
THE
HEFFTER REVIEW


Penso, logo Sou!
Laboratório de Investigação da Consciência

WHAT IS THE HEFFTER RESEARCH INSTITUTE?

Given the paramount importance of the nature of the human mind to global existence, it is curious -- and unsettling -- to realize how little we know about it. The mind is the source of all discovery and invention, yet the relationship between brain and mind remains a mystery. Since our minds are our only means of solving the problems we face on this planet, understanding how the mind works and the nature of its relationship to the brain is an urgent and compelling priority.

Psychedelics have the unique ability to transform fundamentally the very functions that we consider uniquely human: the way we think, feel, communicate, and solve problems. They shift our cognitive and symbolic capacities, our aesthetic and spiritual sensibilities, and our linguistic and imaginative abilities; the very kinds of brain functions that constitute the fabric of what we experience as mind. Because psychedelic agents are similar to natural substances already present in the human brain, the careful study of their effects upon brain function and experiences provides access to primary states of brain and mind and the connections between them. For these reasons, research with psychedelic substances offers an unparalleled opportunity for understanding the relationship of brain to mind in ways not possible using other methods. Indeed, it is the thesis of the Heffter Research Institute that these substances represent an essential technology for this investigation. From the chemical and neurological level, to the psychological and spiritual, psychedelic research is a complex and difficult area of exploration. Nevertheless, the time has come to apply our scientific sophistication to explore the powerful influences of psychedelics on the brain and mind.

For millennia, psychedelics played essential roles in the culture and spiritual practices of advanced civilizations such as the Mayans, Greeks, and Indo-Aryans. These substances hold similar importance today in many traditional non-Western societies. We are at an historic moment. Old social orders are changing rapidly. Economic powers are restructuring for the future. There is widespread popular interest in the brain and mind as never before. Interest in research with psychedelics seems to be growing, and yet organized financial support for this work is on the wane. The Heffter Research Institute is uniquely poised to be a key player in the revival of psychedelic research.

MISSION

The mission of the Heffter Research Institute is to conduct research of the highest scientific quality with psychedelic substances in order to contribute to a greater understanding of the mind, leading to the improvement of the human condition, and the alleviation of suffering. This mission has already begun to attract scientists and researchers of the highest caliber. The information and new knowledge gained will be disseminated to the medical and scientific communities.

The Heffter Research Institute was incorporated in New Mexico in 1993 as a non-profit, 501(c)(3) organization in the belief that such research was not only viable but critically important. The Institute is named after Dr. Arthur Heffter, a turn-of-the century German research pharmacologist who discovered that mescaline was the principal psychoactive component in the peyote cactus.

The current political and intellectual climate offers new opportunities to reopen avenues of research that have been extremely difficult, if not impossible, to pursue in the past within conventional frameworks. Government agencies will provide support to legitimate researchers of psychedelic agents, as the Institute Founders can testify from long periods of research funding. Nevertheless, when it comes to extending the investigations from animal models to human subjects, or to testing hypotheses that the effects of psychedelics may in certain circumstances be beneficial rather than entirely detrimental, the government's role as a supporter of research has been insufficient.

In order for truly uncompromised and creative research in the field of psychedelic neuropsychopharmacology to have any hope of fulfilling its promise, it must be pursued from within the context of a research institute whose operations and research programs are independent of government funding. The Heffter Research Institute will neither condemn psychedelic drugs nor advocate their uncontrolled use. The sole position of the Institute in this regard will be that psychedelic agents, utilized in thoughtfully designed and carefully conducted scientific experiments, can be used to further the understanding of the mind.

The Heffter Research Institute will provide support, facilities, and opportunities to conduct both basic and clinical scientific research on psychedelic drugs that is legitimate and scientifically sound. The Institute is based on the belief that such investigations hold great potential for producing genuine breakthroughs in the understanding of the human mind. The Founders intend that the Heffter Research Institute will be an enduring institution in the service of humankind.

The general objectives of The Heffter Institute include:

- Developing knowledge regarding, and standards of practice for, the appropriate and safe use of psychedelic drugs in a medical context.
- Conducting basic chemical, pharmacological, and neurobiological investigations on psychedelic substances and their mechanisms of action.
- Conducting ethnopharmacological investigations designed to clarify our understanding of the role played by psychoactive plants in the religious, medical, and social institutions of other cultures.
- Conducting phytochemical and pharmacological investigations of plants and other naturally occurring materials, designed to discover, isolate, and characterize novel natural products with psychedelic or other types of psychoactivity.
- Publishing scientific reports, earning grants and awards; organizing and sponsoring scientific conferences to present research results, and providing a forum for discussions of the appropriate medical and scientific uses of psychedelic drugs.
- Conducting clinical research studies to investigate potential therapeutic applications of psychedelic drugs.
- Informing the scientific and medical communities about the issues of safety, adverse effects, and therapeutic potentials related to psychedelic drug use in a medical context.

BE A PARTNER IN THE INSTITUTE'S PROGRESS

The Heffter Research Institute invites the support of those who wish to help realize its unique and valuable mission. Those individuals, corporations, and foundations, having the vision and commitment to help sponsor this research enterprise, do so knowing that their contribution to the Institute and to the field of medicine is a critically important one.

Gifts for research, operating support, and capital funds are welcomed. In addition to gifts of cash, the Institute accepts gifts of securities as well as planned gifts and bequests. The Institute will work with a prospective donor to help realize the fullest tax advantage possible.

THE CHALLENGE

The Heffter Research Institute's Board of Directors has embarked upon an ambitious course. At this initial stage, research and start-up funds are needed to carry out our mission. Significant contributions will be needed to reach the Institute's short and long-term goals. Potential donors are invited to contact the Institute at 330 Garfield, Suite 301 Santa Fe, NM 87501, to explore our World Wide Web site at http://www.heffter.org, or to contact George Greer, M.D., by telephone: (505) 982-0312, Fax: (505) 992-8260, or INTERNET (george@heffter.org), to explore how they might wish to participate in this idea whose time has come.

The Heffter Review of Psychedelic Research

Volume 1, 1998

Editor: David E. Nichols, Ph.D.

Published by:

The Heffter Research Institute
330 Garfield, Suite 301
Santa Fe, NM 87501
www.heffter.org

Cover Art: Genesis I, Benini, 1994, by permission of the artist
Cover design by Mark Plummer

List of Contributors

Callaway, Jace C., Ph.D., Department of Pharmacology and Toxicology, University of Kupio, Kupio, Finland

Carter, Thomas J., Ph.D., Department of Computer Science and Cognitive Studies, California State University, Turlock, California

Geyer, Mark A., Ph.D., Dept of Psychiatry, School of Medicine, University of California at San Diego, La Jolla, California

Gouzoulis-Mayfrank, Euphrosyne, M.D., Psychiatric Department of the Technical University (RWTH), D-52074 Aachen, Germany

Grinenko, A. Ya, M.D., Ph.D., Research Laboratory, Leningrad Regional Dispensary of Narcology, Leningrad Region, Russia

Grob, Charles S., M.D., Dept of Psychiatry, Harbor-UCLA Medical Center, Torrance, California 90509

Hermle, Leo, M.D., Psychiatric and Neurological Hospital “Christophsbad” Faurndauerstrasse 6-28, D-73035 Göppingen, Germany

Krupitsky, Evgeny M., M.D., Ph.D., Research Laboratory, Leningrad Regional Dispensary of Narcology, Leningrad Region, Russia

McKenna, Dennis J., Ph.D., P.O. Box 224, Marine on St. Croix, Minnesota 55047

Myers, Lin S., Ph.D., Departments of Psychology, Computer Science and Cognitive Studies, California State University, Turlock, California

Nichols, David E., Ph.D., Dept of Medicinal Chemistry and Molecular Pharmacology, School of Pharmacy and Pharmacal Sciences, Purdue University, W. Lafayette, Indiana 47907

Schultes, Richard Evans, Ph.D., Director Emeritus, Harvard Botanical Museum, Cambridge, Massachusetts

Vollenweider, Franz X., M.D., Program on neurobiology, University of Zurich Medical Faculty, Psychiatric University Hospital, Research Department, Zurich, Switzerland

Walsh, Roger, M.D., Department of Psychiatry and Human Behavior, College of Medicine, University of California at Irvine, Irvine, California

Watkins, Shelly S., M.A., Department of Neuropharmacology, The Scripps Research Institute, La Jolla, California.

Foreword

There has been an extensive polarization of both political and public opinion over the last ten years in the area of drug use. The phrase "drug abuse" has been promoted into the role of a metaphor for the problems in our society, and it has become the straw man for their solution. If we could win the "war on drugs" we would have no more problems with crime (or poverty, or racism, or street gangs, or illiteracy) and our social system would again become healthy and stable. The blaming of all of our problems on the drug abusers of today is a chilling parallel to the assigned role of the Jews as the target problem in Germany, in the mid-30's. It is as if there are two opposite camps, the drug warriors and the legalizers. If you were to speak against one, you would be branded a member of the other. Neither statesmen nor politicians can dare voice any rationality in these areas of controversy as neither chose to be branded as a spokesman for the other side. Quite literally, the arena has become a, "If you are not for us, you are against us," dichotomy, and there is less and less dialog occurring. At the Congressional level, any new law that mentions the word "drug' in the definition of a crime or the increasing of a penalty against crime, is rarely opposed. Any counter arguer would be seen as "soft on drugs," and would fear losing voter support. In recent years, even the Supreme Court has voted more and more frequently on the side of perceived public response to their decision, rather than on the Constitutional fine print, when an appeal being considered has involved the word, "drug."

Even simple phrases have become loaded sound-bites. A convention on harm reduction in the area of drug use or the potential medical uses of marijuana will be seen by law enforcement and the political establishment as a gathering of drug legalizers, and they will condemn it from a distance. A convention on international precursor control or the neurological risks associated with the use of illegal drugs will be seen by the medical and academic community as a gathering of politically motivated authority figures who wish to limit our freedoms for socially valid reasons. There is no question but that the pendulum is swinging more and more to the side of restrictions and punishment, but any voice that speaks too loudly against this position is condemned as "sending the wrong message."

In the medical area, this division is extreme. The definition of a Schedule I drug is that it has a high abuse potential and no accepted medical utility. Yet there is no provision for any abuse potential other than "high" nor any statutory guidance as to what would constitute "accepted." There is the voice of the "drug warrior" camp that there can be no toleration of any use of a scheduled drug until it has been proven to be safe. There is the counter voice of the "legalizers" that there is no research permitted to establish hazard and, furthermore, there is no definition of the nature of the needed evidence that would constitute proof of safety.

The extremes of this positional separation are just as dramatic in the area of scientific research. In the academic world there has been a gradual shifting of research funding sources from the interests of the University to the interests of the Government. Today a very large percentage of research at both the graduate and the post-doctoral levels is supported by grants from any of several institutes in Washington. And, as the recipients of these grants are increasingly beholden to the political bodies that fund them, they effectively define what is acceptable science. Whereas grant applications were originally chosen to reflect the questions arising out of the curiosity of the experimenter, now they usually reflect the quest for answers that would be of interest to the funder. And again, in the area of drugs this is strongly biased towards the perceived need for information that would support the war on drugs and further justify its escalation. Many grants are awarded specifically to document some negative property of a given drug, rather than simply to search for the properties of that drug.

I would like to propose a middle ground within this turmoil. The perceived "drug" crisis is thought by most people to reflect the use of stimulants and narcotics, with a generous sprinkling of marijuana. There are obvious problems with the stimulants, cocaine and methamphetamine, as well as with the depressants opium and heroin. And marijuana is the favorite bête noire as it is the de facto major justification for our entire law enforcement's existence. Without this plant, our need of drug law enforcement would collapse to about one fifth of where it is today. But, almost unnoticed are the psychedelic drugs which are quite different and distinct. They have been caught up in this anti-drug rubric, even though very few problems have been specifically associated with this minor

category. A few of them, such as LSD and MDMA, have become front-page stuff, and occasionally there are scare stories in the papers concerning novelties such as toad-licking and mushrooms. But to a large measure, this psychedelic fringe is neither newsworthy nor threatening, within the public awareness. It rests there largely as an unknown.

Perhaps we can use this relative anonymity as a modest platform, as a foundation, for the development of a research philosophy that is, truly, on middle ground. The political community, along with the law enforcement and the fundamentalist communities, have all found positions at the extremes, and they cannot take a position that even recognizes a middle ground. When a statement is made by a person in power demanding agreement and compliance concerning some evil drug matter, almost all public figures accept and support his statement. In private, there might be some reservations, but in public there are none. The political position has been lost. But maybe the scientific position has not yet been committed.

Might this community begin to ask questions about a drug such as, "What is its action?" rather than, "Does it have a good or a bad action?" "What is the mechanism of action?" rather than, "What is the mechanism of neurotoxicity?" Small changes such as these would in no way change the intended research protocols, and what is to be observed will still be observed.

Many scientists in the academic community are to some degree intimidated by subtle restraints, and are thus unable to talk with complete candor. But I believe that it is in this very community that the battle-lines of the war on drugs have not yet been cast in stone, and that honest inquiry might still be sought.

Here is a request to the scientists of the world. The next time you submit a grant proposal, state your questions as being from your curiosity, rather than from a search for answers that might bring you government approval. Think twice about framing your question as an answer that you expect to verify experimentally. The excitement of science is in discovery, not in confirmation.

As research scientists, we still command a broad audience, and we do not need to become political lackeys. We must remain articulate. We must remain sincere. And we must retain our integrity. We are the middle ground in a very polarized system, and we must confirm and expand that central position.

Alexander Shulgin
Lafayette, California

Preface

On November 23, 1897, Dr. Arthur Heffter, an outstanding German scientist with training in chemistry, pharmacology, and medicine, performed a careful self experiment with one of the alkaloids that he had isolated from a small cactus. On the 100th anniversary of that date, it seems an auspicious time to be introducing what we hope will be the first of a series of Reviews, named in honor of Dr. Heffter.

The results he obtained on that day established for the first time that a specific chemical substance, which he named mescaline, was responsible for the dramatic and profound psychopharmacological effects that followed the ingestion of a small Southwestern American cactus that had been named peyotl by the Aztec Indians. This cactus, now known as peyote (*Lophophora williamsii*) was the subject of intense intellectual curiosity in the early part of the 20th century. It presently serves as the sacrament for the Native American Church but has been utilized for millenia as the focus of religious rituals by indigenous Indian peoples in the Americas.

In 1943, Dr. Albert Hofmann, a research chemist working at the Sandoz laboratories in Basle, Switzerland, accidentally discovered that a substance he had synthesized in 1938, named LSD-25, had similar profound effects on the psyche. Thus began a relatively short-lived saga that led Dr. Hofmann to isolate and identify a number of active principles from "magical" substances that had been used since antiquity by preindustrial cultures. While mescaline is a simple phenethylamine, perhaps more closely related in structure to the neurotransmitter known as dopamine, it proved to be the case that LSD, certain active principles in the seeds of morning glories and related plants, in various *psilocybe* mushrooms, and in numerous snuffs and plant decoctions used by South American Indians were all built around a chemical scaffold known as tryptamine, the same template upon which the ancient and natural brain neurotransmitter known as serotonin is constructed. The discovery of LSD, and the recognition of this chemical relationship, helped to catalyze the revolution in neuroscience that continues today, and led to early awareness of the importance of the role of serotonin in the brain.

While there was a period during the 1950s where artists and philosophers explored the magical properties of these newly rediscovered but ancient materials, ultimately their profound and ineffable effects on the human psyche have led to widespread use by generations of adolescents. Of course, no one reading this material will be unfamiliar with the fact that these substances, known variously as psychedelics or hallucinogens, are now classified in a restrictive drug category that seems to hold the attention of only a handful of research scientists throughout the world. It has been the aim of the Heffter Research Institute (*http://www.heffter.org*) to foster and maintain research interest in these substances, until the day that their value as research tools and potential therapeutic agents may again be recognized.

There has been no generally recognized forum for the discussion of psychedelic agents by scientists for many years. Many current sources are anonymously authored, and contain anecdotes, the equivalent of old wife's tales, or urban myths, serving only to propagate and create misinformation, something the Heffter Institute adamantly opposes. It is the aim of the Institute, with this inaugural volume, to begin the periodic publication of a series of reviews that will place into perspective current research with psychedelic agents. It is hoped that in these pages, and in future volumes of the Review, a dialogue can be maintained that will convey to readers a real impression of the state of the art in this exciting research arena. Theoretical, practical, and clinical issues will be addressed and as time passes we hope that the number and scope of the contributions to the review will increase.

David E. Nichols
West Lafayette, Indiana

Mark A. Geyer
San Diego, California

November 1997

1. Antiquity of the Use of New World Hallucinogens

Richard Evans Schultes, Ph.D., F.M.L.S

"In the exudates and decoctions from trees and herbs, man has found principles that have permitted him to experience a kinship with the whole of creation." -- William Emboden (1979)

Abstract:

A review of psychoactive plants known from archaeological contexts and artistic representations shows that their use has spanned centuries, continuing in places in Mexico and South America to the present day. The discovery of the unusual properties of these plants took place as part of the exploration of the physical milieu of the Western Hemisphere. That these plants must in some cases be made into infusions in order to be consumed reveals ancient enterprise in manipulating aspects of the environment. The surprising results obtained from treating psychoactive plants allowed their users to communicate more directly with the unseen world which they believed to exist.

It was the great German toxicologist Louis Lewin (1931) who wrote that "from the beginning of our knowledge of man, we find him consuming substances of no nutritive value, but taken for the sole purpose of producing for a certain time a feeling of contentment, ease and comfort."

There is ample material proof that narcotics and other psychoactive plants, such as hallucinogens, were employed in many cultures in both hemispheres thousands of years ago. The material proof exists in some archaeological specimens of the plants in contexts indicating magico-religious use and in art forms such as paintings, rock carvings, golden amulets, ceramic artifacts, stone figurines, and monuments.

Aquifoliaceae Guayusa (Ilex Guayusa)

Guayusa, while probably not hallucinogenic as ordinarily used, is definitely psychoactive, due to its high concentration of caffeine. A tea of the leaves is still used by the Jivaro and other Indians in Ecuador as a stimulant and, in highly concentrated doses, as an emetic for purification before ceremonies or important tribal conferences. These functions were well developed long before the Spanish Conquest, and the Jesuits early established a lucrative market for the leaves in Europe as a cure for syphilis and other diseases; according to their records, they maintained a large plantation of Ilex Guayusa in southern Colombia, the remnants of which can still be seen (Patiño 1968; Schultes 1979). Today, guayusa leaves are sold for medicinal purposes in Quito, Ecuador, and Pasto, Colombia, where they were believed to cure a wide spectrum of ills.

It was with great surprise that an archaeological find indicated the early use of these leaves in distant Bolivia. In the tomb of a medicine man of the culture, dated about A.D. 500, were found several perfectly preserved bundles of flattened leaves neatly tied with fibrous material. In association with these bundles was a snuffing tube, other tubes that have been interpreted as clysters, bamboo storage tubes for powder, spatulas, snuff trays, and a mortar and pestle. The guayusa leaves, which were prepared for the grave with great care, gave positive tests for caffeine after 1500 years (Schultes 1972).

Several caffeine-yielding species of Ilex have been the source of beverages, especially yerba maté in Argentina, yaupon in the southeastern United States, shui-chatze in Tibet and China (Hartwich 1911; Hu 1979). The presence in the Bolivian burial of so much equipment associated with snuffing and the actual remnants of a powder clearly indicate that the leaves were taken as a snuff: there is no reason to believe that caffeine administered in this way would not be absorbed into the general circulation through the nasal mucosa. This discovery is the only one which unequivocally shows that a caffeine-rich product was used as a snuff.

If the extra tubes are correctly interpreted as clysters, they may further indicate application by enema, in which caffeine could likewise be absorbed into the general circulation. No caffeine-rich plant has ever been known to have been used in this way, although rectal administration of tobacco, yopo, and other drugs in the New World is clearly substantiated.

Yaupon (Ilex vomitoria)

In the southeastern part of the United States, the Indians were employing a strong tea of Ilex vomitoria - known as the Black Drink - as a

ceremonial stimulant and emetic when the first Europeans arrived (Hale 1891; Milanich 1979). This tea was made by boiling large doses of leaves for a long time, until the resulting solution was a dark green. In such concentrated infusions, the plant easily acts as an emetic and, so far as we know from early records, this ritualistic cleansing of the body before important tribal convocations was its principal use amongst the American Indians - a custom closely paralleled by the use of guayusa today among the Jivaros of Ecuador.

Evidence of its use in North America from archaeological contexts is circumstantial but convincing. Cult objects from gravesites such as shell drinking cups engraved with cult symbols have been interpreted as vessels for the ceremony of the Black Drink. These shell cups, dating ca. A.D. 1200, were widespread in the Southeast. Residues believed to be from evaporated Black Drink have been found in some (Milanich 1979).

Bolbitiaceae, Strophariaceae

Teonanacatl (Stropharia cubensis; Panaeolus sphinctrinus)

The early Spanish ecclesiastics in conquered Mexico were much disturbed by pagan religions centered upon the sacramental use of several mushrooms known in Nahuatl as teonanacatl ("flesh of the gods"). Divination, prophecy, communion with the spirit world, and curing rituals depended upon the narcotic intoxication induced by these mushrooms and interpretation of the visual and/or auditory hallucinations accompanying the intoxication. Persecution drove these Indian practices into the hinterland, so no archaeological evidence of the magico-religious use of mushrooms was found for a long time. It was even doubted that teonanacatl was a mushroom; the idea that, because a dried mushroom resembled the dried top of the peyote cactus, teonanacatl was but another name for peyote was widely accepted (Safford 1915). Not until the late 1930s and early 1940s were identifiable mushrooms collected from contexts interpreted as ceremonial (Schultes 1939). The modern center of the area in which this mushroom is used is in the Mexican state of Oaxaca, among the Mazatecs.

The velada or mushroom ceremony among the Mazatecs is usually held in response to a request by a person needing to consult the mushrooms about a problem. A complicated diagnostic or curing ritual frequently takes place during an all-night ceremony (Schultes 1939; Wasson et al. 1974). One or two monitors who do not take the mushrooms must be present to listen to what is said. Certain abstinences must be practiced preparatory to the ceremony. It is now known that mushroom ceremonies in southern Mexico use at least two dozen species of mushrooms in several genera, the most important being Stropharia, Psilocybe, and Panaeolus (Guzmán 1959; 1977; Heim 1963; Ott and Bigwood 1978; Schultes 1939; 1969; Singer 1958; Wasson 1973; Wasson and Wasson 1957).

The mushrooms are usually employed fresh and dry. Their shamanistic use is today extraordinarily important, especially among the Indians of Oaxaca. The officiating shaman in tribes of southern Mexico - Mazatecs, Zapotecs, and others - may often be a woman. The all-night ceremony among the Mazatecs of the Sierra Juarez of Oaxaca often includes a curing ritual; the most famous of the shamans of this region, Maria Sabina, sings throughout the night and prays for power from spiritual realms through the mushrooms. Since the modern ceremony is part-Christian, part pagan, all possible help is implored. The following sampling of the night-long chants in Mazatec (translated) shows their variety:

The law which is good
Lawyer woman am I.
Woman of paper work am I.
I go to the sky,
Woman who stops the world am I.
Legendary woman who cures am I.
Father Jesus Christ
I am truly a woman of law,
I am truly a woman of justice...
Woman of space am I,
Woman of day am I,
Woman of light am I...
I give account to my Lord
And I give account to the judge,
And I give account to the government,
And I give account to the Father Jesus Christ,
And my mother princess, my patron mother.
Oh, Jesus, Father Jesus Christ,
Woman of danger am I,
Woman of beauty am I...

The antiquity of sacred mushroom cults in Mexico and adjacent areas is now well established, and they appear to have deep roots in centuries of native tradition. Frescoes from central Mexico dated to AD 300, indicate that mushroom worship goes back at least 1700 years (Wasson 1980). Stylized mushroom caps - undoubtedly Psilocybe aztecorum - decorate the pedestal of a statue of Xochipili (Aztec god of flowers) discovered on the slopes of Mount Popocatepetl and dated to approximately AD 1450 (Wasson 1973). A terra-cotta artifact, ca. 100-300 AD, found in Colimo, shows figures dancing around

a Psilocybe-like mushroom (Furst 1974). Clay figurines with mushroom effigy "horns" from Jalisco are about 1800 years old (Furst 1974). A terra-cotta figurine of the Remojadas style found in Vera Cruz depicts a curandera praying over a mushroom; the artifact is about 2000 years old (Heim 1967).

Even more remarkable are the so-called "mushroom stones" found at highland Mayan sites in Guatemala. These are dated at about 500 BC or earlier. Each consists of on upright stipe with a human or animal figure, the whole crowned with an umbrella-shaped top. Long puzzling to archeologists, they were once interpreted as phallic symbols. Now it is quite widely accepted that they were associated with a mushroom cult, perhaps, as has been suggested, with a Meso-American ball game ritual, itself a religious ceremony. These artifacts appear to indicate a very early sophisticated mushroom cult far beyond the present Mexican geographical limits of the magico-religious use of the fungi (Borhegyi 1961; Furst 1974; Mayer 1977; Ott and Bigwood 1978).

There is today no evidence that hallucinogenic mushrooms are ceremonially employed by Indian groups in South America. It is possible, however, that they were so used in northern Colombia at a period from 100 to 350 AD. In the Gold Museum in Bogota, there are many anthropomorphic pectorals from the Sinú Culture (Schultes and Bright 1979). The earlier, more realistic of these gold artifacts have hemispherical caps separated from the head by definite stipes; in later models, both the human figure and the dome shaped cap become stylized - the domes losing their stipe and becoming affixed directly to the idol. These spherical domes have led to their identification as pectorals for lack of a better explanation of their use, "telephone bell gods", because of the two domes on the heads that suggested old fashioned telephones. Significant is the presence on many of these pectorals of a toad or frog, animals of great magico-religious importance in connection with intoxication in ancient and modern Andean cultures. The discovery in the region of the Sinú Culture of a number of species of Psilocybe, some of which are provided with the hallucinogenic constituent psilocybin, strengthens the suggestion that these pectorals may indicate the ceremonial use of psychoactive mushrooms in magico-religious rituals among the Indians of northern Colombia (Schultes and Bright 1979).

Cactaceae

Peyote (*Lophophora williamsii*) - It has long been suspected that the use of the Mexican hallucinogenic cactus peyote (*Lophophora williamsii*), today widely valued as a sacred intoxicant in magico-religious ceremonies in central and northern Mexico and the basis of a religious cult among Indians of the United States and Canada - was of great age. It is the spineless top of the peyote cactus that is usually taken in Indian ceremonies. Most frequently, it is dried into a so-called "peyote button," but sometimes the freshly severed crown of the plant may be used (Schultes 1938). The Huichol Indians of Mexico, for example, make an annual sacred pilgrimage to Wiricuta - home of the peyote plant - to collect with complex ceremonies enough crowns of the cactus for use during the coming year (Furst 1972; Meyerhoff 1974). In the United States, in regions far removed from areas in which peyote exists, the members of the peyote cult, organized into the Native American Church, may receive their supplies of peyote quite legally in the form of dried peyote buttons (Schultes 1937). These "buttons" are consumed ceremonially with no preparation. Held in the mouth until thoroughly moistened, they are then swallowed; a native worshipper in the all-night peyote ceremony in the United States may consume up to 25 or 30 buttons in one night (La Barre 1964).

There is now firm evidence of the great antiquity of the reverence of this cactus as a divine or sacred plant. The earliest European reports of peyote intimate that the Chicimecos and Toltecs of Mexico were acquainted with it as early as 300 BC, although the accuracy of the dating depends on the interpretation of native calendars (Anderson 1980; Schultes 1938); thus the date may even be earlier.

Recent archeological finds in shelters and caves in the Cuatro Cienegas Basin in Coahuila, Mexico, and trans-Pecos, Texas, dated by ^{14}C and spanning some 8000 years of intermittent human occupation, included, among other plant remains, identifiable specimens of *Lophophora williamsii* - often in abundance and in a context that suggests ritual use. The peyote was accompanied by quantities of seeds of the hallucinogenic red bean (*Sophora secundiflora*) and the toxic Mexican buckeye (*Ungnadia speciosa*) which is suspected to be psychotropic (Adovasio and Fry 1976).

Of great significance are ceramic bowls from Colima, Mexico, dated about 100 BC to 200-300 AD, with four peyote like ornaments and a male hunchbacked figure (also from Colima and of the same age) holding a pair of peyote plants (Furst 1974). It has been suggested that the plants in the Colima peyote effigy may indicate incipient or temporary domestication of the cactus in prehistoric times.

San Pedro Cactus (Trichocereus pachanoi)

There exists today a folk-healing ceremony based in part on the use of the hallucinogenic cactus known in Andean South America as San Pedro, San Pedrillo, aguacolla, and gigantón. A brew of the stems of this tall cactus is prepared, often with other psychoactive plants added (e.g., the Solanaceous Brugmansia candida or floripondio). The brew is employed in magic ceremonies, as a medicine and to protect homes, "as if it were a dog." A drink prepared of the soft interior of the stems of the cactus is also administered in ceremonial contexts. In the highland Indian markets of Peru and Bolivia, cut pieces of the stem of the cactus are sold for preparation of the sacred, intoxicating drink. The San Pedro cactus is now widely employed in Peru and Bolivia in curing ceremonies that combine Christian and pre-Columbian native elements (Davis 1983; Sharon 1972; 1978). The use of this cactus goes far back in prehistory, and there is evidence that its ritual utilization was widespread in the central Andes at the time of the Spanish Conquest. There exist two references to this "plant with which the devil deceived the Indians" from European ecclesiastical reports of the mid-fifteenth century (Sharon 1972).

There are, in addition, artifacts that indicate that its use in Peru goes back at least three thousand years. The oldest known evidence of this kind is a stone excavated at Chavín de Huantar in the northern Peruvian Andes; dating from about 1300 BC, it is carved with a mythological being holding a section of stem of the cactus. Chavín textiles from the south coastal region of Peru show the cactus in association with the jaguar, an animal associated throughout Andean South America with intoxication and hallucinogens; these textiles are dated in the first millennium BC (Sharon 1972). Ceramics dating from 500 to 1000 AD depict sections of the San Pedro cactus together with the jaguar (Furst 1972). The use of this hallucinogen apparently continued on the southern coast of Peru after the decline of the Chavín influence; four ceramic urns in the form of mummy bundles from the Nasca culture, dated from 100 BC to AD 500 have been found with representations of the stem of the cactus protruding from each shoulder (Sharon 1972). In northern Peru, ceramic vessels with representations of San Pedro date to about 400 to 200 BC. (Sharon 1972). At the present time, the ritual is extensively practiced by shamans in the coastal regions of Peru, where it has heavy Christian overtones (Sharon 1972). *Trichocereus pachanoi* has as its active hallucinogenic constituent mescaline, the same alkaloid that is responsible for the visions induced by the peyote cactus (Schultes 1980).

Convolvulaceae

Ololiuqui (Turbina corymbosa, Ipomoea violacea)

A number of Spanish chroniclers of the time of the Conquest of Mexico described in detail the religious and medicinal use of a small lentil-like seed known to the Aztecs as ololiuqui. Its source was a vine called coatlxoxouhqui, which was clearly a morning glory (Reko 1934; Schultes 1941). For nearly four centuries, no species of the Morning Glory Family was found in use as a divinatory hallucinogen, and no psychoactive principle was known until recently in the family Convolvulaceae. Many .writers accepted the suggestion that ololiuqui was a member of the toxic Nightshade Family (a species of Datura), although there were voices of protest (Reko 1934). It was not until the 1930s that identifiable material associated with its magico-religious use as collected in Oaxaca (Schultes 1941). The source plant encountered "in almost all the villages of Oaxaca (where) one finds seeds still serving the natives as an ever present help in time of trouble" (Wasson 1963).

The use of these morning glory seeds as sacred intoxicants in curative ceremonies of ancient origin seems to be focused in Oaxaca, Mexico. In the Mazatec country of that state, the seeds must be ground on a metate (quern) by a maiden and prepared in a cold-water solution. The resulting drink is given to the patient, and the mumblings that he makes during his intoxication are interpreted by on assistant whose task is to listen.

Two species of morning glories are employed in Oaxaca: *Turbina corymbosa* with small, round, brown seeds, and *Ipomoea violacea* with larger, angular, jet black seeds. The chemical constituents in the two species differ. The total ergoline alkaloid content of the seeds of the former species is 0.012 percent, whereas of the latter it is 0.06 percent. This fact explains why Indians use smaller quantities of seeds of *I. violacea* than of *T. corymbosa* (Schultes 1980).

Ololiuqui was one of the most important hallucinogens in ancient Mexico. The plant is depicted in mural painting at Teotihuacan and Tepantitla. These murals show the water goddess with a stylized vine of the sacred hallucinogenic morning glory (Furst 1974).

We know much about the pre-Conquest use of ololiuqui because of the numerous detailed reports made immediately after the arrival of the Spaniards. The personal physician of the king of Spain, Dr.

Francisco Hernández, wrote of the medicinal and magico-religious use of ololiuqui among the Aztecs between 1570 and 1575, a five-year period during which he was studying the native medicinal plants of Mexico; he figured the source plant was a morning glory (Schultes 1941). A painting in the Florentine Codex definitely illustrates a morning glory which the Spanish ecclesiastical authorities considered a gift of the devil (ibid.).

Leguminosae

Red Bean or Mescal Bean (*Sophora secundiflora*)

The red seeds of *Sophora secundiflora*, a beautiful shrub of the dry parts of northern Mexico and the southwestern United States, once formed the basis of a vision-seeking ceremony practiced by a number of Indian tribes (Adovasio and Fry 1976; Schultes 1969; Schultes and Hofmann 1979). The ceremony was known variously as the Red Bean Dance, the Wichita Dance, or the Deer Dance (Campbell 1958). The ingestion of the red beans is extremely dangerous, since the active alkaloid - cytisine - is highly toxic and can cause death by asphyxiation, by attacking the phrenic nerve controlling movement of the diaphragm. As the ritual employment of the safe peyote cactus spread northward from Mexico, the use of the red bean gradually died out, although it is believed that occasionally both hallucinogens were taken together in the early days of peyote use in the United States. It is true, however, that today in certain American tribes part of the ritual dress of the leader of the peyote ceremony consists of a necklace of this once sacred narcotic seed - the only vestige of the former role of this toxic hallucinogen. Cabeza de Vaca, one of the early Spanish explorers of Texas, reported in 1539 that these seeds were an article of trade among the Indians of the region (Schultes 1980). Now, however, there is archaeological evidence for the use of Sophora secundiflore (Adovasio and Fry 1976). Caches of the red bean have been discovered in numerous archaeological sites in northeastern Mexico and trans-Pecos Mexico, often in association with peyote and Mexican buckeye seeds. These sites, dated by ^{14}C, span the period from 7000 BC to AD 1000. The vegetal materials often provided evidence of potential ceremonial use, possibly in a hunting cult (Adovasio and Fry 1976).

Yopo and Vilca

(*Anadenanthera peregrina* and *A. colubrina*)

It is not usual that archaeological remains of plants are found in the wet tropics, although this is true of yopo, a hallucinogenic snuff prepared from the beans of a leguminous tree - *Anadenanthera peregrina*, formerly known by the binomial Piptadenia peregrina (Altschul 1964). This psychoactive powder was widely used in much of the Caribbean (where it was known as cohoba) at the time of the Spanish Conquest (Safford 1916) but it persists now only in the Orinoco of Colombia and Venezuela and adjacent parts of Brazil (Altschul 1972; Safford 1916). Archaeological remains of snuffing tubes and trays can definitely be associated with the use of this hallucinogen (Torres et al. 1991). The first scientific report of yopo was given by the explorer Baron von Humboldt, who witnessed the preparation of the snuff on the Rio Orinoco in 1801 (Schultes and Hofmann 1980). The British botanist Spruce in 1851 offered an extremely detailed description of the preparation and use of the drug (ibid.). The glossy black beans -five to twenty in each pod - are toasted and pulverized. The powder is then sifted and mixed in equal parts with the alkaline ashes of certain barks or leaves, especially ashes of the bark of a wild member of Theobroma, the genus that yields cacao or chocolate (ibid.).

A missionary in the Colombian Orinoco wrote in 1560 that the Indians living along the Rio Guaviare "are accustomed to take yopo and tobacco, and the former is a seed or pip of a tree . . . they become drowsy while the devil, in their dreams, shows them all the vanities and corruptions he wishes them to see and which they take to be true revelations in which they believe, even if told they will die" (Schultes and Hofmann 1979). Yopo was so important in pre-Conquest Colombia that Indians of the highlands, where the tree will not grow, acquired the drug in trade from the tropical lowlands.

Yopo snuff is often token daily as a stimulant, but it is more commonly employed by payés ("medicine men") to induce trances and visions and communicate with the hekula spirits; to prophesy or divine; to protect the tribe against epidemics of sickness; to make hunters and even their dogs more alert. Yopo is quick acting. It first causes a profuse flow of mucous from the nasal passages and occasionally a noticeable quivering of the muscles, particularly of the arms, and a contorted expression of the face. This period soon gives way to one in which the shamans begin to prance, gesticulating and shrieking violently. This expenditure of energy to frighten away the hekula spirits lasts up to an hour. Eventually fully spent, the shamans fall into a trance-like stupor, during which nightmarish hallucinations are experienced.

In the more southerly parts of South America, the Indians prepared a snuff from another species of

Anadenanthera: A. colubrina (Califano 1976). It is still employed by Indians in northern Argentina, where it is known as huilca or vilca and cebil (Altschul 1967). There is evidence from native art that vilca was a plant associated in Peru with mythology.

Concluding Remarks

The discovery of plants with psychoactivity must be attributed to millennia of trial and error experimentation with most or all of the plants in the ambient vegetation of native peoples. There can be no other explanation. When the unearthly and inexplicably weird physical and psychic effects of these few plants were experienced, it did not take long for primitive societies to regard them as sacred elements of the flora, and their use eventually fell into the province of the shamans or medicine men who explained their effects as proof that these species were the home of spirits or spiritual forces enabling man through various hallucinations to communicate with ancestors or with spirits in the outer realms.

Thus, most of these powerful members of the vegetal kingdom became the central figures in magico-religious rituals - rituals which have persisted in many regions to the present time. The role of the plants, as archaeological artifacts and other ancient records attest, has changed little with the passage of time. They remain, in effect, what has been called "plants of the gods."

References

Adovasio, J. M. and G. F. Fry (1976) Prehistoric Psychotropic Drug Use in Northeastern Mexico and Trans-Pecos Texas. *Economic Botany* 30: 94-96.

Altschul, S. von R. (1964) A Taxonomic Study of the Genus Anadenanthera. Contrib. *Gray Herb*. 193. 3-65.

Schultes, R. E., Vilca and its Use. (1967) In: Efron, D.H. (Ed.) Ethnopharmacologic Search for Psychoactive Drugs. Washington, D.C., US. Public Health Service Publ. no. 1645, pp. 307-314

Schultes, R. E., The Genus Anadenanthera in Amerindian Cultures. (1972) Cambridge, Mass., Botanical Museum, Harvard University.

Anderson, E. F. (1980) Peyote - the Divine Cactus. Tucson, University of Arizona Press.

Borhegyi, S. A. (1961) Miniature Mushroom Stones from Guatemala. *American Antiquity* 26: 498-504.

Califano, M. (1976) El Chamanismo Mataco. *Scripta Ethnologica* no. 3, pt. 2- 7-60

Campbell, T. N. (1958) Origin of the Mescal Bean Cult. American Anthropologist 60: 156-160.

Davis E. W (1983) Sacred Plants of the San Pedro Cult. Botanical Museum Leaflets (Harvard University) 29: 367-386

Furst, P. T. (1972) To Find Our Life: Peyote among the Huichol Indians of Mexico. In: Furst, P.T. (Ed.) Flesh of the Gods. New York, Praeger, pp. 136-184.

Furst, P. T. (1974) Hallucinogens in Precolumbian Art. In: King, E.M. and Traylor (Ed.) Art and Environment in Native America. Texas Technical University, Special Publications of the Museum, no. 7, pp. 55-102.

Guzmán, H. G. (1959) Sinopsis de los conocimientos sobre los hongos aluciogenos mexicanos. *Boletin Sociedad Botánico de Mexico* 24: 14-34.

Guzmán, H. G. (1977) Identificación de los Hongos Comestibles y Alucinantes. Mexico City, Editorial Limusa.

Hale, E. M. (1891) Ilex cassine, the Aboriginal North American Tea. U.S.D.A Division of Botany Bulletin 14: 7-22., Washington, D.C., Govt. Printing Office

Hartwich, C. (1911) Die menschlichen Genusmittel. Leipzig, Chr. Herm. Tauchnitz.

Heim, R. (1963) les Champignons toxiques et hallucinogénes. Paris, N. Boubée et Cie.

Hu, Shiu-Ying (1979) The Botany of Yaupon. In: Hudson, C.M. (Ed.) Black Drink - A Native American Tea. Athens, University of Georgia Press, pp. 10-39.

la Barre, W. (1938) The Peyote Cult. Yale University Publications in Anthropology, no. 19. New Haven, Yale University Press; rev. ed., Shoe String Press, Inc., Hamden, Connecticut (1964).

