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Review Paper

A MULTIDISCIPLINARY OVERVIEW OF INTOXICATING ENEMA RITUALS IN THE WESTERN HEMISPHERE

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Introduction

From pre-Hispanic times until the present day the indigenous inhabitants of the Americas have used intoxicating, often hallucinogenic dosage forms as aids to enter supernatural realms, i.e. as facilitating agents in religious trance induction, divination, witchcraft and healing ceremonies (Furst, 1976; Emboden, 1979a; Schultes and Hofmann, 1980a,b; Schultes, 1981). It is equally well known that various Indian tribes and peoples, including several pre-Hispanic ones, employed the enema (Nordenskiöld, 1930; Hallowell, 1935; Heizer, 1944; Wassén, 1972b; Furst and Coe, 1977). While it is therefore not surprising that various publications on American aboriginals contain information about the ritual rectal taking of intoxicating preparations, there does not appear to be an elaborate multidisciplinary survey on this subject. In an attempt to fill this gap, brief articles about South American *Anadenanthera* enemas (de Smet, 1981a) and about enema scenes on ancient Maya pottery (de Smet, 1981b) have been extended to the present more comprehensive overview which offers not only substantial and unsubstantial ethnobotanical data on the ritual use of intoxicating enemas in the western hemisphere, but also a pharmacological view on such practices.

Paricá and the like

Ethnological and botanical data

Many South American Indians valued a snuff, known under the name of paricá, as a ritual intoxicant (Wassén and Holmstedt, 1963; Wassén, 1965, 1967). Several tribes of the Amazon Basin made small rubber syringes which were used occasionally to blow paricá into the nostrils (Métraux, 1949), but most often to administer clysters prepared with the same intoxi-

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cant (Horwitz, 1921; Nordenskiöld, 1930). Unfortunately the ethnological literature on these practices is often vague, generalizing and repetitious.

The Caripuna Indians of the Brazilian Madeira River are said to have provoked a state of trance by taking paricá in the form of an enema (Métraux, 1948a), for which purpose they used a small rubber syringe provided with a bird-bone tube (Horwitz, 1921; Wassén, 1972a).

According to Natterer (quoted by Wassén, 1965), not only the Caripuna but also the Maué and the Mura used seeds of the paricá tree (in Matto Grosso called angico), which were crushed and then mixed with plant ashes to be used for snuffing and as intoxicating clysters. While the Maué use of a paricá enema may not be certain (Nimuendajú, 1948a), the rectal taking of paricá among the Mura is well documented. For this once much feared tribe of the Madeira River the use of paricá, both as a snuff and as an enema, must have been of outstanding importance (Martius, 1867; Nimuendajú, 1948b; Wassén and Holmstedt, 1963). The initiation ceremony of the Mura started with a general mutual flagellation which was followed by the nasal and rectal application of paricá (Marcoy, 1867; Barbosa Rodrigues, 1875). Barbosa Rodrigues (1875) states that "All those who have been flagellated take paricá either as snuff or dissolved in water as a clyster... Taken either way, the effect is terrible and so violent that many die of suffocation or fall unconscious, while still others, resisting, continue the dance... Usually, the clyster causes a violent intoxication". Marcoy (1867) reports that on such occasions the rectal use of paricá was preceded by the snuffing of paricá and the drinking of palm wine in copious amounts. According to Spix and Martius (1831) the Mura clyster had a similar but not so strongly intoxicating effect as the snuff.

The Catawishi or Catauxi Indians of the Purús River are likewise stated to have taken a paricá decoction rectally (Horwitz, 1921; Cooper, 1949; Kennedy, 1982). According to Spruce (1908) paricá was taken as a snuff to induce speedily a sort of intoxication, but "taken in injection, it is a purge, more or less violent according to the dose". This statement clearly opposes the general view that such enemas were intoxicating. Spruce (1908) adds that before the hunt the Catawishi administered the paricá clyster not only to themselves but also to their hunting dogs for a clearer vision and more alertness.

