Ayahuasca: An Ethnopharmacologic History

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*. *Ayahuasca,* or *hoasca*, 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.

What is 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*, particularly *P. viridis.* The leaves of *P. viridis* contains alkaloids which are necessary for the psychoactive effect *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* (McKenna, Towers, & Abbott, 1984). There are also reports (Schultes, 1972) that other *Psychotria* species are similarly utilized in other parts of the Amazon. 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 similar. 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.

Focus of the Present Historical Perspective

The present chapter presents a brief overview of the history of ethnopharmacological investigations of ayahuasca, which has been a topic of fascination to ethnographers, botanists, chemists, and pharmacologists ever since it first became known to science in the mid-19th

century. For expository purposes, the history of ayahuasca ethnopharmacology can be divided into several segments, starting with the prehistorical orgins of the beverage and leading up to the present, where ayahuasca is still an active area of research. The modern history of ayahuasca can be dated from the mid-19th century. The focus of the present chapter is on the ethnopharmacologic history of ayahuasca, though it should be noted that this unique beverage has historically impacted religion, politics, and society, as well as science, (e.g., in the Brazilian goverment's acceptance of the legitimacy of the sacramental use of ayahuasca beverages by the UDV and other Brasilian syncretic sects) and the implications and consequences of its continued and spreading use is likely to be felt on a number of levels now and in the future.

Prehistorical Roots of Ayahuasca

The origins of the use of ayahuasca in the Amazon Basin are lost in the mists of prehistory. No one can say for certain where the practice may have originated, and about all that can be stated with certainty is that it was already spread among numerous indigenous tribes throughout the Amazon Basin by the time ayahuasca came to the attention of Western ethnographers in the mid-19th century. This fact alone argues for its antiquity; beyond that, little is known. Plutarco Naranjo, the Equatorian ethnograper, has summarized what little information is available on the prehistory of ayahuasca (Naranjo, 1979, 1986). There is abundant archeological evidence, in the form of pottery vessels, anthropomorphic figurines, snuffing trays and tubes, etc., that plant hallucinogen use was well established in the Ecuadorian Amazon by 1500 - 2000 B.C. Unfortunately, most of the specific evidence, in the form of vegetable powders, snuff trays, and pipes, is related to the use of psychoactive plants other than ayahuaca, such as coca, tobacco, and the hallucinogenic snuff derived from Anadenanthera species and known as vilka and various other names. There is nothing in the form of iconographic materials or preserved botanical remains that would unequivocally establish the prehistorical use of ayahuasca, although it is probable that these pre-Colombian cultures, sophisticated as they were in the use of a variety of psychotropic plants, were also familiar with ayahuasca and its preparation. The lack of data is frustrating, however, particularly in respect to a question which has fascinated ethnopharmacologists since the late 1960's when its importance was first brought to light through the work of R.E. Schultes and his students. As mentioned above, ayahuasca is unique among plant hallucinogens in that it is prepared from a combination of two plants: The bark or stems of Banisteriopsis species, together with the leaves of Psychotria species or other DMT-containing admixtures. The beverage depends on this unique combination for its activity. There seems small likelihood of "accidentally" combining the two plants to obtain an active preparation when neither is particularly active alone, yet we know that at some point in prehistory, this fortuitous combination was discovered. At that point, ayahuasca was "invented." Just how this discovery was made, and who was responsible, we may never know, though there are several charming myths which address the topic. Mestizo ayahuasqueros in Peru will, to this day, tell you that this knowledge comes directly from the "plant teachers" (Luna, 1984), while the mestres of the Brasilian syncretic cult, the UDV, will tell you with equal conviction that the knowledge came from "the first scientist," King Solomon, who imparted the technology to the Inca king during a little publicized visit to the New World in antiquity. In the absence of data, these explanations are all that we have. All that we can say with confidence is that the knowledge of the techniques for preparing ayahuasca, including knowledge of the appropriate admixture plants, had diffused throughout the Amazon by the time the use of ayahuasca came to the attention of any modern researcher.

Scientific "discovery" of Ayahuasca - the 19th Century

The archeological prehistory of ayahuasca is likely to remain inextricably bound up with its mythical origins for the rest of time, unless some artifact should be uncovered that would unequivocally establish the antiquity of its usage.

By contrast, what might be called the modern or the scientific history of ayahuasca, is traceable to 1851, when the great English botanist Richard Spruce encountered the use of an intoxicating beverage among the Tukano Indians of the Rio Uapes in Brasil (Schultes, 1982). Spruce collected flowering specimens from the large jungle liana used as the source of the beverage, and this collection was the basis for his classification of the plant as Banisteria caapi; it was reclassified as Banisteriopsis caapi by the taxonomist Morton in 1931 as part of his revision of the generic concepts within the family, Malpighiaceae.