Lewin, L. (1931) Phantastica: Narcotic and Stimulating Drugs. London, Kegan Paul, Trench, Trubner & Co., Ltd.

Moyer, K. H. (1977) The Mushroom Stones of Mesoamerica. Ramona, California, Acoma Books.

Meyerhoff, B. G. (1974) Peyote Hunt. The Sacred Journey of the Huichol Indians. Ithaca, Cornell University Press.

Milanich, J. T. (1979) Origins and Prehistoric Distributions of Black Drink and the Ceremoniol Shell Drinking Cup. In: Hudson, C.M. (Ed.) Black Drink - A Native American Tea. Athens, University of Georgia Press, pp. 83-119.

Ott, J. and J. Bigwood, (Eds.) (1978) Teonanacatl. Hallucinogenic Mushrooms of North America, part I: 5-113. Seattle, Washington, Madrona Publishers.

Patiño, V. M. (1968) Guayusa, a Neglected Stimulant from the Eastern Andean Foothills. *Economic Botany* 22: 310-316.

Reko, B. P. (1934) Das mexikanische Rauschgift Ololiuqui. El Mexico Antiguo 3, nos. 3-4: 1-7.

Safford, W. E. (1915) An Aztec Narcotic. *Journal of Heredity* 6: 291-311.

Safford, W. E. (1916) ldentity of Cohoba. *Journal of the Washington Academy of Sciences* 6: 547-562.

Schultes, R. E. (1937) Peyote (Lophophora williamsi) and Plants Confused with It. Botanical Museum Leaflets (Harvard University) 5: 61-88.

Schultes, R. E. (1938) Peyote - an American Indian Heritage from Mexico. *El Mexico Antiguo* 4, nos. 4-6: 199-208.

Schultes, R. E. (1939) Plantae Mexicanae II. The Identification of Teonanacatl, a Narcotic Basidiomycete of the Aztecs. Botanical Museum Leaflets (Harvard University) 7: 37-54.

Schultes, R. E. (1941) . A Contribution to our Knowledge of Rivea corymbosa, the Narcotic Ololiuqui of the Aztecs. Cambridge, Mass., Harvard Botanical Museum.

Schultes, R. E. (1969) Hallucinogens of Plant Origin. *Science* 163: 245-254.

Schultes, R. E. (1972) Ilex Guayusa from 500 AD to the Present. *Etnologiska Studier* 32: 115-138.

Schultes, R. E. (1979) Discovery of an Ancient Guayusa Plantation in Colombia. Botanical Museum Leaflets (Harvard University) 27: 143-153.

Schultes, R. E. and A. Bright (1979) Ancient Gold Pectorals from Colombia: Mushroom Effigies? Botanical Museum Leaflets (Harvard University) 27:113-141. Reprinted in Sweat of the Sun, Tears of the Moon: Gold and Emerald Treasures of Colombia. Natural History Museum of Los Angeles County, Los Angeles: 37-43 (1981)

Schultes, R. E. and A. Hofmann (1979) Plants of the Gods - Origins of Hallucinogenic Use. New York, McGraw-Hill Book Co.

Schultes, R. E. and A. Hofmann (1980) The Botany and Chemistry of Hallucinogens. 2nd ed., Springfield, Illinois, Charles C. Thomas.

Sharon, D. (1972) The San Pedro Cactus in Peruvian Folk Healing. In: Furst P.T. (Ed.) Flesh of the Gods: the Ritual Use of Hallucinogens. New York, Praeger, pp. 114-135.

Singer, H. (1958) Mycological Investigations on Teonanacatl, the Mexican Hallucinogenic Mushroom. Part 1. The History of Teonanacatl, Field Work and Culture Work. *Mycologia* 50: 239-261.

Torres, Constantino M.; Repke, D.; Chan, K.; McKenna, D.; Llagostera, A. and Schultes, R. E. (1991) Snuff powders from Pre-Hispanic San Pedro de Atacama: Chemical and contextual analysis. *Current Anthropology*, vol. 32, no. 5: 640-640.

Wasson, R. G. (1980) The Wondrous Mushroom: Mycolatry in Mesoamerica. New York, McGraw Hill Book Co.

Wasson, R.G. (1963) Notes on the Present Status of Ololiuqui and the other Hallucinogens of Mexico. Botanical Museum Leaflets (Harvard University) 20: 161-193.

Wasson, R.G. (1972) The Divine Mushroom of Immortality. In: Furst, P.T. (Ed.) Flesh of the Gods - the Ritual Use of Hallucinogens. New York, Praeger, pp. 185-200.

Wasson, R.G. (1973) The Role of 'Flowers' in Nahuatl Culture, a Suggested Interpretation. Botanical Museum Leaflet (Harvard University) 23: 305-324.

Wasson, R. G., G. and F. Cowan, and W. Rhodes. (1974) Maria Sabina and the Mushroom Velada. New York, Harcourt Brace Jovanovich.

Wasson, V. P. and R.G. Wasson (1957) Mushrooms, Russia and History. New York, Pantheon.

This article was adapted from an earlier publication that appeared in "Integration 5", in Autumn 1994.

2. Psychiatric Research with Hallucinogens: What have we learned?

Charles S. Grob, M.D.

Psychiatric research with hallucinogens has resumed. After two decades of virtual prohibition, formal authorization from federal regulatory agencies to conduct investigative studies in the United States with these unique mind altering substances has been successfully obtained (Strassman, 1991). The bitter and acrimonious debate that raged through the 1960s and 1970s and into the 1980s has largely subsided. Scientific and health policy makers have determined that these drugs, although possessing an inherent abuse potential, do have a safety profile of acceptable magnitude when compared to drugs currently the subject of formal research investigation as well as others actively dispensed in clinical practice. The U.S. Food and Drug Administration has therefore determined that formal and well controlled investigations designed to assess the risk-benefit ratio of particular hallucinogenic substances may now be pursued. However, for such studies to proceed successfully and for the much heralded (and often vilified) potential of the hallucinogens to be explored, it is imperative that we fully grasp the lessons of the past. For, to paraphrase Santayana, if we fail to understand our history, we will be condemned to repeat the patterns and reactions which will inevitably lead to yet another round of repudiation and rejection of this unique class of psychoactive substances, along with its inherent and inestimable potential for learning and healing.

Shamanistic Roots

Hallucinogens, throughout the breadth of time, have played a vital albeit hidden and mysterious role. They have often, in aboriginal and shamanic contexts, been at the absolute center of culture and world view (Dobkin de Rios, 1984). Opening up the doors to the spiritual planes, and accessing vital information imperative to tribal cohesion and survival, hallucinogenic plants became what some scholars have considered to be the bedrock of human civilization (Wasson, 1968; Wasson et al, 1978; Huxley, 1978). Within the context of shamanic society, these awe inspiring botanicals were utilized to facilitate healing, divine the future, protect the community from danger and enhance learning (e.g. teaching hunters the ways of animals) (Cordova-Rios, 1971). However, with the advent of stratified and hierarchical societies, such plant potentiators came to be viewed as dangerous to the commonweal and controls were placed on direct and revelatory access to the sacred (Dobkin de Rios and Smith, 1976). In some societies (e.g. Aztec civilization) use of psychotropic plants was restricted to the select castes of the religious priesthood. In others, including the progenitors of our own contemporary Euro-American culture, absolute proscriptions on the use of plant drugs for divine purposes were decreed.

Repression of Shamanistic Traditions

To fully understand the enormous resistances to these drugs and the unique experiences they induce, it would be revealing to examine some elements of our historical legacy. A poorly appreciated period from Fourteenth through Seventeenth Century European History has been the persecution of indigenous healers, predominantly woman, during the reign of the Inquisition, particularly in Northern and Western Europe. During a span of three hundred years several million women were accused of practicing witchcraft and condemned to die. The Medieval scholar Jules Michelet has explored the complicity between ecclesiastical and medical authorities in the subjugation of non-sanctioned healing, commenting on the attitude of the Church "that if a woman dare cure without having studied, she is a witch and must die" (Michelet, 1965). To have "studied" in this context is to have faithfully adhered to the precepts and moral authority of the Church, and to have forsworn receiving knowledge from Nature.

A rich heritage of plant lore and applied healing had been passed down from pagan and pre-Christian Europe, rivaling and often surpassing the demonstrated efficacy of Church sanctioned medical practitioners. Hallucinogenic plants with magical as well as healing properties were essential elements of this indigenous pharmacopoeia. Members of the *Solanaceae* family with their alkaloids atropine and scopolamine, including a great number of species of the genus Datura, as well as mandrake, henbane, and belladonna, had wide application as agents of healing and transcendence (Harner, 1973). In taking action against the indigenous use of psychotropic plants, the Church sought to eliminate a perceived threat to its oligarchic powers and reassert its monopoly on legitimate access to the supernatural (O'Neil, 1987). By casting the healer as a witch and the hallucinogenic plants as tools of Satan, the Church succeeded not only in eliminating competition to the elite physician class but also in

virtually eradicating knowledge of these vestiges of pagan and shamanic consciousness.

A second historical period whose examination may be pertinent to understanding our ingrained cultural resistances and aversion to hallucinogens is the European conquest of the New World. Shortly after arrival in Central and South America in the late Fifteenth and early Sixteenth Centuries, the invading Spanish Conquistadors observed an impressive array of psychoactive pharmacopoeia, including morning glory seeds (containing the potent hallucinogen, lysergic acid amide), peyote, and psilocybin mushrooms.

These extraordinary plants were utilized by the native inhabitants to induce an ecstatic intoxication and were an integral component of their aboriginal religion and ritual. As plant hallucinogens were attributed to have supernatural powers, they were quickly perceived by the European invaders as weapons of the Devil designed to prevent the triumph of Christianity over traditional Indian religion (Furst, 1976). An early Seventeenth Century Spanish observer of native customs, Hernando Ruiz de Alarcon, wrote of the idolatries he observed involving the consumption of the morning glory: "Olouihqui is a kind of seed-like lentils produced by a type of vine in this land, which when drunk deprive of the senses, because it is very powerful, and by this means they communicate with the devil, because he talks to them when they are deprived of judgment with the said drink, and deceive them with different hallucinations, and they attribute it to a god they say is inside the seed" (Guerra, 1971).

Identifying the threat not only to consolidating their power and control over the conquered peoples, but also the danger of lower caste immigrant Spaniards developing interest in native rituals and healing practices, The Holy Inquisition of Mexico issued in 1616 a proclamation ordering the persecution and excommunication of those who, under the influence of "herbs and roots with which they lose and confound their senses, and the illusions and fantastic representations they have, judge and proclaim afterwards as revelation, or true notice of things to come. . ." (Guerra, 1967). To continue to engage in native practices and utilize their traditional plant hallucinogens as agents of knowledge and healing would risk indictment of heresy and witchcraft, and inevitably the implementation of the cruelest punishments of the Inquisition, from public flogging to being burned alive at the stake. Unable to accept the indigenous utilization of such psychoactive substances as anything other than idolatry and a threat to their goals of domination and exploitation, the European conquerors denied them legitimacy, endeavoring to expunge their traditions and knowledge. Only by going deeply underground and maintaining their world view and shamanic practices in secret from the dominant Euro-American culture, has this knowledge survived.

Early Research with Hallucinogens

Interest in plant hallucinogens lay dormant until the second half of the Nineteenth Century when growing activities in the new fields of experimental physiology and pharmacology sparked efforts at laboratory analyses of medicinal plants. In the late 1880's German toxicologist Louis Lewin, often called the "father of modern psychopharmacology," received a collection of peyote samples from the Parke-Davis Pharmaceutical Company. Succeeding at isolating several alkaloids from the peyote, Lewin was unable to identify any of them as the psychoactive component through animal testing. The investigation was then taken up by Arthur Heffter, who characterized additional pure alkaloids from the cactus. By ingesting each of them he was able to identify the crucial one, which he named mescaline (Heffter, 1897).

Along with Lewin's published work, interest in plant hallucinogens was encouraged by increasing dissemination of knowledge of the Native American Indian use of peyote, a phenomena of increasing prevalence as the century drew to a close. Obtaining a sample of peyote from the South-Western plains, physician and founder of the American Neurological Association Weir Mitchell, conducted an experiment using himself as the subject. Although overwhelmed with the aesthetic power of the experience, describing that the peyote revealed "a certain sense of the things about me as having a more positive existence than usual," Mitchell expressed alarm that such a profound experience might not be successfully integrated within his contemporary context: "I predict a perilous reign of the mescal habit . . . The temptation to call again the enchanting magic of my experience will, I am sure, be too much for some men to resist after they have once set foot in this land of fairy colors where there seems so much to charm and so little to excite horror or disgust" (Mitchell, 1896).

Inspired by reports of Mitchell's self-experimentation, the prominent English physician Havelock Ellis decided to pursue a similar encounter with the plant hallucinogen, which he later reported as an experience of unparalleled magnitude, asserting that to "once or twice be admitted to the rites of mescal is not only an unforgettable delight but an educational influence of no mean value" (Ellis, 1897). Such unqualified praise of a drug with as yet no proven medical application, however, provoked harsh censure from the editors of the British Medical Journal who

expressed grave concern of peyote's injurious potential and reprimanded Ellis for irresponsibly "putting the temptation before the section of the public which is always in search of new sensation" (British Medical Journal, 1898). Such a vituperative response to Ellis' naive efforts at publicizing and perhaps promoting auto-experimentation with magical plants is an early harbinger of the conflict that mired and paralyzed the field of hallucinogenic research some seventy years later.

Interest in the unusual psychogenic effects of peyote and, following its synthesis in 1919, mescaline, continued through the 1920's. Activities included further exploration of the unique visions induced by the drug by a variety of literary figures and scholars introduced to its exotic phenomena, although when William James experienced a severe gastro-intestinal reaction upon attempting to swallow a segment of peyote he is alleged to have stated: "Henceforth, I'll take the visions on trust" (Stevens, 1987). A comprehensive survey of the effects of mescaline was published by Karl Beringer, a close associate of Hermann Hesse and Carl Jung, in his massive tome "Der Meskalinrausch" (The Mescaline Inebriation) in 1927, followed a year later by Heinrich Kluver's Mescal: The "Divine" Plant and Its Psychological Effects, the first attempt at formal classification and analysis of mescaline visions (Kluver, 1928). And heralding the next phase of hallucinogen research, mescaline was touted by psychiatric researchers as a putative biochemical model for major mental disturbances, particularly schizophrenia (Guttman and Maclay, 1936; Stockings, 1940).

Dr. Hofmann's Serendipitous Discovery

The modern era of hallucinogen research began in the laboratory of Dr. Albert Hofmann, a senior research chemist for the Sandoz Pharmaceutical Company in Basel, Switzerland. In mid April, 1943, Hofmann was engaged in work to chemically modify alkaloids from the rye ergot fungus, *Claviceps purpurea*, in an effort to develop a new analeptic agent (a respiratory stimulant). Acting on a premonition that earlier tests had missed something, he returned to and prepared a fresh batch of a compound he had previously synthesized in 1938, but which had proved at that time to have what were considered to be uninteresting results in animal testing. The chemical compound he had decided to return to after this five year hiatus was the twenty-fifth in a series of lysergic acid amides, and had previously received the designation of LSD-25.

While working with a modest quantity of this compound for further study, Hofmann complained of restlessness and feeling dizzy and decided to return to his home to rest. He subsequently would write that upon reaching home and lying down with his eyes closed he experienced an "extreme activity of the imagination . . . there surged upon me an uninterrupted stream of fantastic images of extraordinary plasticity and vividness and accompanied by an intense kaleidoscope like play of colors. After about two hours, the not unpleasant inebriation, which had been experienced while I was fully conscious, disappeared" (Hofmann, 1983).

Concluding that he had probably accidentally absorbed a small quantity of the compound through his skin, Hofmann set out three days later, on April 19, 1943, to replicate the phenomena by self administering what he considered to be an extremely small and cautious dose, 250 micrograms. Intending to record his subjective experiences of what he had assumed to be a very low dose of the peculiar substance, less than an hour later Hofmann began to feel the onset of what was to be a powerful and indeed frightening altered state of consciousness, and again felt compelled to return to his home. Hofmann would later report "On the way home, my condition began to assume threatening forms. . . Everything in my field of vision wavered and was distorted as if seen in a curved mirror. I also had the sensation of being unable to move from the spot. Nevertheless, my assistant later told me that we had traveled very rapidly. . . My surroundings had now transformed themselves in more terrifying ways. Everything in the room spun around, and the familiar objects and pieces of furniture assumed grotesque, threatening forms. They were in continuous motion, animated, as if driven by an inner restlessness… Even worse than these demonic transformations of the outer world, were the alterations that I perceived in myself, in my inner being. Every exertion of my will, every attempt to put an end to the disintegrations of the outer world and the dissolution of my ego, seemed to be wasted effort. A demon had invaded me, had taken possession of my body, mind and soul." Shortly thereafter, Hofmann would describe, "the climax of my despondent condition had passed. . . the horror softened and gave way to a feeling of good fortune and gratitude. . . now, little by little I could begin to enjoy the unprecedented colors and plays of shapes that persisted behind my closed eyes. Kaleidoscopic, fantastic images surged in on me, alternating, variegated, opening and then closing themselves in circles and spirals, exploding in colored fountains. . . Exhausted, I then slept, to awake next morning refreshed, with a clear head, though still somewhat tired physically. A sensation of well-being and renewed life flowed through me " (Hofmann, 1983). Dr. Hofmann's shocking experience of madness and transcendence, precipitated by an

infinitesimally low dose of what would soon be recognized as the most potent psychoactive substance known to man, heralded the advent of a new era of psychiatric research committed to uncovering the mysteries of the mind and revealing the basis of mental illness.

The Psychotomimetic Model

Albert Hofmann's discovery of LSD soon led to a period of intense interest and activity designed to explore its utility as a model of understanding and treating psychotic illness. Such a direction was consistent with earlier investigations equating the mescaline catalyzed altered state of consciousness with the subjective experience of schizophrenic patients (Guttman and Maclay, 1936; Stockings, 1940). Tayleur Stockings had described the similarities between the two states: "Mescaline intoxication is indeed a true 'schizophrenia' if we use the word in its literal sense of 'split mind,' for the characteristic effect of mescaline is a molecular fragmentation of the entire personality, exactly similar to that found in schizophrenic patients… Thus the subject of the mescaline psychosis may believe that he has become transformed into some great personage, such as a god or a legendary character, or a being from another world. This is a well-known symptom found in states such as paraphrenia and paranoia" (Stockings, 1940). Noting the enormity of perceptual disturbances induced by LSD, coupled with the sensation in some subjects of losing their mind, as had transiently been the case with Dr. Hofmann, Sandoz in 1947 began actively marketing LSD to psychiatric researchers and practitioners as a tool for understanding psychoses. Not only was LSD experimentation in normal subjects proposed as a viable model for studying the pathogenesis of psychotic illness, but psychiatrists were encouraged to self-administer the drug so as to gain insight into the subjective world of the patient with serious mental illness (Stevens, 1987). For a young field struggling to gain credibility as a medical science, this model of chemically controlled psychosis emerged as a propitious sign for the future.

Preoccupation with the hallucinogen induced psychotomimetic model continued through the 1950's. The psychotomimetic position was summarized by one its leading proponents, Harvard psychiatrist Max Rinkel: "The psychotic phenomena produced were predominantly schizophrenia-like symptoms, manifested in disturbances of thought and speech, changes in affect and mood, changes in perception, production of hallucinations and delusions, depersonalizations and changes in behavior. Rorschach tests and concrete-abstract thinking tests showed responses quite similar to those obtained with schizophrenics" (Rinkel and Denber, 1958)., it became increasingly apparent, however, that although an impressive array of psychiatric researchers and theoreticians had elucidated and elaborated upon the startling degree of resemblance between schizophrenia and the hallucinogenic experience, a growing consensus was emerging that the dissimilarities between the two states essentially obviated the value of the chemical psychosis model (Grinspoon and Bakalar, 1979). Speaking at the First International Congress of Neuropsychopharmacology in 1959, the legendary Manfred Bleuler enunciated the central argument in opposition to the psychotomimetic model. He stated that it was the gradual and inexorable progression of a symptom complex that included disturbed thought processes, depersonalization and auditory hallucinations, evolving into a generalized functional incapacitation that was characteristic of schizophrenia. He concluded with the demonstrative declaration that although the psychotomimetic drugs may have strengthened our conceptual understanding of organic psychoses, they have "contributed nothing to the understanding of the pathogenesis of schizophrenia" (Bleuler, 1959).

Hallucinogen Research and the Role of the CIA

Following the end of World War II, as relations with our former ally the Soviet Union began to deteriorate and Cold War tensions heightened, a program was initiated by the U.S. Central Intelligence Agency to develop a speech inducing drug for use in interrogations of suspected enemy agents. Such a search was in part stimulated by knowledge of prior, albeit unsuccessful, efforts by Nazi medical researchers at the Dachau Concentration Camp to utilize mescaline as an agent of mind control (Marks, 1979). By the early 1950's the CIA had acquired from Sandoz Pharmaceutical a large quantity of the highly touted psychotomimetic, LSD, and had begun their own extensive testing program. Early experiments often involved the furtive "dosing" of unwitting subjects, including employees of the CIA and other intelligence organizations, soldiers and customers solicited by prostitutes in the service of the CIA. Given the ill-prepared mental set of the victim, the often adverse setting in which the "experiment" occurred, and the lack of therapeutic aftercare, it is no surprise that highly deleterious outcomes, including suicide, did occur. Although knowledge of this irresponsible and ethically suspect association between the CIA and hallucinogenic substances remained suppressed for the next twenty years, knowledge of such activities was ultimately obtained through the Freedom of Information Act

(Marks, 1979; Lee and Schlain, 1985).

Through the 1950's, as Cold War fears escalated, the CIA began to developed an affinity for the psychotomimetic model then in vogue. In order to further their own goals of investigating the mind control potentials of hallucinogenic drugs, the CIA began to recruit and fund a number of distinguished psychiatric researchers. Included among these was Ewen Cameron, elected President of the American Psychiatric Association in 1953 and first President of the World Psychiatric Association. Capitalizing on the CIA's preoccupation with LSD's purported ability to break down familiar behavior patterns, Cameron received funding to develop a bizarre and unorthodox method for treating severe mental illness. The treatment protocol began with "sleep therapy", where patients were sedated with barbiturates for a several month period, and was followed by a "depatterning" phase of massive electroshock and frequent doses of LSD designed to obliterate past behavior patterns. Patients were then once again heavily sedated, and subsequently subjected to a prolonged "psychic driving" reconditioning phase where they received constant auditory bombardment from speakers under their pillows repeating tape recorded messages, with some patients hearing the same message repeated a quarter of a million times. Given the gross excesses in all modalities of this "treatment", inevitably severe neuro-psychiatric deterioration was incurred by many of Cameron's unconsented subjects (Marks, 1979; Lee and Schlain, 1985). Ultimately, the efforts of the CIA and their contract psychiatrists came to naught as their ill-advised collaboration with hallucinogens yielded little of value to support either the CIA's mind control theories or the psychotomimetic investigations of psychiatric researchers.

The Psycholytic Treatment Model

Early experimentation in Switzerland following Albert Hofmann's discovery in the 1940's had discerned a phenomena quite different than that of the much heralded yet bizarre psychotomimetic mental experience. In subjects given a relatively low dose of LSD, there appeared to occur a release of repressed psychic material, particularly in anxiety states and obsessional neuroses. By allowing this otherwise repressed and threatening material to flow effortlessly into consciousness, investigators surmised that low dose LSD treatment could facilitate the psychotherapy process (Stoll, 1947). Application of the low dose model in Europe as well as the United States ascertained that psycholytic treatment had particular value with patients with rigid defense mechanisms and excessively strict superego structures. By facilitating ego regression, uncovering early childhood memories, and inducing an affective release, psychiatrists claimed to have achieved a breakthrough in reducing the duration and improving the outcome of psychotherapeutic treatment (Chandler and Hartmann, 1960). Problems arose with the psycholytic paradigm, however, as critics noted that the content of regressed material released from the unconscious was extremely sensitive to the psychiatrist's own analytic orientation, in most cases Freudian or Jungian. Questions arose over whether the phenomena observed in the psychotherapeutic sessions, including the often positive treatment outcome, were not simply attributable to the presence of heightened powers of suggestibility. Moreover, with psycholytic treatments, care had to be taken to utilize sufficiently low dosages of the hallucinogen that the patient's ego would not be overwhelmed to the point where verbal analysis would be inhibited. When in the course of psycholytic psychotherapy higher dosages were utilized, the resultant experience could no longer be contained within the intended theoretical framework, thus necessitating delineation of an entirely new paradigm.

The Psychedelic Treatment Model

Psychiatrists utilizing the higher dose model on their patients, as well as self-experimenting on themselves, quickly realized that they had accessed an entirely new and novel dimension of consciousness. As Dr. Hofmann had experienced during his own exploration, this unexpected level of awareness could alternately be rapturous or terrifying. The first psychiatrist to explore this paradigm was the Canadian researcher Humphrey Osmond. Utilizing first mescaline, and later LSD, Osmond devoted his studies to the treatment of alcoholism, a notoriously difficult and refractory condition. Noting that some alcoholics were only able to cease their pathological drinking behaviors after they had experienced a terrifying, hallucinatory episode of delirium tremens during alcohol withdrawal, Osmond set out to replicate this state through utilization of a high dose hallucinogen model. Observing that what distinguished his treatment successes from his treatment failures was whether a transcendent and mystical state of consciousness was attained, Osmond recognized the strong resemblance to states of religious conversion, bringing to mind William James' old axiom that "the best cure for dipsomania is religiomania." Dissatisfied with the prevailing jargon, and arguing that his model demonstrated that hallucinogens did much more than "mimic psychosis", Osmond introduced at the 1957 meeting of the New York Academy of Sciences the term psychedelic, explaining that the "mind manifesting" state did not necessarily produce a predictable and

pathological sequence of events, but rather could catalyze an enriching and life changing vision. And in presaging the cacophonous debate that would shortly fall upon the infant field of hallucinogen research, Osmond concluded that the psychedelic model not only allowed us to escape "Freud's gloomier moods that persuaded him that a happy man is a self-deceiver", but would soon come to the aid of humanity's imperiled existence and "have a part to play in our survival as a species" (Osmond, 1957).

The Prohibition of Hallucinogen Research

With the evolution to the psychedelic model, hallucinogens moved beyond the bounds of control of the medical elite (Neill, 1987). No longer could they be confined to investigations of a model psychosis, nor could they be contained within the framework of conventional psychiatric therapies with implicit prescribed roles for doctor and patient. By blurring the boundaries between religion and science, between sickness and health, and between healer and sufferer, the psychedelic model entered the realm of applied mysticism. As word of the astounding phenomenon induced by the psychedelic model spread into the culture at large, the inevitable backlash occurred. Horrified that this extraordinary investigative probe had been appropriated from their control, the leaders of the psychiatric profession directed harsh criticism at their irrepressible and increasingly evangelistic colleagues. Roy Grinker, the first editor of the prestigious Archives of General Psychiatry, in a 1963 editorial castigated those psychiatric researchers who had become preoccupied with administering "the drug to themselves, and some, who became enamored with the mystical hallucinatory state, eventually in their 'mystique' became unqualified as competent investigators" (Grinker, 1963). And a year later, in the Journal of the American Medical Association, Grinker charged researchers with "using uncontrolled, unscientific methods. In fact, these professionals are widely known to participate in drug ingestion, rendering their conclusions biased by their own ecstasy…The psychotomimetics are being 'bootlegged', and as drugs now under scientific investigation they are being misused" (Grinker, 1964). In moving beyond the boundaries of conventional scientific inquiry, the hallucinogens had "become invested with an aura of magic" (Cole and Katz, 1964), and thus could no longer be provided the status and protection of their elite profession. The covenant had been broken. The hallucinogens, along with the proponents of their continued exploration, were cast out, becoming pariahs in a land and a time that increasingly viewed them as threats to public safety and social order.

By the mid-1960's, the secret was out. Growing interest in hallucinogens had catalyzed, and was catalyzed by, profound cultural shifts. Along with the social upheaval surrounding opposition to an increasingly unpopular war in South-East Asia, hallucinogens assumed a central role in a movement that began to question many of the basic values and precepts of mainstream Euro-American culture. The populace, fueled by sensational media accounts, grew to identify hallucinogens as a prime suspect in inciting the accelerating state of cultural havoc. Along with the drugs themselves, adherents of the experimental and treatment models became increasingly identified as part of the problem. Such circumstances were in no way improved by the rash pronouncements from the radical wing of what had rapidly become identified as an hallucinogen-inspired political movement. The leaders of one notorious research group in particular drew public ire and aroused anxiety and panic by such proclamations as: "Make no mistake: the effect of consciousness-expanding drugs will be to transform our concepts of human nature, of human potentialities, of existence. The game is about to be changed, ladies and gentleman. . . These possibilities naturally threaten every branch of the Establishment. The dangers of external change appear to frighten us less than the peril of internal change. LSD is more frightening than the Bomb!" (Leary and Alpert, 1962).

In response to escalating fears that hallucinogens had become an out of control menace to public safety and cultural stability, the government moved to restrict access to these potent agents of change. Psychiatric leaders, gravely concerned by the threat to public mental health, and perhaps to their professional image as well, vehemently urged government regulating agencies to tighten their controls. Roy Grinker, illustrious psychiatrist and President of the American Medical Association, issued an urgent warning to his colleagues that greater damage lay ahead unless usage of these hazardous chemical agents was contained. Going beyond merely calling for the psychiatry profession to take action against this growing peril, which would include denouncing the renegades within its own ranks, Grinker castigated the government for having been woefully lacking in vigilance and having neglected its duty: "The Food and Drug Administration has failed in its policing functions. The drugs are indeed dangerous even when used under the best of precautions and conditions" (Grinker, 1964).

Driven into action by increasingly lurid media and law enforcement accounts of widespread hallucinogen use among the young, amidst dire warnings that this insidious threat would erode the values and work ethic of future generations, government regulators had no

choice but to act. In 1965 the Congress passed the Drug Abuse Control Amendment, which placed tight restrictions on hallucinogen research, forcing all research applications to be routed through the FDA for approval. In April, 1966, succumbing to mounting adverse publicity, Sandoz Pharmaceuticals ceased the marketing of what their esteemed research chemist Albert Hofmann would come to call "my problem child" (Hoffman, 1983). Also during the spring of 1966, Senator Robert Kennedy called for Congressional Hearings on the problem. Kennedy, whose wife Ethel had reportedly received psychiatric treatments with LSD, expressed concern that potentially vital research was being obstructed, questioning: "Why if they were worthwhile six months ago, why aren't they worthwhile now?… I think we have given too much emphasis and so much attention to the fact that it can be dangerous and that it can hurt an individual who uses it. . . that perhaps to some extent we have lost sight of the fact that it can be very, very helpful in our society if used properly" (Lee and Schlain, 1985). Kennedy's pleas went unheeded, as over the next few years more and more stringent restrictions were imposed on hallucinogen research, culminating in the Bureau of Narcotics and Dangerous Drugs (the predecessor to the Drug Enforcement Agency) decision to place the hallucinogens in the Schedule I class, reserved for dangerous drugs of abuse with no medical value. Research ground to a virtual halt. Government, civic and medical leaders had all responded to their call to duty, permanently expunging, they hoped, what President Lyndon Johnson had declared in his State of the Union address in January, 1968, "these powders and pills which threaten our nation's health, vitality and self-respect" (Stevens, 1987).

Discounting Hallucinogen Research

Hallucinogens, in the guise of an experimental probe into the mysterious world of mental illness, had burst on the scene during the infancy of psychiatric research. They had not only unleashed a firestorm of controversy as a highly touted therapeutic intervention, but had greatly contributed to the development of the exciting new specialty of laboratory neurochemistry research. Access to these unique agents for animal research has been permitted to continue unimpeded, and they have contributed greatly to our understanding of neurotransmitter systems, brain imaging techniques and behavioral pharmacology (Jacobs, 1984; Freedman, 1986). And yet, human research with hallucinogens had, until now, vanished from the scene. Discounted for ever having held value or potential, it is as if they had never been with us. A source of embarrassment and shame, hallucinogen research became a non-issue, virtually disappearing from the professional literature and educational curriculums. By the early 1970's, psychiatric researchers and academicians had perceived that to continue to advocate for human research with hallucinogens, or even to be identified with past interest in their therapeutic potential, might seriously jeopardize their future careers. Difficult decisions had to be made. From the mid 1960's onward, a split began to appear in the ranks of psychiatric hallucinogen researchers. For those who would maintain their enthusiasm for the potentials of these singular substances, a path of professional marginalization would follow. For those who would take a stand against their perfidious threat, accolades and professional advancement would be forthcoming. For most, however, it was to be a process of quietly disengaging, often from what had been a passionate interest, and re-directing their careers towards tamer and less disputable areas. With very few exceptions (Grinspoon and Bakalar, 1979; Grinspoon and Bakalar, 1986; Strassman, 1984), a veil of silence had descended over the putative role of hallucinogen research in psychiatry.

The Future of Hallucinogen Research in Psychiatry

Where are we to go with this most unusual class of psychoactive substances? Some would say it is best to let sleeping dogs lie, that the hallucinogens only brought discord and controversy to the ranks of psychiatry and their re-examination can only lead to further turmoil and acrimony. Psychiatry has moved far beyond the time where hallucinogens were viewed as being on the cutting edge of research investigation. Many psychiatrists graduating from training programs in the last decade are not even aware of the role hallucinogens once did play in the arena of legitimate research. The conventional point of view is that these drugs are potential substances of abuse, nothing more. Within mainstream, academic psychiatry forums for discussion of the relative merits of resuming inquiries into this area have been restricted. What was once a roar of often vituperative debate has receded to barely a whisper.

Perhaps this twenty-five year period of quiescence and retreat into relative obscurity has been necessary to finally give the question of hallucinogens a fair hearing. We have seen in a prior epoch of investigation a playing field painfully polarized between ardent advocates and fervent foes of the hallucinogens' putative role as agents of discovery and healing. The truth has always rested somewhere in between the dichotomous poles of panacea and toxin. The protagonists of the past, whose careers and integrity so often appeared to be interwoven

with the content and outcome of their fierce debate, are exiting the arena. Rumblings of renewed interest are being heard within the halls of academic psychiatry. A new dialogue is slowly starting to emerge. Hopefully, the lessons of the past will be appreciated, and utilized to forge a partnership and collaboration where divergent perspectives will be given a fair and open hearing, and the true potential of the hallucinogens may finally be illuminated.

As the sleeping giant of hallucinogen research emerges from its twenty-five year slumber, it will perceive that the world of psychiatry has vastly changed from when it was put to rest. The once reigning rulers of psychoanalysis have receded to positions of relative obscurity as the field has become progressively dominated by the adherents of biological reductionism. The insights gleaned from the individual case study, once the standard of psychoanalytic investigation, have been devalued and supplanted by the rigorous methodological research design of modern psychiatry. In the future, the putative value of hallucinogens in psychiatry can no longer rest on claims deriving from anecdotal case studies, as inspiring as they may be, but rather must evolve out of the findings of well-structured, controlled, scientific investigation. To achieve relevance and be accepted as a reputable field of study, hallucinogen research must satisfy the standards of contemporary psychiatric research. To maintain an iconoclastic insistence that the very nature of these substances transcends standard research designs would be to prolong their marginalization and deny the opportunity finally to explore their potential utility.

The knowledge base of biological psychiatry and the neurosciences has exploded over the last two decades, facilitated in part by probes and techniques developed with hallucinogen research in animals (Jacobs, 1984; Freedman, 1986). The potential for further advances in our understanding of the mechanisms of brain function has been recognized and enunciated at a technical meeting of the National Institute on Drug Abuse (NIDA) in July, 1992, that concluded that it is now time to move beyond pure animal research into the realm of human investigation. We are now on the threshold of initiating studies utilizing state of the art research techniques, including sophisticated brain imaging scans, neuroendocrine challenge tests, and receptor binding studies in human subjects. The strategy of pursuing such biological investigations will likely not only yield valuable new information in the neurosciences, but facilitate the re-legitimization of human research with hallucinogens and ultimately become a prelude to the re-exploration of their effects on perception, cognition, and emotion.

One of the most controversial arenas of hallucinogen research during the 1950s and 1960s, and persisting as an alluring hope, has been their putative role in alleviating mental suffering. During a mere fifteen year period, over a thousand clinical papers were published in the professional literature discussing the experiences of 40,000 patients treated with hallucinogens (Grinspoon and Bakalar, 1979). While many of these reports were presented in the form of descriptive case studies and are attributed little value by contemporary research standards, they can help point the way for future investigations. A wide variety of psychopathological phenomena were subjected to intervention with hallucinogens, often leading to encouraging reports of positive clinical outcomes. Unfortunately, examining these stimulating accounts in retrospect reveals notable flaws in their design, including primitive and by today's standards deficient measures designed to evaluate therapeutic change, lack of outcome follow-up and unwillingness to utilize appropriate control subjects. As the debate over hallucinogens intensified, it also became apparent that from both warring camps investigators' biases (whether conscious or unconscious) were confounding their results. From our current vantage point, it is often difficult to ascertain the true significance of this past research other than to appreciate that sufficient clinical change appears to have been catalyzed that further investigation is merited. And as we prepare to delve into the question of the hallucinogens' application to treatment models, it will be essential that we control for the flaws that made a previous generation of research suspect. State of the art research methodology must be utilized, including proper attention to set and setting, control populations and measures of short and long term treatment outcome. An atmosphere of active collaboration among investigators with contrasting perspectives needs to be established, avoiding at all costs the schism which led to the collapse of earlier efforts.

The Relevance of the Past

We are on the threshold of initiating explorations which may have considerable ramifications for our future. There is much at stake and much to learn. But in order to take full advantage of this opportunity we must fully understand our past, including that which we know from cultures distant to our own place and time. Plant derived hallucinogens once played a vital, albeit poorly appreciated role in our pre-historical lineage (Furst, 1976; Dobkin de Rios, 1984). While psychiatry has traditionally held a disparaging and pathologizing view towards shamanic belief systems and practices (Devereux, 1958), evidence supplied by transcultural anthropological investigators (Jilek, 1971; Noll, 1983)

demonstrates that shamanic practices may actually be conducive to high levels of psychological health and functioning. To move beyond the commonly held psychiatric viewpoint that shamanism is nothing more than primitivism and the prehistorical wellspring of mental illness, would allow for receptivity to learning from a paradigm that has incorporated for thousands of years the utilization of hallucinogens as a vital facet of belief systems and healing practices (Bravo and Grob, 1989). If we are to assess optimally the true clinical efficacy and safety of the hallucinogens, it is imperative that we be conscious of the critical extrapharmacological variables that we know to be integral to the shamanic model. Ample attention and sensitivity must be given to the preparation for the hallucinogen experience, the powerful expectation effects directed toward predetermined therapeutic goals, the formalized structure of the session and the integration of the altered state experience in the days, weeks and months following the experience. The failure to adhere to any of these aspects of the shamanic paradigm would be to deny hallucinogen research the full opportunity to test its true value.

What removes the shamanic world view so far from our own, and consequently presents the greatest challenges when attempting to incorporate its insights into contemporary research methodology, is the belief that the plant hallucinogens are sacraments of divine origin. However, it is this reverential and spiritual utilization of psychoactive substances that so pointedly distinguishes the practices of tribal and shamanic peoples from our own contemporary profaned and pathologized context of drug abuse. Hallucinogens in the shamanic world have traditionally played a critical role in rites of initiation, providing personal regeneration and radical change, and are perceived as essential to the process of growth and maturity and the acquisition of meaning (Grob and Dobkin de Rios, 1992; Zoja, 1989). They are not mis-used or abused, and are not agents of societal chaos and destruction. Their use is fully sanctioned and integrated into the mainstream of society, and commonly utilized in ritually prescribed and elder facilitated ceremonies. The hypersuggestible properties of the hallucinogens, utilized within a highly controlled set and setting, achieves a powerful effect, reinforcing cultural cohesion and commitment. These apparent beneficial effects of shamanic hallucinogen use contrast markedly with the destructive outcomes often observed in our own contemporary contexts (Dobkin de Rios and Grob, 1993).

An Illustrative Model

One of the most exciting areas of investigation from the past era of hallucinogen research was the treatment of severe, refractory alcoholism. In the 1950s psychiatric researchers had identified the similarities between the spectrum of the LSD experience and the phenomenology of delirium tremens (Osmond, 1957; Ditman and Whittlesey, 1959). As alcoholism was notorious for its lack of responsiveness to conventional treatment approaches, great interest and energies were directed towards this area of study. Highly impressive short term results of treatment with hallucinogens (Chwelos et al, 1959; MacLean et al, 1961; Van Dusen et al, 1967) gave impetus to a surge of enthusiasm that a dramatic and effective intervention had finally been found. Additional support was forthcoming from Bill Wilson, the founder of Alcoholics Anonymous, who revealed that his own carefully supervised experiences with LSD had not only been a highly valuable personal experience, but were also fully compatible with the tenets of the movement he had started (Grof, 1987). However, as the level of discord within the psychiatric profession and the degree of alarm in the public heightened, resistance to accepting the hallucinogen model for alcoholism intensified. As mainstream psychiatry could no longer stand idly by in the face of threatened radical upheaval, so the Board of Trustees of Alcoholics Anonymous felt compelled to reject their creator Bill Wilson's proposed endorsement.