The Casharari or Cacharary Indians, an Arawakan tribe of the western Amazon Basin, are reputed to have known paricá clysters (Métraux, 1948b, 1949). Drawing from a Portuguese source on these Indians (Mâso, 1919), Nordenskiöld (1930) describes the effects of the paricá enema as follows: "After about five minutes it acts in about the same way as intoxication from opium, inducing lovely and blissful dreams. Twenty minutes later the dreamer is fully normal again, and does not appear to suffer from any after-discomfort as is the case after snuffing paricá".

To the north of the Casharari lived the Omagua or Umaua Indians and further west the Cocama Indians. These Tupian tribes are said to have used

powdered curupa leaves which were blown into the nose or administered as a clyster with the help of small rubber syringes (Métraux, 1948c). Usually only the Omagua are implicated as curupa users (Veigl, 1785; Marcoy, 1867; Martius, 1867) and there seems to be some doubt about the curupa use among the Cocama (Wassén, 1967). The Omagua are stated to have employed enema syringes especially at feasts, when an obliging host distributed them to all his guests (De La Condamine, 1778).

Other South American tribes which are explicitly claimed to have taken paricá clysters, are the Maina Indians (Métraux, 1949) who are known to have made rubber syringes (Chantre y Herrera, 1901; Nordenskiöld, 1930), the Poruporo Indians (Horwitz, 1921) and the Pasé, Juri and Uainuma Indians (Métraux, 1948c).

The vagueness of the ethnological literature on páricá enemas is especially evident from the absence or insufficient reliability of botanical data. Sometimes the source is not identified at all (Horwitz, 1921; Métraux, 1948b,c; Natterer, quoted by Wassén (1965)) and sometimes the source is said to be *Piptadenia* (Métraux, 1948a, 1949) or more specifically *Piptadenia* seeds (Nordenskiöld, 1930). The paricá seeds which the Mura used for their clysters (Martius, 1867; Barbosa Rodrigues, 1875; Nimuendajú, 1948b) as well as the curupa leaves from which the Omagua prepared their enemas (Marcoy, 1867; Martius, 1867; Lowie, 1948; Métraux, 1948c) have been attributed to a plant named *Mimosa acacioides* or *Acacia niopo*. This leguminous tree has also been known under the binomial *Piptadenia peregrina* (List and Hörhammer, 1977) and is now considered to belong to the genus *Anadenanthera* which comprises the two species *A. peregrina* and *A. colubrina* (von Reis Altschul, 1967). These botanical identifications of paricá clysters correspond well with the once common view that paricá snuffs generally were prepared from seeds of a *Piptadenia* species, especially *P. peregrina* (Roth, 1924; Lowie, 1948; Cooper, 1949; Wassén and Holmstedt, 1963; Schultes, 1967b). Cooper (1949) has rightly cautioned, however, that some of these attributions may not be correct, since in some cases exact botanical evidence is lacking. It has become clear now that the vernacular term paricá is not used exclusively for the genus *Anadenanthera*, for it also refers to *Virola* preparations (Schultes, 1954; Seitz, 1967) and to snuffs containing harmine (Holmstedt and Lindgren, 1967). Furthermore it is uncertain that *Anadenanthera peregrina* is the species used throughout the Amazon. Schultes (1972) who speaks of a widespread rectal administration of *Anadenanthera* in South America, points out in a personal communication that "Other species may be used, such as *A. colubrina*. I believe that *A. peregrina* is a species primarily of the Orinoco and adjacent parts of the northern Amazonia of Brazil. Whether the species used in the Peruvian Amazon or the central Amazon of Brazil are *A. peregrina* is questionable. The reason is that snuffs, etc. have not been accompanied by voucher herbarium specimens". In other words, the geographical distribution of *Anadenanthera peregrina* is now assumed to be far more limited than it

was previously believed to be (Schultes, 1967b; Schultes and Hofmann, 1980b). It is likely, although not absolutely certain (Wassén, 1972a), that the Maué and other tribes of the Madeira area knew snuffs prepared from *A. peregrina*, since this tree occurs in this region (Schultes, 1967b). On the other hand it is unknown anywhere near the area of the Omagua, so its use by this tribe of Amazonian Peru must be open to serious question (Schultes and Hofmann, 1980b).