Seven years later, Spruce again encountered the same liana in use among the Guahibo Indians on the upper Orinoco of Colombia and Venezuela, and, later the same year, found the Záparo Indians of Andean Peru taking a narcotic beverage, prepared from the same plant, which they called ayahuasca. Although Spruce's discovery predates any other published accounts, he did not publish his findings until 1873, when it was mentioned in a popular account of his Amazon explorations (Spruce, 1873). A fuller exposition was not to appear until Spruce published his account in A.R. Wallace's anthology in 1908, Notes of a Botanist on the Amazon and Andes (Spruce, 1908). Credit for the earliest published reports of ayahuasca usage belongs to the Ecuadorian geographer Manuel Villavicencio, who, in 1858, wrote of the use of ayahuasca in sorcery and divination on the upper Rio Napo (Villavicencio, 1858). Although Villavicencio supplied no botanical details about the plant used as the source of the beverage, his account of his own self-intoxication left no doubt in Spruce's mind that they were writing about the same thing.

Throughout the remainder of the 19th century, various ethnographers and explorers continued to report on their encounters of the use of an intoxicating beverage prepared by various indigenous Amazonian tribes, and purportedly prepared from the "roots" (Crévaux, 1883), of various "shrubs" (Koch-Grünberg, 1909) or "lianas" (Rivet, 1905) of uncertain botanical provenance. Unlike Spruce, who had the presence of mind not only to collect botanical voucher specimens, but also materials designated for eventual chemical analysis, these later investigators did not collect specimens of the plants they observed, and hence their accounts are now of little more than historical importance. One notable exception was Simson's (1886) publication of the use of ayahusca amongst Ecuadorian Indians, noting that they "drank ayahuasca mixed with yage, sameruja leaves, and guanto wood, an indulgence which usually results in a broil between at least the partakers of the beverage." None of the ingredients were identified, nor were voucher specimens collected, but this report is the earliest indication that other admixture species were employed in the preparation of ayahuasca.

While Richard Spruce and other adventurous Amazonian explorers were collecting the first field reports of ayahuasca from 1851 onward, the groundwork was already being laid for important work on the chemistry of ayahuasca that would take place in the second decade of the twentieth century. The 19th century witnessed the birth of natural products chemistry, starting with the isolation of morphine from opium poppies by the German pharmacist Sërtuner in 1803. A disproportionate number of natural products isolated for the first time during this period were alkaloids, probably because these bases are relatively easy to isolate in a pure form, and partly because the plants which contain them were and are important drug plants with obvious and often dramatic pharmacological properties. It was during this period of feverish alkaloid discovery that German chemist H. Göbel isolated harmaline from the seeds of the Syrian Rue, Peganum harmala. Six years later, his colleague, J. Fritsch isolated harmine from the seeds in 1847. More than 50 years later, a third alkaloid, harmalol, was also isolated from Syrian Rue seeds by Fisher in 1901. Harmine, like the other ß-carbolines named after the species epithet of Peganum harmala, would later turn out to be identical to the major ß-carboline found in Banisteriopsis caapi; the definitive establishment of the equivalence of the ayahuasca ß-carboline to harmine from Syrian Rue however, would not take place until the 1920s, after harmine had been independently isolated by several investigators and given a variety of names.

The final 19th century event of signicance in the scientific history of ayahuasca took place in 1895, with the first investigations of the effects of harmine on the central nervous system in lab animals by Tappeiner; his preliminary results were followed up more systematically by Gunn in 1909, who reported that the major effects were motor stimulation of the CNS with tremors and convulsions, followed or accompanied by paresis and slowed pulse (Gunn, 1935).

Ayahuasca In the Early 20th century (1900-1950)

The early decades of the twentieth century witnessed the publication of Spruce's detailed accounts of his Amazonian explorations and his observations of the use of the narcotic beverage among several tribes that he contacted. Although brief reports had been published earlier by Spruce and others, it was Spruce's account of his travels in a volume edited by the famed naturalist and co-discoverer of evolution A.R. Wallace in 1908 that may have rescued the knowledge of ayahuasca from the depths of academic obscurity and brought it to the attention of educated lay people.

During this early twentieth century period, progress in the understanding of ayahuasca took place mainly on two fronts: Taxonomic, and chemical. With some notable exceptions, pharmacological investigations of the properties of ayahuasca were relatively quiescent during this period.

The botanical history of ayahuasca during this period is an amusing combination of excellent taxonomic detective work by some, and egregious errors compounded upon errors by others. Safford, in 1917, asserted his belief that ayahuasca and the beverage known as caapi were identical,and derived from the same plant. The French anthropologist Reinberg (1921) compounded the confusion by his assertion that ayahuasca was referable to *Banisteriopsis caapi*, but that yajé was prepared from an Apocyanaceous genus, *Haemadictyon amazonicum*, now correctly classified as *Prestonia amazonica*. This error, which apparently originated from an uncritical reading of Spruce's original field notes, was to persist and propagate through the literature on ayahuasca for the next forty years. It was finally put to rest when Schultes and Raffauf published a paper specifically refuting this misidentification (Schultes and Raffauf, 1960), however it still crops up occasionally in technical literature.