It soon became apparent that the methodological shortcomings of the research alleging to demonstrate unequivocally positive results in the treatment of alcoholism would undermine progress in the field. Poorly controlled research design, with questionable measures of change and inadequate follow-up led to charges that hallucinogen advocates had been blinded by their own enthusiasm and had mis-interpreted and mis-represented their findings. Opponents of the hallucinogen treatment model would subsequently conduct their own clinical trials, designed to refute what they perceived as dangerous and exaggerated claims of therapeutic success (Smart et al, 1966; Hollister et al, 1969; Ludwig, Levine and Stark, 1970). These studies, which purported to demonstrate an entire lack of treatment efficacy of models utilizing hallucinogens, were received by the psychiatric establishment with great relief. In fact, the Ludwig, Levine and Stark study provided such reassurance to a profession so shaken by its own iconoclasts, as well as satisfying contemporary formal medical research standards with such aplomb, that it was awarded the prestigious Lester N. Hofheimer Prize for Research from the American Psychiatric Association.

Nevertheless, the investigations designed to provide the last word on the "failed" hallucinogen treatment model have themselves come under scathing attack. Not only have the investigators' lack of appreciation of set and setting, failure to adequately prepare their patients for the experience and refusal to allow for follow-up integration been identified (Grinspoon and Bakalar, 1979), but the capricious nature of medical research has itself been implicated. "At a time when LSD was popular, Levine and Ludwig (1967) had reported positive results… When LSD fell out of favor and the positive results became politically unwise, they obtained negative results. Unconsciously or consciously they built into their study a number of antitherapeutic elements that guaranteed a therapeutic failure" (Grof, 1980).

The discussion of the potential role of hallucinogens in the treatment of alcoholism, and by inference its application to other psychiatric disorders as well, would not be complete without an examination of the role of the plant hallucinogen, peyote, in the treatment of Native American Indians. Evidence exists that peyote was in widespread use in Central America and revered as a medicine and religious sacrament as early as 200 B.C. (Furst, 1976). After the American Civil War, the use of peyote moved north of the Rio Grande River and quickly spread to dozens of native tribes throughout the United States and Canada. During the 1870s and 1880s a peyote vision religion developed in reaction to the inexorable encroachment of non-native peoples onto the Indian lands and the associated, deliberate destruction of native culture. With the defeat and subjugation of the Native American people, alcoholism became epidemic. Although until recently faced with unrelenting political repression by the U.S. government, the Native American Church, a syncretistic church combining elements of traditional Indian religion and Christianity and utilizing peyote as its ritual sacrament, has been recognized by anthropologists and psychiatrists as being the only effective treatment for endemic alcoholism (Schultes, 1938, La Barre, 1947, Bergman, 1971, Albaugh and Anderson, 1974). Karl Menninger, a revered figure in the development of American Psychiatry in the 20th Century, has stated: "Peyote is not harmful to these people; it is beneficial, comforting, inspiring, and appears to be spiritually nourishing. It is a better antidote to alcohol than anything the missionaries, the white man, the American Medical Association, and the public health services have come up with" (Bergman, 1971).

Integral to the positive treatment outcome with peyote has been its sacramental utilization within the ritual context of mystical-religious experience. The Native American Church is a clear contemporary example of the successful application of the shamanic model to the treatment of severe, refractory illness. Although the Native American Church applies to a circumscribed and relatively homogenous population, it provides a valuable lesson on the importance of the shamanic model and the need for attentiveness to set and setting, intention, preparation and integration, as well as group identification. If we are to develop optimal research designs for evaluating the therapeutic utility of hallucinogens, it will not be sufficient to adhere to strict standards of scientific methodology alone. We must also pay heed to the examples provided us by such successful applications of the shamanic paradigm. It will only be then, when we have wedded our state of the art research designs to the wisdom accrued from the past, that we will adequately appreciate what role hallucinogens may have in our future.

Conclusion

After a twenty-five year period of virtual prohibition, formal psychiatric research with hallucinogenic drugs has resumed. This article has reviewed the process by which hallucinogens came to be viewed as beyond the pale of respected and sanctioned clinical investigation, and has directed attention to the importance of fully understanding the lessons of the past so as to avoid a similar fate for recently approved research endeavors. The shamanistic use of hallucinogenic plants as agents designed to facilitate healing, acquire knowledge and enhance societal cohesion were brutally repressed in both the Old and New Worlds by the progenitors of our own contemporary Euro-American culture, often with complicity of the medical professions. Knowledge of the properties and potentials of these consciousness altering plants was forgotten or driven deeply underground for centuries. It was not until the late 1800s that German pharmaceutical researchers investigating the properties of peyote re-discovered the profound and highly unusual effects of these substances. A dispute anticipating the virulent controversies of the 1960s ensued, however, pitting proponents of this new model of consciousness exploration against those who questioned the propriety of their colleagues enthusiasm for self experimentation and penchant for sweeping proclamations. The history of hallucinogen research in the 20th century has revolved around this regrettable polarization, and as such has impeded the evolution of the field.

Developments in the second half of the 20th century were catalyzed by the remarkable discoveries of the Swiss research chemist, Albert Hofmann. In the

wake of his synthesis of the extraordinarily potent psychoactive substance, lysergic acid diethylamide, a period of active investigation ensued. Notable gains were accomplished utilizing the psychotomimetic model for understanding mental illness and the low dose psycholytic approach for the treatment of a variety of psychiatric conditions. It soon became apparent however, that these models possessed inherent limitations when applied to the orthodox psychiatric constructs then in vogue. The implementation of the high dose psychedelic model, in spite of its apparent utility in treating resistant conditions such as refractory alcoholism, presented even greater difficulties in conforming to the boundaries of conventional theory and practice. Acceptance of hallucinogens as reputable tools for investigation and agents for treatment were dealt a further and near fatal blow when they became embroiled in the cultural wars of the 1960s. Together with revelations of unethical activities of psychiatric researchers under contract to military intelligence and the CIA, the highly publicized and controversial behaviors of hallucinogen enthusiasts led to the repression of efforts to investigate formally these substances. For the next twenty-five years research with hallucinogens assumed pariah status within academic psychiatry, virtually putting an end to formal dialogue and debate.

We now have before us the opportunity to resurrect the long dormant field of hallucinogen research. However, if the debacle of the past is to be avoided, it is imperative that we learn from the lessons of prior generations of researchers who saw their hopes and accomplishments dissipate under the pressures of cultural apprehension and the threat of professional ostracism. It is essential that the mistakes of the past not be replicated. Definitive steps to end the protracted period of silence and inactivity have been initiated. Contemporary investigators will need to proceed tactfully however, and with respect for the anxieties that this work may provoke in their colleagues. Serious effort must be taken to facilitate active dialogue and collaboration. Current and accepted models of research design must be rigorously adhered to, for to disregard the state of contemporary scientific investigation would ultimately undermine the goals of fully exploring the rich potential of these substances. It will also be critical to learn from the wisdom accrued over the ages in cultures with world views quite different from our own. Although much of the knowledge of the shamanic utilization of plant hallucinogens has been lost with the passage of time, investigators must appreciate the vital role that set and setting have on determining outcome, and incorporate such parameters in their research designs. An opening now exists to explore this fascinating yet poorly understood class of psychoactive substances. Whether we can successfully take advantage of this opportunity will depend ultimately on how well we have learned the lessons of the past.

References

Albaugh, BJ (1974) Peyote in the treatment of alcoholism among American Indians. *Am J Psychiatry* 131, 1247-1250.

Bergman, RL (1971) Navajo peyote use: Its apparent safety. *Amer J Psychiatry* 128, 695-699.

Berringer, K (1927) Der Mescalinrausch. Springer, Berlin.

Bleuler, M (1958) Comparison of drug-induced and endogenous psychoses in man. In, PB Breatly, R Deniker, Raduco-Thomas,D (Eds): Proceedings of the First International Congress of Neuropsychopharmacology. Elsevier, Amsterdam.

Bravo, G, Grob, C (1989) Shamans, sacraments and psychiatrists. *J Psychoactive Drugs* 21, 123-128.

Chandler, AL, Hartman, MA (1960) Lysergic acid diethylamide (LSD-25) as a facilitating agent in psychotherapy. *Arch Gen Psychiatry* 2, 286-299.

Chwelos, N, Blewett, DB, Smith, CM, Hoffer, A (1959) Use of d-lysergic acid diethhylamide in the treatment of alcoholism. *Quarterly J Studies Alcohol* 20, 577-590.

Cole, JO, Katz, M (1964) The psychotomimetic drugs. *JAMA* 187, 182-185.

Cordova-Rios, M (1971) The Wizard of the Upper Amazon. Atheneum, New York.

De Rios, MD, Smith, DE (1976) Using or abusing? An anthropological approach to the study of psychoactive drugs. *J Psychedel Drugs* 8, 263-266.

De Rios, MD, Grob, CS (1993) Hallucinogens, suggestibility and adolescence in cross-cultural perspective. Yearbook of Ethnomedicine 3, 113-132.

Devereux, G (1958) Cultural thought models in primitive and modern psychiatric theories. *Psychiatry* 21, 359-374.

Ditman, KS, Whittlesey, JRB (1959) Comparisons of the LSD experience and delirium tremens. *Arch Gen Psychiatry* 1, 47.

Ellis, H (1897) Mescal: A new artificial paradise. Annual Report of the Smithsonian Institution, pp. 537-548.

Freedman, DX (1986) Hallucinogenic drug research - if so, so what?: Symposioum summary and commentary. *Pharmacol Biochem Behav*: 24, 407-415.

Furst, PT (1976) Hallucinogens and Culture. Chandler and Sharp, Novato, CA.

Grinker, R (1963) Lysergic acid diethylamide. *Arch Gen Psychiatry* 8, 425.

Grinker, R (1964) Bootlegged ecstasy. *JAMA* 187, 192.

Grinspoon, L, Bakalar, JB (1979) Psychedelic Drugs Reconsidered. Basic Books, New York.

Grinspoon, L Bakalar, JB (1986) Can drugs be used to enhance the psychotherapeutic process? *Amer J Psychotherapy* 40, 393-404.

Grob, C, De Rios, MD (1992) Adolescent drug use in cross-cultural perspective. *J Drug Issues* 22, 121-138.

Grof, S (1980) LSD Psychotherapy. Hunter House, Pomona, CA.

Grof, S (1987) Spirituality, addiction, and western science: *ReVision* 10(2), 5-18.

Guerra, F (1967) Mexican phantastica - A study of the early ethnobotanical sources on hallucinogenic drugs. *Br J Addict* 62, 171-187.

Guerra, F (1971) The Pre-Columbian Mind. Seminar Press, London.

Guttman, E, Maclsy, WS (1936) Mescaline and depersonalization: Therapeutic experiments. *J Neurol Psychopath* 16, 193-212.

Harner, MJ (1973) The role of hallucinogenic plants in European witchcraft. In, Harner MJ (Ed): Hallucinogens and Shamanism. PP. 125-150. London, Oxford University Press.

Heffter, A. (1897) Uber Pellote. *Arch. Exp. Path. Pharmakol* 40, 418-425.

Hofmann, A (1985) LSD - My Problem Child: Reflections on Sacred Drugs, Myasticism, and Science. J.P. Tarcher, Los Angeles.

Hollister, LE, Shelton, J, Krieger, G (1969) A controlled comparison of lysergic diethylamide (LSD) and dextroamphetamine in alcoholics. *Amer J Psychiatry* 125, 1352-1357.

Huxley, A (1977) Moksha: Writings on Psychedelics and the Visionary Experience. J.P. Tarcher, Los Angeles.

Jacobs, BL (1984) Hallucinogens: Neurochemical, Behavioral and Clinical Perspectives. Raven Press, New York.

Jilek, WG (1971) From crazy witchdoctor to auxiiary psychotherapist: The changing image of the medicine man. *Psychiatrica Clinica* 4, 200-220.

Kluver, H (1928) Mescal: The 'Divine' Plant and its Psychological Effects. Keegan-Paul, London.

LaBarre, W (1947) Primitive psychotherapy in native American cultures: Peyotism and confession. *J Abnormal Soc Psychol* 42, 294-309.

Leary, T, Alpert, R (1962) The politics of consciousness. Harvard Review 1(4), 33-37.

Lee, MA, Shlain, B (1985) Acid Dreams: The CIA, LSD and the Sixties Rebellion. New York, Grove Weidenfeld.

Levine, J, Ludwig, AM (1967) The hypnodelic treatment technique. In, HA Abramson (ed), The Use of LSD in Psychotherapy and Alcoholism. New York, Bobbs-Merrill.

Ludwig, AM, Levine, J, Stark, LH (1970) LSD and Alcoholism: A Clinical Study of Treatment Efficacy. Springfield, Illinois, Charles C. Thomas.

Maclean, JR, Macdonald, DC, Byrne, UP, Hubbard, AM (1961) LSD in treatment of alcoholism and other psychiatric problems. *Quarterly J Studies Alcohol* 22, 34-45.

Marks, J (1979) The Search for the "Manchurian Candidate". New York, Dell.

Michelet, J (1965) Satanism and Witchcraft: A Study in Medieval Superstition (1862). Translated by A.R. Allinson. New York, Citadel.

Mitchell, SW (1896) Remarks on the effects of Abhelonium lewinii (the mescal button). *Br Med J* 2, 1625-1629.

Neill, JR (1987) "More than medical significance": LSD and American psychiatry 1953-1966. *J Psychoactive Drugs*, 19, 39-45.

Noll, R (1983) Shamanism and schizophrenia: A state-specific approach to the "schizophrenia metaphor" of shamanic states. *American Ethnologist* 10, 443-459.

O'Neil, M (1987) Magical healing, love magic and the Inquisition in late sixteenth-century Modena. In, S. Haliczer (Ed): Inquisition and Society in Early Modern Europe, pp. 88-114. Croom Helm, London.

Osmond, H (1957) A review of the clinical effects of psychotomimetic agents. *Ann NY Acad Sci* 66, 418-434.

Rinkel, M, Denber, HCB (Eds) (1958) Chemical Concepts of Psychosis. McDowell, New York.

Schultes, RE (1938) The appeal of peyote (Lophophora williamsii) as a medicine. *American Anthropologist* 40, 698-715.

Smart, RG, Storm, T, Baker EFW, Solursh, L (1966) A controlled study of lysergide in the treatment or alcoholism. *Quarterly J Studies Alcohol* 27, 469-482.

Stevens, J: Storming Heaven (1988) LSD and the American Dream. Harper and Row, New York.

Stockings, GT (1940) A clinical study of the mescaline psychosis, with special reference to the mechanism of the genesis of schizophrenia and other psychotic states. *J Mental Science* 86, 29-47.

Stoll, WA (1947) Lysergaure-diathylamid, ein phantastikum aus der mutterkorngruppe. *Schweizer Archiv fur Neurologie und Psychiatrie* 60, 279-323.

Strassman, RJ (1984) Adverse reactions to psychedelic drugs: A review of the literature. *J Nervous Mental Disease* 172, 577-595.

Strassman, RJ (1991) Human hallucinogenic drug research in the United States: A present-day case history and review of the process. *J Psychoactive Drugs* 23, 29-37.

Van Dusen, W, Wilson, W, Miners, W, Hook, H (1967) Treatment of alcoholism with lysergide. *Quarterly J Studies Alcohol* 28, 295-304.

Wasson, RG (1968) Soma: Divine Mushroom of Immortality. Harcourt, Brace and World, New York.

Wasson, RG, Ruck, CAP, Hofmann, A (1978) The Road to Eleusis. Harcourt, Brace, Jovanovich, New York.

A slightly abbreviated version of this article first appeared in the Yearbook for Ethnomedicine and the Study of Consciousness 3:91-112, 1994

3. Recent Advances and Concepts in the Search for Biological Correlates of hallucinogen-induced Altered States of Consciousness

Franz X. Vollenweider, M.D.

Introduction

Hallucinogens and related substances constitute a powerful experimental basis to investigate biological correlates of altered states of consciousness (ASC) (Hermle et al. 1988; Javitt and Zukin 1991; Vollenweider, 1994). In combination with functional brain imaging techniques and pharmacological methodologies, they are remarkable molecular probes to study the functional organization of the brain and to generate chemical hypotheses of ASC. The study of hallucinogens in humans is important because these substances affect a number of brain functions that typically characterize the human mind, including cognition, volition, ego, and self-consciousness. They can elicit a clinical syndrome that resembles in various aspects the first manifestation of schizophrenic disorders, but is different in other respects (Fischman, 1983; Gouzoulis et al. 1994; Vollenweider et al. 1997d). The various forms of ego-disorders are especially prominent features of psychedelic and naturally occurring psychoses. For example, they can produce a form of ego-dissolution that is experienced with heightened awareness, en-hanced introspection, sublime happiness, as well as a form that is experienced with anxiety and fragmentation. Hence, studies of the neuronal mechanisms of action of hallucinogens should provide not only novel insights into the pathophysiology of psychiatric disorders and their treatments, but in a more wider sense into the biology of consciousness as a whole, e.g. into the biology of ego structuring processes.

In the present discussion, I wish to summarize some of the recent advances in hallucinogen research that have resulted from human studies conducted in our group. In the first part, a human model of sensory gating deficits, the cortico-striato-thalamo-cortical (CSTC) loop model of psychosensory processing, is introduced to provide a perspective on how current scientific knowledge about hallucinogen drug action could be visualized within a synthetic framework to explain their subjective effects in humans. The CSTC model is based on the assumption that psychedelic and psychotic symptoms can be conceptualized by failure to inhibit or "gate" intrusive mental activity. Specifically, the CSTC loop model suggests that a deficient thalamic "filter" function leads to sensory overload of the cortex which in turn results in cognitive fragmentation and sensory flooding as seen in hallucinogen-induced states and naturally occurring psychoses (Vollenweider, 1994).

The theoretical conception of the "thalamic filter" theory is comparable to animal models of sensory gating deficits such as the prepulse inhibition paradigm (PPI), although the PPI paradigm does not explicitly refer to the thalamus as an anatomical structure responsible for filtering deficits. However, both the CSTC model and the PPI paradigm suggest that perturbations in cortico-striato-thalamic pathways are critical for the loss of inhibition processes and the pathogenesis of psychotic symptoms. This assumption is supported by increasing preclinical evidence demonstrating that hallucinogens specifically interfere with neurotransmitter systems within the limbic cortico-striatal-thalamic circuitry and produce PPI-deficits comparable to those seen in several neuropsychiatric disorders characterized by failure to inhibit irrelevant cognitive, motor or sensory information.

Positron emission tomography (PET) was used to test the hypothesis that hallucinogens may lead to a disruption of "filter" functions and produce a sensory overload of the frontal cortex. Moreover, a correlational analysis between hallucinogen-induced changes in neuronal activity and specific dimensions of ASC was carried out to elucidate the neuronal substrates of psychedelic states. Psychometric measures and PET investigations with specific receptor ligands were and are performed to investigate the effects of hallucinogens on brain functions before and after pretreatment with specific neuroreceptor antagonists. These studies provide a paradigm shift where interactions of different neurotransmitter systems are seen as the basis for the psychological effects of hallucinogens. The PPI paradigm is used as a second measure to characterize the putative effects of hallucinogens on inhibition processes in humans and functional interactions of neurotransmitter systems in ASC. Clearly, among the many topics that could be considered in this

context, I have to make some selection, and some of the subjects unavoidably will remain sketchy.

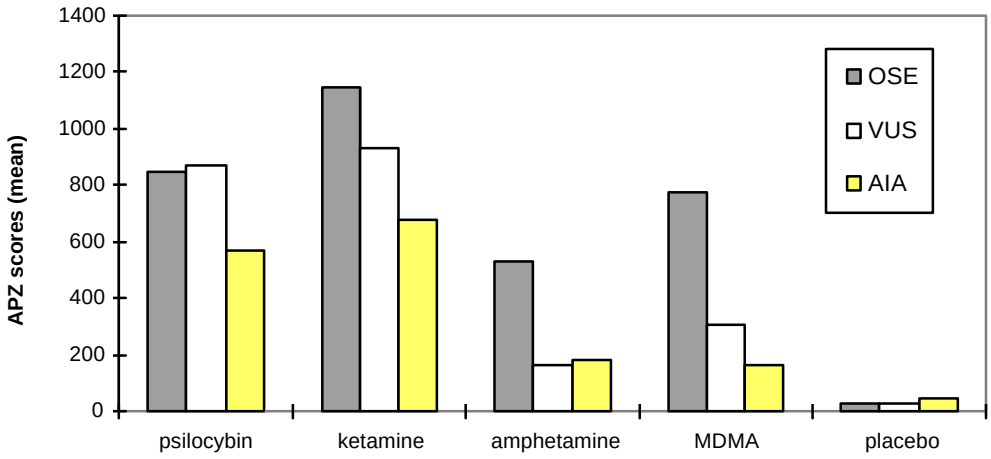

Figure 1. APZ Profiles in healthy volunteers (n = 20).

Measurement of psychological dimensions of ASC

In the context of the present theme -relating psychological and biological effects of hallucinogens- the assessment and characterization of altered states of consciousness (ASC) is of fundamental importance. Among several rating scales, the APZ questionnaire, which has become the standard in Europe for measuring specific states of consciousness and which has been used on a routine basis by our group, is to be described. In short, the APZ questionnaire was developed based on a large prospective study done with 393 subjects tested with cannabinoids, dimethyltryptamine, psilocybin, mescaline, harmaline, nitrosoxide, hypnosis, autogenic training, and meditation techniques (Dittrich, 1994). It measures three primary and one secondary etiology-independent dimensions of ASC. The first dimension, designated as "oceanic boundlessness" (OSE), measures derealization phenomena and ego-dissolution which are associated with enhanced sensory awareness and a positive basic mood ranging from heightened feelings to sublime happiness and exaltation. Ego-dissolution can include or start with a mere loosening of ego-boundaries, but may end up in a feeling of merging with the cosmos, where the experience of the sense of time is changed or completely vanished. This state might be comparable to a mystical experience, if fully developed. The second dimension "dread of ego-dissolution"(AIA) measures thought disorder, ego-disintegration, loss of autonomy and self-control variously associated with arousal, anxiety, and paranoid feelings of being endangered. The third subscale "visionary restructuralization"(VUS), refers to auditory and visual illusions, hallucinations, synaesthetic phenomena, as well as to changes in the meaning of various precepts.

The intercultural consistency of the APZ dimensions OSE, AIA and VUS has been rigorously tested in a subsequent study, the International Study on Altered States of Consciousness (ISASC), and the dimensions have been shown to be altered consistently in a manner that is independent of the particular treatment, disorder, or condition that led to the ASC (Dittrich et al. 1985; Dittrich, 1994). The APZ rating scale is now available in an English version and it is important to emphasize the need for a quantitative instrument such as the APZ to exchange and integrate further research into the effects of hallucinogens on an international level.

So far, the APZ questionnaire has been used to characterize the psychological effects of hallucinogens, dissociative anesthetics, stimulants, and entactogens. For example, using the APZ questionnaire, we recently demonstrated in a double-blind placebo-controlled study that the psychological effects of MDMA in normals can be clearly differ-

entiated from those seen in comparable studies with

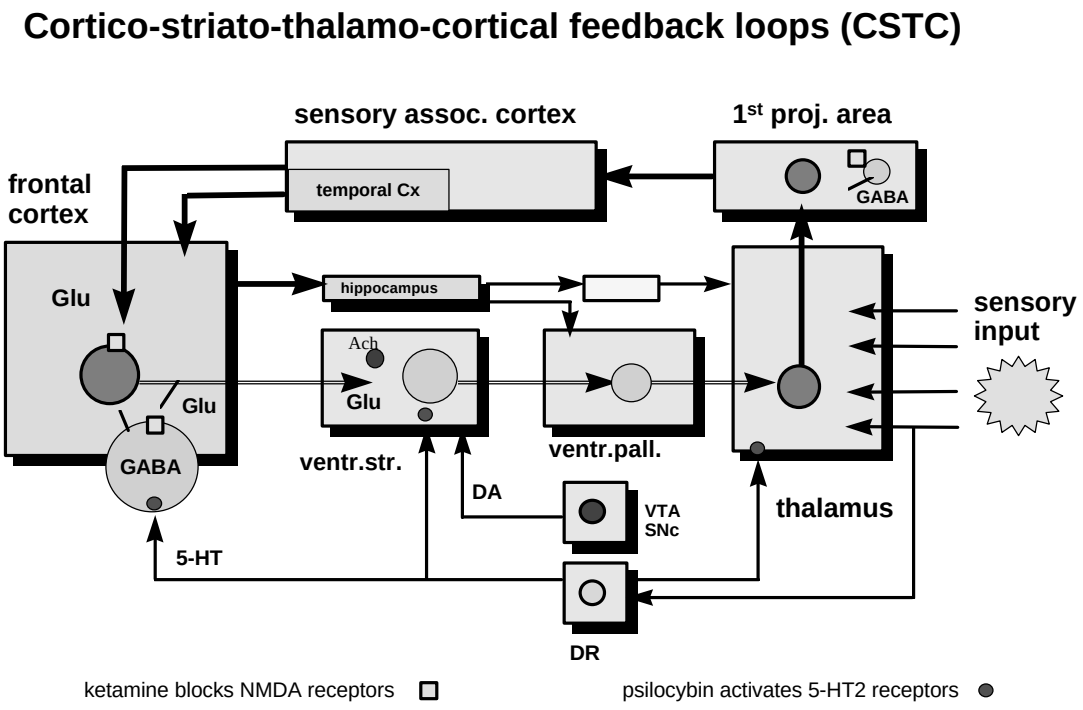

Figure 2. Cortico-striato-thalamo-cortical feedback loops.

ketamine, psilocybin, and amphetamine (Vollenweider et al. 1997e) (Figure 1).

As seen in figure 1, MDMA (1.7 mg/kg p.o.) produced a unique pattern of APZ scores. Although the OSE scores in MDMA subjects were approximately similar (80%) to those seen after psilocybin and ketamine, the VUS and AIA scores were only about 30-50% of the values seen in psilocybin and ketamine subjects (Vollenweider et al. 1997b; Vollenweider et al. 1997b). In contrast to psilocybin and ketamine subjects, loosening of ego-boundaries and perceptual changes produced by MDMA were generally not experienced as problematic or psychotic fusion, but instead as a positive or pleasurable state in which the distinction between self and nonself was reduced and a sense of enhanced empathy existed. Furthermore, MDMA subjects noted that this state allowed them to feel "more united with the world" and less "separated from others". Unlike psilocybin and ketamine, both of which produced comparable increases in hallucinations as indicated by the VUS scores, MDMA did not produce hallucinations, but instead what was typically described was an intensification of sensory perception ("colors were more intense," "objects appeared more detailed," sound was more clear, etc.), and visual illusions ("3D-vision of flat objects," micropsia and macropsia, etc.). Finally, with regard to psychostimulants, euphorigenic doses of d-amphetamine produced similar AIA scores, but lower OSE and VUS scores than those seen in the study with MDMA (Vollenweider et al. 1997a). Although additional studies using multiple doses are needed to confirm these conclusions, the present findings are suggestive of appreciable differences in the psychological profiles produced by MDMA relative to psilocybin, ketamine, or d-amphetamine.

Certainly, several types of ASCs possibly may have etiology-specific dimensions, e.g. acoustic-hallucinatory phenomena, memory disturbances etc., besides those mentioned above. The identification of such specific dimensions will be pertinent to a more comprehensive description of ASC's. Moreover, since individual reaction differences on ASC-inducing agents are high, even when experimental conditions are kept constant, research into other

factors such as personality traits, genetic predispositions, environmental factors, etc., influencing the course of ASC is mandatory. Such studies were performed (Dittrich, 1994) or are in progress (Vollenweider et al., in preparation). Another important need, particularly for exploring pathophysiological commonalties of ASC and naturally occurring psychoses, is the systematic assessment of similarities and differences of psychotic symptoms seen in drug-induced ASC and psychiatric patients, using the same psychometric instruments, e.g. such as the APZ, HRS or IPP rating scales (Dittrich, 1994; Scharfetter 1995; Strassman, 1995).

The CSTC model of sensory information processing and ASC

Based on the available neuroanatomical evidence and pharmacological findings of psychedelic drug actions, we proposed a cortico-subcortical model of psychosensory information processing that can be used as a starting working hypothesis to analyze and integrate the effects of different chemical types of hallucinogens at a system level. The model conceptualizes psychedelic states as complex disturbances that arise from more elementary deficits of sensory information processing in cortico-striato-thalamo-cortical (CSTC) feedback loops. The model was not entirely new; it incorporates the idea that psychotic symptoms might relate to a dopaminergic and/or dopaminergic-glutamatergic neurotransmitter dysbalance in mesolimbic and/or mesolimbic-corticostriatal pathways, but it enlarges this hypothesis, insofar as serotonergic and GABAergic neurotransmission are also brought into the scheme (Vollenweider, 1992; Vollenweider, 1994).

In short, five CSTC loops have been identified and each loop, functioning in parallel, is thought to mediate a different set of functions; the motor, the oculomotor, the prefrontal, the association and the limbic loop. The limbic loop is involved in memory, learning, and self-nonself discrimination by linking of cortical categorized exteroceptive perception and internal stimuli of the value system. The limbic loop originates in the medial and lateral temporal lobe and hippocampal formation, projects to the ventral striatum including the nucleus accumbens, the ventromedial portions of the caudate nucleus and putamen. Projections from these nuclei then converge on the ventral pallidum and feedback via the thalamus to the anterior cingulate and the orbitofrontal cortex (Figure 2).

The model includes the view that the thalamus acts a filter or gating mechanism for the extero- and interoceptive information flow to the cerebral cortex and that deficits in thalamic gating may lead to a sensory overload of the cortex, which in turn may ultimately cause the sensory flooding, cognitive fragmentation and ego-dissolution seen in drug-induced altered mental states and psychotic disorders. The filter capability of the thalamus is thought to be under the control of cortico-striato-thalamic (CST) feedback loops. Specifically, it is hypothesized that the striatum, comprising the dorsal and the ventral striatum (including the nucleus accumbens) and the corresponding dorsal and ventral pallidum, excerts an inhibitory function on the thalamus. Inhibition of the thalamus should theoretically result in a decrease of sensory input to the cortex and in a reduction of arousal, protecting the cerebral cortex from sensory overload and breakdown of its integrative capacity. The model suggests that striatal activity is modulated by a number of subsidiary circuits, with their respectively neurotransmitter systems. The mesostriatal and mesolimbic projections provide an inhibitory dopaminergic input to the striatum including the nucleus accumbens. Under physiological conditions, the inhibitory influence of dopaminergic systems on the striatum is, however, thought to be counter-balanced by the glutamatergic excitatory input from cortico-striatal pathways. This assumption implies that an increase in dopaminergic tone, as well as a decrease in glutamatergic neurotransmission should theoretically lead to a reduction of the inhibitory influence of the striatum on the thalamus and result in an opening of the thalamic “filter” and, subsequently, in a sensory overload of the cerebral cortex, resulting in psychotic symptom formation. Finally, the reticular formation, which is activated by input from all sensory modalities, gives rise to serotonergic projections to the components of the CST loops, namely the frontal cerebral cortex, cingulate cortex, hippocampus, striatum, nucleus accumbens, thalamus, and amygdala. Excessive activation of the postsynaptic elements of these serotonergic projection sites should also result in a reduction of the thalamic gating mechanism and, consequently, in a sensory overload of frontal cortex resulting in psychosis.

First results testing the CSTC model

Although the CSTC model is an oversimplification, it provides a set of testable hypotheses. Specifically, according to the CSTC model we have

hypothesized, the reduction of glutamatergic functions, for example by the NMDA antagonist ketamine, should lead to a sensory overload and metabolic activation of the cerebral cortex, presumably of the frontal cortex (hyperfrontality). If the CSTC model is valid, stimulation of the serotonergic system, for example by the mixed 5-$HT_{2A/2C/1A}$ agonist psilocybin, should lead to activation of the frontal cortex similar to that seen with ketamine (see figure 2).

- Factor I: frontomedial, frontolateral, cingulate ant. and post., parietal, and sensorimotor Cortex
- Factor II: occipitomedial and -lateral Cortex
- Factor III: temporomedial and lateral Cortex
- Factor IV: caudate nucleus, putamen
- Factor V: thalamus

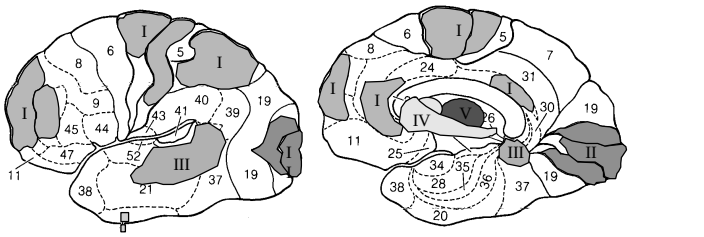

Figure 3. Five clusters of brain regions (factors 1-5) that can be interpreted as functional "units" or "modules." Each unit comprises a number of functionally highly intercorrelated brain regions. For example, the "fronto-parietal factor"(I)includes the frontomedial, frontolateral, anterior and posterior cingulate, parietal, and sensorimotor cortex. The integrity of this factor structure is not disrupted in ASC, but the activity of brain regions within such an unit alters with psychedelic states. The "fronto-parietal factor" appears to play a fundamental role as a "central supervision and execution system" insofar as this unit is involved in ego-structuring processes and self-representation by interpretation and integration of extra- and intrasensory information, planning and execution of motor functions.

The hyperfrontality hypothesis of ketamine- and psilocybin-induced mental states has been tested in healthy volunteers using positron emission tomography (PET) and the radioligand [^{18}F]fluoro-deoxyglucose (FDG). PET with FDG enables one to explore directly the interactive organization of the human brain, via the coupling of cerebral glucose metabolism and neuronal activity. In fact, the central hypothesis of a frontocortical activation in psychedelic states could be confirmed. Both ketamine and psilocybin led to a marked metabolic activation of the frontal cortex and a number of overlapping metabolic changes in other brain regions (Vollenweider et al. 1997c; Vollenweider et al. 1997d). To elucidate the relationship between regional metabolic activation of the brain and specific states of consciousness a correlational analysis was performed. One of the main findings of this computation was that ego dissolution and derealization phenomena correlated with the increase of metabolic activity in the frontal cortex including the anterior cingulate, and also with changes in the temporal cortex and basal ganglia. These findings demonstrated that not a single brain region, but distributed neuronal networks are involved in psychedelic and psychotic symptom formation.

Nevertheless, the hyperfrontality finding observed in these studies is potentially important. First, the marked stimulation of the frontal cortex, the anterior cingulate, the temporomedial cortex and the thalamus seen in both psilocybin and ketamine subjects is in line with the thalamic filter theory, suggesting that a disruption of the limbic cortico-striato-thalamic (CST) loop should theoretically lead to a sensory overload of the frontal cortex and its limbic relay stations. This interpretation is also supported by the recent finding that ketamine administration in haloperidol-stabilized schizophrenics resulted in an increase of cerebral blood

flow in the thalamus, frontomedial and anterior cingulate cortex, concomitant with the exacerbation of psychotic symptoms (Lahti et al. 1995). Second, the hyperfrontality is of particular interest because it appears to parallel similar findings in acutely ill schizophrenic and non-schizophrenic psychotic patients, but contrasts with the hypofrontality finding seen in chronic schizophrenics. Third, the common hyperfrontality finding also supports the idea that the psychedelics used in these studies may mediated their effects through a common neurotransmitter system. As 5-HT_2 and NMDA receptors have been located on GABAergic neurons in the frontal cortex, GABAergic neurons in cortico-striatal pathways may provide a common anatomical substrate involved in the genesis of ketamine- and psilocybin-induced hyperfrontality and psychosis. On the other hand, both psilocybin and ketamine have been reported to activate either directly or indirectly the dopaminergic system. As activation of dopaminergic pathways could theoretically lead to disruption of the information flow in CST-loops, the possibility remains that dopamine also contributes to the pathophysiology of hyperfrontality and acute psychotic symptom formations (Kehr, 1977; Meltzer et al. 1978; Meltzer et al. 1981; Hiramatsu et al. 1989). Certainly, such hypotheses need substantial prospectively acquired corroborative evidence and carefully designed mechanistic studies (see below).

Patterns of cortical activity in Altered states of consciousness

The correlational analysis between cortical activity and psychological dimensions of ASC of our psilocybin and ketamine studies clearly indicated that complex neuronal networks are involved in the formation of ASC. This implies that a multivariate analysis of metabolic and psychological data and relatively large sample size, e.g. 50 -100 subjects, is mandatory to identify the common neuroanatomical substrates of ASC with accurate precision. Therefore, a number of additional placebo-controlled FDG-PET experiments with *S*-ketamine, *R*-ketamine, and amphetamine were performed in normal subjects to explore further the relationship between hallucinogen-induced patterns of cortical activity and the psychological dimensions of ASC (Vollenweider et al. 1997; Vollenweider et al. 1997b). To identify the interactive organization of the brain in resting states and ASC, normalized metabolic PET data from placebo and corresponding drug conditions were subjected to a factor analysis and factor scores for each individual subjects was computed. Surprisingly, this computation revealed that the "cortical-subcortical organization" (based on a five-factor solution) during ASC was very similar to that seen under placebo condition, indicating that the functional integrity of interrelated brain regions (factors), which might be interpreted as functional "units" or "modules", is not disrupted in ASC (see Figure 3). According to their content, the factors were labeled "fronto-parietal cortex," "temporal cortex," "occipital cortex," "striatum" (which included the nucleus caudate and putamen), and "thalamus." Subsequent comparison of the factor score values of the drug and placebo condition revealed, however, that subjects during hallucinatory states had significantly higher scores on the "frontal-parietal" and "striatal" network, and lower scores on the "occipital cortex" than in resting states. This finding indicates that neuronal activity within these modules (factors) and the more global relationship between these units (factors) is markedly different in ASC than in the normal waking state.

Moreover, multiple regression analysis between psychological scores (APZ scores) and factor score values (normalized metabolic activity) revealed first that the dimension OSE (oceanic boundlessness) relates to changes in metabolic activity in the frontal-parietal, temporal, and occipital cortex. Second, that VUS (visionary restructuralization including hallucinatory phenomena) is associated with metabolic alterations of a fronto-parietal, temporal, striatal, and occipital network, and third that anxious ego-disintegration (AIA) is primarily associated with metabolic changes in the thalamus, as shown by the following regression equations:

OSE = 0.32 F1* - 0.20 F2* + 0.11 F3 + 0.20 F4* + 0.05 F5

VUS = 0.20 F1* - 0.27 F2* + 0.17 F3* + 0.32 F4* + 0.10 F5

AIA = 0.00 F1 + 0.09 F2 + 0.01 F3 + 0.17 F4 + 0.28 F5*

*F1 is the fronto-parietal factor, F2 is the occipital factor, F3 is the temporal factor, F4 is the striatal factor, and F5 is the thalamic factor; *denotes significance at the level of $p < 0.05$.*

The present results suggest that hallucinogens in combination with functional brain imaging techniques (PET, SPECT, fMRI etc.) are promising research tools for exploring the biological correlates

of ego-structuring processes. It appears that the more positively experienced form of ego-dissolution (OSE) can functionally and metabolically be differentiated from the more fragmented and anxious ego-dissolution AIA. The present data also indicate that the CSTC model used here provides a satisfactory starting point to approach the functional organization of the brain in ASC. It should be noted, however, that the present correlations, which are based on an aggregation of observations over time (APZ ratings, metabolism) and space (brain regions) though probably correct in the order of magnitude, might be inadequate at a finer level of resolution. To explore further the circuitry dynamics of the CSTC model during ASC, we have started making use of a new three dimensional EEG-based functional brain tomo-

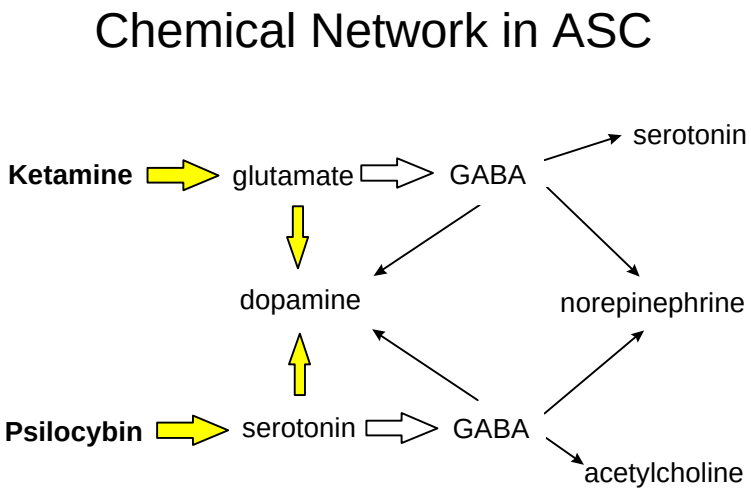

Figure 4. Chemical Network in Altered States of Consciousness (see text).

graphy for localizing the electric activity in the brain, which is called LORETA (low resolution electromagnetic tomography) (Pasqual-Marqui et al. 1994). LORETA allows locating differences in the distribution of electrically active neuronal populations with the advantage of the high time resolution of the EEG. A first aim of an ongoing study is to explore the course of the functional relationship between the thalamus and cortical regions, particularly the frontal cortex, during MDMA or psilocybin administration in healthy volunteers (Vollenweider, Gamma and Frei, in preparation). It is proposed that the combination of LORETA and PET will bring further insight into the functional organization of the brain in ASC.