Among the investigators who helped to clarify, rather than cloud, the taxonomic understanding of ayahuasca botany must be mentioned the works of Rusby and White in Bolivia in 1922 (White, 1922) and the publication by Morton in 1930 of the field notes made by the botanist Klug in the Colombian Putumayo. From Klug's collections, Morton described a new species of *Banisteriopsis*, *B. inebriens*, used as a hallucinogen, but he also asserted that at least three species, *B. caapi*, *B. inebriens*, and *B. quitensis*, were used similarly and that two other species, *Banisteria longialata*, and *Banisteropsis rusbyana* may have been used as admixtures to the preparation. Curiously, it was two chemists, Chen and Chen (1939) who did the most to clarify the early taxonomic confusion about the identity of the ayahuasca source plants. These investigators, working on the isolation of the active principles of yagé and ayahuasca, supported their investigations with authentic botanical voucher specimens (a rare practice at that time) and, after a review of the literature, concluded that caapi, yagé, and ayahuasca were all different names for the same beverage, and that their source plant was identical: *Banisteriopsis caapi*. Subsequent work by Schultes and others in the 1950's would establish that, in fact, Malpighiaceous species other than *B. caapi* were implicated in the preparation of the beverage, but considering the reigning confusion of the time, Chen and Chen's contribution was a rare light in the forest of prevailing darkness. From subsequent fieldwork, it is now quite clear that the two main botanical sources of the beverage variously known as caapi, ayahuasca, yagé, natéma, and pinde are the barks of *B. caapi* and *B. inebriens*.

The first half of the 20th century was also the period in which the first serious chemical investigations of the active principals of ayahuasca were carried out; and, like much of the initial taxonomic work taking place during this same period, scientific progress on this front was marked at first by confusion arising from the simultaneous investigations of several independent groups of investigators. Gradually, as these investigations found their way into the scientific literature, clarity began to emerge from a fairly murkey picture.

Harmine, which consensus would eventually establish as the major ß-carboline alkaloid of *Banisteriopsis* species, had been isolated from the seeds of *Peganum harmala* in 1847 by the German chemist Fritsch. Its unequivocal indentification was still several decades in the future when an alkaloid named "telepathine" was obtained from unvouchered botanical material called "yajé" by Zerda and Bayón in 1905 (quoted in Perrot and Hamet, 1927). In 1923, an alkaloid was again isolated from unvouchered botanical materials by the Colombian chemist Fisher Cardenas (1923), and was also named telepathine; at the same time, another Colombian team, chemist Barriga-Villalba and Albarracin (1925) isolated an alkaloid, yageine. This may also have been harmine in an impure form, but the formula assigned at the time and the melting point were inconsistent for a ß-carboline structure. To compound the confusion, the vine with which Barriga-Villalba worked had been "identified" as *Prestonia amazonica*, but he later revised this identification to *Banisteriopsis caapi*. In all of these instances, the lack of botanical reference specimens rendered the work of dubious value.

Things began to get slightly better from 1926 into the 1950s. Michaels and Clinquart (1926) isolated an alkaloid which they called yageine from unvouchered materials. Shortly afterward, Perrot and Hamet (1927) isolated a substance which they called telepathine and suggested that it was identical to yageine. Lewin, in 1928, isolated an alkaloid which he named banisterine; this was shown to be identical with harmine, previously known from the Syrian Rue, by chemists from E. Merck and Co. (Elger, 1928; Wolfes & Rumpf 1928). Elger worked from vouchered botanical materials which had been identified at Kew Gardens as *Banisteropsis caapi*. At Lewin's urging, based on his own animal studies, the pharmacologist Kurt Beringer (1928) used samples of "banisterine" donated by Lewin in a clinical study of 15 post-encephalitic Parkinson's patients, and reported dramatic positive effects (Beringer, 1928). This was the first time that a reversible MAO inhibitor had been evaluated for the treatment of Parkinson's Disease, though harmine's activity as a reversible MAOI was not discovered until nearly 30 years later. It also represents one of the few instances where a hallucinogenic drug has been clinically evaluated for the treatment of any disease (Sanchez-Ramos, 1991).