Further explorations into the role of serotonin and dopamine in ASC

The CSTC model suggests that serotonergic pathways modulating cortico-striatal-thalamic loops of sensory and cognitive information processing are critical to hallucinogenic drug action, as well as for the treatment and pathogenesis of schizophrenia (Carlsson and Carlsson 1990; Vollenweider et al. 1997d). Indeed, both indoleamine (psilocybin, LSD) and phenylalkylamine (mescaline, DOI) hallucinogens, which produce schizophrenia-like syndromes in humans, primarily bind to 5-HT_1, 5-HT_2, 5-HT_5 and 5-HT_7 receptors in various animal tissue preparations (Peroutka, 1994). Furthermore, it has been suggested that the common effects of these two classes of hallucinogens may be mediated by agonist actions at 5-HT_2 receptors: first, because the potency of hallucinogens correlates with 5-HT_2 receptor binding affinity in animals (Titeler et al. 1988); and second, because the behavioral effects of hallucinogens in animals can be blocked by 5-HT_2 antagonists (Sanders-Bush et al. 1988; Meert et al. 1989; Wing et al. 1990; Schreiber et al. 1995). Furthermore, the affinity of LSD for D_2 receptors (Watts et al. 1995) and other influences of hallucinogens on dopamine (DA) functions (Smith et al. 1975; Haubrich and Wang 1977) suggest some contribution of DA systems to hallucinogen effects. The role of the serotonin and dopamine systems in

the generation of hallucinogen-induced ASC has never been systematically tested in human studies. With respect to understanding and development of novel pharmacological treatments of psychoses, human studies are, however, essential, particularly since more recent data indicate that some animal models of hallucinogenic drug action may not reflect hallucinogenic properties in man (Koerner and Appel 1982).

To test the hypotheses that 5-HT_2 and/or DA D_2 receptors contribute to hallucinogen action in humans, we studied the influences of pretreatment with the preferential 5-HT_{2A} antagonist ketanserin (Hoyer and Schoeffter 1991), the D2 antagonist haloperidol (Burt et al. 1976), or the mixed 5-HT_2/D_2 antagonist risperidone (Leysen et al. 1996) on the psychological and cognitive effects of psilocybin in normal subjects, using a placebo-controlled, within-subject design (Vollenweider et al. 1996). The APZ rating scale and a neuropsychological test were used to assess the subjective effect of psilocybin and putative working memory deficits. As seen in figure 5, the subjective effects of psilocybin were blocked dose-dependently by the serotonin 5-HT_{2A} antagonist ketanserin or the atypical antipsychotic risperidone, but were increased by the dopamine antagonist and typical antipsychotic haloperidol. These data are consistent with animal studies and provide the first evidence in humans that psilocybin-induced ASC's are primarily due to serotonin 5-HT_{2A} receptor activation. Given the evidence that psilocybin does not act directly upon DA receptors (Creese et al. 1975) and the fact that haloperidol partially ameliorated the OSE score including positively experienced derealization and depersonalization phenomena, but markedly increased cognitive deficits and anxious ego-dissolution as measured by the AIA score, it appears that psilocybin also has a complex indirect influence on dopaminergic systems (Figure 4, 5). Nevertheless, our results show that 5-$HT_{2A/C}$ receptor activation can lead to psychotic symptoms that do not depend on DA systems. This finding together with our previous observation that psilocybin stimulates frontocortical glucose metabolism in normals (Vollenweider et al. 1997d) similar to that seen in acutely ill schizophrenic patients, supports the hypothesis that excessive serotonergic activity may be a critical factor in psychedelic and naturally occurring psychoses, at least in a subset of schizophrenic patients, and that specific 5-HT_{2A} antagonists may be useful in normalizing such imbalances (Meltzer, 1991). With respect to hallucinogen-assisted psychotherapy, specific 5-HT_{2A} antagonists may also prove valuable to antagonize prolonged or unwanted side effects of indole hallucinogens.

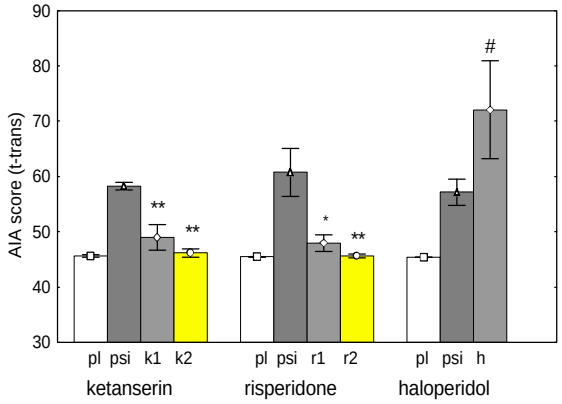

Figure 5. Placebo (pl) and psilocybin (psi) effects on AIA scores. Pretreatment with the selective 5-HT_{2A} receptor antagonists ketanserin (k1, k2) and risperidone (r1, r2) significantly blocks psilocybin-induced increased AIA scores, while haloperidol (h) markedly increased the cognitive deficits and anxious ego-dissolution score.

Whether psilocybin increases dopaminergic activity through 5-HT_2 receptor stimulation alone or in combination with 5-HT_1 receptors or via another receptor system needs to be further investigated and is the main scope of an ongoing PET study on serotonin-dopamine interactions (Vollenweider et al. 1997g). The clarification of this issue is important, since more recent studies suggest that atypical neuroleptics mediate their antipsychotic effects through 5-HT_2 and D_2 antagonism (Meltzer and Gudelsky 1992).

The sensorimotor gating model and ASC

Another important research concept that allows one to explore the neuropharmacology of hallucinogens and cognitive and sensorimotor gating or "filtering" deficits in ASC is the prepulse inhibition paradigm of the startle response (PPI) (for review see (Swerdlow et al. 1992; Geyer and Markou 1995). The PPI paradigm is based on the observation that a startle response to an intensive stimulus is inhibited or gated when the startling cue is preceeded 30-500 msec earlier by a weak prepulse. Theoretically, and as similarly proposed by the CSTC loop model, impairments in inhibition processes lead to sensory overload, attentional deficits, and cognitive fragmentation. PPI has been used as an operational

measure of cognitive and sensorimotor gating in both human and animal studies. PPI deficits have been found in patients with schizophrenia, obsessive compulsive disorder (OCD), Huntington's disease, and psychosis-prone normals compared to normals, reflecting failure to gate sensory, cognitive, or motor information (Geyer et al. 1990; Swerdlow et al. 1994; Swerdlow et al. 1995). More importantly, the PPI deficits seen in these psychiatric patients can be mimicked in rats treated with hallucinogenic 5-HT agonists (psilocybin, DOI, etc.) or NMDA antagonists (ketamine, PCP, or MK 801), giving support to the idea that the sensory flooding seen in ASC and psychotic patients may have a common underlying neurobiological basis (Mansbach and Geyer 1989; Sipes and Geyer 1994) (see above). In fact, the similarity of PPI deficits in animal studies and schizophrenic patients, in combination with other findings, has revitalized interest in hallucinogens in the 1990s and prompted a concerted search into the neurotransmitter systems involved in modulating PPI in rodents (for review see Geyer and Markou 1995).

Studies into the PPI-disruptive effects of hallucinogens and related drugs contributed to the development of specific hypotheses about the primary locus that may be responsible for the psychological effects of hallucinogens in humans. For example, animal studies subsequently demonstrated that the PPI-disruptive effects of both hallucinogenic 5-HT_2 agonists, such as DOI (Sipes and Geyer 1995a; Sipes and Geyer 1997a) and serotonin (5-HT) releasing compounds, such as MDMA ("Ecstasy"), could be blocked with selective 5-HT_{2A} antagonists (Padich et al. 1996). These findings gave substantial support to the idea that indole- and phenylethylamine hallucinogens, but presumably also “entactogens” such as MDMA may mediate their psychological effects in humans through action at a common site, 5-HT_{2A} receptors, although other subtypes of serotonin receptors are also implicated in the modulation of PPI (Sipes and Geyer 1994; Sipes and Geyer 1995; Sipes and Geyer 1996).

The hypothesis that indoleamine hallucinogens such as psilocybin mediate their psychedelic effects primarily via 5-HT_2 receptor activation has been confirmed more recently in a human study (see above, (Vollenweider et al. 1996)). However, whether and how indoleamine hallucinogens and entactogens affect PPI in humans, has not yet been tested. Moreover, it is unclear whether the 5-HT_2 receptor system contributes to the psychological effects of entactogens in humans, since entactogens, unlike hallucinogens, do not produce hallucinations or psychotic symptoms in man.

To explore and compare the putative effects of a typical indoleamine hallucinogen and entactogen on PPI, we have begun to investigate the effects of psilocybin, a 5-HT_2 agonist, and MDMA, a 5-HT releaser, on PPI of acoustic startle in normal laboratory rats versus healthy human volunteers (a collaboration with Mark Geyer, UCSD) (Vollenweider et al. 1997e). To illustrate the need of such comparison studies, the major results of the MDMA study shall briefly be given here. Based on previous studies in rats and mice, the hypothesis was that MDMA would disrupt PPI in both rats and humans.

Surprisingly, our preliminary data indicate that MDMA produces opposite effects on PPI in animals and humans: (1) MDMA decreased PPI of acoustic startle in a dose-related fashion in rats, as expected from previous studies; and (2) a typical recreational dose of MDMA (1.7 mg/kg) increased PPI measured under comparable conditions. The multiple doses of MDMA used in rats ranged from the same 1.7 mg/kg dose used in humans to one order of magnitude higher, in keeping with the typical differences in effective doses between these species. The dose of MDMA used in the human study was shown to have substantial psychological effects in the same subjects, characterized by an easily controlled affective state with feelings of relaxation, heightened mood, euphoria, increased sensory awareness, and elevated psychomotor drive, as detailed elsewhere (Vollenweider et al. 1997f).

The time between administration and testing was selected to be at or near the time of peak effects observed in rats and humans, given the respective routes of administration (subcutaneous injection vs oral). Thus, despite attempts to maximize the comparability of the tests in rats and humans, MDMA produced opposite behavioral effects in rats versus humans, using a measure of sensorimotor gating that is thought to have a high degree of cross-species homology (Geyer and Markou 1995). In the absence of mechanistic studies, no firm conclusions can be drawn regarding the mediation of the observed MDMA effects in humans. Hence, considerably more research will be required to determine whether this disparity between drug effects in rats and humans reflects a species-specific difference in the mechanism of action of MDMA or in the behavioral expression of a similar pharmacological effect, or both. Furthermore, these findings demonstrate the importance of conducting

mechanistic studies of pharmacological agents in healthy humans as well as in experimental animals.

Outlook

In conclusion, the present data indicate that human hallucinogen research with PET and PPI offers a powerful research strategy for studying brain function and neurotransmitter interactions in ASC. The data indicate that neuronal substrates of normal and abnormal thought and behavior are associated with an interactive neuronal network of multiple neurotransmitter systems. The data also corroborate the view that the hallucinogen challenge paradigm not only constitutes a powerful tool to bridge the gap between the mental and the physical, but will also enhance our understanding of the pathophysiology of neuropsychiatric disorders.

Acknowledgments

The author especially thanks Prof. Mark Geyer, UCSD, and Dr. M.F.I. Vollenweider-Scherpenhuyzen, Zürich, for critical comments on the manuscript.

References

Beart PM, McDonald D. (1982): 5-hydroxytrypt-aminergic-dopaminergic interactions in the ventral tegmental area of rat brain. *J Pharm Pharmacol* 34:591-593

Burt DR, Creese I, Snyder SH. (1976): Properties of [3H]Haloperidol and [3H]Dopamine binding associated with dopamine receptors in calf brain membranes. *Mol Pharmacol* 12:800-812

Carlsson M, Carlsson A. (1990): Schizophrenia: A subcortical neurotransmitter imbalance syn-drome? *Schizophrenia Bull* 16:425-432

Creese I, Burt DR, Snyder SH. (1975): The dopamine receptor: differential binding of d-LSD and related agents to agonist and antagonist states. *Life Sci* 17:1715-1720

Dittrich A, von Arx S, Staub S. (1985): International study on altered states of consciousness (ISASC). Summary of the results. *Germ J Psych* 9:319-339

Dittrich A. (1994): Psychological aspects of altered states of consciousness of the LSD type: measurements of their basic dimensions and prediction of individual differences. In Pletscher A, Ladewig D (eds), 50 years of LSD. Current status and perspectives of hallucinogens. New York, Parthenon Publishing, pp.101-118.

Fischman LG. (1983): Dreams, hallucinogenic drug states, and schizophrenia: a psychological and biological comparison. *Schizophrenia Bull* 9:73-94

Geyer MA, Swerdlow NR, Mansbach RS, Braff DL. (1990): Startle response models of sensorimotor gating and habituation deficits in schizophrenia. *Brain Res Bull* 25:485-498

Geyer MA, Markou A. (1995): Animal models of psychiatric disorders. In Bloom FE, Kupfer DJ (eds), The fourth generation of progress. New York, Raven Press, pp.787-798.

Gouzoulis E, Hermle L, Sass H. (1994): (Psychedelic experiences at the onset of productive episodes of endogenous psychoses). *Nervenarzt* 65:198-201

Haubrich DR, Wang PFL. (1977): N,N-dimethyltryptamine lowers rat brain acetyl-choline and dopamine. *Brain Res* 131:158-161

Hermle L, Oepen G, Spitzer M. (1988): Zur Bedeutung der Modellpsychosen. *Fortschr Neurol Psychiat* 56:48-58

Hiramatsu M, Cho AK, Nabeshima T. (1989): Comparison of the behavioral and biochemical effects of the NMDA receptor antagonists, MK-801 and phencyclidine. *Eur J Pharmacol* 166:359-366

Hoyer D, Schoeffter P. (1991): 5-HT receptors: Subtypes and second messengers. J Receptor Res 11:197-214

Javitt DC, Zukin SR. (1991): Recent advances in the phencyclidine model of schizophrenia. *Am J Psychiatry* 148:1301-1308

Kehr W. (1977): Effect of lysuride and other ergot derivatives on monoaminergic mechanism in rat brain. *Eur J Pharmacol* 41:261-273

Koerner J, Appel JB. (1982): Psilocybin as a discriminative stimulus: lack of specificity in an animal behavior model for 'hallucinogens'. *Psychopharmacology* (Berlin) 76:130-135

Lahti AC, Holcomb HH, Medoff DR, Tamminga CA. (1995): Ketamine activates psychosis and alters limbic blood flow in schizophrenia. *NeuroReport* 6:869-872

Leonard BE. (1994): Serotonin receptors--where are they going? *Int Clin Psychopharmacol* 9 Suppl 1:7-17

Leysen JE, Janssen PA, Gommeren W, Wynants J, Pauwels PJ, Janssen PAJ. (1996): In vitro and in vivo receptor binding and effects on monoamine turnover in rat brain regions of the novel antipsychotics risperidone and ocaperidone. *Mol Pharmacol* 41:494-508

Mansbach RS, Geyer MA. (1989): Effect of phencyclidine and phencyclidine biologs on

sensorimotor gating in the rat. *Neuropsychopharm* 2:299-308

Meert TF, de Haes P, Janssen PA. (1989): Risperidone (R 64 766), a potent and complete LSD antagonist in drug discrimination by rats. *Psychopharmacology* (Berlin) 97:206-212

Meltzer HY, Fessler RG, Simonovic M, Fang VS. (1978): Stimulation of rat prolactin secretion by indolealkylamine hallucinogens. *Psychopharmacology* (Berlin) 56:255-259

Meltzer HY, Sturgeon RD, Simonovic M, et al. (1981): Phencyclidine as an indirect dopamine agonist. In Domino EF (ed), PCP (Phencyclidine): Historical and Current Perspectives. Ann Arbor, NPP Books, pp.207-242. Meltzer HY. (1991): The mechanism of action of *novel antipsychotic drugs. Schizophrenia* Bull 17:263-287

Meltzer HY, Gudelsky GA. (1992): Dopaminergic and serotonergic effects of clozapine -Implications for a unique profile. *Arzneim Forsch* 42:268-272

Padich RA, McCloskey TC, Kehne JH. (1996): 5-HT modulation of auditory and visual sensorimotor gating:II. effects of the 5-HT_2A antagonist MDL 100,907 on disruption of sound and light prepulse inhibition produced by 5-HT agonists in Wistar rats. *Psychopharmacology* (Berlin) 124:107-116

Pasqual-Marqui RD, Michel CM, Lehmann D. (1994): Low resolution electromagnetic tomography: a new method for localizing electrical activity in the brain. *Int J Psychophysiol* 18:49-65

Peroutka SJ. (1994): 5-hydroxytryptamine receptor interactions of D-lysergic acid diethylamide. In Pletscher A, Ladewig D (eds), 50 Years of LSD. New York, The Parthenon Publishing Group, pp.19-26.

Sanders-Bush E, Burries KD, Knoth K. (1988): Lysergic acid diethylamide and 2,5-dimethoxy-4-methylamphetamine are partial agonists at serotonin receptors linked to phosphoinositide hydrolysis. *J Pharmacol Exp Ther* 246:924-928

Scharfetter C. (1995) The self-experience of schizophrenics. Empirical studies of the ego/self in schizophrenia, borderline disorders and depression. Zürich, University of Zürich.

Schreiber R, Brocco M, Audinot V, Gobert A, Veiga S, Millan MJ. (1995): (1-(2,5-dimethoxy-4 iodophenyl)-2-aminopropane)-induced head-twitches in the rat are mediated by 5-hydroxytryptamine (5-HT) 2A receptors: modulation by novel 5-HT2A/2C antagonists, D1 antagonists and 5-HT1A agonists. *J Pharmacol Exp Ther* 273:101-112

Sipes TA, Geyer MA. (1994): Multiple serotonin receptor subtypes modulate prpuls inhibition of the starle respons in rats. *Neuropharmacology* 33:441-448

Sipes TA, Geyer MA. (1995a): DOI disruption of prepulse inhibition of startle in the rat is mediated by 5-HT2a and not by 5-HT2C receptors. *Behavioural Pharmacology* 6:839-842

Sipes TA, Geyer MA. (1995b): 8-OH-DPAT disruption of prepulse inhibition in rats; reversal with (+)WAY 100,135 and localization of site of action. *Psychopharmacology* 117:41-48

Sipes TE, Geyer MA. (1996): Functional behavioral homology between rat 5-HT1B and guinea pig 5-HT1D receptors in the modulation of prepulse inhibition of startle. *Psychopharmacology* 125:231-237

Sipes TE, Geyer MA. DOI disrupts prepulse inhibition of startle in rats via 5-HT2A receptors in the ventral pallidum. [In Press] *Brain Res* (1997):

Smith RC, Boggan WO, Freedman DX. (1975): Effects of single and multiple dose LSD on engogenous levels of brain tyrosine and catecholamine. *Psychopharmacologia* 42:271-276

Strassman RJ. (1995): Hallucinogenic drugs in psychiatric research and treatment. *J Nerv Ment Dis* 183:127-138

Swerdlow NR, Caine SB, Braff DL, Geyer MA. (1992): The neural substrates of sensorimotor gating of the starle reflex: a review of the recent findigs and their implications. Journal of *Psychopharmacology* 6:176-190

Swerdlow NR, Braff DL, Taaid N, Geyer MA. (1994): Assessing the validity of an animal model of deficient sensorimotor gating in schizophrenic patients. *Arch Gen Psychiatry* 51:139-154

Swerdlow NR, Filion D, Geyer MA, Braff DL. (1995): "Normal" personality correlates of sensorimotor cognitive, and visuospatial gating. *Biol Psychiatry* 37:286-299

Titeler M, Lyon RA, Glennon RA. (1988): Radioligand binding evidence implicates the brain 5-HT2 receptor as a site of action for LSD and phenylisopropylamine hallucinogens. *Psychopharmacology* (Berlin) 1988; 94:213-216

Vollenweider FX. (1992): Die Anwendung von Psychotomimetika in der Schizophrenie-

forschung unter besonderer Berücksichtigung der Ketamin/PCP-Modell-Psychose. *SUCHT* 38:389-409

Vollenweider FX. (1994): Evidence for a cortical-subcortical dysbalance of sensory information processing during altered states of consciousness using PET and FDG. In Pletscher A, Ladewig D (eds), 50 Years of LSD: State of the Art and Perspectives of Hallucinogens. Symposium of the Swiss Academie of Medical Sciences, October 21-22, 1993, Lugano-Agno, Switzerland. London, Parthenon Publishing, pp. 67-86.

Vollenweider FX, Gamma A, Baer T, et al. (1996) Ketanserin, a 5-HT2 antagonist, but not haloperidol, effectively blocks psilocybin-induced model psychosis in healthy volunteers. [Abstract] WPA-Abstractbook: 116

Vollenweider FX, Antonini A, Leenders KL, Mathys K. (1997a) Effects of high amphetamine doses on mood and cerebral glucose metabolism in normals using positron emission tomography (PET). [submitted] *Psychiatry Research: Neuroimaging.*

Vollenweider FX, Antonini A, Leenders KL, Oye I, Hell D, Angst J. (1997b): Differential Psychopathology and patterns of cerebral glucose utilisation produced by (S)- and (R)-ketamine in healthy volunteers measured by FDG-PET. *Eur Neuropsychopharmacol* 7:25-38

Vollenweider FX, Leenders KL, Scharfetter C, Antonini A, Maguire P, Missimer J, Angst J. (1997c): Metabolic hyperfrontality and psychopathology in the ketamine model of psychosis using positron emission tomography (PET) and [F-18]-fluorodeoxyglocose (FDG). *Eur Neuropsychopharmacol* 7:9-24

Vollenweider FX, Leenders KL, Scharfetter C, Maguire P, Stadelmann O, Angst J. (1997d): Positron emission tomography and fluorodeoxyglucose studies of metabolic hyperfrontality and psychopathology in the psilocybin model of psychosis. *Neuropsychopharm* 16:357-372

Vollenweider FX, Liechti M, Gamma A, Hell D, Geyer M. (1997e) Effects of MDMA ("ecstasy") on sensorimotor gating, attention, and mood in healthy volunteers. [Abstract] The State of the Art in Psychiaty/Abstracts 1997: 28

Vollenweider FX, Liechti M, Gamma A, Huber T. (1997f): Psychological and cardiovascular effects and short-term sequale of MDMA ("Ecstasy") on MDMA-naive healthy volunteers. [submitted] *Neuropsychopharm*.

Vollenweider FX, Vontobel P, Hell D, Leenders KL (1997g) Evidence for 5-HT2 mediated increase of basal ganglia dopamine release in human model psychosis - a PET study with [11C]raclopride [Abstract] The State of the Art in Psychiaty/Abstracts 1997: 39.

Watts VJ, C.P. Lawler CP, Fox DR, K.A. Neve KA, D.E. Nichols DE, Mailman RB (1995): LSD and structural analogs: pharmacological evaluation at D_1 dopamine receptors. *Psychopharmacology*, 118: 401-409.

Wing LL, Tapson GS, Geyer MA. (1990): 5HT-2 mediation of acute behavioral effects of hallucinogens in rats. *Psychopharmacology* (Berlin) 100:417-425

4. Why Study Hallucinogenic Drugs in Animals?

Mark A. Geyer, Ph.D

Introduction

What can we learn from studies of hallucinogenic drugs in animals? The Church of Scientology has labelled such studies funded by the National Institute on Drug Abuse (NIDA) and the National Institute of Mental Health (NIMH) as worthless wastes of the taxpayers' money. This year, the Council for Citizens Against Government Waste has joined in the fight against the Federal funding of such research, singling out a 25 year study of hallucinogen mechanisms in animals, supported by NIMH, as being particularly wasteful. In years past, my research grant from NIDA supporting behavioral studies of hallucinogens in rats has been targeted by animal rights activists, including a candle-light vigil protesting a study of 102 rats given phencyclidine. Nevertheless, I and many other scientists believe that we can learn important information from basic studies of hallucinogen action in animal models and that this information may lead to the alleviation of human sufferring. The present essay will illustrate how such benefits may be realized. From the outset, it should be acknowledged that there are many reasons one might wish to understand the mechanisms responsible for the fascinating and often profound effects of hallucinogens. Many believe that exploring the effects of hallucinogens has the potential to teach us important lessons regarding the nature of consciousness and the way it relates to the brain. Here, the focus is specifically on the possible applications of such an understanding to the treatment of mental illness, a more limited but still important domain.

Antipsychotic Medications

Some 40 years ago, the advent of antipsychotic medications that helped treat patients with schizophrenia led to a revolution in our mental health care system. Due in large part to the effectiveness of these medications in many patients, the longstanding practice of institutionalizing schizophrenia patients for their lifetime in state-run mental hospitals gradually came to an end. Indeed, few of these state mental hospitals remain today. Nevertheless, these medications are not without unfortunate serious side-effects and are not effective in treating all schizophrenia patients. Schizophrenia has long been thought to include a group of disorders having different etiologies and requiring different treatments for different patients. Virtually all of our current array of antipsychotic drugs, however, work via a common mechanism of blocking receptors for the neurotransmitter dopamine. Dopamine is the neurotransmitter that is believed to mediate the behavioral actions of drugs such as amphetamine and cocaine. Despite the fact that very little evidence exists for a causal abnormality in dopamine systems in the brains of schizophrenia patients, the vast majority of these patients are treated currently with dopamine antagonists, that is, drugs that block the actions of dopamine. Many of these treatments are sufficiently successful to enable patients to live and often work in society rather than face a lifetime of hospitalization, but they may not be the optimal treatments, are certainly not cures, and have proven ineffective in a large number of patients. Dopamine antagonists also produce unwanted side effects in the form of serious Parkinsonian-like symptoms such as muscle rigidity.

In the past decade, we have come to recognize that many of these patients who did not benefit from treatment with dopamine antagonists can be treated effectively with another drug, clozapine, that is relatively weak as a dopamine antagonist but is also an antagonist at receptors for several other neurotransmitters, including serotonin. Serotonin is the neurotransmitter that is believed to mediate the psychological effects of both hallucinogens and entactogens. Clozapine has also proven to be remarkable in that it achieves its therapeutic effects in schizophrenia patients without producing Parkinsonian-like side-effects. It does, however, produce potentially fatal blood abnormalities in perhaps 1% of patients and is, therefore, both risky and costly. Given the devastating lifetime nature of schizophrenia, these risks and costs are often deemed acceptable by patients, families, and physicians, largely because the clozapine treatment can be so remarkably effective. Thus, the key message is that these treatment-resistant patients, who have failed to respond to any number of dopamine antagonists, can be treated pharmacologically and can again lead relatively productive lives. Accordingly, the search has been intense to understand the therapeutic mechanism(s) of action of clozapine and to identify new drugs that would have similar therapeutic effects without the potentially fatal side-effects. One of the candidates for such a drug is what could aptly be called a hallucinogen antagonist that has been identified directly by animal studies of hallucinogen mechanisms.

Schizophrenia

Theories regarding the abnormalities responsible for the symptomatology of the group of disorders we call schizophrenia have often suggested the importance of deficits in early forms of filtering, gating, and information processing. Such theories posit that deficient gating of sensory and cognitive information results in an overloading inundation of information and consequent disorganization of thought processes (the hallmark of schizophrenia) (e.g. Braff and Geyer, 1990). In parallel, the actions of hallucinogens have often been related to changes in filtering mechanisms, e.g. the doors of perception described by Aldous Huxley. Many investigators have suggested that an understanding of the mechanisms contributing to effects of these drugs could provide insight into the abnormalities of brain function that lead to psychotic disorders. It is not necessary to argue that hallucinogens mimic all the symptoms of a complex disorder such as schizophrenia to believe that they affect some of the same brain systems that can be disturbed in psychiatric illnesses (Geyer and Markou, 1995). Thus, an understanding of hallucinogen actions may be relevant to specific aspects of schizophrenia rather than the entire complex syndrome. In recent years, this idea of gating or filtering deficits in schizophrenia has been studied successfully using measures of startle responses. A number of experiments have used laboratory animals to explore the similarities between the effects of so-called psychotomimetic drugs and the abnormalities of information processing observed in patients with schizophrenia or related disorders. Our group has taken advantage of the opportunity for cross-species studies of information processing provided by startle response tests. Specifically, two examples of fundamental filtering mechanisms we have studied using the startle response are habituation and prepulse inhibition (PPI).

Startle Measures of Information Processing

The startle reflex is a collection of responses to sudden intense stimuli that has provided a useful approach to studying the neural control of simple behaviors. One major advantage of startle response paradigms is that similar behavioral phenomena can be studied in a variety of species (Geyer and Markou, 1995). In humans, the blink reflex component of the startle response is measured using EMG. In small animals, a movement sensor is used to measure the whole-body flinch elicited by startling stimuli. Of importance for the present work is not the reflex phenomenon itself, but two conceptually important forms of information processing - habituation and PPI - that can be demonstrated using measures of startle. One is habituation, which is often considered to be the simplest form of learning. Habituation is defined as the decrease in responding when the same stimulus is presented repeatedly. For example, habituation enables us to learn to ignore the repetitive but unimportant ticking of a clock. The process of habituation is essential to the selectivity of attention, since only by learning to ignore irrelevant stimuli (i.e. habituate) can one focus attention specifically on significant events. Another form of information processing is PPI, which is the normal suppression of the startle reflex when the intense startling stimulus is preceded by a weak prestimulus. In PPI, a weak prepulse inhibits the behavioral response to a powerful sensory stimulus. In all animals tested, PPI occurs when the prepulse and startling stimuli are in the same or different sensory modalities. It does not appear to be a form of learning, since it occurs on the first exposure to the prepulse and pulse stimuli, and it does not exhibit habituation over multiple tests. PPI is considered to be an example of a pre-attentive and largely involuntary filtering mechanism because of the very short time interval between the prepulse and the startle stimulus (i.e. 30-300 msec) that is sufficient to produce the inhibition. In contrast, habituation operates at much longer time frames and involves the cognitive processing of the information content of the stimuli.

Startle Habituation in Schizophrenia

In keeping with the theory that schizophrenia is characterized by an inability to inhibit responding to unimportant events, the habituation of acoustic startle (startle elicited by bursts of noise presented through headphones) is deficient in patients with schizophrenia (Geyer and Braff, 1982; Braff et al., 1992). Relative to either normal controls or non-psychotic psychiatric patients, actively ill patients with schizophrenia were found to exhibit a slower rate of habituation, that is, they continued to respond to the noises longer than the controls even though the noises had no particular meaning. It is important to note that all three groups were similar in response to the initial presentations of the startling noises. Thus, the deficit in habituation was seen in the absence of any change in startle reactivity, consistent with the notion that the abnormality involves the processing of information rather than basic sensory reactivity. Others have reported similar deficits in the habituation of cutaneous startle (elicited by tiny electric shocks) in psychotic patients, also in the absence of differences in startle reactivity (Bolino et al., 1994). The observation of deficits in both acoustic and cutaneous startle habituation indicates some generality in the phenomenon. Deficits in habituation in schizophrenia patients do not simply result from medications or psychotic behavior per se, since schizotypal patients who exhibit behavioral abnormalities but are not receiving antipsychotic medications and are not grossly psychotic also show

habituation deficits (Cadenhead et al., 1993). If such deficits in habituation can be generalized to other sensory input and response output systems, perhaps even including thoughts to which most of us readily habituate, patients having such an abnormality would be expected to have difficulties in organizing a coherent view of the world - they would literally be unable to differentiate important from unimportant events or direct their attention selectively to specific stimuli or thoughts.

Startle Habituation in Animals

Studies in rats have suggested that brain serotonergic systems, which are defined by the neurons that use serotonin as their neurotransmitter, control startle habituation. These effects appear to be due to the activation specifically of one of the several subtypes of the brain's receptors for serotonin, the serotonin-2 receptor. The effects of hallucinogens are believed to be due largely to their actions as serotonin-2 agonists, that is, they mimic the effects of serotonin at these particular receptors. Hallucinogens have often been suggested to enhance one's ability to see familiar things as novel and to increase the perceptual impact of both external events and internal thoughts. While such an experience may be desirable in one who knows that the distortion of information processing is due to the ingestion of a drug and is time-limited, it must be quite a different experience to recognize that this condition reflects the permanent status of one's brain. In animals, of course, we study effects of these drugs in the absence of insight about the source of the perceived abnormality - rather like studies of LSD in which the drug was given to subjects without their knowledge. Relatively early studies demonstrated that the hallucinogens LSD and mescaline impaired the habituation of tactile startle (elicited by small puffs of air) in rats (Geyer et al., 1978; Geyer and Tapson 1988). Similarly, Davis et al. (1986) demonstrated robust increases in acoustic startle in rats treated with mescaline that were not associated with any change in the initial level of startle reactivity and appeared to be attributable to a specific effect on the habituation of startle. In contrast, amphetamine increased startle on all trials, reflecting a more generalized increase in startle reactivity (Davis et al., 1986). This study was among the first to implicate serotonin-2 receptors in startle habituation, as the effect of mescaline, but not that of amphetamine, was abolished by pretreatment with the serotonin-2 antagonist ritanserin. Subsequent studies with a variety of serotonin-2 antagonists demonstrated that the antagonists by themselves could accelerate tactile startle habituation (Geyer and Tapson, 1988). Thus, the opposite effects of hallucinogenic serotonin-2 agonists and serotonin-2 antagonists in the modulation of startle habituation provide strong support for the use of these hallucinogens as models of the parallel deficits in gating functions observed in schizophrenic and schizotypal patients. Furthermore, they support the idea that the special therapeutic actions of the antipsychotic clozapine may be related to its serotonin-2 antagonist properties and that selective serotonin-2 antagonists (i.e. hallucinogen antagonists) might help at least some patients with schizophrenia.

The effects of "entactogens" on habituation in rats further implicate the serotonergic system in the control of startle habituation. These drugs, including 3,4-methylenedioxy-N-methyl amphetamine (MDMA or "Ecstasy") and alpha-ethyltryptamine (AET or "Love Pearls"), are potent releasers of serotonin from neurons in the brain and robustly impair the habituation of startle responses (Kehne et al., 1992; Martinez and Geyer, 1997). The anti-habituation effects of serotonin releasers are prevented by pretreatment with serotonin reuptake inhibitors, such as fluoxetine ("Prozac"), which prevent the drug-induced release of serotonin from serotonergic (but not dopaminergic) neurons (Kehne et al., 1992; Martinez and Geyer, 1997). Thus, it appears that these entactogens impair habituation by releasing serotonin, which then presumably acts upon serotonin-2 receptors.

The psychotomimetic agent phencyclidine (PCP) also impairs the habituation of startle responding in rats, especially at relatively low doses (Geyer et al., 1984). Thus, impairments of startle habituation appear to constitute a behavioral effect in rats that is common to hallucinogenic serotonin agonists, entactogenic serotonin releasers, or psychotomimetic PCP-like drugs.

Prepulse Inhibition in Schizophrenia

Prepulse inhibition of acoustic startle is deficient in schizophrenia patients (Braff et al., 1978). Theoretically, such a deficit in a fundamental form of pre-attentive filtering may distort information and produce a form of sensory overload which may lead to the disorganized thought processes that are the hallmark symptoms of schizophrenia. This deficit in PPI has been confirmed in studies of medicated, but still-ill patients with schizophrenia in various countries and by investigators using different methods (Bolino et al., 1994; Braff et al., 1992; Grillon et al., 1992). As with habituation, non-medicated schizotypal patients also show PPI deficits (Cadenhead et al., 1993). Furthermore, there is some evidence that PPI deficits in schizophrenia may be reversed by successful treatment with antipsychotic drugs (Hamm et al., 1995; Weike et al., 1996). Only recently have studies attempted to relate these observed deficits in sensorimotor gating functions to measures of thought disorder. Perry and Braff (1994) have reported a significant correlation within a group

of schizophrenia patients between deficits in PPI and thought disorder as assessed by psychological tests. Further studies in this vein will be important in relating the abnormalities in basic forms of information processing, such as PPI or habituation, to more complex symptoms, treatment outcomes, or quality of life.

Prepulse Inhibition in Animals

In rats, hallucinogenic serotonin agonists have been found to disrupt PPI, mimicking the deficit in PPI observed in schizophrenia patients. LSD, which mimics the effects of serotonin (i.e. has agonist effects) at multiple serotonin receptors, dose-dependently reduces PPI (Geyer, in press). Similarly, PPI is reduced by hallucinogens that have more selective agonist effects at serotonin-2 receptors, such as 2,5-dimethoxy-4-iodoamphetamine (DOI). Importantly, the PPI-disruptive effects of hallucinogenic serotonin-2 receptor agonists are blocked by pretreatment with serotonin-2 antagonists including MDL 100907 (Padich et al., 1996; Sipes and Geyer, 1994, 1995), but not by the dopamine antagonist and traditional antipsychotic haloperidol (Padich et al., 1996). Such findings have contributed to the current investigation of MDL 100907 as a possible non-dopaminergic antipsychotic in patients with schizophrenia. Because MDL 100907 is devoid of dopamine antagonist properties, it will not produce the Parkinsonian-like side-effects that plague the current class of antipsychotics. This drug is currently (1997) being tested in clinical trials; early reports from these trials have been promising. If it does prove to be antipsychotic, it will represent one of the very few novel treatments used to treat schizophrenia that is not based on any dopamine antagonist effects. Thus, it may be particularly effective in the subgroup of schizophrenia patients for whom dopamine antagonists are ineffective. Clearly, if this promise is realized, it will be a direct benefit of animal studies on the mechanisms responsible for the effects of hallucinogens.

PPI in rats is also reduced by systemic treatment with serotonin releasers, or "entactogens", including MDMA, N-ethyl-3,4-methylenedioxy-amphetamine (MDEA or "Eve"), fenfluramine, and AET (Kehne et al., 1992, 1996; Mansbach et al., 1989; Martinez and Geyer, 1997). The PPI-disruptive effects of serotonin releasers are prevented by pretreatment with the serotonin reuptake inhibitor fluoxetine, which prevents the drug-induced release of serotonin from serotonin neurons while having little effect by itself. As with the classical hallucinogens, the serotonin-2 antagonist MDL 100907 and possible new antipsychotic is also effective in blocking the effects of serotonin releasers on PPI (Padich et al., 1996). Thus, it appears that these entactogens disrupt PPI by releasing serotonin which, in turn, acts upon serotonin-2 receptors.

In rats, PPI is reduced dose-dependently by the administration of the psychotomimetic PCP or related drugs such as ketamine (Mansbach and Geyer 1989, 1991). Importantly, the effects of PCP are <u>not</u> reversed by typical antipsychotics such as haloperidol, but <u>are</u> reversed by atypical antipsychotics including clozapine (Bakshi et al., 1994; Geyer et al., 1990). Thus, the PCP-disruption of PPI may be a useful model for identifying novel atypical antipsychotic treatments. In humans, this class of drugs produces symptoms that mimic some features of schizophrenia (Javitt and Zukin, 1991). Specifically, PCP-induced clinical effects have been linked to the characteristics and pathophysiology of the "deficit" symptoms of schizophrenia that are the most difficult to treat with the typical antipsychotics that work via dopamine antagonism. Furthermore, ketamine has been shown to produce a schizophrenia-like deficit in PPI in normal control subjects (Karper et al., 1994), induce psychotic symptoms in normal volunteers (Malhotra et al., 1996), and exacerbate psychotic symptoms in schizophrenia patients (Lahti et al., 1995), providing some validation of the similar animal studies.

Conclusions

The study of gating or filtering deficits in schizophrenia and parallel animal models based on startle measures of information processing has demonstrated considerable utility in the exploration of the phenomenology and neurobiology of schizophrenia in general and the drug-induced models of psychosis in particular. In rats, hallucinogens, entactogens, and PCP-like drugs mimic both the impairments of habituation and disruptions in PPI observed in patients with schizophrenia. Either of these abnormalities could be responsible for the thought disorder that is central to the symptoms of schizophrenia. The effects of hallucinogens and entactogens on both habituation and PPI have been related to their particular mechanisms of action within serotonergic systems. These observations in rats have led directly to the development of serotonin-2 antagonists for the treatment of schizophrenia. The effects of PCP and related psychotomimetics in rats appear to be sensitive specifically to atypical antipsychotics and may aid in the identification of novel antipsychotic therapeutics. By virtue of the extensive knowledge regarding the neurobiological substrates involved in the modulation of such gating functions as habituation and PPI in laboratory animals, the further application of these measures may enable the elucidation of both the mechanisms of action of psychotomimetics in humans and their possible relevance to the abnormalities that lead to schizophrenia and related psychotic disorders.

Shortly after the discovery of the neurotransmitter serotonin, it was suggested that LSD might owe its profound effects to actions on serotonin systems in the brain, due to structural similarities between LSD and serotonin. It was also suggested that we might learn something about the causes and/or treatment of psychotic disorders by discovering the mechanisms of action of LSD and related hallucinogens. While European psychiatrists have continued to explore this possibility (Hermle et al., 1993), most American psychiatrists dismissed the idea some 30 years ago because of largely specious arguments (Geyer and Markou, 1995). In retrospect, one can argue that the current excitement regarding the potential effectiveness of a serotonin-2 antagonist such as MDL 100907 in the treatment of schizophrenia could and would have been explored long ago if animal studies of hallucinogens had been supported more widely. Instead, progress has been slow, being based on the work of relatively few laboratories. For many years, it was thought that LSD functioned as a serotonin antagonist and that serotonin acted as a tranquilizing neurotransmitter in opposition to the activations associated with the neurotransmitter dopamine. Subsequent studies in animals revealed that LSD and related compounds actually act as serotonin agonists, that is, they mimic some actions of serotonin (at the serotonin-2 subtype of serotonin receptors). Although entrenched ideas fade slowly, informed neuroscientists are now recognizing that serotonin and dopamine are not simply reciprocal neurotransmitter systems and often work in concert. Hence, it is now acknowledged that both serotonin antagonism and dopamine antagonism may contribute importantly to the treatment of psychosis. This new insight, with its practical consequence being the current testing of a hallucinogen antagonist in schizophrenia patients, has evolved directly from multidisciplinary studies of laboratory animals. These animal studies may not have been motivated explicitly by the possible discovery of new treatments for any disease; most were designed simply to further our basic knowledge of serotonin systems and the mechanisms of action of hallucinogenic drugs. Without such basic knowledge, however, one can be confident that biomedical science will not advance and new treatments for psychiatric disorders will not be developed. Thus, despite the fact that such research is subject to ridicule by those who would stop animal research, I contend that animal studies of hallucinogen mechanisms have the potential to alleviate human sufferring.

References

Bakshi VP, Swerdlow NR, Geyer MA. Clozapine antagonizes phencyclidine-induced deficits in sensorimotor gating of the startle response. J Pharmacol Exp Ther 271: 787-794, 1994.

Bolino F, Di Michele V, Di Cicco L, Manna V, Daneluzzo E, Cassachia M. Sensorimotor gating and habituation evoked by electrocutaneous stimulation in schizophrenia. Biol Psychiat 36: 670-679, 1994.

Braff DL, Geyer MA. Sensorimotor gating and schizophrenia: Human and animal model studies. Arch Gen Psychiatry 47:181-188, 1990.

Braff DL, Grillon C, Geyer M. Gating and habituation of the startle reflex in schizophrenic patients. Arch Gen Psychiat 49: 206-215, 1992.

Braff D, Stone C, Callaway E, Geyer M, Glick I, Bali L. Prestimulus effects on human startle reflex in normals and schizophrenics. Psychophysiology 15: 339-343, 1978.

Cadenhead KS, Geyer MA, Braff DL. Impaired startle prepulse inhibition and habituation in schizotypal patients. Am J Psychiat 150: 1862-1867, 1993.

Davis M, Cassella JV, Wrean WH, Kehne JH. Serotonin receptor subtype agonists: Differential effects on sensorimotor reactivity measured with acoustic startle. Psychopharmacol Bull 22:837-843, 1986.

Geyer MA, Peterson L, Rose G, Horwitt D, Light R, Adams L, Zook J, Hawkins R, Mandell AJ. Effects of LSD and mescaline derived hallucinogens on sensory integrative function: Tactile startle. J Pharmacol Exp Ther 207:837-847, 1978.

Geyer MA, Braff DL. Habituation of the blink reflex in normals and schizophrenic patients. Psychophysiol 19:1-6, 1982.

Geyer MA, Segal DS, Greenberg BD. Increased startle responding in rats treated with phencyclidine. Neurobehav Toxicol Teratol 6:161-164, 1984.

Geyer MA, Tapson GS. Habituation of tactile startle is altered by drugs acting on serotonin-2 receptors. Neuropsychopharmacol 1:135-147, 1988.

Geyer MA, Swerdlow NR, Mansbach RS, Braff DL. Startle response models of sensorimotor gating and habituation deficits in schizophrenia. Brain Res Bull 25: 485-498, 1990.

Geyer MA, Markou A. Animal models of psychiatric disorders. In: Psychopharmacology: The Fourth Generation of Progress (FE Bloom and DJ Kupfer, eds), Raven Press, Ltd, New York, pp. 787-798, 1995.

Geyer MA. Behavioral studies of hallucinogenic drugs in animals: Implications for schizophrenia research. Pharmacopsychiatry, in press.

Grillon C, Ameli R, Charney DS, Krystal J, Braff DL. Startle gating deficits occur across prepulse intensities in schizophrenic patients. Biol Psychiat 32: 939-943, 1992.

Hamm A, Weike A, Bauer U, Vaitl D, Gallhofer B. Prepulse inhibition in medicated and unmedicated schizophrenics. Psychophysiology, 33 (Suppl 1): S65, 1995.

Hermle L, Funfgeld M, Oepen G, Botsch H, Borchard D, Gouzoulis E, Fehrenbach RA, Spitzer M. Mescaline-induced psycho-pathological, neuropsychological, and neuro-metabolic effects in normal subjects: Experimental psychosis as a tool for psychiatric research. Biol Psychiat 32:976-991.

Javitt DC, Zukin SR. Recent advances in the phencyclidine model of schizophrenia. Am J Psychiat 148: 1301-1308, 1991.

Karper LP, Grillon C, Charney DS, Krystal JH. The effect of ketamine on pre-pulse inhibition and attention. Abstr ACNP, 124, 1994.

Kehne JH, McCloskey TC, Taylor VL, Black CK, Fadayel GM, Schmidt CT. Effects of serotonin releasers 3,4 Methylenedioxymethamphetamine (MDMA), 4-chloroamphetamine (PCA) and fenfluramine on acoustic and tactile startle reflexes in rat. J Pharmacol Exp Ther 260: 78-89, 1992.

Kehne JH, Padich RA, McCloskey TC, Taylor VL, Schmidt CJ. 5-HT modulation of auditory and visual sensorimotor gating: I. Effects of 5-HT releasers on sound and light prepulse inhibition in Wistar rats. Psychopharmacology 124: 95-106, 1996.

Lahti AC, Koffel B, LaPorte D, Tamminga CA. Subanesthetic doses of ketamine stimulate psychosis in schizophrenia. Neuropsychopharmacol 13: 9-19, 1995.

Malhotra AK, Pinals DA, Weingartner H, Sirocco K, Missar CD, Pickar D, Breier A. NMDA receptor function and human cognition: the effects of ketamine in healthy volunteers. Neuropsychopharmacol 14: 301-307, 1996.

Mansbach RS, Braff DL, Geyer MA: Prepulse inhibition of the acoustic startle response is disrupted by N-ethyl-3,4-methylenedioxy-amphetamine (MDEA) in the rat. Eur J Pharmacol 167: 49-55, 1989.

Mansbach RS, Geyer MA. Effects of phencyclidine and phencyclidine biologs on sensorimotor gating in the rat. Neuropsychopharm, 2: 299-308, 1989.

Mansbach RS, Geyer MA. Parametric determinants in pre-stimulus modification of acoustic startle: interaction with ketamine. Psychopharm 105: 162-168, 1991.

Martinez DL, Geyer MA. Characterization of the disruptions of prepulse inhibition and habituation of startle induced by alpha-ethyltryptamine. Neuropsychopharm 16:246-255, 1997.

Padich RA, McCloskey TC, Kehne JH. 5-HT modulation of auditory and visual sensorimotor gating: II. Effects of the serotonin-2A antagonist MDL 100,907 on disruption of sound and light prepulse inhibition produced by 5-HT agonists in Wistar rats. Psychopharmacology 124: 107-116, 1996.

Perry W, Braff DL. Information-processing deficits and thought disorder in schizophrenia. Amer J Psychiat 151: 363-367, 1994.

Sipes TA, Geyer MA. Multiple serotonin receptor subtypes modulate prepulse inhibition of the startle response in rats. Neuropsychopharm 33: 441-448, 1994.

Sipes TE, Geyer MA. DOI disruption of prepulse inhibition of startle in the rat is mediated by serotonin-2A and not by serotonin-2C receptors. Behav Pharmacol 6:839-842, 1995.

Weike A, Globisch J, Hamm A, Bauer U. Prepulse inhibition and habituation of skin conductance responses in schizophrenics: Neuroleptic drug effects. Psychophysiol 33 (Suppl 1): S88, 1996.

5. The Medicinal Chemistry of Phenethylamine Psychedelics

David E. Nichols, Ph.D.

I am sometimes asked, "how would you describe your research?" After many years my standard response has evolved to, "I design molecular probes of brain function." While the readers of this essay may know that I have worked with psychedelics for nearly thirty years, my laboratory also is studying the development of potential new treatments for depression, as well as carrying out significant efforts to create new therapies for end-stage Parkinson's disease. In each case, we are using relatively small chemical molecules to interact with various brain targets to gain information that may enhance our understanding of the underlying importance of those targets to normal brain function. In the latter two examples, it is clear what the end point should be. We should find better and faster ways to treat depression, and we should find new drugs to restore function to Parkinson patients who presently have no further hope. While the molecules we design often start out as experimental probes, if we have understood well the nature of our target, these structures may eventually become therapeutic entities.

What about probes of the brain receptors for hallucinogens? What is the end point there, and how is it relevant? There is one line of reasoning that says these peculiar substances can only be assayed in man, and that any other approach is inherently invalid. While off the record one may occasionally be forced to admit to the essential core truth of this premise, it does *not* necessarily follow that any other type of research is completely and utterly useless. Readers will find further confirmation of this fact in the chapter in this volume by Dr. Mark Geyer. I have occasionally been challenged that the structure-activity studies I carry out have no relevance to the real world; that studies in rats have no meaning. I do not believe this to be the case, and I shall explain why. We can very well use receptor assays, and models employing trained laboratory animals (mostly rats) to tell us whether a new molecule may have the essential molecular features that would ultimately allow it to be classified as a psychedelic, were it to be tested in man. What we cannot do with animals, or with any other nonhuman models, is to predict whether a particular molecule will open the gates of heaven or stoke up the fires of hell. We must maintain a clear distinction between these two positions. On the one hand, we can design and study molecules in model systems that allow us to predict that the structure will have psychedelic activity, but on the other we absolutely *cannot* know the full psychopharmacological complexity of their effects in the absence of clinical studies.

Discussions of psychedelics as chemical molecules, interacting with brain receptors, also tends to "demystify" psychedelics for those who view them as sacraments. It is not my mission to gore anyone's sacred cow. In the realm of psychedelics, hard core science will say that these substances simply activate certain parts of the brain that produce effects that might be predictable, if only we had a complete understanding of the brain and its neurobiology. At the other end of the spectrum are sincere people who believe that psychedelics are sacred substances, that can produce genuine nirvana, union with the cosmos, and the like--ecstatic states that they believe have very little to do with brain anatomy or chemistry. These are the folks who talk about a new paradigm of mind, quantum consciousness, and the like. I do not plan to enter this debate, but rather only to present a fundamentally reductionistic view of how these substances are now believed to interact with the physical brain. My objective in this essay is to provide some basic information about the medicinal chemistry of psychedelic agents.

At its heart, medicinal chemistry (what I do) attempts to draw clear and meaningful relationships between the molecular features of a chemical structure and the biological events subsequent to its administration to a living organism. Inherent in this approach is the assumption that a relationship exists between chemical structure and biological effect. In the context of psychedelic agents a relationship certainly exists. It is in clearly and explicitly defining this relationship that problems may arise.

Perhaps it would be helpful here to employ a crude analogy. One can clearly see that a relationship exists between gasoline and automobile travel. What one cannot predict is whether a particular tank of gasoline is destined to propel a car toward Canada, Mexico, the Northeast, etc. The outcome is dependent on the whims of the owner of the vehicle. Similarly, one can predict that

psychoactive substances such as LSD will move the psyche from what has been called consensus reality, to some altered state of consciousness. What cannot be predicted is the nature of that change or the "direction" the altered state will take. It is an erroneous assumption to believe that medicinal chemistry can design in elements of molecular structure that will lead the psyche in a particular direction. The state of the art in medicinal chemistry is not so advanced! This would be akin to assuming that a particular blend of gasoline could somehow determine the direction that the car will be driven.

What I am leading up to is the fact that there are key recognition elements within the structures of all psychedelic molecules that lead to their activity; phenethylamines have them, tryptamines have them, and LSD and other related ergolines have them. Essential chemical features of these molecular recognition elements activate a key brain target. This activation then "enables" the brain to shift its processing from ordinary waking consciousness and enter into whatever state is produced by all psychedelic drugs. Most scientists now believe the target, or "switch" for psychedelic molecules is a site known as the serotonin 5-HT_{2A} receptor (Nichols 1997). Just as turning on the power switch of a television enables the TV to display images, *but is not responsible for what is seen*, psychedelic molecules, by activating this brain receptor, "turn on" some other set of amplifiers and processors that allow nonordinary feelings and states of consciousness to occur.

While this may sound reductionistic to many readers, it may also be useful to envisage an analogy between this receptor and an automobile's ignition system, that must be switched on with a key before the car may go in any direction. It is up to the motivations of the driver, the power of the engine, the condition of the roads, etc. (i.e. the "set" and the "setting") to determine where and when the journey will actually begin and end.

It is believed that during ordinary circumstances the brain 5-HT_{2A} receptor is not highly activated. That is, the daily ebb and flow of serotonin molecules does not produce an LSD-like state in us because not many serotonin molecules are released by neurons onto these receptors. When a psychedelic molecule enters the brain however, it binds very tightly to these receptors, producing an extensive and prolonged activation state. In fact, the brain is so sensitive to activation of these receptors that when they are overstimulated, as for example when one ingests a psychedelic such as LSD, they quickly decline in density so as to reduce the numbers of targets for any additional neurotransmitter that might be released (or any additional LSD molecules that may happen to arrive). This is the reason that LSD loses its effects when taken too often. The number of receptors for it just rapidly decreases!

What my research has done is to focus on key sites in the brain, and attempt to identify the recognition elements that are necessary to bind to and activate them. This was a goal when I started research in this field in 1969, and it remains unattained in 1997. But, I think we are getting closer to understanding. To begin with, until a few years ago no one really had a good idea of what a receptor might look like. Today, we know that the vast majority of neurotransmitter receptors are bundles of protein helices embedded in and spanning the neuronal cell membrane. The receptor, therefore, can act as a "conduit" to allow information to pass *through* the neuronal membrane.

One of the stable forms that proteins can adopt is called an alpha helix. This is somewhat the shape of a Slinky toy, or the shape of the threads around a bolt. It is now widely believed that most of the serotonin receptors exist as a bundle of seven such alpha helices inserted into the neuron membrane. These seven helices are connected both on the outside and on the inside of the neuron membrane with continuing loops of proteins, so that the whole receptor, if it could be unwound and stretched out, would simply be one very long chain of amino acids, the basic building blocks of all proteins. A schematic view of this type of receptor is presented in figure 1.

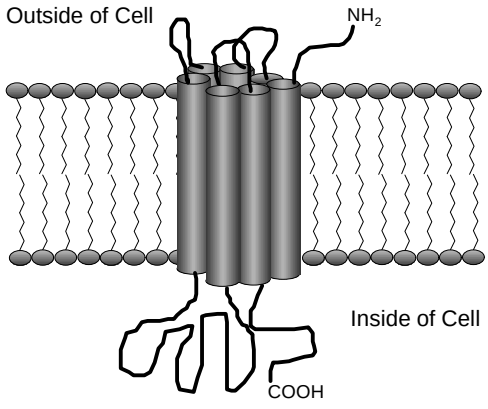

Figure 1. *A schematic representation of a membrane-bound G-protein coupled receptor, of which the serotonin 5-HT_{2A} receptor is an example. The receptor consists of 7 alpha helices, represented here by tubes, connected on the inside and outside with continuing loops of protein.*

The process of neurotransmission involves the release of neurotransmitter molecules from the terminal of a neuron. These diffuse through the solution in the space between the two neurons (called the synapse), and are attracted to the receptor, probably due to electrostatic fields generated by the charges on the amino acids in the receptor and charges on the neurotransmitter. The neurotransmitter molecule fits into the ligand recognition domain of the receptor, where a series of events is then initiated. It is believed that when the neurotransmitter "docks" into the receptor, the seven alpha helices rearrange the way they are oriented with respect to each other. That is, they twist, turn, and bend, undergoing what is called a "conformational change," in order to achieve a new packing arrangement that is compatible with the presence of the neurotransmitter in their midst. This is a reasonable hypothesis, and could be explained in a very technical way if time and space permitted.

What is not adequately represented in figure 1 is the relatively large piece of receptor protein that is used to connect the seven alpha helices on the *inside* of the receptor. These protein chains, particularly a large loop that connects helices 5 and 6, as well as the end of the protein chain that follows helix 7 on the inside of the receptor, adopt a shape that allows them to bind to another type of protein, called a GTP-binding protein (G protein for short). When the neurotransmitter molecule binds to its recognition domain in part of the receptor on the *outside* of the membrane, it causes changes in the shape of the receptor, and the movement of the receptor helices then apparently causes large shape changes in the loops and chains on the part of the receptor that is *inside* of the neuron. When this occurs, the G proteins dissociate from the receptor because the fit between them is no longer complementary, they bind to molecules of GTP in the cytoplasm, and then initiate a series of biochemical changes in the neuron that constitutes the actual "message" of the neurotransmitter; calcium levels in the neuron change, certain proteins are activated that attach phosphate groups to other proteins, etc. The whole process is a complex sequence of events known as a signaling cascade. All these biochemical changes produced in the interior alter the state of the neuron, making it more or less easy to send a signal itself. Ultimately, at least for psychedelics, these changes in brain biochemistry somehow lead to an alteration in consciousness. How this occurs will remain a mystery for many years to come, if we can ever discover it!

The assumption in my laboratory has been that all the various types of psychedelic agents, at a minimum, interact with brain serotonin 5-HT_{2A} receptors in this way, and what we have tried to do is to understand how the *chemical features* of these molecules lead to their binding to this receptor. We shall now move on to a more chemical discussion of what properties are possessed by the molecules themselves, that may allow them to activate receptors.

Following more than two decades of work, in several laboratories, there are now some ideas about what is required for activity, at least in some classes of molecules. For example, as a crude representation, figure 2 shows some of the structural features that may be important within the phenethylamine type hallucinogens for receptor recognition and activation (Monte et al. 1996). First of all, the cyclic hexagonal ring in the center of the figure is called a phenyl ring. The letter N in the NH_3 to the right of that represents the nitrogen atom. The lines connecting the two represent two carbon atoms attached together, called an ethyl group. Hence, these molecules, in general, are called phenethylamines or sometimes phenylethylamines: a phenyl ring separated by an ethyl grouping from an amine.

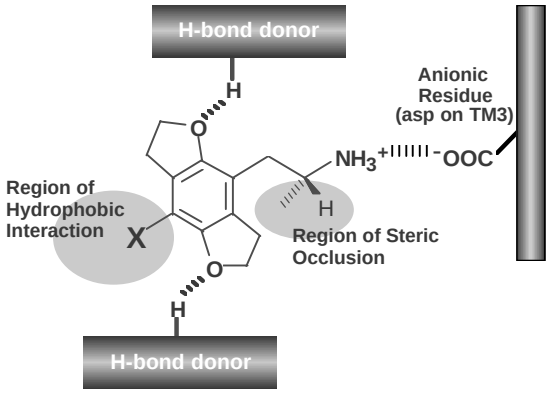

Figure 2*. A schematic representation of a phenethylamine hallucinogen similar to DOB interacting with the ligand binding domain of the serotonin 5-HT_{2A} receptor. Important sites for chemical interaction include the amino group, the two oxygen atoms, the hydrophobic "X" group, and the central phenyl ring itself. Taken from Monte et al. 1996*

The nitrogen atom has the property of being basic, in the context of acid-base chemical reactions. Ammonia is a common household base. Bases are neutralized by chemical reaction with acids.

Common household acids are vinegar and soft drinks. Since acids neutralize bases, in the body the basic amino group of the phenethylamines is also "neutralized" by reacting with weak acids. This means that the basic amino group, which is normally represented by an NH_2, has added an extra hydrogen atom, or proton (i.e. the acid), and now is an NH_3^+, the plus sign denoting that the hydrogen atom brought a positive charge with it to the molecule.

This positive charge is believed to lead to an attraction for an amino acid in the serotonin receptor called an aspartic acid residue. This key aspartic acid residue is located on one of the membrane-spanning alpha helices designated as transmembrane helix 3. This amino acid is a weak acid, similar in acidity to vinegar, but it too has lost it's hydrogen atom by neutralization in the body. The characteristic feature of weak organic acids is the presence of a COOH grouping of atoms. Since molecules prefer to be neutral, and not carry a charge on them, the departure of it's hydrogen atom with a positive charge left behind a corresponding negative charge. Thus, the aspartic acid is shown not as a -COOH, but rather as a $-COO^-$, indicating that the hydrogen atom is gone, and that a negative charge was left behind. It is the attraction between the amino group, with the positive charge, and the aspartic acid residue, with the negative charge, that is believed to be one of the most powerful forces in causing a neurotransmitter to bind to its receptor. This attraction is denoted by the series of short vertical lines between the NH_3^+ and the $-OOC^-$ in the figure. As a crude analogy, one can appreciate the force that occurs between the two poles of a magnet.

On the left side of the phenethylamine molecule, a large "X" is pictured above an elliptical area labeled as a "Region of Hydrophobic Interaction." Hydro is a prefix denoting water, and phobic comes from the same root as phobia, or fear of something. Thus, hydrophobic is a term meaning that something is "water-hating." Not surprisingly, therefore, hydrophobic molecules typically have an oily or greasy texture. This is an important place in the receptor that seems to prefer to bind to atoms or groups that have an oily, non-water soluble nature. Extremely potent phenethylamine hallucinogens have atoms attached at this position such as bromine, iodine, or sulfur. Indeed, if the rest of the structure is completely identical, the changing of what is attached only at this location of the phenyl ring can give compounds that begin to approach the potency of LSD on a dosage basis!

Another important feature of these compounds is the two oxygen atoms. These are shown near the top and bottom of the structure, as the letter O, with the dashed lines toward the Hs. These oxygen atoms are essential to binding and activation of the receptor. Alexander Shulgin carried out a number of studies where he replaced these oxygen atoms with other atoms such as sulfur, and in each case the activity was greatly reduced or lost completely. In the simplest compounds, these oxygen atoms are not part of a ring system, as shown here, but rather are freely swinging. They are hooked to the phenyl ring, and then another carbon atom called a methyl group is attached. This grouping looks like this: $-OCH_3$. Because of the numbering system for the locations around the phenyl ring, these methoxy groups are attached at positions numbered 2 and 5. The "X" group is attached at the position numbered 4. Thus, these compounds are often called 2,5-dimethoxy-4-substituted phenethylamines.

In figure 2, however, both oxygen atoms are shown incorporated into pentagonal rings (known as dihydrofurans), that have common edges with the central phenyl ring (i.e. they are "fused" to the phenyl ring). This has the effect of "locking" the oxygen atoms so they cannot undergo rotational movement. Experiments in my laboratory have shown that this gives the most active orientation of the oxygen atoms in producing hallucinogenic effects. We believe that the oxygen atoms interact with the receptor through hydrogen bonds, represented as the dashed lines connecting the oxygen atom to a hydrogen atom (denoted by the letter H) arising from a hydrogen bond donating site in the receptor. Because oxygen atoms have extra electrons in their outer shell, and certain types of hydrogen atoms attached to oxygen or nitrogen atoms have a slight "deficiency" of electrons, there is a fairly strong attraction between them that is called a hydrogen bond.

Finally, there is also a small area shown in figure 2 labeled "Region of Steric Occlusion." In the phenethylamines, there is only a hydrogen atom (H) at the end of the dashed line in this region. These are representatives of compounds that Shulgin has named 2C compounds (e.g. 2C-B, 2C-T, etc.). The 2C represents the fact that there are only two carbons between the phenyl ring and the amine. However, if a third carbon atom is attached, that is, a $-CH_3$ group is attached at the end of the dashed line that is lying over the region of steric occlusion, these compounds are typically called amphetamines. This carbon in the ethyl group is called the alpha position because it is the first carbon atom attached to the amine nitrogen. (The second carbon atom from the amine, next to the phenyl ring, is called the beta position.)

Nothing larger than a single carbon atom with its attached hydrogens, called a methyl group, can be attached here. In organic chemistry, the word steric is used to refer to the size or bulk of a portion of the molecule. We have therefore designated this portion of the receptor as an area that cannot tolerate steric bulk. In other words, it is a region of steric occlusion.

So, the molecule binds through a combination of forces, to the amino group, the two oxygen atoms, and the hydrophobic "X" group, and in addition, the receptor has many hydrophobic amino acid groups within the ligand binding domain that simply embrace the phenyl ring and the ethyl group which themselves are hydrophobic. The molecule just becomes as snug as a bug in a rug! In the process of being attracted to, and wrapping around the psychedelic molecule, the receptor changes and moves itself, and sets off the sequence of biochemical events described earlier.

The same thing cannot be said for molecules related to mescaline, however. We recently (Monte et al. 1997) showed that carrying out the same types of chemical modifications that led to high activity in the DOB type compounds, gave molecules that appear inactive in our animal models when applied to mescaline. Illustrated in figure 3 below are the relevant examples. Locking the methoxy groups of DOB into rings (as also shown earlier in the "receptor" model) gives an increase in potency. On the other hand, locking the distal methoxy groups of mescaline into rings in the same way led to inactive compounds!

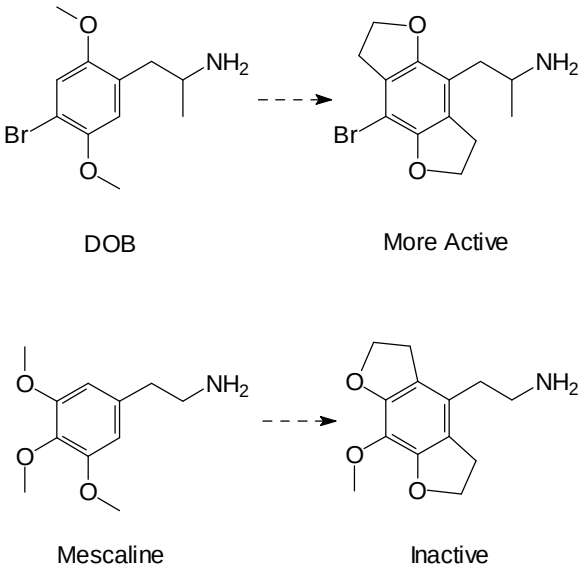

Figure 3. *Rigidification of the methoxy groups in DOB leads to compounds with increased activity while a similar transformation in mescaline leads to inactive compounds.*

While it has generally been assumed that mescaline activates the same receptors as all of the other types of psychedelics, there are clearly some important differences when one actually looks at the molecular architecture of mescaline compared with DOB-like molecules. This is an issue that continues to perplex us, and will be the focus of additional studies as we attempt to identify the active shape of mescaline-like molecules when they bind to the receptor.

These might appear, at first glance, to be easy questions to solve, but in fact the design of molecular probes to study this question is quite problematic. When a change is made in the structure of a molecule, many variables are changed simultaneously and one often cannot know which one was responsible for the observed effect. For example, in figure 3, incorporation of the methoxy groups into the pentagonal furan rings does not simply "lock" the orientation of the oxygen atom. It also introduces new pieces of molecular 'baggage.' That is, a methoxy group is $-OCH_3$, while the corresponding part of the furan ring structure is $-OCH_2CH_2-$. Furthermore, in mescaline, the positions in the phenyl ring (the hexagonal central ring) that are adjacent to the ethylamine chain are occupied only by hydrogen atoms, while in the rigid analogue on the right, they serve as the anchor points for the cyclic ring structures. In the usual circumstance, one cannot know what effect these additional modifications have on overall activity. Our analogy to the DOB molecule however, suggests that incorporation of the oxygen atoms into these ring structures should not affect activity, *if the oxygen atom in the methoxy group possesses the same orientation as in the ring structure upon binding to the receptor*. Our extension of this approach to mescaline, leading to inactive compounds, suggests therefore that the oxygen atoms of mescaline do not adopt the orientation of the rigid analog shown on the right, and that perhaps the methoxy groups of mescaline may rotate into some different, and as yet undefined orientation. What is this orientation? That is a question we will attempt to address in future studies.

What's next?

The missing piece(s) of the puzzle are now the links between these biochemical events, and the parts of the brain that must be involved in changing consciousness. It will probably be a long time before this connection can be made. In the meantime, however, there are a number of scientifically valid approaches that will give useful information. Recently, for example, we have "stumbled" upon a simple phenethylamine molecule that has affinity for the 5-HT_{2A} receptor nearly 100-fold higher than any other compound discovered to date, including LSD itself! There is no particular reason to search for more potent compounds, but often such molecules prove to be quite useful as research tools. For example, when a molecule has very high affinity for a receptor, it is often possible to introduce radioactive atoms into the molecule that allow one to visualize sites where the molecule binds in the brain. This has already been done with molecules such as DOB, DOI, and LSD. However, a molecule with even higher affinity can be used at lower concentrations and dosages to detect and visualize receptors. This new molecule, with exceedingly high affinity for the 5-HT_2 class of receptors will no doubt be useful to label and visualize these receptors in the brain. Indeed, we have already begun discussions with a firm that supplies radioactive molecules to prepare radioactive forms of this molecule for evaluation.

Literature reports now also suggest that a tentative 3-dimensional structure for the family of G-protein coupled receptors may not be far off. This is the receptor family to which nearly all of the serotonin receptors belong. Perhaps within the next year or two a good structure may become available. With that event, we would begin computer modeling studies to dock our molecules into this receptor structure in attempts to gain an appreciation of which structural features of the molecule are necessary for binding and activation of the receptor. If this can be accomplished, we should also be able to design new molecules to test hypotheses about which molecular features are necessary for receptor binding. That would be a very exciting development because it would be the first time that it might become possible to design a molecule, *de novo*, to fit a particular receptor. Clearly, if we can retain our research funding, the most exciting developments in the medicinal chemistry of psychedelic agents are yet to come.

References

Nichols, D.E., Snyder, S.E., Oberlender, R. Johnson, M. and Huang, X. (1991) 2,3- Dihydrobenzofuran Analogues of Hallucinogenic Phenethylamines, *J. Med. Chem.*, **34**, 276-281.

Monte, A.P. Marona-Lewicka, D. Cozzi, N.V. Nelson, D.L. and Nichols, D.E. (1995) Conformationally restricted tetrahydro-1-benzoxepin analogs of hallucinogenic phenethylamines, *Medicinal Chemistry Research*., **5**, 651-663.

Monte, A.P. Marona-Lewicka, D. Parker, M. Wainscott, B. Nelson, D.L. and Nichols, D.E. (1996) Dihydrobenzofuran analogues of hallucinogens. 3. Models of 4-Substituted (2,5-dimethoxyphenyl)alkylamine derivatives with rigidified methoxy groups, *J. Med. Chem.*, **39**, 2953-2961.

Monte, A.P. Waldman, S.R. Marona-Lewicka, D. Wainscott, D.B. Nelson, D.L. Sanders-Bush, E. and Nichols, D.E. (1997) Dihydrobenzofuran analogues of hallucinogens. 4. Mescaline Derivatives," *J. Med. Chem.*, **40**, 2997-3008.

Nichols, D.E. (1997) Role of Serotonergic Neurons and 5-HT Receptors in the Action of Hallucinogens," in *Handbook of Experimental Pharmacology. Serotoninergic Neurons and 5-HT Receptors in the CNS*, H.G. Baumgarten and M. Göthert, Eds., Springer-Verlag GmbH & Co., Heidelberg, Germany, pp 563-585.

.

6. Are The "Entactogens" a Distinct Psychoactive Substance Class? The Contribution of Human Experimental Studies to the Classification of MDMA and Other Chemically Related Methylenedioxyamphetamine Derivatives

Euphrosyne Gouzoulis-Mayfrank, M.D. and Leo Hermle, M.D.

Introduction

MDMA (methylenedioxymethamphetamine; "Ecstasy") and its analogs MDE (methylenedioxy-ethylamphetamine; "Eve"), methylenedioxybenzo-dioxoylbutanamine (MBDB) and methoxymethylene-dioxyamphetamine (MMDA) are ring-substituted amphetamine-derivatives. Their chemical structures are closely related to both the stimulant amphetamines and the psychedelic phenethylamines and methoxyamphet-amines like mescaline, DOM and DOB (Figure 1). However, they are thought to exert unique psychological effects in humans, distinguishing them both from the stimulant and the psychedelic amphetamines (Shulgin and Nichols 1978, Shulgin 1986). During the last decade, there has been an intensive controversial discussion of MDMA in the scientific and general media. The dimension of this still ongoing discussion is motivated by the popularity of MDMA as an illegal recreational drug (Seymour 1986, Beck and Morgan 1986, Beck 1990), its neurotoxic potential (Price et al 1989, Grob et al 1990) and its claimed medical usefulness as an adjunct in insight-oriented psychotherapy (Grinspoon and Bakalar 1986, Greer and Tolbert 1986, 1990).

Studies with laboratory animals demonstrated that high and repeated doses of MDMA cause long-lasting or even irreversible degeneration of brain cells containing the endogenous transmitter serotonin (Ricaurte et al 1992). This is not a unique finding with MDMA, because a similar or even stronger neurotoxic potential can be shown in animal studies for many amphetamines. The clinical significance of these experimental data is unclear. However, they built a strong argument for the scheuling of MDMA in 1985.

According to anecdotal evidence MDMA possesses anxiolytic and antidepressive properties. It evokes a subtle, easily controllable altered state of consciousness with an emphasis on emotional aspects, relaxation, feelings of happiness, heightened self-acceptance and empathy, openness for communication and decrease of fear responses. In contrast, perceptual alterations, alterations of thinking and orientation and amphetamine-like stimulatory effects are not generally reported (Greer and Tolbert 1986). This psychotropic profile makes MDMA, in the view of some psychotherapists, a valuable tool for psycholytic psychotherapy. Psycholytic therapies with psyche-delics (mostly LSD) were performed in many European and American centers in the 1950s and 1960s. The rationale of psycholytic therapy has its analogy in dream analysis: during the psychedelic state defense mechanisms diminish and defended, unconscious conflict material is visualized in a symbolic way; facilitating the approach to this material for analysis and interpretation after the psycholytic session. Before MDMA was scheduled in 1985 it was used by some therapists, predominantly on the west coast, in indi-vidual settings and in marital therapy (Greer and Tolbert 1990). In Switzerland, a small group of psychotherapists with psychoanalytic background founded the Swiss Medical Society for Psycholytic Therapy in 1988. They obtained time-limited licences for the use of LSD and MDMA in psycholytic sessions and treated over a hundred patients with neurotic and psychoreactive disorders during the years 1988 till 1994 (Styk 1994). Both U.S. and Swiss psycho-therapists gave enthusiastic reports of the beneficial effects of MDMA sessions on the therapeutic process (Greer and Tolbert 1986, Widmer 1989). According to these reports, MDMA helps overcome strong defenses, enables the therapist to confront the patient with deep conflicts by reducing his/her anxiety and may even be the only possibility to overcome stagnation of the psychotherapeutic process in treatment-resistant cases with substantial chronicity. A recent follow-up study of 121 treated patients in Switzerland demonstated improvement in 90% of the cases (Gasser, in press).

It was hypothesized that MDMA, MBDB and MDE constitute a novel psychoactive substance class. Animal drug discrimination experiments and pharmacological studies on the structure-activity relationships of MDMA and related compounds support the hypothesis of a distinct pharmacological class (Nichols 1986, Nichols and Oberlender 1990). Nichols (1986) proposed that the hypothetical new class be designated "entactogens." This new term is composed of the roots "en," "tactus," and "gen" and makes a strong reference

.

to the psychotherapeutic usefulness of the substances.

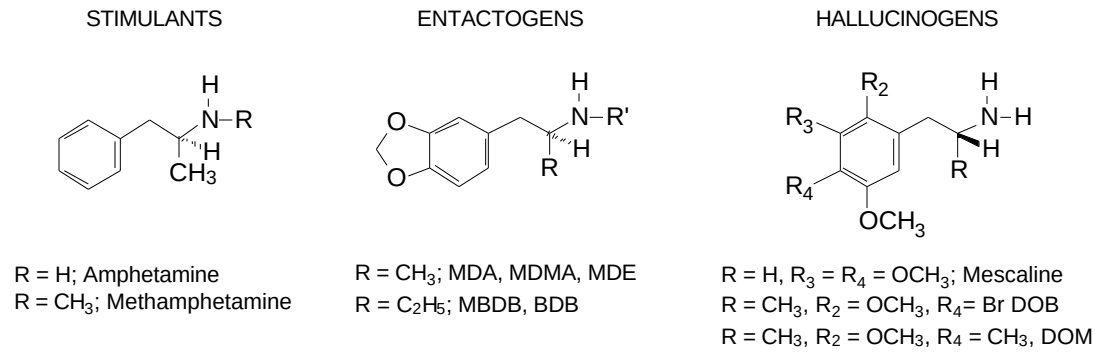

Figure 1. Chemical structures of stimulant amphetamines, entactogens, and phenethylamine psychedelics.

Nichols (1986): "Just as the word "tact" has the connotation of communicating information in a senstitive and careful way so as to avoid offense, it seemed that the Latin root of this word, tactus, would be appropriate as part of the term. Addition of the Greek roots en (within or inside) and gen (to produce) created the term entactogen, having the connotation of producing a touching within."

However, there are also reports of panic reactions, amphetamine-like stimulation and perceptual alterations with recreational MDMA use (Peroutka et al 1988, Whitaker-Azmitia and Aronson 1989, Dowling et al 1987). Reports of recreational users are difficult to interpret because of the various influences of the set and setting (personality, personal and environmental situative factors) on the effects of the drug and because of the frequent concomitant use of other substances or alcohol. Moreover, tablets sold as "Ecstasy" may contain mixtures of MDMA with amphetamines or even psychedelics or in some cases may lack MDMA altogether. In consequence, the position of the entactogens within the range of the chemically related psychotropic drugs is uncertain.

Human experimental studies with MDE ("Eve")

The most direct way to explore the question of a distinct pharmacological entity is to assess the effects of an entactogen in a standardized human experimental setting. Due to the current legal situation, human studies with hallucinogens and related psychoactive substances are difficult to realize. However, it is not impossible to obtain the approvals needed from the responsible state authorities. Our group has already performed a pilot study on the subjective and neurobiological effects of MDE in healthy volunteers. Further studies are currently in progress. We chose to work with MDE, because it was shown to be less neurotoxic than MDMA in animal studies (Schmidt 1987, Ricaurte et al 1987, Gibb et al 1990). The experimental design was random double-blind, placebo-controlled, cross-over, i.e. every volunteer took part in one active (a single 140 mg oral dose) and one placebo experiment.

Fourteen healthy volunteers participated in this first study. The psychological effects of MDE were assessed using several questionnaires and scales. In addition, we studied the neurohormonal influences of the drug in eight of the fourteen subjects. The remaining six subjects participated in a sleep EEG study in order to assess the effects of MDE on sleep architecture.

Neurobiological effects of MDE

Effects on hormonal secretion

The secretion of cortisol, prolactin, and growth hormone is regulated by endogenous transmitters such as serotonin and norepinephrine acting in the hypothalamus and hypophyseal gland of the brain. Drugs interacting with these endogenous transmitters (e.g. amphetamines and psychedelics) alter neurohormonal secretion. Thus, to compare the neuroendocrine effects of psychotropic drugs is one possible approach to their pharmacologic characterization.

Eight healthy male volunteers took 140 mg of MDE or placebo at noon time after a standardized light lunch. For the following 3.5 hours blood samples were taken every 20 minutes for an analysis of the time-course of the effects on neurohormonal secretion. After the intake of MDE, there were sharp rises in cortisol and prolactin plasma levels, which declined after about two hours, but were still above the pre-drug level at the

end of the experiment. In contrast, growth hormone levels did not rise above the pre-drug level (Gouzoulis et al 1993a). From previous studies of other groups it is known that stimulant amphetamines and psychedelic amphetamine derivatives enhance cortisol and prolactin secretion. So, these effects do not differentiate between the entactogens and the other chemically related substances. However, amphetamines are also known to enhance the secretion of growth hormone. In our study, this was not true for MDE. Our growth hormone data might be indicative of distinct pharmacological mechanisms supporting the hypothesis of a novel psychoactive substance class (Gouzoulis et al 1993a), but have to be replicated before further interpretations are made.