Working from vouchered botanical materials supplied by Llewellyn Williams of the Chicago Field Museum, Chen and Chen (1939) succeeded in confirming the work of Elger and Wolfes and Rumpf; these workers isolated harmine from the stems, leaves, and roots of B. caapi, and confirmed its identity with banisterine, previously isolated by Lewin. In 1957 Hochstein and Paradies analyzed vouchered material of ayahuasca collected in Peru and isolated harmine, harmaline, and tetrahydroharmine. The investigations of the constituents of other *Banisteriopsis* species was not undertaken until 1953, when O'Connell and Lynn (1953) confirmed the presence of harmine in the stems and leaves of vouchered specimens *of B. inebriens* supplied by Schultes. Subsequently Poisson (1965) confirmed these results, by isolating harmine and a small amount of harmaline from "natema" from Peru, identified by Cuatrecasas as *B. inebriens*.

Mid-20th Century (1950-1980)

The first half of the 20th century witnessed the initial scientific studies of ayahuasca and began to shed some light on the botanical sources of this curious hallucinogen and the nature of its active constituents. During the three decades from 1950 to 1980, botanical and chemical

studies continued apace, and new discoveries laid the groundwork for an eventual explanation of the unique pharmacological actions of ayahuasca.

On the chemical front, the work of Hochstein and Paradies (1957) confirmed and extended the previous work of Chen and Chen (1939) and others. The active alkaloids of *Banisteriopsis caapi* and related species were now firmly established as harmine, tetrahydroharmine, and harmaline. In the late 60's however, the first detailed reports of the use of admixtures as a regular, if not invariant, component of the ayahuasca brew began to emerge (Pinkley, 1969), and it soon became apparent that at least two of these admixtures, *Banisteriopsis rusbyana* (later reclassified by Bronwen Gates as *Diplopterys cabrerana*) and *Psychotria* species, particularly *P. viridis*, (Schultes, 1967) were added to the brew to "strengthen and extend" the visions. A further surprise came when the alkaloid fractions obtained from these species proved to be the potent short-acting (but orally inactive) hallucinogen N,N-dimethyltryptamine (DMT) (Der Marderosian, et al. 1968). This compound had been known as a synthetic for some decades following Manske's initial synthesis; but its occurrence in nature and its hallucinogenic properties had only come to light a few years earlier, when Fish, Johnson, and Horning (1955) had isolated it as the putative active principle in *Piptadenia peregrina* (later reclassified as *Anadenanthera peregrina*), the source of a hallucinogenic snuff used by Indians of the Carribean, as well as the Orinoco basin of South America.

The pharmacological rationale for the discovery by Schultes, Pinkley, and others in the late 60's that ayahuasca depended for its activity on a synergistic interaction between the MAO-inhibiting ß-carbolines in *Banisteriopsis* with the psychoactive but peripherally inactivated tryptamine, DMT had already been provided in 1958 by Udenfriend and coworkers (Udenfriend, et al., 1958) These researchers in the Laboratory of Clinical Pharmacology at NIH were the first to demonstrate that ß-carbolines were potent, reversible inhibitors of MAO. During this same period, clinical work and self-experimentation by the Hungarian psychiatrist and pharmacologist Stephen Szara (1957) with the newly synthesized DMT lead to the publication of the first reports of its profound, though short-lasting, hallucinogenic actions in humans. Szara's experiments also lead to the first recognition that the compound is not orally active, though the mechanisms of its inactivation on oral administration were not fully understood. Ironically, several decades later, the DMT pioneer Szara would be appointed as the head of NIDA (National Institute on Drug Abuse).

In 1967, during the height of the Summer of Love in the Haight Ashbury, a unique symposium was held in San Francisco under the sponsorship of what was at the time the U.S. Department of Health, Education, and Welfare. Entitled Ethnopharmacologic Search for Psychoactive Drugs (the proceedings were later published under that title as U.S. Public Health Service Publication #1645, issued by the U.S. Government Printing Office) (Efron, et al., 1967) this conference brought together the leading lights of the day in the emerging field of psychedelic ethnopharmacology. Participants included toxicologist Bo Holmstedt of the Karolinska Institute in Stockholm, ethnobotanist Richard Evans Schultes, chemist Alexander Shulgin, newly credentialed M.D. and marijuana researcher Andrew Weil, and others. It was the first time that a conference on the botany, chemistry and pharmacology of psychedelics had been held, and as it happened, it was certainly the last time that such a conference would be held under government sponsorship! This landmark conference, and the publication issuing from it which was to become a classic of psychedelic literature, was the first forum where the state of the art at the time regarding ayahuasca in its multidisciplinary aspects were revealed to the world. The symposium volume included chapters on the chemistry of ayahuasca (Deulofeu, 1967) , the ethnography of its use and preparation (Taylor, 1967) , and the human psychopharmacology of the ß-carbolines of ayahuasca (Naranjo, 1967). It is an ironic commentary on the paucity of knowledge of ayahuasca at the time that the uses of tryptamine-containing admixtures, and their activation via MAO-inhibition, did not even surface for discussion at the symposium; the

prevailing assumption was that the psychoactivity of ayahuasca was due primarily if not entirely to the ß-carbolines.