Alteration of sleep architecture

In the sleep laboratory study MDE caused mostly, but not exclusively, amphetamine-like effects. Subjects took 140 mg MDE or placebo at 11:00 p.m. and lights were switched off immediately. After a normal sleep onset latency and sleep duration of about one hour, all subjects awoke due to the drug effects and stayed awake for at least 2.5 hours during the night on MDE (Gouzoulis et al 1992). There was a clear reduction of total sleep time and an increase in intermittent time awake after MDE. REM sleep, the sleep phase with the most prominent dream activity, was completely suppressed and did not occur at all after again falling asleep. The effects described so far are amphetamine-like. The overall reduction of sleep time affected all sleep stages, but was more prominent for the functionally less important light sleep (sleep stage 2). In contrast, there was a trend towards increase of deep sleep (sleep stage 4) during the second part of the night after MDE compared to placebo, i.e. subjects caught up with this most restorative sleep phase. Moreover, the cyclic sleep architecture was preserved during the second part of the night. The missing suppression of deep sleep and cyclic sleep architecture in the context of otherwise amphetamine-like effects is unusual and might indicate a distinct effect pattern of MDE on sleep, supporting the hypothesis of a novel psychoactive substance class. Interpretation of these data, however, as well as the data on growth hormone secretion, must be cautious because of the limited number of subjects (Gouzoulis et al 1992).

Psychological effects

There was a strong interindividual variability in the psychological effects of MDE (Hermle et al 1993a, b). Effects began 30 to 90 minutes after ingestion of the drug and lasted two to three hours.

All subjects displayed a significant stimulation with increased vigilance, drive and pressure of speech, together with sympathomimetic vegetative signs like sweating, slight tremor and moderate rises in blood pressure and heart rate Most subjects expressed subjective feelings of increased physical and mental vitality. This amphetamine-like effect pattern was the only uniform effect of the drug

The emotional quality of the experience was variable. Eleven subjects had an overall pleasant experience, which was free of anxiety and included feelings of euphoria, happiness, relaxation, security, and self-acceptance. Four out of these eleven subjects were engaged with important personal themes and were remarkably open for communication in a way that reminded us of the definition of an "entactogen." It may sound contradictory, but these subjects described their mood as being "sad." However, they felt at the same time a deep self-acceptance, so the overall experience was very positive. Three out of the eleven subjects additionally described cosmic-mystic feelings (unity with other people and the universe, religious feelings) during the experiment.

The experience of the remaining three subjects was very different and included negative emotional feelings. One subject reported marked depersonalization and derealization, blocking of normal thinking and attenuated emotionality. Another subject had an unpleasant experience of MDE-induced amphetamine-like psychomotor excitement and he felt very dysphoric. Finally, one volunteer experienced a psychosis with hallucinations, delusional ideas, anxious behavior and loss of insight and control of the situation for the duration of three hours (Gouzoulis et al 1993b). All other subjects except this one kept control over their altered state and insight into the experimental nature of their experience. However, half of the subjects did have some minor perceptual alterations including mainly visual, but also tactile and auditory phenomena e.g. colors were percieved as being more bright, their own own body felt heavier or lighter, etc. These phenomena and the one case of psychotic reaction are indicative of the underlying hallucinogenic potential of MDE.

One of the scales we used is the APZ-Questionnaire (Dittrich 1985) for the assessment of altered states of consciousness (ASC), which can be induced by psychedelic drugs as well as by various psychological conditions such as sensory deprivation or overstimulation and certain meditation techniques. The items of the questionnaire build three subscales: the subscale "oceanic boundlessness" (OSE) refers to positive emotional states, mystic experiences of unity and feelings of happiness. The subscale "Dread for

Ego-Dissolution" (AIA) refers to negative emotional experiences with anxiety and panic reactions like a horror trip. The subscale "Visionary Restructuralization" (VUS) includes hallucinatory behavior and ideas of reference. We compared the mean values of the 14 subjects of our MDE study to the mean values of 12 volunteers of a former study of our group with the hallucinogenic phenethylamine mescaline (Hermle et al 1992). The intake of mescaline resulted in significant effects on all three subscales. The effects of MDE were also significant, but less marked than the effects of mescaline (Figure 2), the difference being stronger for the "negative" and "hallucinogenic" subscales AIA and VUS (Hermle et al 1993a). The MDE-induced state was generally milder, more easy to control and with an emphasis on emotional aspects compared to the state induced by a classic hallucinogen like mescaline.

In summary, the data of our first pilot study with MDE are indicative of the close relation of the entactogens to both psychedelics and stimulants (Hermle et al 1993b). MDMA, MDE and MBDB probably take an intermediate position within the range of chemically related stimulant amphetamines and hallucinogenic phenethylamines. The entactogenic effects (reduction of anxiety and defenses, self-acceptance, empathy, peacefulness) are a major and unique part of the spectrum of action of the entactogens. However, this spectrum also includes amphetamine-like and mild hallucinogenic effects.

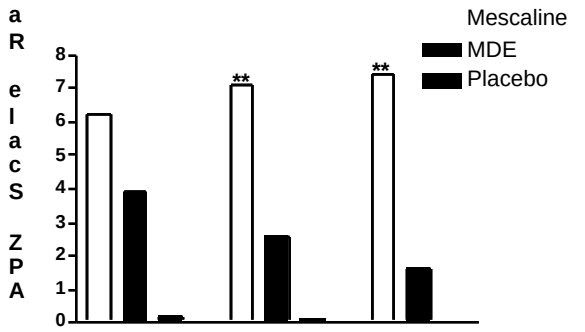

Figure 2. Comparison of the altered state of consciousness (ASC) induced by mescaline (n = 12) and MDE (n = 14) in healthy volunteers (subscales of the APZ questionnaire (Hermle et al 1993a))

Ongoing direct comparative studies with MDE and other psychoactive phenethylamines

A disadvantage of our placebo-controlled studies with MDE is that we can directly compare the drug´s actions only to placebo. Comparisons to the effects of other psychoactive substances can be drawn from literature data, but this procedure has significant methodological problems. Direct comparative studies with an entactogen and representatives of the other two categories of chemically related phenethylamines will provide us with stronger evidence for or against the case of a distinct pharmacological class. At present, our group is conducting an experimental project of this kind in collaboration with the Department of Nuclear Medicine in Aachen (U. Büll), the Psychiatric Department of the University of Heidelberg (M. Spitzer), the Pharmaceutical Department of the University of Tübingen (K.-A. Kovar) and the Psychiatric Department of UC San Diego (M. Geyer).

Every volunteer of our ongoing project participates in two experimental sessions with the same substance; this may be MDE, methamphetamine (representative of the stimulant class), psilocybin (representative of the psychedelic class), or placebo. Both the volunteer and our team are blind concerning the substance (double-blind design). Subjects undergo a series of examinations during the experiments: those include standardized psychopathological assessments, computer-based neuropsychological studies of attention and memory, PET studies of regional cerebral metabolism, electrophysiological studies of habituation and pre-pulse inhibition of the startle reflex, assessments of the neuroendocrine secretion and studies of pharmacokinetics and drug metabolism. With this project, we hope that we will be able to make a substantial contribution to the understanding of the mechanism of action of the entactogens, as well as the mechanism of action of stimulants and psychedelics.

References:

Beck, J. (1990) The public health implications of MDMA use. In: Peroutka, S.J. (ed.), Ecstasy: The clinical, pharmacological and neurotoxicological effects of the drug MDMA. Kluwer Academic Publishers, pp 77-103.

Beck, J., and Morgan, P.A. (1986) Designer drug confusion: A focus on MDMA. *J Drug Educ* 16, 287-302.

Dittrich, A., von Arx, S., and Staub, S. (1985) International study on altered states of consciousness (ISASC). Summary of the results. *German J Psychol* 9, 319-339.

Dowling, G.P., McDonough, E.T., and Bost, R.O. (1987) "Eve" and "Ecstasy": a report of five deaths associated with the use of MDEA and MDMA. *JAMA*257, 1615-1617.

Ensslin, H.K., Maurer H.H., Gouzoulis, E., Hermle, L., Kovar, K.-A. (in press) Metabolism of racemic 3,4-methylenedioxyethylamphetamine (MDE) in

humans. Isolation, identification, quantification and synthesis of urine metabolites. *Drug Metabolism and Disposition.*

Gasser P. (in press) Die psycholytische Psychotherapie in der Schweiz von 1988-1993. *Schweizer Archiv Neurol Psychiat*.

Gibb, J.W., Stone, D., Johnson, M., and Hanson, G.R. (1990) Neurochemical effects of MDMA. In: Peroutka, S.J. (ed), Ecstasy: The clinical, pharmacological and neurotoxicological effects of the drug MDMA. Boston, Kluwer Academic Publishers, pp 133-150.

Gouzoulis, E., Steiger, A., Ensslin, H., Kovar, K.-A., and Hermle, L. (1992) Sleep-EEG effects of 3,4-Methylenedioxyethamphetamine (MDE; "Eve") in healthy volunteers. *Biol Psychiatry* 32, 1108-117

Gouzoulis, E., Bardeleben, U.v., Rupp, A., Kovar, K.-A., and Hermle, L. (1993a) Neuroendocrine and cardiovascular effects of MDE in healthy volunteers. *Neuropsychopharmacology* 8, 187-193.

Gouzoulis, E., Borchardt, D., and Hermle, L. (1993b) A case of toxic psychosis induced by "Eve" (3,4-Methylenedioxyethylamphetamine). *Arch Gen Psychiatry* 50, 75.

Greer, G., and Tolbert, R. (1986) Subjective reports of the effects of MDMA in a clinical setting. *J Psychoactive Drugs* 18, 319-327.

Greer, G., and Tolbert, R. (1990) The therapeutic use of MDMA. In: Peroutka, S.J. (ed), Ecstasy: The clinical, pharmacological and neurotoxicological effects of the drug MDMA. Kluwer Academic Publishers, pp 21-35.

Grinspoon, L., and Bakalar, J.M. (1986) Can drugs be used to enhance the psychotherapeutic process? *Am J Psychotherapy* XL, 393-404.

Grob, C., Bravo, G., and Walsh, R. (1990) Second thoughts on 3,4-methylenedioxymeth-amphetamine (MDMA) neurotoxicity. *Arch Gen Psychiatry* 47,288.

Hermle, L., Fünfgeld, M., Oepen, G., Bosch, H., Borchardt, D., Gouzoulis, E., Fehrenbach R. A., Spitzer, M. (1992) Mescaline-induced psychopathological, neuropsychological, and neurometabolic effects in normal subjects: Experimental psychosis as a tool for psychiatric research. *Biol Psychiatry* 32, 976-991.

Hermle, L., Gouzoulis, E., Oepen, G., Spitzer, M., Kovar, K.-A., Borchardt, D., Fünfgeld, M., Berger, M. (1993a) The significance of hallucinogenic research in psychiatry: history and present status. *Nervenarzt* 64, 562-571.

Hermle, L., Spitzer, M., Borchardt, D., Kovar, K.-A., and Gouzoulis, E. (1993b) Psychological effects of MDE in normal subjects. Are entactogens a new class of psychoactive agents? *Neuropsychopharmacology* 8, 171-176.

Nichols, D.E. (1986) Differences between the mechanism of action of MDMA, MBDB, and the classic hallucinogens. Identification of a new therappeutic class: Entactogens. *J Psychoactive Drugs* 18, 305-313.

Nichols, D.E., and Oberlender, R. (1990) Structure-Activity relationships of MDMA and related compounds: a new class of psychoactive agents?. In: Peroutka, S.J. (ed), Ecstasy: The clinical, pharmacological and neurotoxicological effects of the drug MDMA. Kluwer Academic Publishers, pp 105-131.

Peroutka, S.J., Newman, H., and Harris, H. (1988) Subjective effects of 3,4-methylenedioxymethamphetamine in recreational users. *Neuropsychopharmacology* 1, 273-277.

Price, L.H., Ricaurte, G.A., Krystal, J.H., and Heninger, G.R. (1989) Neuroendocrine and mood responses to intravenous L-tryptophan in MDMA users. *Arch Gen Psychiatry* 46, 20-22.

Ricaurte, G.A., Finnegan, K.F., Nichols, D.E., DeLanney, L.E., Erwin, I., and Langston, J.W. (1987) MDE, a novel analogue of MDMA, produces long-lasting depletion of serotonin in rat brain. *Eur J Pharmacol* 137, 265-268.

Ricaurte, G.A., Martello, A.L., Katz, J.L., Martello, M.B. (1992) Lasting effects of MDMA on central serotonergic neurons in nonhuman primates: neurochemical observations. *J Pharmacol Exp Ther* 261, 616-622.

Schmidt, C.J. (1987) Acute administration of methylenedioxymethamphetamine: comparison with the neurochemical effects of its N-desmethyl and N-ethyl analogs. *Eur J Pharmacol* 136, 81-88.

Seymour, R.B. (1986) MDMA. San Francisco, Haight-Ashbury Publications.

Shulgin, A.T., and Nichols, D.E. (1978) Characterization of three new psychotomimetics. In: Stillman, R.C., and Willette, R.E. (eds), The Psychopharmacology of Hallucinogens. Pergamon Press, New York, pp 74-83.

Shulgin, A.T. (1986) The background and chemistry of MDMA. *J Psychoactive Drugs* 18, 291-304.

Styk, J. (1994) Rückblick auf die letzten sieben Jahre der Schweizerischen Ärztegesellschaft für Psycholytische Therapie. In: Dittrich, A., Hofmann, A., and Leuner, H.C. (eds). Welten des Bewußtseins, Band 4. Verlag für Wisenschaft und Bildung, Berlin, pp 149-154.

Widmer, P.S. (1989) Fallbeispiel einer

psycholytischen Psychotherapie. In: Schlichting, H., and Leuner, H.C. (eds) Psychoaktive Substanzen und veränderte Bewußtseinszustände in Forschung und Therapie. ECBS Göttingen, pp 163-168.

Whitaker-Azmitia, P.A., and Aronson, T. (1989). Panic attacks associated with MDMA (ecstasy). *Am J Psychiatry* 146, 119.

7. Flashbacks in Theory and Practice

Lin S. Myers, Ph.D., Shelly S. Watkins, M.A., and Thomas J. Carter, Ph.D.

Hallucinogenic drugs have been used by humankind for at least five thousand years. In our society during the past thirty to fifty years there has been tremendous growth of interest in and use of psychoactive substances. The most common use of hallucinogenic drugs today is recreational, although they have also been used in therapeutic and religious settings. The popular press, governmental and law enforcement agencies, and some researchers have reflected society's concerns about possible dangers of drug use. The fact that hallucinogenic drugs lack addictive qualities has led to a focus on possible long term effects such as flashbacks, a reappearance of the drug experience, possibly years later. Among the issues we will discuss in this article are what might constitute a flashback, current clinical definitions, some research into the phenomena, and the implications for therapeutic and recreational uses of hallucinogens. Making sense of flashback phenomena can be difficult because it involves issues of definitions, consciousness, how we recognize qualities of our own mental processes, and interactions between physiological and psychological functioning.

We attempt to understand the world through our conscious experience. Most people take it for granted that their perceptions are a direct and reliable reflection of reality. However, how we perceive the world is a function of both what we take in through our senses and how our brains process our perceptions. Without conscious effort, we habitually compensate for irregularities in our perceptual processing. For example, if a myopic person removes their glasses, they don't normally assume that the world has actually become fuzzy. We recognize that a stick in the water is not really bent, although it may look that way. We must remember, though, that our ability to accommodate perceptual variations depends on factors such as cognitive development, brain chemistry, personality, previous experience, and our internal models of reality.

As we think about the issues raised by perceptual variations such as optical illusions, a number of questions come to mind: what is "normal" consciousness? To what extent can we assume that our experiences are similar to those of others'? Is there an objective reality independent of our experience and perception? What role do social and cultural systems and expectations play? To what extent and in what ways do our senses and cognitive processes filter our perceptions and, given the overwhelming variety and quantity of perceptual stimuli available to us, how important are those filters? How are we aware of variations in our own consciousness? Might there be reasons to actively alter our consciousness either through drugs, meditation, or other means?

These questions, and many others, gain additional importance as we try to understand the effects of what have been called mind-altering drugs, and possible long term consequences of their use. Among known hallucinogenic substances are LSD, mescaline, peyote, psilocybin, ayahuasca, and ololiuqui. There is a conservative estimate of one million hallucinogen users in the United States alone (Ott, 1993). The number of students, both in high school and college, who have used LSD is rising. These current reports have further contributed to concern about safety issues and possible adverse consequences resulting from drug use.

Generally, hallucinogenic drugs are so classified largely because of their ability to alter visual perceptions, with eyes open or closed, inducing experiences such as geometric patterns, trails of moving objects, rippling effects, intensification of colors, and spontaneous formation of objects. However, users frequently report a variety of other psychological and perceptual changes including alteration of time sense, intense experience of emotion (e.g., anxiety, ecstatic experiences), mood changes (e.g., euphoria, fear), a feeling of unreality or dissociation (out of body experience), and alterations in the other sensory systems of smell, taste, touch, and hearing. Combination or crossing of sensory experiences, sometimes called synesthesia (e.g., "seeing" sounds), has also been reported.

As can be seen in the above list, experiences may be reported as positive, negative, or both. A variety of internal and external factors are known to influence a drug experience. One of the most common factors influencing a person's response to psychoactive substances is the situation associated with the drug experience. The user's expectations about the drug experience are known as the "set," with the physical location of the experience known as the "setting." These conceptions help to explain some of the variation in subjective reports of hallucinogen effects. If one expects to feel relaxed after smoking marijuana or expects enlightenment via a mystical experience after ingesting psilocybin, then a set has been established. In addition, the expectations and attitudes toward a drug experience may be shared among a group and this may have an effect on experiences of members of the group as well as on inexperienced users joining the group.

Other psychological effects that can be experienced with any drug are known as placebo effects. That is, a person may experience psychological and/or physical effects from a substance, independent of the usual physiological effects of the substance. This may include responses to inactive substances (e. g., sugar pills) or unusual responses to active substances. For example, heavy users of marijuana may get high smoking marijuana from which all of the active THC ingredient had been removed. This expectation or presumption of effect can be powerful and may influence an individual's response to a drug. In the 1960s when hallucinogen use was becoming mainstream, inexperienced users were given instructions to facilitate a positive mental set and careful consideration was given to the setting in which the drug experience occurred. Some researchers have suggested that many of the negative experiences with hallucinogens (bad trips) occurred in users who were not as careful in their attention to set and setting. Negative experiences have been said to include acute adverse psychological reactions, chronic persistent anxiety, and long term physiological or perceptual changes.

More general social and cultural factors may also play a significant role in drug experiences. Various cultures have integrated hallucinogen use into their religious and social practices. In these cultures the set and setting of drug use fit into a larger context. Visionary and mystical experiences are expected and considered an important and positive outcome. There are few reports of long term negative consequences of hallucinogen use in these cultures. This may be a function of adequate preparation to take these types of drugs, or it may be that such long term effects occur but either are not considered adverse, are not noticed, or are not reported because of limited opportunities for investigation or treatment. In general, our culture, particularly through the popular press, has come to interpret possible long term perceptual or psychological changes experienced by hallucinogen users to be consequences of drug use,

and typically they are considered adverse effects.

One of the reported primary long term effects occurring with previous hallucinogen use is sudden and unexpected recurrence of some or all of the drug experience, called a flashback. The phenomena associated with hallucinogenic drug flashbacks have been reported to include relived intense emotion, a feeling of unreality, and visual distortions such as geometric patterns, trails of moving objects, or a rippling effect. Wesson and Smith (1976) classified flashbacks from self-reports of patients as including perceptual, somatic, and emotional types.

The current clinical definition of a drug flashback is Hallucinogen Persisting Perception Disorder (HPPD) described in the Diagnostic and Statistical Manual, 4th edition (DSM-IV), of the American Psychiatric Association (1994). The definition specifies the re-experiencing of perceptual symptoms, primarily visual, which must also cause significant social, occupational, or other distress before this diagnosis can be made. The visual disturbances listed include geometric hallucinations, flashes of color, false perceptions of movement in the visual field, intensified color, trails of images of moving objects, halos around objects, positive afterimages, macropsia and micropsia. The DSM-IV diagnosis is not applicable when the symptoms are associated with another general medical or mental condition such as visual epilepsy or schizophrenia. It is worth noting that other symptoms reported in research, or which have been associated in the popular press with flashback phenomena such as anxiety, fear, paranoia, suicidal thoughts, or other emotional or sensory experiences, are not included in the diagnostic criteria. The HPPD diagnosis appears to be based almost exclusively on research by Abraham and his colleagues (1982; 1983; 1988; 1993).

Abraham suggests, based on his research, that visual disturbances occur at a higher rate in people with a history of LSD use. Abraham (1982) examined the possibility of impairments in color discrimination after prior exposure to LSD. Volunteers selected from the outpatient adult psychiatric department at Massachusetts General Hospital in Boston were given a color discrimination test that involved identifying a white disk, surrounded by a yellow halo, as being white. The distance at which the correct identification was made was recorded. Following the test, a drug history was taken and the 77 volunteers were divided into three categories: nonusers of LSD (31), and users with and without a clinical history of LSD-related flashbacks (10 & 34, respectively). LSD users were defined as persons who reported having used any drug called LSD and having had subsequent changes in mood and perception lasting at least 6 hours. Those who had ever used LSD needed to be significantly closer to the target to identify it as white compared to controls; however there was no significant difference between LSD users with and without reported flashbacks. Abraham interpreted these results as suggesting that some LSD users have chronic, irreversible impairments in color perception. In 1988, Abraham and Wolf published an additional study of direct measures of visual perception in which they found that compared to a control group of 20 psychiatric outpatients, 24 LSD users, primarily from the same clinic, had impairments in peripheral vision function and had more difficulty adjusting to a dark environment.

In a 1983 paper that foreshadowed what he later defined as HPPD, Abraham reports on data collected a decade earlier. In two phases, he had interviewed 123 people with a history of LSD use. All participants were referred to the study in response to a notice in the Acute Psychiatric Service

requesting any person ever having used LSD. All referrals were made by residents in the Department of Psychiatry of Massachusetts General Hospital in the acute service and the inpatient unit. The volunteers had drug abuse as the most common diagnosis. The 53 volunteers in the first phase underwent unstructured, open ended interviews about any and all conditions they considered resulting from the use of LSD. Of all the symptoms reported, 16 visual disturbances considered by Abraham most compatible with reports in the literature of flashbacks were chosen for study in phase two, essentially excluding all other reported symptoms from further study. These visual disturbances included phenomena such as geometric hallucinations, illusions of movement, trails, flashes of color, and prolonged intensification of color. In phase two, 70 additional volunteers from the same clinic and a control group of 40 individuals matched for a variety of variables were given a questionnaire. About 54% of the 70 users reported having had subjective symptoms which they labeled as flashbacks. A number of issues make it difficult to assess Abraham's interpretation of these data. Of the 16 targeted visual disturbances, ten were reported significantly more often in users than in nonusers. Abraham then selected the top four and found them to have a significant positive correlation with the participants' clinical description of flashbacks, but he may have also decided thereafter to use these four items as *his* criteria for "flashback". Interpretation of his further analyses of variables such as number of uses of LSD and time since last use and their correlation with "flashback" becomes problematic since it is unclear if he means the four visual symptoms or the participants' own definition of flashback.

This lack of clarity points to a variety of methodological concerns regarding the interpretation of these studies. A major methodological concern is the makeup of the sample populations. For example, the majority of the participants in these studies were white males and either psychiatric inpatients or people who had sought acute psychiatric treatment. Number of times the drug was taken and time since last use varied considerably. Many were polydrug users and were currently receiving treatment for substance abuse or other acute psychiatric problems. Other long term physiological or psychiatric problems may have been present. These factors contribute to a lack of generalizability of the results to the general population of hallucinogen users.

Abraham interprets his results as implying a causal link between a history of LSD use and impairments in color discrimination and peripheral vision. However, these individuals may or may not have had these visual disturbances prior to their drug use. Since no pre-test was completed, this is impossible to determine. It is also possible that the dramatic perceptual changes during acute hallucinogen intoxication allow the individual later to recognize more readily, non-pathologic, transient changes in ordinary perception. Finally, while differences in perceptual factors may be present, it was not determined if they were actually interfering with the person's occupational or social functioning in any way.

The DSM-IV classification of HPPD is problematic for a variety of reasons. First is the parenthetical labeling denoting HPPD as "flashbacks". While Abraham's research shows a statistically significant correlation between ever having used LSD and the visual disturbances listed under HPPD, the explanatory power of this correlation, that LSD is the sole factor involved in these visual phenomena, is only about 10% of the variance. In other words, other factors might have explained his findings in 90% of the cases, including genetic,

environmental, psychological and personality factors, etc. Furthermore, at no time does he tie a currently experienced "flashback" to a difficulty in discerning visual stimuli during testing. The common conception of a drug flashback is a sudden, unexpected reoccurrence of the drug experience that is disabling or significantly disturbing. His research, which apparently forms the basis for the DSM-IV classification of HPPD, shows no evidence for this sort of phenomenon and he specifically remarks on the stability of the disturbances over time. Second, the classification suggests any of the hallucinogens may be implicated when the majority of Abraham's work has focused solely on LSD use.

In determining other possible long term physiological effects, the time since the drug was last used (as well as other drugs used) may be important. For example, users who refrained from using LSD for at least 48 hours before testing scored lower on spatial orientation and visual perception tests when compared to nonusers (Cohen & Edwards, 1969). However, when these tests were administered to LSD users who had not used within one year prior to testing, no significant differences were found between the users and nonusers (McGlothlin et al. 1969). This lack of support for the former study suggests that visual and perceptual effects may persist for a short time following LSD use, but are not permanent.

We should also consider other factors that may contribute to both acute and long term responses to hallucinogens. Naditch (1974) concluded that adverse reactions to marijuana, LSD, and/or mescaline were related to psychopathology. Others have reported that people at highest risk for adverse reactions tend to have a history of psychiatric illness, typically ingest high doses more frequently, and are polydrug users (e. g., Robbins et al. 1967; Smart & Bateman, 1967; Ungerleider et al. 1968). In a 1967 study of 25 emergency room patients seen for LSD-related disorders, over half of them had diagnoses falling within the schizophrenia spectrum (Blumenfield & Glickman, 1967). Individuals who may be predisposed to schizophrenia or who have disorganized thought processes are at the highest risk for LSD-related disorders. Conversely, this danger appears to be low when hallucinogenic drugs are used by emotionally stable individuals in a safe, protected setting (McWilliams & Tuttle, 1973). An understanding of other personality characteristics that may be related to drug experiences, reports of long term effects, similar symptom reporting in nonusers, and even likelihood of drug use itself, is important.

The research examining the flashback phenomenon provides conflicting reports of incidence, ranging from 15 to 77 percent among LSD users. Typically, the samples have been gathered from clinical populations and studies have focused on psychopathology. In the extant literature, information from less restricted populations is sparse. Little research has explored the relationships between more general personality characteristics and symptoms associated with drug experiences.

Our recent study (Watkins et al. 1995) in a nonclinical sample found that of 207 users 21% report ever having had a drug flashback, while 3.3% of the 153 nonusers also reported having had a drug flashback. Users were defined as anyone who had reported having ever used an hallucinogen. Over half of the users reporting drug flashbacks said they were not disturbed by them and none reported being unable to function. In contrast, within the nonuser group, those reporting drug flashbacks were all either moderately bothered or unable to function. Overall, the incidence of flashback reports in this sample is at the low end of the range described in the literature.

Interestingly, we found that the frequency of hallucinogen use, time since last hallucinogen use, and total number of uses had little or no relationship to drug flashback reports. Time since last use was significantly negatively correlated with reports of HPPD symptoms and not related to self reports of flashbacks. We also examined how personality variables were related to a variety of symptoms from a sample of DSM-IV diagnostic categories, including HPPD symptoms, and found that in users, scoring higher on measures of fantasy and openness to experience were related to reports of having experienced more HPPD symptoms. This study will be reported more fully elsewhere, but underscores the importance of studying nonclinical samples and investigating other variables that may be relevant to flashback phenomena.

In this short review we have raised some important issues relevant to future research into hallucinogen flashback phenomena. Examples of some of the research in this area that we have reviewed should underscore the need for caution in assuming we already know what the long term positive or negative effects of hallucinogen use may be. Much of the published literature (see for example Strassman's 1984 review for a summary) concerning persistent organic changes or alterations of personality or attitudes remains controversial but tends to suggest that most such possible changes are relatively benign. As previously mentioned, in our study of nonclinical participants who were hallucinogen users none reported having experienced flashbacks which rendered them unable to function, and most considered the experience not to be bothersome. While care must certainly be taken in the use of psychoactive substances of any type in therapeutic, experimental, and recreational contexts, concerns about devastating flashback experiences appear not to be warranted from current research reports.

References

American Psychiatric Association. (1994). Diagnostic and Statistical Manual for Mental Disorders, (4th ed.). APA, Washington, D. C.

Abraham, H. D. (1982) A chronic impairment of color vision in users of LSD. *Brit J Psychiat*, **140**, 518-520.

Abraham, H. D. (1983) Visual phenomenology of the LSD flashback. *Arch Gen Psychiat*, **40**, 884-889.

Abraham, H. D. and Wolf, E. (1988) Visual function in past users of LSD: Psychosocial findings. *J Abn Psych*, **97**, 443-447.

Abraham, H. D. (1993) Adverse consequences of lysergic acid diethylamide. *Addiction*, **88**, 1327-1334.

Blumenfield, M. and Glickman, L. (1967) Ten months' experience with LSD users admitted to a county psychiatric receiving hospital. *NY State J Med*, **67**, 1849-1853.

Cohen, S. and Edwards, A. (1969) LSD and organic brain impairment. *Drug Dependence*, **2**, 1-4.

McGlothlin, W., Arnold, D., and Freedman, D. (1969) Organicity measures following repeated LSD ingestion. *Arch Gen Psychiat*, **21**, 704-709.

McWilliams, S. and Tuttle, R. (1973) Long-term psychological effects of LSD. *Psych Bull*, **79**, 341-351.

Naditch, M. (1974) Acute adverse reactions to psychoactive drugs, drug usage, and psychopathology. *J Psychoactive Drugs*, **22**, 305-311.

Ott, J. (1993) Pharmacotheon. Kennewick, WA. Natural Products, CO.

Ungerleider, J. and Fisher, D. (1967) The problems of LSD-25 and emotional disorders. *Cal Med*, **106**, 210-211.

Watkins, S., Carter, T. J., and Myers, L. S. (1995) Hallucinogen flashbacks:

Reality or myth? Poster (88.5) presented at the Society for Neuroscience meeting, November, 1995.

Wesson, D. R. and Smith, D. E. (1976) An analysis of psychedelic drug flashbacks. *Amer J Drug Alcohol Abuse*, **3**, 425-438.

8. Ten Year Study of Ketamine Psychedelic Therapy (KPT) of Alcohol Dependence

Evgeny M Krupitsky, M.D., Ph.D. and A.Ya Grinenko, M.D., Ph.D.

Psychedelic psychotherapy was shown to be a potential benefit for alcoholism treatment in the "60s," but different methodologies made it difficult to generalize across studies. The requisite development of appropriate sophistication for these studies was not possible to do after they were scheduled in 1970 and their use was strictly limited. However, at about this time, ketamine was being shown to elicit "psychedelic" emergent phenomena in patients. This property of ketamine was exploited by our use of ketamine-assisted therapy of alcoholism. Ketamine has some advantages over other psychedelics as an adjunct to psychotherapy. It is safe and short acting (the psychoactive effects lasting about an hour). In addition, ketamine is not scheduled like other psychedelics. In lower doses (about one sixth to one tenth of that usually used in surgery for a general anaesthesia) it induces a profound psychedelic experience.

Psychotherapy in our model consists of the preparation of patients for the psychedelic session, the psychotherapeutic facilitation of the session and special post-session psychotherapy (Krupitsky, 1992). This post-session work is intended to help the patient integrate insights from the psychedelic experience to the everyday life and relate the experience to his life and personality problems. Moreover, psychotherapy in this manner acquires a special quality. It is considered here not only as a process of resolution of certain psychological problems, but also as an important stage in spiritual maturation. The uniquely profound and powerful psychedelic experience often helps our patients to generate new insights that enable them to integrate new, often unexpected meanings, values and attitudes about their individual selves and the world.

We carried out a controlled clinical trial of the efficacy of KPT. To determine the efficiency of the treatment, we collected follow-up information about all the patients who had taken part in this study a year after their release. According to the data, abstinence of more than 1 year was observed in 73 out of 111 people (65.8%) who had undergone the KPT. Thirty people (27.0%) had relapsed. We could not obtain data on eight patients (7.2%). In the control group of 100 patients whose treatment consisted only of conventional methods, only 24 patients (24%) remained sober for more than 1 year ($p < 0.01$). Thus, the data from the follow-up study demonstrated that ketamine-assisted psychedelic therapy increases the efficacy of conventional alcoholism treatment.

Two-year follow-up data had been collected for the 81 patients who had undergone the KPT (because at the moment of the follow-up study only 81 out of 111 patients had a two-year follow-up period after KPT). According to the data, abstinence of more than 2 years was observed in 33 out of these 81 patients (40.7%). Thirty-eight patients (46.9%) had relapsed. We could not obtain two-year follow-up data on 10 patients (12.4%). Three-year follow-up data had been collected for the 42 patients who had undergone KPT. According to the data, abstinence of more than 3 years was observed in 14 out of these 42 patients (33.3%). Twenty-four patients (57.2%) had relapsed. We could not obtain three-year follow-up data on four patients (9.5%). These two- and three-year follow-up data are also evidence of the high efficacy of KPT.

We also carried out psychological, biochemical, and neurophysiological studies of the different possible underlying mechanisms of KPT.

Psychological underlying mechanisms

MMPI

All patients in each experimental group were examined with the Minnesota Multiphasic Personality Inventory (MMPI) (adapted in Russia by Sobchik (1990)) before and after KPT.

According to the MMPI data, our analysis of psychological changes in the experimental group points to definite, rather expressed dynamics in the patient's MMPI profiles. Particularly, after KPT the indices were decreased for the majority of the main MMPI scales. The most expressed, statistically significant decrease in the profile was in the scale "hypochondria," "depression," "hysteria," "psychastenia," "schizophrenia," "sensitivity-repression," and also in Taylor's scale of anxiety. At the same time, the estimate in the Ego strength scale increased. On the whole, such favorable psychological dynamics testify to the fact that the patients became more sure of themselves, their possibilities, their future, less anxious and neurotic, and more emotionally open after KPT. Against the background of these general tendencies, we saw in the majority of cases some essential individual variations (e.g. concerning changes in such scales as "masculinity-femininity," "paranoia," hypomania," and "sensitivity-repression") that reflected, as a rule, a certain harmonization of the patient's personality profiles.

Locus of Control

Thirty alcoholic patients treated with KPT were examined with the Locus of Control Scale (LCS) developed by J.Rotter (Phares, 1976) and adapted in Russia by Bazhin et al. (1993). All patients were assessed with the LCS twice: before and after KPT.

It was established that locus of control in the personality of alcoholic patients became significantly more internal after KPT (from 11.1 ± 4.8 to 30.3 ± 5.3; P<0,01). This means patients became more sure about the ability to control and manage different situations of their life, they became more responsible for their life and future after KPT.

Psychosemantic Changes

Color Test of Attitudes and Personality Differential

We also studied changes in the psychosemantic domain induced by KPT. The study used the data from 69 alcoholic in-patients treated with KPT in our hospital. All patients were examined by the personality differential test (PD) (Bazhin and Etkind, 1983) (a personality oriented version of Osgood's semantic differential (Osgood et al., 1957)) and also by the color test of attitudes (CTA) (Etkind, 1980) before and after the treatment.

The analysis of the CTA results revealed that after KPT there occurred significant positive changes in the nonverbal emotional attitude to a psychotherapist, close relatives, to the ideal image of self, and to the image "Me sober," At the same time, the attitude to the image "Me drunk" became more negative. According to the PD data, significant positive changes occurred after KPT only in respect to the attitude toward the person himself (Krupitsky, 1992).

After KPT there occurred a considerable decrease in differences between certain indicies of the CTA and that of PD in respect to the same images. This decrease was evidenced by the reduction of the difference between the verbal (realized) and nonverbal (unrealized) assessments of personal attitudes. Such reduction was mainly related to the change in the CTA indices and appeared to be the strongest for the sphere of attitudes to a psychotherapist, relatives, the image "Me sober," and the ideal image of self.

Thus, KPT produced considerable and significant positive changes in the domain of personality attitudes, which took place due to the transformation of nonverbal (unrealized) emotional attitudes. KPT resulted in a decreased level of dissonance between isosemantic indices as measured by CTA and PD which could be interpreted as a reduction of dissonance between verbal/conscious and non-verbal/unconscious thoughts and feelings regarding alcohol use and personality characteristics and relationships.

One should also underline the fact that, according to the CTA data, there occurred strong positive changes in patients' nonverbal (unrealized) assessments of the attitudes toward the psychotherapist, close relatives, to the image "Me sober," and to the ideal image of self. This means that the patient has internally grown to emotionally accept these images and, in turn, the attitudes toward sobriety connected with them. Thus KPT of alcoholism may be of benefit by transforming unconscious attitudes, particularly those related to sobriety. The enhancement of the relationship to the therapist may have enhanced transference issues which may also have had a therapeutic effect.

A special note should be made of the discrepancies between the verbal and nonverbal estimates of a patient's personal attitudes registered before KPT. These discrepancies, obviously, reflect the presence of an essential discord between the conscious and unconscious estimates of a personality's attitudes. This discord reflects a peculiar difference between the subject's unconscious and conscious mind, and possibly characterizes the ambivalence of the patient's position and the disagreement between what is declared at the verbal level and what takes place at the level of the immediate emotional experience. Such discord may give rise to psychological discomfort, internal tension, to difficulties in communication with the environment, i.e. to the reduction of a person's adaptation, which after all leads to alcoholism relapse. Therefore, the reduction of such discord due to KPT should be considered as an achievement of a personality's psychologial status which favors sobriety.

A study with repertory grids (Kelly matrixes)

Ten alcoholic patients were tested with verbal and special nonverbal (color) repertory grids before KPT and after it. Then we calculated the mean verbal repertory grid (MVRG) and mean color (nonverbal) repertory grid (MCRG) for all 10 patients together. Four MVRG and MCRG (2 before KPT and 2 after KPT) were processed by the standard programs of repertory grid computer-assisted analysis (Fransella and Bannister, 1977), and then semantic spaces of the personality were built (Fig. 1 and 2). The semantic space of the personality (built on the basis of multidimentional assessments of elements with constructs) shows semantic interrelationships and interconnections between elements and/or constructs of the repertory grid.

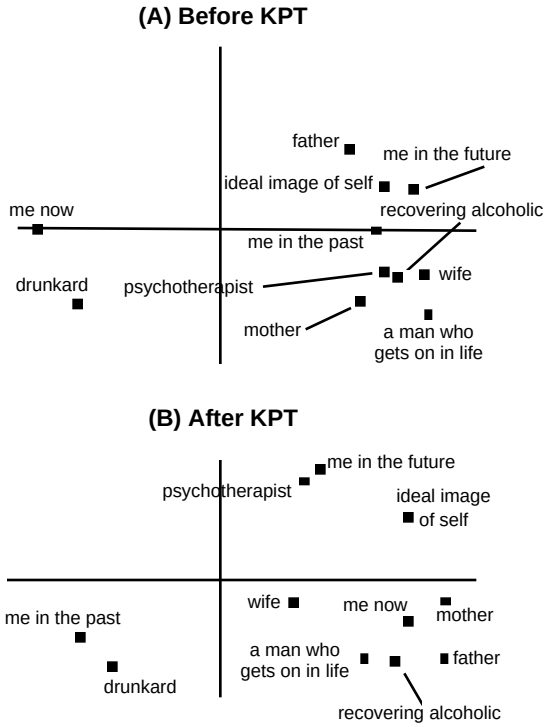

Figure 1. Semantic space of the mean color repertory grid of alcoholic patients

The results of this study have demonstrated some positive changes in the semantic space of the personality of alcoholic patients, particularly in the space of personality characteristics of the color repertory grids. The image "Me now" was close to the image "Drunkard" and far from the group of such positive images as "Recovery alcoholic," "Ideal image of self," "Wife," "A man who gets on in life," and others in the semantic space of the MCRG before KPT (Fig.1A). After KPT the image "Me now" became close to the group of positive images described above and far from the image "Drunkard" in the space of MCRG (Fig.1B). At the same time the image "Drunkard" became closer to the image "Me in the past." These data indicate that alcoholic patients emotionally perceived (identified) themselves as drunkards before KPT. After KPT their emotional perception of themselves had been changed: they emotionally identified themselves with "recovery alcoholic" and other positive images in the semantic space of personality characteristics and value orientations, and identified themselves as drunkards only in the past.