In the five years following this conference, progress was made in understanding ayahausca pharmacology and chemistry. Schultes and his students Pinkley and der Marderosian published their initial findings on the DMT-containing admixture plants (Der Marderosian et al., 1968; Pinkley, 1969), fueling speculation that DMT, orally activated by ß-carbolines, was responsible for much of the activity of the brew. This notion, although plausible, would not be scientifically confirmed for another decade.

In 1972, Rivier and Lindgren (1972) published one of the first interdisciplinary papers on ayahuasca, reporting on the alkaloid profiles of ayahuasca brews and source plants collected among the Shuar people of the upper Rio Purús in Peru. At the time, their paper was one of the most thorough chemical investigations of the composition of ayahuasca brews and source plants that referenced vouchered botanical collections. It also discussed numerous admixture plants other than the *Psychotria* species and *Diplopteris cabrerana*, and for the first time provided evidence indicating that ayahuasca admixture technology was complex, and that many species were on occasion used as admixtures.

In the later 1970's a team of Japanese phytochemists became interested in the chemistry of Banisteriopsis, and reported the isolation of a number of new ß-carbolines and the pyrrolidine alkaloids shihunine and dihydroshihunine (Hashimoto and Kawanishi, 1975, 1976; Kawanishi et al. 1982). Most of the newly reported ß-carbolines were isolated in extreme trace amounts, however, and the possibility was later raised that they might be artifactsresulting from the isolation procedures (McKenna, et al., 1984).

Late 20th Century (1980-present)

Following publication of Rivier's and Lingren's paper, there was little further progress on the scientific front for the remainder of the 1970's. There was no comparable follow-up to Rivier and Lindgren's work until McKenna et al., (1984) published the results of their chemical, ethnobotanical, and pharmacological investigations of ayahuasca and its admixtures, based on vouchered botanical specimens and samples of brews used by mestizo ayahuasqueros in Peru. This paper was significant because it represented the first time that the theory proposed to explain the oral activity of the beverage, i.e., that the active principle was DMT, rendered orally active by ß-carboline-mediated blockade of peripheral MAO, was experimentally confirmed. Assays of ayahuasca fractions in rat-liver MAO systems showed that the brews were extremely potent MAO inhibitors even when diluted many orders of magnitude compared to full strength. A further important discovery was the finding that the levels of alkaloids typically found in the mestizo ayahuasca brews exceeded the levels found in the upper Rio Purús ayahuasca by Rivier and Lindgren, sometimes by an order of magnititude or more. Based on the known human pharmacology of DMT and ß-carbolines, McKenna and co-workers showed that a typical dose (100 ml) of the mestizo ayahuasca samples contained enough DMT to constitute an active dose. The investigators suggested that the lower levels of alkaloids found in the Shuar samples of Rivier and Lindgren (1972) may have resulted from the different methods used in preparation. The Shuar typically soak the Banisteriopsis and admixture plants in cold water; they do not boil the plants, nor do they reduce the volume of the final extract, as is typically done in mestizo practice. These factors explained the discrepancies in alkaloid concentration found in the two different studies, or at least provided a plausible rationale to explain the differences.

The decade of the 1980's also witnessed the early contributions of the anthropologist, Luis Eduardo Luna. Working among mestizo ayahuasqueros near the cities of Iquitos and Pucallpa in

Peru, Luna's work was the first to articulate the importance of the strict diet followed by apprentice shamans, as well as the specific uses of some of the more unusual admixture plants (Luna, 1984a; 1984b; 1986). He was also the first to report on the concept of "plant teachers," (plantas que enseñan), which is how many of the admixture plants are viewed by the mestizo ayahuasqueros. In 1986, McKenna, Luna, and Towers published the first comprehensive tabulation of the species used as admixtures and the biodynamic constituents contained in them, pointing out that these relatively uninvestigated species comprise an extensive folk pharmacopoeia worthy of closer scrutiny as potential sources of new therapeutic agents (McKenna, et al., 1995).

While conducting fieldwork together in the Peruvian Amazon in 1985, McKenna and Luna first began discussing the possibility of conducting a biomedical investigation of ayahuasca. The superior health of the ayahuasqueros, even at advanced ages, seemed remarkable and something that could be amenable to scientific study. The logistical challenges of carrying out such work in Peru, however, seemed daunting, since access to storage facilities for plasma samples was limited and local concepts of witchcraft made it unlikely that ayahuasqueros would submit to medical procedures such as collection of blood and urine samples. The workers wrote a preliminary proposal for the project following their return from the field but did not pursue funding.