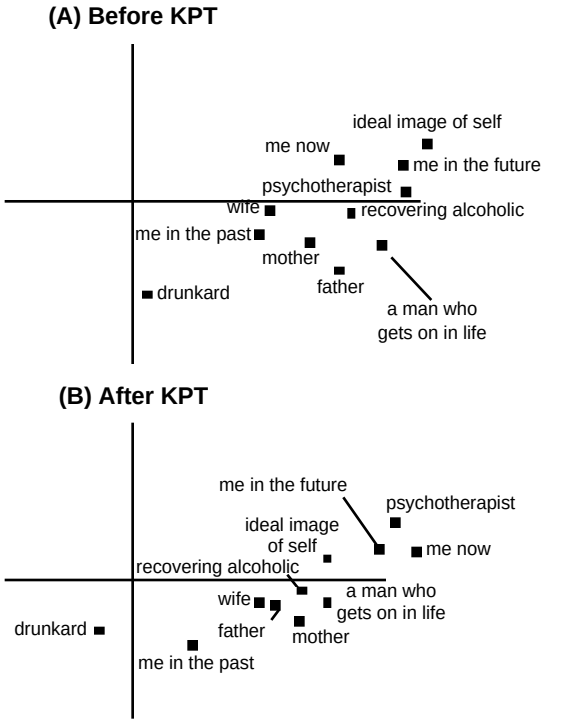

Figure 2. Semantic space of the mean verbal repertory grid of alcoholic patients

The changes in the verbal repertory grids were not so significant as in the color repertory grids (Fig.2A and 2B). The image "Drunkard" only became a little bit more distant from the group of positive images and closer to the image "Me in the past." It is interesting to note that patients already identified themselves with positive images at the level of verbal self-identification in the semantic space of personality characteristics and value orientations before KPT, whereas they identified themselves in the same way at the level of nonverbal (unaware, mostly emotional) perception only after KPT. This can be interpreted to mean, first of all, that KPT creates a profound nonverbal association with the sobriety self-concept, and second, that KPT brings about the attainment of similarity (resemblance) of verbal (realized) and nonverbal (unaware) perception by the patients of their individual self and the world.

These data show that KPT positively transformed primarily the nonverbal (unaware, mainly emotional) perception by alcoholic patients of their individual self. Thus, it is possible to conclude that KPT positively transformed mostly the emotional self-identification (self-concept) of alcoholic patients.

Content Analysis Data

We also carried out content-analysis of psychedelic experiences written down by our patients after their KPT sessions. It is of interest to note that a content analysis from the written self-reports of 108 male alcoholic patients whose personality

characteristics were defined by the MMPI demonstrated a number of statistically reliable correlations between some MMPI scales and the content of the psychedelic experience described in self-reports. Thus, one may conclude that the ketamine psychedelic experiences are to a certain extent determined by the personality characteristics of patients.

In addition we also have demonstrated the relationship (statistically reliable correlations) between the content of the ketamine session experiences and the MMPI profile changes caused by KPT. That is, the content of the ketamine session experiences to a certain extent determines the personality changes caused by KPT.

Effect on Life Values

Thirty patients assessed with the LCS were also examined with the Questionnaire of Terminal Life Values (QTLV) developed by Senin (1991) and based on Rokeach's approach to human values and beliefs (Rokeach, 1972, 1973). Patients were examined with QTLV twice: before and after KPT.

This study has demonstrated a number of significant positive changes in patient's values as a result of KPT. KPT enhanced the importance of such life values as creativity, self-perfection, spiritual contentment, social recognition, achievement of life purposes and individual independence. These changes were mostly expressed in such areas of life values actualization as family, education and social life. It is evident that such a positive transformation of a patient's life values system brings about enhanced motivation for a sober life and favors sobriety.

Effect on grasping the meaning of life (purposes in life)

Ten alcoholic patients were studied before and after KPT with the Purpose-in-Life Test (PLT) elaborated by Crumbaugh (1968) and based on Frankl's concept of man's aspiration for the meaning of life. The PLT was adapted in Russia by Leontiev (1992) in the Department of Psychology of the Moscow State University.

This study has shown that KPT causes a significant increase in the index of grasping the meaning of life in alcoholic patients (from 89.7 ± 5.7 to 115.3 ± 3.2; $p < 0.01$). Before KPT, the index was below the average normal level, but after KPT it was greater. These changes mean that after KPT patients were able to grasp better the meaning of their lives, their life purposes, and perspectives. Their life became more interesting, emotionally saturated, and filled with meaning for them after KPT. They felt themselves more able to live in accordance with their concept of the meaning of life and life purposes as a result of KPT. Such changes favor a sober life, particularly from the standpoint of Frankl's approach which considers alcoholism as an "existential neurosis," as a consequence of losing the meaning of life and the appearance of a specific "existential void" (Frankl, 1978), which KPT we believe is able to fill, at least to some extent.

Effect on Spirituality

We have studied the influence of a profound mystical (transformative) experience during KPT on the level of spiritual development of the alcoholic patients in this study. For the assessment of changes of spirituality we used our own special Spirituality Scale based on a combination of the Spirituality Self-Assessment Scale developed by Charles Whitfield, who studied the importance of spirituality in alcoholism therapy in Alcoholic Anonymous (Whitfield, 1984), and the Life Changes Inventory developed by Ken Ring to estimate the changes of values and purposes of life produced by near-death experiences (Ring, 1984). It was demonstrated by our Spirituality Scale that the increase in the level of spiritual development of our alcoholic patients due to KPT was comparable to the increase induced in healthy volunteers by a special course of meditation and was much greater than the changes in spiritual development induced in alcoholics by a training program of relaxation techniques and self hypnosis (autogenic training). It is evident that the increased spiritual development induced by KPT in alcoholic patients is very auspicious for sobriety. Moreover, the results of the study of KPT's influence on spirituality demonstrate that KPT is much more than simply the creation of an attitude in alcoholic patients toward a sober life. These results show that KPT brings about profound positive changes in life values and purposes, in attitudes toward the different aspects of life and death, and, in turn, in the alcoholic's world view. Many reports suggest religious or spiritual conversion as an important factor in "spontaneous" recovery from drug abuse, and Alcoholic Anonymous programs have a distinct spiritual/religious orientation (Whitfield, 1984; Corrington, 1989; Grof, 1990). A therapy that enhances the likelihood for a conversion type experience therefore might have utility in the treatment of substance abuse. Psychedelic drug-assisted psychotherapy may represent one method to elicit religious spiritual experience in patients with chemical dependence.

Thus, KPT brings about positive changes in personality characteristics, nonverbal emotional attitudes and self-concept, positive transformation of value orientations and grasping the meaning of life, and also spiritual growth. All these psychological changes favor a sober life.

Underlying Biochemical Mechanisms

We also carried out biochemical investigations of the underlying mechanisms of KPT. The results of

the biochemical investigations have shown that during the ketamine session there occurred a real decrease in the activity of MAO-A in blood serum and MAO-B in blood platelets, and there also was an increased dopamine level in blood. Plasma serotonin and GABA concentrations were not altered significantly. An increase of ceruloplasmin activity was statistically significant and the (-endorphin level increased during the KPT session (Krupitsky et al., 1990).

Changes in neurotransmitter metabolism could have some notable aspects. First, they allow some speculations about the underlying neurochemical mechanisms of the psychedelic action of ketamine (Krupitsky et al., 1990). For example, an increase of ceruloplasmin activity causes a corresponding increase in the conversion of monoamines into adrenochromes which have been speculated to possess hallucinogenic activity. This would be particularly true under conditions of inhibited MAO activity and increased dopamine levels. It is of interest that such conditions occur during the action of many hallucinogens (Hamox, 1984; McKenney et al., 1984).

Second, the fact that the pharmacological action of KPT affected both monoaminergic and opioidergic systems, i.e. those neurochemical brain systems that are involved in the development (pathogenesis) of alcohol dependence, is an important result of this biochemical investigation. It is possible that these changes are related to a certain extent to the efficiency of this method.

Underlying Neurophysiological Mechanisms

According to the data from computer-assisted EEG analysis we discovered that ketamine increases delta activity (a 1.5-2 fold increase) and particularly theta activity (a 3-4 fold increase) in all regions of the cortex. This is evidence of limbic system activation during ketamine sessions, as well as evidence for the reinforcement of the limbic-cortex interaction. This fact can also be considered to a certain extent to be indirect evidence for the strengthening of the interactions between the conscious and subconscious levels of the mind during the KPT.

Clinical observations

Our clinical observations suggest that KPT might also be helpful for the treatment of dependence on other drugs (e.g. heroin, ephedrone). Our method involves the repeated injection of small doses of ketamine, which allows for the maintenance of a constant verbal relationship with the patient. We believe that KPT might induce in some drug abusing patients the same psychotherapeutic effects that we have seen in alcoholics.

Ketamine psychedelic therapy proved to be effective for the treatment of personality disorders in alcoholic patients (Ivanov et al., 1995). Sixty-four alcoholic patients with different personality disorders (avoidant - 20 patients, histrionic - 21 patients, and borderline - 23 patients) were treated with KPT. Data from clinical (Bekhterev Psychoneurological Research Institute rating scales) and psychological (MMPI, Spielberger State-Trait Anxiety Scale, T. Leary test of interpersonal relationships) studies showed the differential efficacy of ketamine psychedelic psychotherapy in the different groups of patients. KPT proved to be very effective in patients with avoidant personality disorders, less effective in patients with histronic personality disorders and least effective in patients with borderline personality disorders. It should be noted that KPT positively influenced on the personality characteristics assessed by MMPI in all groups of alcoholic patients with personality disorders.

The potential of ketamine-assisted psychedelic therapy is not restricted to the treatment of addiction. According to data from our pilot study (20 patients, 7 male and 13 female), ketamine-assisted psychedelic therapy is also quite effective in treating neurotic disorders. This research has demonstrated that the efficacy of ketamine psychotherapy differed with various forms of neuroses: psychedelic therapy proved most effective in treating neurotic (reactive) depression and post-traumatic stress disorders, and least effective in treating obsessive-compulsive and phobic neuroses. Hysterical neurosis appeared to be most resistant to psychedelic therapy.

Conclusion

We have been working with KPT since 1985 and have already treated more than 1000 alcoholic patients with KPT without any complications such as protracted psychoses, flashbacks, agitation, or ketamine abuse. KPT appears to be a safe and effective method for treatment of alcohol dependence. It seems to be an especially powerful tool in Russia, where there was no psychedelic revolution in the 1960s, where almost no one knows the meaning of "psychedelic," or can even imagine that this drug might be used for recreation, or for fun. In Russia, therefore, KPT looks particularly unusual and powerful.

References

Bazhin, E.F., Golynkina, E.A. and Etkind, A.M. (1993). Locus of Control Questionnaire. Smysl, Moscow (in Russian).

Bazhin, E.F. and Etkind, A.M. (1983). A Manual for Personality Differential. Leningrad (in Russian).

Corrington, J.E. (1989) Spirituality and recovery: relationships between levels of spirituality, contentment and stress during recovery from

alcoholism in AA. *Alcoholism Treatment* Quarterly 6, 151-165.

Crumbaugh, J.S. (1968) Cross-validation of Purpose-in-Life Test based on Frankl's concept. *J. Individual Psychology* 24, 74-81.

Etkind, A.M. (1980) Color test of attitudes and its use in the study of neurotic patients. In: Social-Psychological Studies in Psychoneurology (Bazhin, E.F., ed.), pp.110-114. Leningrad Research Psychoneurological Inst., Leningrad (in Russian).

Frankl, V. (1978) The unheared cry for meaning. New York.

Fransella, F. and Bannister, D. (1977) A Manual for Repertory Grid Technique. Academic Press, London, New York.

Grof, C. (1990) The impoverished soul: addiction as spiritual emergency. *Spiritual Emergency Network. J.* 2, 20-29.

Hamon, M. (1984) Common neurochemical correlates to the action of hallucinogens. In: Hallucinogens: Neurochemical, Behavioral and Clinical Perspectives, Vol.4, pp.143-169. Raven Press, New York.

Ivanov, V.B., Krupitsky, E.M., Romanova, T.N., Dunaevsky, I.V. and Grinenko, A.Ya. (1995) Ketamine psychedelic therapy of personality disorders in alcoholic patients. In: Abstract Book, 3rd International Conference "AIDS, Cancer and Related Problems", p. 45. St. Petersburg.

Krupitsky, E.M. (1992) Ketamine psychedelic therapy (KPT) of alcoholism and neurosis. Multidisciplinary Association for Psychedelic Studies Newsletter 3, 24-28.

Krupitsky, E.M., Grinenko, A.Ya., Karandashova, G.F., Berkaliev, T.N., Moshkov, K.A. and Borodkin, Yu.S. (1990) Metabolism of biogenic amines induced by alcoholism narcopsychotherapy with ketamine administration. *Biogenic Amines* 7, 577-582.

Leontiev, D.A. (1992) Test of the meaning of life orientations. Smisl, Moscow (in Russian).

McKenney, T.D., Towers, G.H.W. and Abbots, T.S. (1984) Monoamine oxidase inhibitors in South American hallucinogenic plants. Part 2: Constituents of orally-active Myristicaceous hallucinogens. *J. Ethnopharmacol.* 12, 179-211.

Osgood, Ch., Susi, C.J. and Tannenbaum, P.M. (1957). The Measurement of Meaning. Urbana.

Phares, E.J. (1976) Locus of Control in Personality. New York.

Ring, K. (1984) Heading Toward OMEGA. William Morrow and Company, Inc., New York.

Rokeach, M. (1972) Beliefs, Attitudes and Values. Josey-Bass Co., San Francisco.

Rokeach, M. (1973) The Nature of Human Values. Free Press, New York.

Senin, I.G. (1991) Questionnaire of Terminal Life Values. Yaroslavl (in Russian).

Sobchik, L.N. (1990) Standardized Multiphasic Method of the Research of Personality, Moscow (in Russian).

Whitfield, C.L. (1984) Stress management and spirituality during recovery: a transpersonal approach. Part 1: Becoming. *Alcoholism Treatment Quarterly* 1, 3-54.

9. New Views of Timeless Experiences: Contemporary Research on the Nature and Significance of Transpersonal Experiences

Roger Walsh, M.D., Ph.D.

If there is one thing that is clear about psychedelics it is that they can unleash an awesome variety of experiences. Some of the most powerful, as well as the most profound and transformative are also some of the most controversial: specifically transpersonal experiences in which the self-sense expands beyond (trans) the personal or personality to encompass wider aspects of humankind, life, the world and the universe.

Some of these echo experiences that have long been the goal of the world's great spiritual-contemplative traditions and in certain cases appear phenomenologically indistinguishable from full blown mystical experiences, as Walter Pahnke demonstrated in his famous Harvard chapel Good Friday study. Some researchers, e.g. Zaehner, have argued that drug induced experiences could not possibly be the same as those that contemplatives labor for decades before tasting. However the religious scholar Huston Smith (1964/1993) seems to have demolished this claim in his classic paper "Do drugs have religious import?" and theoretical arguments for their identity have also been advanced (Stace, 1987; Walsh, 1991).

Yet even if some psychedelic experiences are phenomenologically indistinguishable from classic contemplative and mystical experiences this is certainly not enough to establish their significance and value in the eyes of many contemporary academicians and mental health professionals. For to many such people religious experiences themselves are suspect and may even be taken as evidence of psychopathology. Such views reflect both the history of psychiatry and much of the modern and postmodern cultural zeitgeist. Yet it is increasingly clear that such pathologizing interpretations are no longer tenable in the light of recent research. The aim of this article is therefore to trace the evolution of our understanding and to make clear that observations of the power and potential benefits of transpersonal experiences, whether psychedelically or contemplatively induced, are fully consistent with contemporary research and theory.

The Evolution of Our Understanding

In psychiatry, it was Freud who set the original tone. The title of his book *The Future of an Illusion* left little doubt about his views on the nature of religion. He regarded it as a developmental relic to be outgrown and mystical experiences as severely regressive. Nor were Western religions the only ones to be dismissed. In a well known text *The History of Psychiatry*, Alexander & Selesnick (1966) pointed to "the obvious similarities between schizophrenic regressions and the practices of yoga and Zen."

Of course such views were understandable, given that mental health practitioners were seeing disturbed individuals whose relationships to, and use of, religion were often also correspondingly disturbed. Moreover, this dismissive trend also reflected a larger, centuries-long trend in Western culture. Beginning with the age of enlightenment, the rise of science had performed the healthy and much needed function of freeing European civilization from the stifling grip of the church's dogmatic control. Within a mere evolutionary blink of the eye the dominant arbiters of reality shifted from church and clergy to science and scientists.

The peak--or nadir, depending on your perspective--of this shift was symbolized by Auguste Comte, founder of positivism. To satisfy the needs of the unsophisticated masses, Comte proposed a new church complete with scientists as saints. Comte modestly allowed that he would be willing to serve as pope; but alas, he became increasingly grandiose and died deranged. Yet Comte notwithstanding, science continued to pour forth its marvels and the human vision of the universe expanded from leagues to light years, and from countries to the cosmos.

Yet in other ways the human vision of the universe and of ourselves was curiously diminished. Whereas the scope of the known universe kept expanding, its meaning and significance kept contracting. Comforted by the great religious myths, humans had once felt themselves to be children of God, at home in a coherent, divinely ordered world designed expressly for their wellbeing. Now they saw themselves as meaningless blobs of protoplasm, adrift on an uncaring speck of dust in a remote unchartered corner of one of uncountable billions of galaxies. Human beings were increasingly demoted to mere sophisticated machines: the "stimulus-response machines" of behaviorists, the "wet

computers" of artificial intelligence, or for evolutionary biologists "a pecularily baroque example of the lengths to which nuclear acid is prepared to go to copy itself" (Chedd, 1973).

Of course mind and transcendental experiences were similarly deflated. Mind came to be regarded as merely "an epiphenomenon of the neuronal machinery of the brain" and transcendental experiences were dismissed as the disordered fire-works of that machinery. Francis Crick, discoverer of the nature of DNA, epitomized this view with his suggestion that belief in the existence of God might be due to mischievous mutant molecules that he named "theotoxins."

Consequently, all meaning, purpose and values--no matter how venerated or venerable -- suddenly seemed groundless. The net result was what Lewis Mumford described as "a disqualified universe," and what the sociologist, Max Weber, called "the disenchantment of the world." This disenchanted world was now reduced, as the Nobel Laureate philosopher of science Alfred North Whitehead (1967) lamented, to merely "a dull affair, soundless, scentless, colorless; merely the hurrying of material, endlessly, meaninglessly."

And yet, as Whitehead pointed out "this position on the part of the scientist was pure bluff." Scientists had made the understandable but disastrous mistake of sliding from science into scientism; from believing that science was a superb way of gaining some information about some things to believing it was the best or only way of obtaining information about all things; from saying that what science can't observe it can't observe to saying that what science can't observe doesn't exist (Wilber, 1983).

Contemporary Understandings

Yet as with so many things, the times are changing, and with them our views of science, religion and transpersonal experiences. It is now increasingly clear that the reductionistic dismissal of religion by science and its pathologization by psychiatry are largely based on unsophisticated views of science, religion and transpersonal experiences. While there is much in religion that is problematic there is also much that is beneficial.

Science is only one way of obtaining valid information. For a comprehensive view of ourselves and the world, it needs to be complimented by experiential, interpretive (hermeneutical), and introspective modes of knowing. In addition, a materialistic, reductionistic, disqualified worldview of nature and humans--so long assumed to follow naturally and necessarily from science--is only one of many possible views.

It is now clear that the terms religion and spirituality can refer to so many different behaviors, values and institutions that understanding them and their psychological significance requires bringing order into this semantic chaos. One useful approach is to look at religion and spirituality from a developmental life-span perspective.

Researchers increasingly divide development into three major phases: preconventional, conventional and transconventional; or prepersonal, personal, and transpersonal. Whether it is the development of cognition, morality, faith, motivation or a self-sense, it is clear that we enter the world unsocialized (at a preconventional stage) and are gradually acculturated into a conventional worldview and modus operandi. A few individuals develop further into postconventional stages of post-formal operational cognition (see, for example, the work of Flavell and Arieti), transconventional morality (Lawrence Kohlberg), universalizing faith (James Fowler), self-actualizing and self-transcending motives (Abraham Maslow), and a transpersonal self-sense (Ken Wilber). These diverse studies have been synthesized into a remarkably comprehensive theory of transpersonal development by Ken Wilber (1981, 1986).

What is crucial for a contemporary psychological understanding of religion is the recognition that religious belief, behavior and experience can occur at any stage --preconventional, conventional or post-conventional-- and can vary dramatically in form, function and value according to the stage. There is no question that religion can be tragically misused in the service of, for example, egocentricity, bias and fanaticism. But the great mistake of many scientists and mental health practitioners who dismissed religion wholesale was to mistake parts of preconventional or conventional religion for all of religion; to equate dogmatic mythical or magical thinking with all religious thinking; to fixate on religion as a defensive maneuver and overlook religion as a developmental catalyst; to conflate preconventional regression with transconventional progression; and to confuse the schizophrenic's prepersonal loss of ego boundaries with the mystic's transpersonal recognition of the unity of existence.

The net effect is what is now known as "the pre/trans fallacy": the confusion and conflation of preconventional/prepersonal religious developmental stages with transconventional/transpersonal stages. Henceforth we will need to be far more precise in identifying the function and developmental level of religious behavior, belief and experience.

Fortunately, relevant research on religion, spirituality and transpersonal experiences is expanding dramatically and includes some of the following helpful background findings.

Growing numbers of contemporary psychoanalytic thinkers are forging new psychoanalytic perspectives of religion and no longer see psychoanalysis and authentic spirituality as incompatible. People who have transpersonal or mystical experiences, far from

being necessarily pathological, score above average on multiple measures of well-being.

Several hundred studies of meditation confirm that, in addition to inducing the transpersonal experiences that are its goal, it can produce wide-ranging psychological, physiological and biochemical effects and therapeutic benefits. Intriguing findings include evidence for enhanced creativity, perceptual sensitivity, empathy, marital satisfaction, lucid dreaming, sense of self-control, and self-actualization. Developmentally, several studies suggest it may foster maturation on scales of ego, moral and cognitive development. Clinical research suggests that it can be therapeutic for several psychological and psychosomatic disorders including anxiety, phobias, posttraumatic stress, insomnia, drug abuse, chronic pain and mild depression (West, 1987; Walsh & Vaughan, 1993).

Near-death experiences can be profound transpersonal experiences and whatever their precise nature may finally turn out to be, are far from being signs of severe pathology as was once widely assumed. Rather they seem to be followed by surprisingly large, long lasting and beneficial psychological changes, especially associated with decreased concern with materialism and increased interest in love and learning.

In the new psychiatric diagnostic manual, DSM-IV, a new category for religious or spiritual problems refers to religiously based difficulties that do not reflect pathology. This new code is an important step in institutionalizing the recognition that religious interests, concerns and experiences are not synonymous with pathology.

Together, these findings make abundantly clear that transpersonal experiences are far from being synonymous with pathology. Rather, they can be surprisingly beneficial and transformative and are most likely to occur in people of exceptional psychological health and maturity. These facts, plus their remarkable frequency and power in psychedelic sessions, suggest that they deserve to be a focus of further psychedelic research.

References

Alexander, F., Selesnich S. (1973) The History of Psychiatry. New York: New American Library.

Chedd, G. (1973) *New Scientist*. 58:606-608.

Freud, S. (Trans. W.D. Robson-Scott). (1928/1955) The Future of an Illusion. New York: H. Liveright Publishing Corporation.

Smith, H. (1964) Do drugs have religious import? (1993) *The Journal of Philosophy*, LXI, 517-530. Reprinted in R. Walsh & F. Vaughan eds. Paths Beyond Ego: The Transpersonal Vision. Los Angeles: J. Tarcher, pp 91-93.

Stace, W. (1987) Mysticism and Philosophy. Los Angeles: J. Tarcher.

Walsh, R. (1990) The Spirit of Shamanism. Los Angeles: J. Tarcher.

Walsh, R., Vaughan F., eds. (1993) Paths Beyond Ego.. Los Angeles: J.P. Tarcher.

West, M, ed. (1987) The Psychology of Meditation. Oxford:Clarenden Press

Whitehead, A. (1967) Science and the Modern World. New York: Macmillan.

Wilber, K. (1980) The Atman Project. Wheaton, IL:Quest.

Wilber, K. (1983) Eye to Eye: The Quest for the New Paradigm. Garden City: Anchor/Doubleday.

Wilber, K., Engler, J., Brown, D., eds. (1986) Transformations of Consciousness: Conventional and Contemplative Perspectives on Development. Boston: New Science Library/ Shambhala.

10. The Scientific Investigation of Ayahuasca: A Review of Past and Current Research

Dennis J. McKenna,[1] Ph.D., J. C. Callaway, Ph.D.,[2] and Charles S. Grob. M.D.[3]

Introduction

Of the numerous plant hallucinogens utilized by indigenous populations of the Amazon Basin, perhaps none is as interesting or complex, botanically, chemically, or ethnographically, as the hallucinogenic beverage known variously as *ayahuasca* , *caapi*, or *yage*. The beverage is most widely known as *ayahuasca*, a Quechua term meaning "vine of the souls," which is applied both to the beverage itself and to one of the source-plants used in its preparation, the Malpighiaceous jungle liana, *Banisteriopsis caapi* (Schultes, 1957). In Brazil, transliteration of this Quechua word into Portuguese results in the name, *Hoasca. Hoasca*, or *ayahuasca*, occupies a central position in Mestizo ethnomedicine, and the chemical nature of its active constituents and the manner of its use makes its study relevant to contemporary issues in neuropharmacology, neurophysiology, and psychiatry.

Traditional and Indigenous Uses of Ayahuasca

The use of *ayahuasca* under a variety of names is a widespread practice among various indigenous aboriginal tribes endemic to the Amazon Basin (Schultes, 1957). Such practices undoubtedly were well established in pre-Columbian times, and in fact may have been known to the earliest human inhabitants of the region. Iconographic depictions on ceramics and other artifacts from Ecuador have provided evidence that the practice dates to at least 2000 B.C. (Naranjo, 1986). Its widespread distribution among numerous Amazonian tribes also argues for its relative antiquity.

Considerable genetic intermingling and adoption of local customs followed in the wake of European contact, and *ayahuasca*, along with a virtual pharmacopoeia of other medicinal plants, gradually became integrated into the ethnomedical traditions of these mixed populations. Today the drug forms an important element of ethnomedicine and shamanism as it is practiced among indigenous Mestizo populations in Peru, Colombia, and Ecuador. The sociology and ethnography of the contemporary use of *ayahuasca* (as it is most commonly termed) in Mestizo ethnomedicine has been extensively described (Dobkin de Rios, 1972, 1973; Luna, 1984, 1986)

Syncretic Religious Use of Ayahuasca

From the perspective of the sociologist or the ethnographer, discussion of the use of *ayahuasca* or *ayahuasca* can conveniently be divided into a consideration of its use among indigenous aboriginal and mestizo populations, and its more recent adoption by contemporary syncretic religious movements such as the União do Vegetal (UDV), Barquena, and Santo Daime sects in Brazil. It is within the context of acculturated groups such as these that questions regarding the psychological, medical, and legal aspects of the use of *ayahuasca* become most relevant, and also, most accessible to study.

The use of *ayahuasca* in the context of mestizo folk medicine closely resembles the shamanic uses of the drug as practiced among aboriginal peoples. In both instances, the brew is used for curing, for divination, as a diagnostic tool and a magical pipeline to the supernatural realm. This traditional mode of use contrasts from the contemporary use of *ayahuasca* tea within the context of Brazilian syncretic religious movements. Within these cults, the members consume *ayahuasca* tea at regular intervals in group rituals in a manner that more closely resembles the Christian Eucharist than the traditional aboriginal use. The individual groups of the UDV, termed *nucleos*, are similar to a Christian Hutterite sect, in that each group has a limited membership, which then splits to form a new group once the membership expands beyond the set limit. The *nucleo* consists of the congregation, a group leader or mestre, various acolytes undergoing a course of study and training in order to become mestres, and a temple, an actual physical structure where the sacrament is prepared and consumed at prescribed times, usually the first and third Saturday of each month. The membership of these newer syncretic groups spans a broad socio-economic range and includes many educated, middle-class, urban professionals (including a number of physicians and other health professionals). Some older members have engaged in the practice for 30 or more years without apparent adverse health effects. The UDV and the Santo Daime sects are the largest and most visible of several syncretic religious movements in Brazil that have incorporated the use of *ayahuasca* into their ritual practices. Of the two larger sects, it is the UDV that possesses the strongest organizational structure as well as the most highly disciplined membership. Of all the *ayahuasca* churches in Brazil, the UDV has also been the most pivotal in convincing the government to remove *ayahuasca* from its list of banned drugs. In 1987, the government of Brazil approved the ritual use of

[1] Heffter Research Institute, Santa Fe, NM
[2] Department of Pharmaceutical Chemistry, University of Kuopio, Finland
[3] Heffter Research Institute, Santa Fe, NM, and Department of Psychiatry, Harbor/UCLA Medical Center Torrance, CA

hoasca tea in the context of group religious ceremonies. This ruling has potentially significant implications, not only for Brazil, but for global drug policy, as it marks the first time in over 1600 years that a government has granted permission to its non-indigenous citizens to use a psychedelic in the context of religious practices.

Botanical, Chemical, and Pharmacological Aspects of *Ayahuasca*

Ayahuasca is unique in that its pharmacological activity is dependent on a synergistic interaction between the active alkaloids in the plants. One of the components, the bark of *Banisteriopsis caapi*, contains ß-carboline alkaloids, which are potent MAO-A inhibitors; the other component, the leaves of *Psychotria viridis* or related species, contains the potent short-acting psychoactive agent N,N-dimethyltryptamine (DMT). DMT is not orally active when ingested by itself, but can be rendered orally active in the presence of a peripheral MAO inhibitor - and this interaction is the basis of the psychotropic action of *ayahuasca* tea (McKenna, Towers, & Abbott, 1984).

1. Botanical sources of ayahuasca

In a traditional context, *Ayahuasca* is a beverage prepared by boiling - or soaking - the bark and stems of *Banisteriopsis caapi* together with various admixture plants. The admixture employed most commonly is the Rubiaceous genus *Psychotria*, (Rubiaceae), particularly *P. viridis*. The leaves of *P. viridis* contains alkaloids which are necessary for the psychoactive effect (see the sections on chemistry and pharmacology, below). There are also reports (Schultes, 1972) that other *Psychotria* species, *especially P. leiocarpa* or *P. carthaginensis*, are used instead of *P. viridis*, but such reports may be due to a botanical misidentification; in any case, use of *Psychotria* species other *than P. viridis* is rare. In the Northwest Amazon, particularly in the Colombian Putumayo and Ecuador, the leaves of *Diplopterys cabrerana*, a jungle liana in the same family as *Banisteriopsis*, are added to the brew in lieu of the leaves of *Psychotria.* The alkaloid present in *Diplopterys*, however, is identical to that in the *Psychotria* admixtures, and pharmacologically, the effect is the same. In Peru, various admixtures in addition to *Psychotria* or *Dipolopterys* are frequently added, depending on the magical, medical, or religious purposes for which the drug is being consumed. Although a virtual pharmacopoeia of admixtures are occasionally added, the most commonly employed admixtures (other than *Psychotria*, which is a constant component of the preparation) are various Solanaceous genera, including tobacco (*Nicotiana* sp.), *Brugmansia* sp., and *Brunfelsia* sp. (Schultes, 1972; McKenna, et al., 1995). These Solanaceous genera are known to contain alkaloids, such as nicotine, scopalamine, and atropine, which effect both central and peripheral adrenergic and cholinergic neurotransmission. The interactions of such agents with serotonergic agonists and MAO inhibitors are essentially unknown in modern medicine.

2. Chemistry of Ayahuasca and its source plants

The chemical constituents of *ayahuasca* and the source-plants used in its preparation have been well characterized (McKenna, et al., 1984; Rivier & Lindgren, 1972). *Banisteriopsis caapi* contains the ß-carboline derivatives harmine, tetrahydroharmine, and harmaline as the major alkaloids (Callaway, et al., 1996). Trace amounts of other ß-carbolines have also been reported (McKenna, et al., 1984; Rivier & Lindgren, 1972; Hashimoto and Kawanishi, 1975, 1976) as well as the pyrrolidine alkaloids shihunine and dihydroshihunine (Kawanishi et al. 1982). The admixture plant, *Psychotria viridis*, contains a single major alkaloid, N,N-dimethyltryptamine (DMT), while N-methyl tryptamine and methyl-tetrahydro-ß-carboline have been reported as trace constituents (McKenna, et al., 1984; Rivier & Lindgren, 1972). The admixture plant *Psychotria carthagenensis* has been reported to contain the same alkaloids (Rivier & Lindgren, 1972) but a subsequent investigation could not confirm the presence of DMT in the single collection examined (McKenna, et al., 1984). The concentrations of alkaloids reported in *Banisteriopsis caapi* range from 0.05 % dry weight to 1.95 % dry weight; in *Psychotria*, the concentration of alkaloids ranged from 0.1 to 0.66 % dry weight (McKenna, et al., 1984; Rivier & Lindgren, 1972). Similar ranges and values were reported by both groups of investigators.

The concentrations of alkaloids in the *ayahuasca* beverages are, not surprisingly, several times greater than in the source plants from which they are prepared. Based on a quantitative analysis of the major alkaloids in several samples of *ayahuasca* collected on the upper Rio Purús, Rivier & Lindgren (1972) calculated that a 200 ml dose of *ayahuasca* contained an average of 30 mg of harmine, 10 mg tetrahydroharmine, and 25 mg DMT. Callaway, et al., determined the following concentrations of alkaloids in the *hoasca* tea utilized in the biomedical study with the UDV (mg/ml): DMT, 0.24; THH, 1.07; harmaline, 0.20; and harmine 1.70. A typical 100 ml dose of hoasca thus contains in mg: DMT, 24; THH, 107; harmaline, 20; harmine, 170. Interestingly, these concentrations are above the threshold of activity for i.v. administration of DMT (Strassman & Qualls, 1994).

McKenna et al. (1984) reported somewhat higher values for the alkaloid content of several samples of Peruvian ayahausca. These investigators calculated that a 100 ml dose of these preparations contained a total of 728 mg total alkaloid, of which 467 mg is harmine, 160 mg is tetrahydroharmine, 41 mg is harmaline, and 60 mg is DMT. This is well within the range of activity for DMT administered i.m. (Szara, 1956) or i.v. (Strassman & Qualls, 1994) and is also well within the range for harmine to act effectively as a monoamine oxidase inhibitor (MAOI).

In vitro, these ß-carbolines function as MAOI at approximately 10 nM (e.g., harmine's IC_{50} for MAOI is ~1.25 x 10^{-8} M; cf. McKenna, et al., 1984; Buckholtz & Boggan, 1977). In mice, harmaline administered i.p. at 5 mg/kg causes 100% inhibition by 2 hours post-injection, the activity falling off rapidly thereafter (Udenfriend et al. 1958) This dose corresponds to approximately 375 mg in a 75 kg adult, but, based on the measured concentration of harmine in the liver, it is likely that one half this dose or less would also be effective. The reasons for the discrepancy in alkaloid concentrations between the samples examined by Rivier & Lindgren (1972) and those examined by McKenna, et al. (1984) are readily explained by the differences in the methods of preparation. The method employed in preparing *ayahuasca* in Pucallpa, Peru, where the samples analyzed by McKenna et al. (1984) were collected, results in a much more concentrated brew than the method employed on the upper Rio Purús, the region which was the source of the samples examined by Rivier & Lindgren. The concentrations and proportions of alkaloids can vary significantly in different batches of *ayahuasca,* depending on the method of preparation, as well as the amounts and proportions of the source-plants.

The notion that the ß-carbolines, by themselves, are hallucinogenic and thus contribute to the overall hallucinogenic activity of the ayahuasca beverage, was based on flawed earlier research (Naranjo, 1967) and has been discredited (Callaway, et al., 1997). As MAO inhibitors, ß-carbolines can increase brain levels of serotonin, and the primarily sedative effects of high doses of ß-carbolines are thought to result from their blockade of serotonin deamination. The primary action of ß-carbolines in the ayahuasca beverage is their inhibition of peripheral MAO-A, which protects the DMT in the brew from peripheral degradation and thus renders it orally active. There is some evidence, however, that tetrahydroharmine (THH), the second most abundant ß-carboline in the beverage, acts as a weak 5-HT uptake inhibitor and MAOI. Thus, THH may prolong the half-life of DMT by blocking its intraneuronal uptake, and hence, its inactivation by MAO, localized in mitochondria within the neuron. On the other hand, THH may block serotonin uptake into the neuron, resulting in higher levels of 5HT in the synaptic cleft; this 5-HT, in turn, may attenuate the subjective effects of orally ingested DMT by competing with it at post-synaptic receptor sites (Callaway, et al., 1997).

3. Pharmacological actions of Ayahuasca and its Active Alkaloids

The hallucinogenic activity of *ayahuasca* is a function of the peripheral inactivation of MAO by the ß-carboline alkaloids in the mixture. This action prevents the peripheral oxidative deamination of the DMT, which is the primary hallucinogenic component, rendering it orally active and enabling it to reach its site of action in the CNS in an intact form. (McKenna, et al 1984; Schultes, 1972). DMT alone is inactive following oral administration at doses up to 1000 mg (Shulgin, 1982; Nichols, et al. 1991). DMT is active by itself following parenteral administration starting at around 25 mg (Szara, 1956; Strassman & Qualls, 1994). Because of its oral inactivity, various methods of parenteral administration are employed by users. For example, synthetic DMT is commonly smoked as the free base; in this form, the alkaloid volatilizes readily and produces an immediate, intense psychedelic episode of short duration (5 -15 min), usually characterized by multicolored, rapidly moving visual patterns behind the closed eyelids (Stafford, 1977). The Yanomamo Indians and other Amazonian tribes prepare a snuff from the sap of various trees in the genus *Virola*, which contain large amounts of DMT and the related compound, 5-methoxy-DMT, which is also orally inactive (McKenna, et al. 1985; Schultes and Hofmann, 1980). The effects of the botanical snuffs containing DMT, while not as intense as smoking DMT free base, are similarly rapid in onset and of limited duration [unpublished data]. The *ayahuasca* beverage is unique in that it is the only traditionally used psychedelic where the enzyme-inhibiting principles in one plant (ß-carbolines) are used to facilitate the oral activity of the psychoactive principles in another plant (DMT). The psychedelic experience that follows ingestion of *ayahuasca* differs markedly from the effects of parenterally ingested DMT; the time of onset is approximately 35-40 minutes after ingestion, and the effects, which are less intense than parenterally administered synthetic DMT, last approximately four hours. The subjective effects of *ayahuasca* include phosphene imagery seen with the eyes closed, dream-like reveries, and a feeling of alertness and stimulation. Peripheral autonomic changes in blood pressure, heart-rate, etc., are also less pronounced in *ayahuasca* than parenteral DMT. In some individuals, transient nausea and episodes of vomiting occur, while others are rarely affected in this respect. When *ayahuasca* is taken in a group setting, vomiting is considered a normal part of the experience and allowances are made to accommodate this behavior (Callaway, et al., 1997).

The amounts of ß-carbolines present in a typical dose of *ayahuasca* are well above the threshold for activity as MAOI. It is likely that the main contribution of the ß-carbolines to the acute effects of *ayahuasca* results from their action as peripheral MAO inhibitors, rendering DMT orally active. It is worthy of note that ß-carbolines are highly selective inhibitors of MAO-A, the form of the enzyme for which serotonin, and presumably other tryptamines, including DMT, are the preferred substrates (Yasuhara, et al., 1972; Yasuhara, 1974). This selectivity of ß-carbolines for MAO-A over MAO-B, combined with their relatively low affinity for liver MAO compared to brain MAO, may explain why reports of hypertensive crises following the ingestion of *ayahuasca* have not been documented. On the other hand, Suzuki et al. (1981) has reported that DMT is primarily oxidized by MAO-B; it is

possible, therefore, that high concentrations of ß-carbolines, partially inhibit MAO-B as well as MAO-A; but the greater affinity of tyramine for MAO-B enables it to compete for binding to the enzyme and displace any residual ß-carbolines. This mechanism would explain the lack of any reports of peripheral autonomic stimulation associated with the ingestion of *ayahuasca* in combination with foods containing tyramine (Callaway, et al., 1997).

DMT and its derivatives and the ß-carboline derivatives are widespread in the plant kingdom (Allen & Holmstedt, 1980) and both classes of alkaloids have been detected as endogenous metabolites in mammals, including man (Bloom, et al. 1982; Barker, et al. 1981a; Airaksinen & Kari, 1981). Methyl transferases which catalyze the synthesis of DMT, 5-methoxy-DMT, and bufotenine have been characterized in human lung, brain, blood, cerebrospinal fluid, liver, and heart, and also in rabbit lung, toad, mouse, steer, guinea pig, and baboon brains, as well as in other tissues in these species (McKenna & Towers, 1984). Although the occurrence, synthesis, and degradative metabolism of DMT in mammalian systems has been the focus of recent scientific investigations (Barker, et al. 1981b). Endogenous psychotogens have been suggested as possible etiological factors in schizophrenia and other mental disorders, but the evidence remains equivocal (Fischman, 1983). The candidacy of DMT as a possible endogenous psychotogen essentially ended when experiments showed comparable levels in both schizophrenics and normals; at present the possible neuroregulatory functions of this "psychotomimetic" compound are incompletely understood, but Callaway (1988) has presented an interesting hypothesis regarding the possible role of endogenous DMT and ß-carbolines in regulating sleep cycles and REM states.