In 1991, however, a fresh opportunity to initiate such a study presented itself in Brasil. McKenna and Luna were among several foreigners invited to participate in a conference in São Paulo by the Medical Studies section of the União do Vegetal (UDV), a Brasilian syncretic religion that used ayahuasca in their ceremonies. The group's use of ayahuasca in a ritual context (under the name hoasca, vegetal, or simply cha, tea), while permitted by the Brasilian regulatory authorities, was subject to provisional review. Many members of the UDV were themselves physicians, psychiatrists, or had other kinds of medical expertise, and so were most receptive to the notion of conducting a biomedical study of ayahuasca when it was proposed to them by Luna and McKenna. It turns out that this had been a part of their own unspoken agenda all along and was part of the reason for inviting the foreign investigators to the first Medical Studies Conference on Hoasca. Besides the opportunity to satisfy scientific curiousity about the human pharmacology of hoasca, the UDV had a political motive for carrying out such a study; they wanted to be able to demonstrate to the Brasilian health authorities that the long-term use of hoasca tea was safe, and did not cuase addiction or other adverse reactions. The UDV physicians were hoping to enlist foreign scientists to collaborate in the study. The question of how the study was to be funded had yet to be answered.

Following the 1991 conference, McKenna returned to the United States and drafted a proposal describing the objectives of the study that was to become known as the Hoasca Project. Initially, the objective was to submit the proposal to the National Institute on Drug Abuse, but as the proposal took shape it became clear that funding for the study would be unlikely to originate from any government agency; not only were there legal, logistical, and political problems with securing NIH funds for a study to be carried out in Brasil, it was also clear that given the nature of government drug policy, the NIH would not look favorably on a proposal that was not aimed at demonstrating serious harmful consequences resulting from the use of a psychedelic drug. Fortunately, McKenna had affiliations with Botanical Dimensions, a non-profit organization dedicated to the investigation of ethnomedically important plants, and through this venue he was able to solicit generous grants from several private individuals.

With sufficient funding assured for at least a modest pilot study, McKenna enlisted the collaborative talents of various colleagues in the medical and academic communities. Eventually, a truly international, interdisciplinary study team was formed, consisting of scientists from UCLA, the University of Miami, the University of Kuopio in Finland, the

University of Rio de Janeiro, University of Campinas near São Paulo, and the Hospital Amazonico in Manuas.

The team returned to Manaus in the summer of 1993 to begin the field phase of the research, which was conducted using volunteers who were members of the Nucleo Caupari in Manaus, one of the oldest and largest UDV congregations in Brasil. The team spent five weeks in Brasil administering test doses of hoasca tea to the volunteers, collecting plasma and urine samples for later analysis, and carrying out a variety of physiological and psychological measurements.

The result was one of the most comprehensive multi-faceted investigations of the chemistry, psychological effects, and psychopharmacology of a psychedelic drug to be carried out in this century. Both the acute and the long-term effects of regular ingestion of hoasca tea were measured and characterized; extensive psychological evaluations, and in-depth structured psychiatric interviews were conducted with all volunteers; the nature of the serotonergic response to ayahuasca was measured and characterized; and the pharmacokinetics of the major hoasca alkaloids were measured for the first time in human plasma. Since completion of the field phase of the study, the results have been published in a number of peer-reviewed papers (Grob, et al., 1996; Callaway, et al., 1994, 1996, 1998), and have recently been summarized in a comprehensive review (McKenna, et al., 1998). Among the key findings were that long-time members of the UDV commonly underwent life-changing experiences that changed their lives and behavior in positive and profound ways; that there was a persistent elevation in serotonin uptake receptors in platelets, possibly indicative of similar long-term serotonergic modulation occurring in the central nervous system that may reflect long-term adaptive changes in brain functions. The study did establish that the regular use of hoasca, at least within the ritual context and supportive social environment which exists within the UDV, is safe and without adverse long-term toxicity, and, moreover, apparently has lasting, positive influences on physical and mental health.

The Future History of Ayahuasca

The field and laboratory phases of the Hoasca Project have been completed for sometime, and now that the last and final major paper resulting from the work has been accepted for publication, the Project is in its final stages. Always conceived as a pilot study, the objectives of the hoasca study were modest and intended to indicate directions for future research. In this regard, the study was a remarkable success; like all good science, the study raised more questions than it answered, and suggested several promising directions for future research. Now that ayahuasca has been clearly shown to be safe, non-toxic, and therapeutically useful as medicine, it is to be hoped that future researchers will devote sufficient interest, as well as funds, to the exploration of its healing potential.

Some Speculative Issues

With the completion of the Hoasca Project, there now exits a solid foundation of basic data to serve as the underpinning of future scientific investigations as their focus moves from the field to the laboratory and the clinic. But outside the perimeter of the cold light of reason cast by scientific scrutiny, there remain a number of issues surrounding ayahuasca that are unlikely be resolved by science alone, at least not by scientific methods as they are now understood. Ayahuasca is a symbiotic ally of the human species; its association with our species can be traced at least as far back as New World prehistory; the lessons we have acquired from it, in the course of millenia of coevolution, may have profound implications for what it is to be human, and to be an intelligent, questioning species within the biospheric community of species. Although we have no certain answers, the question of the nature and meaning of the relationship between humanity and this visionary vine, and by extension with the entire universe of plant

teachers, persistently troubles us. Why should plants contain alkaloids that are close analogs of our own neurotransmitters, and that enable them to "talk" to us? What "message" are they trying to convey, if any? Was it purely happenstance, purely accident, that led some early, experiment-minded shaman to combine the ayahuasca vine and the chacruna leaf, to make the tea that raised the curtain on the Invisible Landscape for the first time? It seems unlikely (neither of the key ingredients are particulary inviting as food), and yet what else could it have been? The ayahuasqueros themselves will simply tell you that "the vine calls." Others, trying to be more sophisticated and "rational" but proffering no more satisfying explanation, will talk about plant alkaloids as interspecies pheromonal messengers and the carriers of sensoritropic cues that enabled early humans to select and utilize the biodynamic plants in their environment. Still others, such as the McKenna brothers in their early work, and a more recent reformulation of a similar theory by anthropologist Jeremy Narby (McKenna & McKenna, 1975; Narby, 1998) argue that by some as yet obscure mechanism, the visionary experiences afforded by plants such as ayahuasca give us an insight, an intuitive understanding, of the molecular bedrock of biological being; and that this intuitive knowledge, only now being revealed to the scientific worldview by the crude methods of molecular biology, has always been available as direct experience to shamans and seers with the courage to forge symbiotic bonds with our mute but infinitely older and wiser plant allies.

Such notions are surely speculative and are certainly not science; but to an observer of the contemporary world, who has been involved both scientifically and personally with ayahuasca for many years now, I find it very interesting that such "wild" speculations keep reasserting themselves, no matter how much we try to "desacralize" the tea and render it down to a matter of chemistry and botany, receptor sites and pharmacology. All of those things are important, certainly; but none of them will ever "explain" the undeniable and profound mystery that is ayahuasca.

References

Barriga-Villalba, A.M. (1925) Yajeine. A new alkaloid. J. of the Society of Chemistry and Industry 44:205-207

Beringer, K. (1928) Über ein neues, auf das extrapyramidal-motorische System wirkendes Alkaloid (Banisterin). Nervenarzt 1:265-275.

Callaway, J. C., D. J. McKenna, , G. S. Brito, L. P. Raymon, R.E. Poland, E. N. Andrade, E. O. Andrade, D. C. Mash (1998) Pharmacology of Hoasca alkaloids in Healthy Humans. Journal of Ethnopharmacology. 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

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

Chen, AL & Chen, KK (1939) Harmine: the alkaloid of caapi. Qtly J. Pharm. Pharmacol. 12:30-38

Crévaux, J. (1883) Voyages dans l'Amerique du Sud. Librairie hachette & Cie, Paris.

Deulofeu, V. (1967) Chemical compounds isolated from Banisteriopsis and related species. In: Efron, D. H., B. Holmstedt, N.S. Kline (eds.) (1967) Ethnopharmacological Search for Psychoactive Drugs. U.S. Public Health Service Publication #1645. U.S. Government Printing Office.

Der Marderosian, A. H., Pinkley, H.V., Dobbins, M.F. (1968) native use and occurrence of N,N-dimethyltryptamine in the leaves of Banisteriopsis rusbyana. American J. of Pharmacy 140:137

Efron, D. H., B. Holmstedt, N.S. Kline (eds.) (1967) Ethnopharmacological Search for Psychoactive Drugs. U.S. Public Health Service Publication #1645. U.S. Government Printing Office.

Elger, F. (1928) Über das Vorkommen von Harmin in einer südamerikanischen Liane (Yagé). Helvetica Chemica Acta 11:162

Fischer, C. G. (1923) Estudio Sobre el Principio Activo de Yagé. Unpublished Thesis, Université Nacional, Bogotá

Fish, M.S., Johnson, N.M., Horning, E. C. (1955) Piptadenia alkaloids. Indole bases of Piptadenia peregrina (L.) Benth and related species. J. American Chemical Society 77:5892-5895.

Grob, C. S., D. J. McKenna, , 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 psychopharmacology of hoasca, a plant hallucinogen used in ritual context in Brasil: Journal of Nervous & Mental Disease. 184:86-94.

Gunn, J.A. (1935) Relationship between chemical constitution, pharmacological actions, and therapeutic uses in the harmine group of alkaloids. Arch. Int. Pharmacodyn. 50:379-96

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

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

Hochstein, F.A. & Paradies A. M. (1957) Alkaloids of Banisteriopsis caapi and Prestonia amazonica. J. American Chemical Society 79: 5735ff

Kawanishi, K. Y. Uhara, Y. Hashimoto (1982) Shihunine and dehydroshihunine from *Banisteriopsis caapi*. Journal of Natural Products 45:637-638.