ß-carbolines are tricyclic indole alkaloids that are closely related to tryptamines, both biosynthetically and pharmacologically. They are readily synthesized by the condensation of indoleamines with aldehydes or alpha-keto acids, and their biosynthesis probably also proceeds via similar reactions (Callaway et al., 1994). ß-carbolines have also been identified in mammalian tissue, including human plasma and platelets, and rat whole brain, forebrain, arcuate nucleus, and adrenal glands (Airaksinen and Kari, 1981). 6-methoxy-tetrahydro-ß-carboline has been recently identified as a major constituent of human pineal gland (Langer et al. 1984). This compound inhibits the high-affinity binding of [^{3}H]-imipramine to 5-HT receptors in human platelets (Langer et al. 1984), and also significantly inhibits 5-HT binding to type 1 receptors in rat brain; the compound has a low affinity to type 2 receptors, however (Taylor et al. 1984). 2-methyl-tetrahydro-ß-carboline and harman have been detected in human urine following ethanol loading, (Rommelspacher, et al., 1980) and it has been suggested that endogenous ß-carbolines and other amine-aldehyde condensation products may be related to the etiology of alcoholism (Rahwan, 1975). At least one ß-carboline has been identified as a by-product of the oxidative metabolism of DMT in rat brain homogenates (Barker, et al. 1980).

ß-carbolines exert a variety of neurophysiological and biological effects (McKenna and Towers, 1984). ß-carboline derivatives are selective, reversible, competitive inhibitors of MAO-A (Buckholtz and Boggan, 1976, 1977). Other neurophysiological actions of ß-carbolines include competitive inhibition of the uptake of 5-HT, dopamine, epinephrine, and norepinephrine into synaptosomes (Buckholtz and Boggan, 1976; Pähkla, et al., 1997)), inhibition of Na^+ dependent membrane ATPases (Canessa, et al. 1973), interference with biosynthesis of biogenic amines (Ho, 1977), and vasopressin-like effects on sodium and water transport in isolated toad skin (de Sousa and Gross, 1978). ß-carboline-3-carboxylate and various esterified derivatives have been implicated as possible endogenous ligands for benzodiazepine receptors (Lippke et al. 1983). ß-carboline ligands of these receptors can induce epileptiform seizures in rats and in chickens homozygous for the epileptic gene (Morin, 1984, Johnson, et al. 1984); this proconvulsant action can be blocked by other receptor ligands, including diazepam and ß-carboline-carboxylate propyl ester (Morin, 1984, Johnson, et al. 1984).

ß-carbolines also exhibit other biological activities in addition to their effects on neuro-physiological systems. For instance Hopp and co-workers found that harmine exhibited significant anti-trypanosomal activity against *Trypanosoma lewisii* (Hopp et al., 1976). This finding may explain the use of *ayahuasca* in mestizo ethnomedicine as a prophylactic against malaria and internal parasites (Rodriguez, et al. 1982). Certain ß-carbolines are known to exert mutagenic or co-mutagenic effects, and the mechanism responsible may be related to their interactions with nucleic acids (Umezawa, et al. 1978; Hayashi, et al. 1977). The ultra-violet activated photocytotoxic and photogenotoxic activity of some ß-carbolines has also been reported (McKenna & Towers 1981; Towers & Abramosky, 1983).

Recent Biomedical Investigations of Ayahuasca

Although achieving some notoriety in North American literature through the popular press and the writings of William Burroughs and Allan Ginsberg (Burroughs and Ginsberg, 1963), the psychological and physiological phenomena induced by *ayahuasca* have received little or no rigorous study. Various travelers to the Amazon have reported their own first hand experiences with *ayahuasca* (Weil, 1980), while both formal and informal ethnographic narratives have excited the public imagination (Lamb, 1971; Luna and Amaringo, 1991). Interest in the exotic origins and effects of ayahuasca have attracted a steady stream of North American tourists, often enticed by articles and advertisements in popular and New Age magazines (Krajick, 1992; Ott, 1993). Concern over possible adverse health effects resulting from the use of *ayahuasca* by such naive travelers has recently been expressed by a noted authority on Mestizo

ayahuasca use (Dobkin de Rios, 1994). These concerns are in marked contrast to testimonials of improved psychological and moral functioning by the adherents of the syncretic *ayahuasca* churches in Brazil.

The individuals who are attracted to the UDV seem to belong to a slightly more professional socio-economic class than those who join the Santo Daime. Of the approximately 7000 members of the UDV in Brazil, perhaps 5 - 10 % are medical professionals, among them physicians, psychiatrists, psychologists, chiropracters, and homeopathic physicians. Most of these individuals are fully aware of the psychologically beneficial aspects of the practice, and evince a great interest in the scientific study of *hoasca*, including its botany, chemistry, and pharmacology. The medically educated members can discuss all of these aspects with a sophistication equal to that of any U.S.-trained physician, botanist, or pharmacologist. At the same time they do have a genuine spiritual reverence for the *hoasca* tea and the experiences it evokes. The UDV places a high value on the search for scientific truth, and sees no conflict between science and religion; most members of the UDV express a strong interest in learning as much as possible about how the tea acts on the body and brain. As a result of this unique circumstance, the UDV presents an ideal context in which to conduct a biomedical investigation of the acute and long-term effects of *hoasca.* (In the parlance of the UDV, the tea is sometimes called *hoasca*, which is a Portguese transliteration of *ayahuasca.* The term as used here applies specifically to the tea used within the UDV, while *ayahuasca* is used to denote non-UDV sources of the brew.)

Due to a fortunate combination of circumstances, we were invited to conduct such a biomedical investigation of long-term drinkers of hoasca by the Medical Studies section of the UDV (Centro de Estudos Medicos). This study, which was conducted by an international consortium of scientists from Brazil, the United States, and Finland, was financed through private donations to various non-profit sponsoring groups, notably Botanical Dimensions, which provided major funding, the Heffter Research Institute, and MAPS, (Multidisciplinary Association for Psychedelic Studies). Botanical Dimensions is a non-profit organization dedicated to the study and preservation of ethnomedically significant plants, and MAPS and the Heffter Research Institute are non-profit organizations dedicated to the investigation of the medical and therapeutic uses of psychedelic agents. The field phase of the study was conducted during the summer of 1993 at one of the oldest UDV temples, the Nucleo Caupari located in the Amazonian city of Manaus, Brazil. Subsequent laboratory investigations took place at the respective academic institutions of some of the principle investigators, including the Department of Psychiatry, Harbor UCLA Medical Center, the Department of Neurology, University of Miami School of Medicine, the Department of Psychiatry, University of Rio de Janeiro, Department of Internal Medicine, University of Amazonas Medical School, Manaus, and the Department of Pharmaceutical Chemistry, University of Kuopio, Finland.

Since this study was the first of its kind, there was virtually no pre-existing data on the objective measurement of the physical and psychological effects of ayahuasca in human subjects. As a result, this study was in some respects a pilot study; its primary objectives were modest, representing an effort to collect a basic body of data, without attempting to relate the findings to either possible detrimental effects of ayahuasca, or to possible therapeutic effects. The study had four major objectives:

- Assessment of Acute Psychological and Physiological Effects of *Hoasca* in Human Subjects
- Assessment of Serotonergic Functions in Long-term Users of *Hoasca* Tea
- Quantitative Determination of Active Constituents of *Hoasca* Teas in Plasma
- Quantitative Determination of Active Constituents of *Hoasca* Teas

Most of these objectives were achieved, and the results have been published in various peer-reviewed scientific journals (Grob, et al., 1996; Callaway, et al., 1994; Callaway, et al., 1996;. Callaway, et al., 1997). The results are summarized briefly below.

Assessment of Acute and Long-term Psychological Effects of Hoasca Teas (Grob, et al., 1996)

The subjects in all of the studies consisted of a group of fifteen healthy, male volunteers, all of whom had belonged to the UDV for a minimum of ten years, and who ingested hoasca on average of once every two weeks, in the context of the UDV ritual. None of the subjects actively used tobacco, alcohol, or any drugs other than hoasca. For some comparative aspects of the study, a control group of fifteen age-matched males was also used; these individuals were recruited from among the friends and siblings of the volunteer subjects, and like them were local residents of Manaus having similar diets and socio-economic status. None of the control subjects were members of the UDV, and none had ever ingested hoasca tea.

The psychological assessments, administered to both groups, consisted of structured psychiatric diagnostic interviews, personality testing, and neuropsychological evaluations. Measures administered to the UDV hoasca drinkers, but not to the hoasca-niave group, included semistructured and open-ended life story interviews, and a phenomenological assessment of the altered state elicited by hoasca, was quantified using the Hallucinogen Rating Scale developed by Dr. Rick Strassman in his work with DMT and psilocybin in human subjects (Strassman, et al., 1994).

The UDV volunteers showed significant differences from the hoasca-naive subjects in the Tridimensional Personality Questionnaire (TPQ) and the WHO-UCLA Auditory Verbal Learning Test. The TPQ assesses three general areas of behavior,

viz., novelty-seeking, harm avoidance, and reward dependence. With respect to novelty-seeking behaviors, UDV members were found to have greater stoic rigidity vs exploratory excitability, greater regimentation vs disorderliness, and a trend toward greater reflection vs impulsivity; but there was no difference between the groups on the spectrum between reserve and extravagance. On the harm reduction scale, UDV subjects had significantly greater confidence vs fear of uncertainty, and trends toward greater gregariousness vs shyness, and greater optimism vs anticipatory worry. No significant differences were found between the two groups in criteria related to reward-dependence.

The fifteen UDV volunteers and the control subjects were also given the WHO-UCLA Auditory Learning Verbal Memory Test. Experimental subjects performed significantly better than controls on word recall tests. There was also a trend, though not statistically significant, for the UDV subjects to perform better than controls on number of words recalled, delayed recall, and words recalled after interference.

The Hallucinogen Rating Scale, developed by Strassman et. al (1994) for the phenomenological assessment of subjects given intravenous doses of DMT, was administered to the UDV volunteers only (since control subjects did not receive the drug). All of the clinical clusters on the HRS were in the mild end of the spectrum compared to intravenous DMT. The clusters for affect, intensity, cognition, and volition, were comparable to an intravenous DMT dose of 0.1 to 0.2 mg/kg, and the cluster for perception was comparable to 0.1 mg/kg intravenous DMT, and the cluster for somatesthesia was less than the lowest dose of DMT measured by the scale, 0.05 mg/kg.

The most striking findings of the psychological assessment came from the structured diagnostic interviews, and the semi-structured open-ended life story interviews. The Composite International Diagnostic Interview (CIDI) was used for the structured diagnostic interview. None of the UDV subjects had a current psychiatric diagnosis, whereas two of the control subjects had an active diagnosis of alcohol abuse and hypochondriasis. Only one subject among the controls had a past psychiatric disorder that was no longer present; an alcohol abuse disorder that had remitted two years previously. However, prior to membership in the UDV, eleven of the UDV subjects had diagnoses of alcohol abuse disorders, two had had past major depressive disorders, four had past histories of drug abuse (cocaine and amphetamines), eleven were addicted to tobacco, and three had past phobic anxiety disorders. Five of the subjects with a history of alcoholism also had histories of violent behavior associated with binge drinking. All of these pathological diagnoses had remitted following entry into the UDV. All of the UDV subjects interviewed reported the subjective impression that their use of hoasca tea within the context of the UDV had led to improved mental and physical health, and significant improvements in interpersonal, work, and family interactions.

Assessment of Serotonergic Functions in Long-term Users of Hoasca (Callaway, et al., 1994)

Another objective of the study was to investigate whether long-term use of hoasca resulted in any identifiable "biochemical marker" that was correlated with hoasca consumption, particularly with respect to serotonergic functions, since the hoasca alkaloids primarily affect functions mediated by this neurotransmitter. Ideally, such a study could be carried out on post-mortem brains of long-term drinkers in comparison to those of non-drinkers. In this study, this ideal could not be attained due to the fact that the subjects were still alive and using their brains! We settled on looking at serotonin transporter receptors in blood platelets as the next best alternative, using [^{3}H]-citalopram to label the receptors in binding assays. The up-or down regulation of peripheral platelet receptors is considered indicative of similar biochemical events occurring in the brain, although there is some controversy about the correlation between platelet receptor changes and changes in CNS receptors medications (Stahl, 1977; Pletscher and Laubscher, 1980; Rotman, 1980). However, platelet receptors were deemed suitable for the purposes of our study, as our objective was not to resolve this controversy but simply to determine if some kind of long-term biochemical marker could be identified. Neither did we postulate any conclusions about the possible "adverse" or "beneficial" implications of such a marker, if detected. We conducted the assays on platelets collected from the same group of 15 volunteers after they had abstained from consuming the tea for a period of three weeks. We also collected platelet specimens from the age-matched controls who were not hoasca drinkers. We were surprised to find a significant up-regulation in the density of the citalopram binding sites in the hoasca drinkers compared to control subjects. While the hoasca drinkers had a higher density of receptors, there was no change in the affinity of the receptors for the labelled citalopram. The significance of this finding, if any, is unclear. There is no other pharmacological agent which is known to cause a similar upregulation, although chronic administration of 5-HT uptake inhibitors has been reported to decrease both Bmax (the density of binding sites) and 5-HT transporter RNA in rats (Hrinda 1987; Lesch et al., 1993). Increases in Bmax for the uptake site in human platelets have been correlated with old age (Marazziti et al, 1989) and also the dark phase of the circadian cycle in rabbits (Rocca et al., 1989). It has been speculated (Marazziti et al, 1989) that upregulation of 5-HT uptake sites in the aged may be related to the natural course of neuronal decline. Although our sample size was limited, we found no correlation with age, and the mean age of the sample was 38 years. Also, none of our subjects showed evidence of any neurological or psychiatric deficit. In

fact, in view of their exceptionally healthy psychological profiles, one of the investigators speculated that perhaps the serotonergic upregulation is associated, not simply with age, but with "wisdom" -- a characteristic often found in the aged, and in many hoasca drinkers.

Another interesting self-experiment related to this finding was carried out by one of the investigators, Jace Callaway, following his return to Finland after the field phase of the study was completed. Dr. Callaway has access to Single Photon Emission Computerized Tomography (SPECT) scanning facilities in the Department of Pharmacology at the University of Kuopio. Suspecting that the causative agent of the unexpected upregulation might be tetrahydroharmine (THH), Dr. Callaway took SPECT scans of his own brain 5-HT uptake receptors prior to beginning a six week course of daily dosing with tetrahydroharmine, repeating the scan after the treatment period. He did indeed find that the density of central 5-HT receptors in the prefrontal cortex had increased; when he discontinued THH, their density gradually returned to previous levels over the course of several weeks. While this experiment only had one subject, if it is indicative of a general effect of THH that can be replicated and confirmed, the implications are potentially significant. A severe *deficit* of 5-HT uptake sites in the frontal cortex has been found to be correlated with aggressive disorders in violent alcoholics; if THH is able to specifically reverse this deficit, it may have applications in the treatment of this syndrome. These findings are especially interesting when viewed in the context of the psychological data collected in the hoasca study (Grob, et al., 1996). The majority of the subjects had had a previous history of alcoholism, and many had displayed violent behavior in the years prior to joining the UDV; virtually all attributed their recovery and change in behavior to their use of hoasca tea in the UDV rituals. While it can be argued that their reformation was due to the supportive social and psychological environment found within the UDV, the finding of this long-term change in precisely the serotonin system that is deficient in violent alcoholism, argues that biochemical factors may also play a role

Assessment of the Acute Physiological Effects of Hoasca Tea (Callaway, et al., 1997)

The major focus of the biochemical and physiological measurements carried out for the study was on the acute effects subsequent to consuming hoasca tea. One of the objectives was simply to measure the effects of hoasca on standard physiological functions, such as heart rate, blood pressure, and pupillary diameter, subsequent to ingestion. We found that all of these responses were well within normal parameters. Hoasca, not surprisingly, caused an increase in pupillary diameter from baseline (pre-dose) levels of 3.7 mm to approximately 4.7 mm at 40 minutes, which continued to 240 minutes after ingestion at which point measurements were discontinued. Breaths per minute fluctuated throughout the 240 minutes, from a low of 18.5 at baseline to a high of 23 breaths per minute at 100 minutes. Temperature rose from a baseline low of 37 ° C at baseline to a high of 37.3 °C at 240 min (although the ambient temperature also increased comparably during the course of the experiments, which were conducted from 10:00 - 16:00). Heart rate increased from 71.9 bpm at baseline to a maximum of 79.3 bpm by 20 minutes, decreased to 64.5 bpm by 120 minutes, then gradually returned toward basal levels by 240 minutes. There was a concomitant increase in blood pressure; both systolic and diastolic pressure increased to maxima at 40 minutes (137.3 and 92.0 mm Hg respectively) over baseline values (126.3 and 82.7 mm Hg respectively) and returned to basal values by 180 minutes. We also measured nueroendocrine response for plasma prolactin, cortisol, and grwoth hormone; all showed a rapid and dramatic increases over basal values from 60 minutes (cortisol) to 90 minutes (growth hormone) to 120 minutes (prolactin) after ingestion. The observed response, typical of serotonergic agonists, are comparable to the values reported by Strassman & Qualls (1994) in response to injected DMT. In our study, however, the response to oral DMT was delayed by a factor of four or five. Dr. Russell Poland, of the Harbor-UCLA Medical Center, carried out the neuroendocrine measurements.

Characterization of the Pharmacokinetics of Hoasca Alkaloids in Human Subjects (Callaway, et al., 1996; 1997)

The fourth objective of the study was to measure pharmacokinetic parameters of the hoasca alkaloids in plasma following ingestion of hoasca tea, and to correlate this to the amounts of alkaloids ingested. The UDV collaborators held a special "preparo" to prepare the sample of hoasca that was used for all subjects in the study. The mestres confirmed the activity in the usual manner, via ingestion, and pronounced it active and suitable for use in the study. Subsequent analysis by HPLC found the tea to contain, in mg/ml: harmine, 1.7; harmaline, 0.2; THH, 1.07; and DMT 0.24. Each subject received an aliquot of tea equivalent to 2 ml/kg body weight, which was consumed in a single draught. Based on the average body weight (74.2 ± 11.3 kg), the average dose of tea was 148.4 ± 22.6 ml, containing an average of 35.5 mg DMT, 158.8 mg THH, 29.7 mg harmaline, and 252.3 mg harmine. These doses are above the threshold level of activity for DMT as a psychedelic, and for harmine and THH as MAO inhibitors; harmaline is essentially a trace constituent of hoasca tea (Callaway, et al., 1996, 1997).

Only 12 of the 15 volunteers had sufficient plasma levels of DMT to permit pharmacokinetic measurements, possibly due to early emesis during the course of the session. Of these, the maximum plasma concentration (Cmax) (15.8 ng/ml) occurred at 107 minutes after ingestion, while the half-life ($T_{1/2}$

was 259 minutes. THH was measured in 14 of the 15 subjects; the Cmax was 91 ng/ml, reached at 174 min. This compound displayed a prolonged half-life of 532 minutes, in contrast to harmine which had a half-life of 115.6 min. The Cmax for harmine and harmaline was 114.8 and 6.3 ng/ml, respectively, and time of maximum concentration (Tmax) was 102 and 145 minutes, respectively. The $T_{1/2}$ for harmaline could not be measured (Callaway, et al.,1997).

In many ways this study was conceived because of the need to collect some basic data on the physiological and pharmacokinetic characteristics of ayahuasca, since none had previously existed. The conclusions to be drawn from the results, if any, are interesting and potentially significant, particularly in that these findings may offer a physiological rationale for the marked improvements in psychological health that is correlated with long-term hoasca use. Not surprisingly, the highest plasma concentrations of DMT correlated with the most intense subjective effects; however, the psychological measurement (Hallucinogen Rating Scale) indicated that comparable plasma levels of injected DMT in the study by Strassman & Qualls (1994) gave effects that were more intense than those reported from the hoasca tea. One possible explanation is that THH, by acting as a 5-HT reuptake inhibitor, may have resulted in a greater availability of 5-HT at the synapse, and this may have competed with DMT for occupancy at serotonergic synapses.

Another point worthy of remark is that the activity of THH in hoasca is apparently more a function of its inhibition of 5-HT uptake than to its action as an MAOI. THH is a poor MAOI compared to harmine (EC_{50} = 1.4 x 10^{-5} M vs 8 x 10^{-8} M for harmine), and while the plasma levels for harmine are well above the EC_{50} values, those for THH are well below the EC_{50} value for this compound as an MAOI.

Future Studies

The major objectives of the initial biomedical investigation of hoasca have been met, including the overall objective, that of developing a basic body of descriptive information on the physiological and psychopharmacological characteristics of the tea. But, like all good science, these investigations raise more question than they have answered. It seems clear that ayahuasca is relatively safe; it can be taken on a regular schedule for months or even years without producing any adverse effect. Indeed, all of our subjects were highly functional individuals who attribute much of their "coping" skills to the tea and the lessons it has taught them, albeit within the doctrinal context of the UDV. None of them showed any signs of physical disease, or neurological or psychological deficits, indeed, many had higher scores in some of the psychometric testing regimes than comparable control subjects who had never imbibed hoasca. Yet many questions remain, and it is to be hoped that future investigations will be done, and that some of the most relevant questions will be at least partially answered. Among areas which suggest themselves for future research, the following seem obvious:

- **Effect of hoasca on women, particularly pregnant and/or lactating women.** For simplicity's sake, our initial study included only male subjects who had imbibed the tea on a regular basis for at least ten years. Thus our sample was deliberately restricted; it included only experienced hoasca drinkers, and only men, just to minimize the number of variables. But women also drink hoasca, and moreover, most do so throughout pregnancy and lactation; indeed, children in the UDV are baptized with a tiny spoonful of hoasca, although they are not usually exposed to pharmacologically active amounts until at least age 13. There are many issues here worthy of study. For example, women claim that hoasca has positive benefits both in managing their pregnancy, and in assisting birth; many will take hoasca during labor to facilitate the process. The role of hoasca during pregnancy and lactation, whether adverse or positive, is just one of a score of questions which could be answered by follow-up studies using women hoasca drinkers.
- **Prospective studies, with children and new members.** For similar reasons, our study did not include any recent converts to the UDV, nor any children, who, if they choose, are allowed to attend UDV sessions and imbibe smaller amounts of hoasca as early as age 13. Nor did the study include any recent adult converts to the UDV. Clearly, prospective studies of both groups could add a great deal to our knowledge. In view of our finding that hoasca apparently brings about long-term increases in serotonin uptake receptor densities, the implications of this need to be further investigated, and prospective studies may clarify this question. For instance, is the increase in serotonin uptake sites a consequence of regular imbibition of hoasca, as would seem the obvious conclusion, or are hoasca drinkers as a group biased toward those who are predisposed toward naturally high receptor densities? And what are the implications of either finding? Similar questions, as well as a host of sociological and developmental questions, could be addressed in a prospective study of children of UDV members who remain in the group and start to imbibe hoasca regularly in adolescence. An obvious question to answer in this context would be an assessment of children and adolescents who were exposed to hoasca in utero, to determine the impact, if any, of prenatal hoasca exposure on their subsequent neurological and psychological development. Another question germane to the possible long-term health benefits of regular hoasca use is that of whether the practice might prove to be prophylactic against alcohol and drug abuse for adolescents who consume the tea within the UDV structure.

- **Brain imaging and electrophysiological studies** To the degree that facilities can be made available, brain imaging and electrophysiological studies of the acute and chronic effects of hoasca would further fill in the picture of its pharmacological characteristics.
- **Therapeutic applications of hoasca in treatment of substance abuse and alcoholism** The experience of UDV members, recounted in the structured "life-story" interviews, would seem to indicate that hoasca has real potential as a therapeutic agent in treating substance abuse and/or alcoholism as well as other psychopathologies. Most of the subjects interviewed were involved with substance abuse prior to joining the UDV, and have since ceased. Most attribute their recovery to the tea; it would seem that confirmation of their experience and further information could be collected relatively easily, perhaps through a prospective study using recent converts to the UDV having prior involvement with substance abuse or other addictive disorders.
- **Immunomodulatory effects of hoasca** Another parameter that could be easily assessed, that may have important implications for the long-term health effects of hoasca, is the question of its possible effects on the immune system. Hoasca may be an immunostimulant, and thus potentially beneficial in maintaining resistance to disease; on the other hand, it could be an immunosuppressant, and this would also have serious implications for long-term or frequent use. Although hoasca tea is customarily used as a ritual sacrament rather than a medicine, anecdotal reports suggesting that hoasca may facilitate recovery from serious illnesses such as cancer, and well-designed studies are needed to investigate this question. One possibility is that discontinuation of the use of alcohol, tobacco, and drugs of abuse, as is common in UDV members, may contribute to long-term salutary effects on health.

Summary

Ayahuasca, or hoasca, whether known by these names, or any of numerous other designations, has long been a subject of fascination to ethnographers, botanists, psychopharmacologists, and others with an interest in the many facets of the human relationship with, and use of, psychoactive plants. With its complex botanical, chemical, and pharmacological characteristics, and its position of prime importance in the ethnomedical and magico-religious practices of indigenous Amazonian peoples, the investigation of ayahuasca in its many aspects has been an impetus to the furtherence of our scientific understanding of the brain/mind interface, and of the role that psychoactive plant alkaloids have played, and continue to play, in the quest of the human spirit to discover and to understand its own trancendent nature.

Now, the process that has unfolded in Western culture since Richard Spruce first reported on ayahuasca use among the Indians of the Norwthwest Amazon in 1855 (Anon, 1855; Spruce, 1873) has reached a new stage. Ayahuasca has emerged from the Amazonian jungles where it has remained cloaked in obscurity for thousands of years, to become the sacramental vehicle for new syncretic religious movements that are now diffusing from their center of origin in Brazil to Europe, the United States, and throughout the world. As the world observes this process unfolding (with joyous anticipation for some, and with considerable trepidation for others), the focus for the scientific study and understanding of ayahuasca has shifted from the ethnographer's field notes and the ethnobotanist's herbarium specimens, to the neurophysiologist's laboratory and the psychiatrist's examining room. With the completion of the first detailed biomedical investigation of ayahuasca, science now has the basic corpus of data needed to ask further questions, regarding the pharmacological actions, the toxicities and possible dangers, and the considerable potential Ayahuasca has to heal the human mind, body, and spirit. Humanity's relationship with ayahuasca is a long-term commitment, expressed on an evolutionary time scale, that has already taught us much, and from which we can still learn much, provided we have the courage, and the tools, to ask the right questions.

References

Airaksinen, M. M. and I. Kari, (1981) ß-carbolines, psychoactive compounds in the mammalian body. *Medical Biology* 59: 21-34.

Allen, J. R. F. & B. Holmstedt (1980) the simple ß-carboline alkaloids. *Phytochemistry* 19:1573-1582

Anonymous (1855) Journal of a voyage up the Amazon and Rio Negro by Richard Spruce, San Carlos del Rio Negro, June 27, 1853. Hooker Journal of Botany and Kew Garden Miscellany, Nos. 6&7.

Barker, S. A. J. A. Monti, and S. T. Christian (1980) Metabolism of the hallucinogen N,N-dimethyltryptamine in rat brain homogenates. *Biochemical Pharmacology* 29: 1049-1057.

Barker, S. A. J. A. Monti, and S. T. Christian (1981a) N,N-dimethyltryptamine: An endogenous hallucinogen. *International Review of Neurobiology* 22: 823-110.

Bloom, F., J. Barchus, M. Sandler, and E. Usdin (eds). (1982) *ß-carbolines and Tetrahydro-isoquinolines*. Alan R. Liss; New York.

Buckholtz, Neil S., & W. O. Boggan (1976) Effects of tetrahydro-ß-carbolines on monoamine oxidase and serotonin uptake in mouse brain. *Biochemical Pharmacology* 25: 2319-2321.

Buckholtz, Neil S., & W. O. Boggan (1977) Monoamine oxidase inhibition in brain and liver produced by B-carbolines: structure-activity relationships and substrate specificity. *Biochemical Pharmacology* 26:1991-1996

Burroughs, W.S., & A. Ginsberg (1963) The Yage Letters. City Lights Books, San Francisco.

Callaway, J.C. (1988) A proposed mechanism for the visions of dream sleep. *Medical Hypotheses* 26: 119-124.

Callaway, J.C., M. M. Airaksinen, Dennis J. McKenna, Glacus S. Brito, & charles S. Grob (1994) Platelet serotonin uptake sites increased in drinkers of ayahuasca. *Psychopharmacology* 116: 385-387

Callaway, J.C., J. Gynther, A. Poso, A. Vepsäläinen, M.M. Airaksenin (1994) The Pictet-Spengler reaction and biogenic tryptamines: formation of tetrahydro-β-carbolines at physiological pH. *J. Hetero. Chem*. 31: 431-435.

Callaway, J. C., D. J. McKenna, C. S. Grob, G. S. Brito, L. P. Raymon, R.E. Poland, E. N. Andrade, E. O. Andrade, D. C. Mash (1997) Pharmacology of Hoasca alkaloids in Healthy Humans. *Journal of Analytical Toxicology*. In Press.

Callaway, J. C., L. P. Raymon, W. L. Hearn, D. J. McKenna, C. S. Grob, G. S. Brito, D. C. Mash (1996) Quantitation of N,N-dimethyltryptamine and harmala alkaloids in human plasma after oral dosing with Ayahuasca. *Journal of Analytical Toxicology* 20: 492-497

Canessa, M., E. Jaimovich, and M. de la Fuente (1973) Harmaline: a competitive inhibitor of Na^+ ion in the (Na^+/K^+)ATPase system. *Journal of Membrane Biology* 13:263-282.

de Rios, M. Dobkin (1972) Visionary vine: Psychedelic healing in the Peruvian Amazon. *International Journal of Social Psychiatry* 17: 256-269.

de Rios, M. Dobkin (1973) Curing with *ayahuasca* in an urban slum. In Harner, M. (ed.) *Hallucinogens and Shamanism*. Oxford University Press. London.

de Rios, M. Dobkin (1994, January) Drug tourism in the Amazon. Omni, p. 20.

de Sousa, R. C., & A. Grosso; (1978) Vasopressin-like effects of a hallucinogenic drug - harmaline - on sodium and water transport. *Journal of Membrane Biology* 40: 77-94

Fischman, L. G. (1983) Dreams, hallcinogenic drug states, and schizophrenia: a psychological and biological comparison. *Schizophrenia Bulletin* 9: 73-94.

Grob, C. S., D. J. McKenna, J. C. Callaway, G. S. Brito, E. S. Neves, G. Oberlender, O. L. Saide, E. Labigalini, C. Tacla, C. T. Miranda, R. J. Strassman, K. B. Boone (1996) Human pharmacology of hoasca, a plant hallucinogen used in ritual context in Brasil: *Journal of Nervous & Mental Disease*. 184:86-94.

Hashimoto, Y. & K. Kawanishi (1975) New organic bases from Amazonian Banisteriopsis caapi. *Phytochemistry* 14: 1633-1635.

Hashimoto, Y. & K. Kawanishi(1976) New alkaloids from Banisteriopsis caapi. *Phytochemistry* 15: 1559-1560.

Hayashi, K., M. Nagao, & T. Sugimura (1977). Interactions of harman and norharman with DNA. *Nucleic Acids Research* 4:3679-3685.

Ho B. T. (1977) Pharmacological and biochemical studies with ß-carboline analogs. In Essman, W. B. and L. Vazelli (eds.) *Current Developments in Psychopharmacology* Vol 4. Spectrum Press, New York.

Hopp, K.H., L. V.. Cunningham, M. C. Bromel, L. J. Schermeister, & S. K. W. Kahlil (1976) In vitro antitrypanosomal activity of certain alkaloids against *Trypanosoma lewisi*. *Lloydia* 39:375-77

Hrinda P.D. (1987) Regulation of high- and low-[^{3}H]-imipramine sites in rat brain by chronic treatment with antidepressants. European Journal of Pharmacology 138:159-168.

Johnson, D. D., T. E. Fisher, J. M. Tuchek, & R. D. Crawford (1984) Pharmacology of methyl- and propyl-B-carbolines in a hereditary model of epilepsy. *Neuropharmacology* 23:1015-1017

Kawanishi, K., Y. Uhara, and Y. Hasimoto (1982) Shinunine and dihydroshihunine from Banisteriopsis caapi. *Journal of Natural Products* 45: 637-38.

Krajick, K. (1992, June 15). Vision quest. Newsweek, pp. 44-45

Lamb, F.B. (1971) Wizard of the Upper Amazon: the Story of Manuel Cordova-Rios. Houghton-Miflin, Boston.

Langer, S. Z, R. Raisman, M. S. Briley, D. Schecter, and E. Zarafian (1980) Platelets from depressed patients have a decreased number of ^{3}H-imipramine binding sites. *Federation Proceedings, Federation of American Society for Experimental Biology* 30:1097.

Langer, S. Z., C. R. Lee, A. Segnozac, T. Tateishi, H. Esnaud, H. Schoemaker, & B. Winblad (1984) Possible endocrine role of the pineal gland for 6-methoxytetrahydro-ß-carboline, a putative endogenous neuromodulator of the [^{3}H]imipramine recognition site. *European Journal of Pharmacology* 102:379-380

Lesch, K. P., C.S. Aulakh, B.L. Wolozin, T.J. Tolliver, J.L. Hill, D. L. Murphy (1993) Regional brain expression of serotonin transporter mRNA and its regulation by reuptake inhibiting antidepressants. Molecular Brain Research 17:31-35.

Lippke, K. P., W. G. Schunack, W. Wenning, & W. E. Muller (1983) ß-carbolines as benzodiazepine receptor ligands: 1. Synthesis and benzodiazepine receptor interaction of esters of ß-carboline-3-carboxylic acid. *Journal of Medicinal Chemistry* 26:499-503

Luna, Luis E. (1984) The healing practices of a Peruvian shaman. *Journal of Ethnopharmacology* 11:123-133

Luna, Luis E. (1986) *Vegitalismo: Shamanism Among the Mestizo Population of thePeruvian Amazon.* Stockholm: Almqvist and Wiksell International.

Luna, Luis E., & Pablo Amaringo (1991) Ayahuasca Visions: The Religious Iconography of a Peruvian Shaman. North Atlantic Books, Berkeley, CA

Marazziti, D., M. Falcone, A. Rotondo, P. Castrogiovanni (1989) Age related differences in human platelet 5-HT uptake. Naunyn-Schmiedeberg's Arch. Pharmacol. 340:593-594.

McKenna D. J. & G. H. N. Towers (1981) Ultra-violet mediated cytotoxic activity of ß-carboline alkaloids. *Phytochemistry* 20(5):1001-1004.

McKenna, D. J. & G. H. N. Towers (1985) On the comparative ethnopharmacology of the Malpighiaceous and Myristicaceous hallucinogens. *Journal of Psychoactive Drugs*, 17:35-39.

McKenna, D., G. H. N. Towers, & F. S. Abbott. (1984) Monoamine oxidase inhibitors in South American hallucinogenic plants: Tryptamine and ß-carboline constituents of ayahuasca. *Journal of Ethnopharmacology* 10:195-223

McKenna, D.J., & G. H. N. Towers (1984). Biochemistry and pharmacology of tryptamines and ß-carbolines: A minireview. *Journal of Psychoactive Drugs* 16:347-358

McKenna, Dennis J., L. E. Luna, & G. H. N. Towers, (1995) Biodynamic constituents in Ayahuasca admixture plants: an uninvestigated folk pharmacopoeia. In: von Reis, S., and R. E. Schultes (eds). Ethnobotany: Evolution of a Discipline. Dioscorides Press, Portland

Melchior, C. & M. A. Collins (1982) The route and significance of endogenous synthesis of alkaloids in animals. *CRC Critical Reviews in Toxicology* 9: 313-356

Morin, A. M. (1984) ß-carboline kindling of the benzodiazepine receptor. *Brain Research* 321:151-154

Naranjo, C. (1967) Psychotropic properties of the harmala alkaloids. in D. H. Efron, B. Holmstedt, & N. S. Kline (eds.) *Ethnopharmacologic Search for Psychoactive Drugs.* U.S. Public Health Service Publication # 1645

Naranjo, P. (1986) El *ayahuasca* in la arqueología ecuatoriana. *America Indigena* 46: 117-128.

Nichols, D. E., Robert Oberlender, and McKenna, D. J. (1991) Stereochemical Aspects of Hallucinogenesis. Chapter 1, pp. 1-39 in R. R. Watson (ed.) *Biochemistry and Physiology of Substance Abuse, Vol. III*. CRC Press, Boca Raton, FL.

Ott, J. (1993) Pharmacotheon: Entheogenic Drugs, their Plant Sources and History. Natural Products, Kennewick, WA.

Phäkla, R., L. Rago, J.C. Callaway, M.M. Airaksinen (1997) binding of pinoline on the 5-hydroxytryptamine transporter: competitive interaction with [^{3}H]-citalopram. Pharmacol & Toxicol. 80: 122-126.

Pletscher, A. and A. Laubscher (1980) Use and limitations of platelets as models for neurons: Amine release and shape change reaction. In *Platelets: Cellular response Mechanisms and Their Biological Significance*. Rotman, A. et al. (eds) pp. 267-276

Rahwan, R. G. (1975) Toxic effects of ethanol - possible role of acetaldehyde, tetrahydroisoquino-lines, and tetrahydro-ß-carbolines. *Toxicology and Applied Pharmacology* 24: 3-27.

Rivier, L., & J. Lindgren (1972) *Ayahausca,* the South American hallucinogenic drink: Ethnobotanical and chemical investigations. *Economic Botany* 29:101-129

Rocca, P. A-M Galzin, S. A. Langer (1989) Light-dark differences in [^{3}H]-paroxetine binding in rabbit platelet membranes. . Naunyn-Schmiedeberg's Arch. Pharmacol. 340:41-44.

Rodriguez, E., J. C. Cavin, and J. E. West (1982) The possible role of Amazonian psychoactive plants in the chemotherapy of parasitic worms: a hypothesis. *Journal of Ethnopharmacology* 6: 303-309.

Rommelspacher, H., S. Strauss & J. Lindemann (1980) Excretion of tetrahydroharmane and harmane into the urine of man after a load with ethanol. *FEBS Letters* 109:209-212

Rotman, A. (1980) The use of blood platelets serotonin uptake as a model in the study of mental illness. In: *Enzymes and Neurotransmitters in Mental Disease.* Usdin, E., T. L. Sourkes, and M. B. H. Youdim (eds) pp. 65-76. John Wiley and Sons.

Schultes, R. E. (1957) The identity of the Malpighiaceous narcotics of South America. *Harvard Botanical Museum Leaflets* 18:1-56

Schultes, R. E. (1972) Ethnotoxocological significance of additives to New World hallucinogens. *Plant Science Bulletin* 18: 34-41

Schultes, R. E. and A. Hofmann (1980) *The Botany and Chemistry of Hallucinogens*, 2nd. Edition. Charles C. Thomas, Publishers, Springfield, Ill.

Shulgin, A. T. (1982) Psychotomimetic drugs: structure-activity relationships. In *Handbook of Psychopharmacology* Vol. 11. L. L. Iversen, S. D. Iversen, and S. H. Snyder (eds.) Plenum Press, New York.

Spruce, R.A. (1873) On some remarkable narcotics of the Amazon Valley and Orinoco. Ocean Highways. Geographical Magazine 1:184-193.

Stafford, P. (1977) Psychedelics Encyclopedia. And/Or Press, Berkeley, CA.

Stahl, Stephen M. (1977) The human platelet: a diagnostic and research tool for the study of biogenic amines in psychiatric and neurologic disorders. *Archives of General Psychiatry* 34: 509 516.

Suzuki, O. Y., Katsumata, Y., Oya, M. (1981) Characterization of eight biogenic indolamines as substrates for type A and type B monoamine oxidase. *Biochem. Pharmacol.* 30: 1353-1358.

Strassman, R. J. & C. R. Qualls (1994) Dose-response study of N,N-dimethyltryptamine in humans I: Neuroendocrine, autonomic, and cardiovascular effects. Arch. Gen. Psychiatry 51:85-97.

Szara, S. (1956) Dimethyltryptamine: its metabolism in man; the relation of its psychotic effect to the serotonin metabolism. *Experientia* 12: 411-441.

Taylor, D. L., P. B. Silverman, B. T. Ho (1984) Effects of 6-methoxytetrahydro-ß-carboline on 5-hydroxytryptamine binding in rat brain. *Journal of Pharmacy and Pharmacology* 1984. 36: 125-127.

Towers, G. H. N. and Z. Abramosky (1983) UV-mediated genotoxicity of furanoquinoline and of certain tryptophan-derived alkaloids. *Journal of Natural Products* 46 576-581.

Udenfriend, S., B. Witkop, B. G. Redfield, & H. Weissbach (1958) Studies with reversible inhibitors of monoamine oxidase: Harmaline and related compounds. *Biochemical Pharmacology* 1:160-165

Umezawa, K., A. Shirai, T. Matsushima, & T. Sugimura (1978). Co-mutagenic effect of harman and norharman with 2-acetyl-aminoflourine derivatives. *Proceedings of the National Academy of Sciences USA* 75:928-930

Weil, A.T. (1980) In the land of yage. In: *The Marriage of the Sun and Moon: A Quest for Unity in Consciousness.* Houghton-Mifflin, Boston.

Yasuhara, H (1974) Studies on monoamine oxidase (report XXIV). Effect of harmine on monoamine oxidase. *Japanese Journal of Pharmacology* 24: 523-533

Yasuhara, H, S. Sho, & K. Kamijo (1972) Differences in the actions of harmine on the oxidations of serotonin and tyramine by beef brain mitochondrial MAO. *Japanese Journal of Pharmacology* 22: 439-441.