Koch-Grünberg, T (1909) Zwei Jahre unter den Indianern Vol. 1: 298ff.

Lewin, L. (1928) Sur une substance envirante, la banisterine, extraite de Banisteria caapi Spr. Comptes Rendeus 186: 469ff

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

Luna, L. E. (1984b) The concept of plants as teachers among four mestizo shamans of Iquitos, northeast Peru. Journal of Ethnopharmacology 11:135-156.

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

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

McKenna, D.J., C. S. Grob, J. C. Callaway (1998) The Scientific Investigation of Ayahuasca: A Review of Past and Current Research. Heffter Review of Psychedelic Research 1:??-??

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

Dennis J. McKenna & Terence K. McKenna (1975) The Invisible Landscape. Seabury Press, New York.

Michaels, M. & Clinquart, E. (1926) Sur des réactions chemiques d'identificacion de la yageine. Bulletin de Academie Royale Médicin Belgique Series 5, Vol. 6: 79ff

Morton, C.V. (1930) Notes on Yagé, a drug plant of Southeastern Colombia. Journal of the Washington Academy of Science 21:485

Naranjo, C. (1967) Psychotropic properties of the harmala alkaloids. In: Efron, D. H., B. Holmstedt, N.S. Kline (eds.) (1967) Ethnopharmacological Search for Psychoactive Drugs. U.S. Public Health Service Publication #1645. U.S. Government Printing Office.

Naranjo, P. (1979) Hallucinogenic plant use and related indigenous belief systems in the Ecuadorian Amazon. J. of Ethnopharmacology 1:121-145.

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

Narby, Jeremey (1998) The Cosmic Serpent: DNA and the Origins of Knowledge. Jeremy Tracher/Putnam Publishers, New York.

O'Connell, F.D. & Lynn, E. V. (1953) The alkaloids of Banisteriopsis inebriens Morton. J. American Pharmaceutical Association 42:753

Perrot E. and Hamet, R. (1927) Le yagé, plante sensorielle des Colombie. Comptes Rendues de al Academie Scientifique 184:1266.

Pinkley, H.V. (1969) Plant admixtures to ayahuasca, the South American hallucinogenic drink. Lloydia 32:305ff

Poisson, J. (1965) Note sur le "natem," boisson toxique péruvienne. Annales Pharmacia Francaise 23:241ff

Reinberg, P. (1921) Contribution à l'étude des boissons toxiques des indiens du Nord-ouest de l'Amazon, l'ayahuasca, le yagé, le huanto. Journal de la Societé des Americanistes, Paris. Vol. 4:49ff

Rivet, P., (1905) Les indiens colorados. Journal de la Societé des Americanistes, Paris. Vol. 2:201ff

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

Sanchez-Ramos, J.R. (1991) Banisterine and Parkinson's Disease. Clinical Neuropharmacology 14:391-402

Schultes, R.E. & R. Raffauf (1960) Prestonia: An Amazonian narcotic or not? Botanical Museum Leaflets, Harvard University 19:109-122.

Schultes, R.E. (1982) The beta-Carboline hallucinogens of South America. J. of Psychoactive Drugs 14:205-219

Schultes, R.E., (1967) The place of ethnobotany in the ethnopharmacologic search for psychoactive drugs. In: Efron, D.H. (ed). Ethnopharmacologic Search for Psychoactive Drugs. U.S. Public Health Service Publication # 1645. U.S. Government Printing Office, Washington, D.C.

Simson, A. (1886) Travels in the Wilds of Ecuador. Lowe, Livinston, Marston & Searle, London.

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

Spruce, R.A. (1908) In: Wallace, A.R. (ed) Notes of a Botanist on the Amazon and Andes. MacMillan. London.

Szára, S.I., (1957) The comparison of the psychotic effects of tryptamine derivatives with with the effects of mescaline and LSD-25 in self-experiments. In: Garratini, S. & V. Ghetti (eds.) Psychotropic Drugs. Elsevier, New York, pp. 460-467.

Taylor, D. (1967) The making of the hallucinogenic drink from Banisteriopsis caapi in northern Peru. In: Efron, D. H., B. Holmstedt, N.S. Kline (eds.) (1967) Ethnopharmacological Search for Psychoactive Drugs. U.S. Public Health Service Publication #1645. U.S. Government Printing Office.

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

Villavicencio, M. (1858) Geografía de la República del Ecuador. Craighead, New York.

White, O.E. (1922) Botanical exploration in Bolivia. Brooklyn Botanical Garden Record 11:102ff

Wolfes, O. & Rumpf, K. (1928) Über die Gewinnung von Harmin aus einer südamerikanischen Liane. Archive für Pharmakologie 266:188ff