It is sometimes claimed that the Incas, well known inhabitants of ancient Peru, intoxicated themselves with rectal infusions of wilka or huilca seeds (Furst, 1976; Furst and Coe, 1977). The early chronicler Poma de Ayala (1969) indeed refers to such enemas and another early writer states that Inca witch doctors foretold the future by speaking with the devil, for which office they intoxicated themselves with villca, pouring its juice into the alcoholic beverage chicha or taking it another way (von Reis Altschul, 1967). Most early records, however, including the original report on the vilca clyster, emphasize the laxative properties of vilca seeds (von Reis Altschul, 1967) and it is not sufficiently clear whether the seeds helped to produce visions or were taken only for purgative qualities (Rowe, 1946). Poma de Ayala (1969) says that the Incas purged themselves once a month with bilca tauri, half of which was drunk and half of which was taken "por debajo" to give strength, health and a 200 years life span. Larrain Barros (n.d.) suggests that the phrase "por debajo" implicates nasal administration, but it is far more likely to indicate the rectal route, not in the least since various forms of the word vilca meant enema, syringe or the giving of an enema (von Reis Altschul, 1967; Wassén, 1972b). The botanical source of the vilca clyster is usually thought to be *Anadenanthera* (Larrain Barros, n.d.), in particular *A. colubrina* (Rowe, 1946; Furst and Coe, 1977). It should be noted that the evidence for this attribution is circumstantial rather than conclusive (von Reis Altschul, 1967; Schultes and Hofmann, 1980a,b) and that *A. colubrina* occurs in eastern Brazil, whereas from Peru the variety *A. colubrina* var. *cebil* is known (Schultes and Hofmann, 1980b).

Chemical and pharmacological data

Seeds of *Anadenanthera peregrina* (*Piptadenia peregrina*) were found to contain one or more of the following indole alkaloids: *N,N*-dimethyltryptamine (DMT); its corresponding *N*-oxide (DMT-*N*-oxide); 5-hydroxy-*N,N*-dimethyltryptamine or bufotenin (5-OH-DMT); its corresponding *N*-oxide (5-OH-DMT-*N*-oxide); 5-methoxy-*N,N*-dimethyltryptamine (5-MeO-DMT) (Holmstedt and Lindgren, 1967; Schultes et al., 1977). The question arises of whether the *N*-oxides might be artifacts, as Saxton (1965) points out that DMT is readily oxidized on exposure to air. During storage DMT and 5-MeO-DMT may transform into 5-OH-DMT (Schultes et al., 1977). A Venezuelan sample has been reported to contain as much as 7.4% of 5-OH-DMT (Chagnon et al., 1971). According to Schultes (pers. commun.), this report is not

based on identified herbarium voucher specimens and is open to question. In other samples 5-OH-DMT was present in lower amounts of 0.94% (Saxton, 1965) or up to 3.5% (Schultes et al., 1977). DMT, DMT-*N*-oxide, 5-OH-DMT and 5-OH-DMT-*N*-oxide were reported to be present in seeds of *Piptadenia macrocarpa* (Holmstedt and Lindgren, 1967), now considered to be *Anadenanthera colubrina* var. *cebil* (Schultes, 1967b), whereas from seeds of *Anadenanthera colubrina* (*Piptadenia colubrina*) 5-OH-DMT could be isolated (Holmstedt and Lindgren, 1967) in amounts up to 2.1% (Saxton, 1965).

DMT is a well-established hallucinogen, which elicits a brief but profound LSD-like response when given in intramuscular doses ranging from 0.7 to 1.1 mg/kg, i.e. 49—77 mg/70 kg (Szára, 1956; Rosenberg et al., 1963; Kaplan et al., 1974). Intramuscular administration of 0.25 mg/kg (17.5 mg/70 kg) has similar effects on certain tests measuring psychoticism as the *Cannabis* constituent delta-9-tetrahydrocannabinol (Bickel et al., 1977). In schizophrenics, intramuscular doses of 25—50 mg can induce psychological changes (Turner and Merlis, 1959), such as exacerbation of the psychosis (Gillin and Wyatt, 1977).

Human experiments with 5-MeO-DMT seem to have been conducted only by Shulgin (1970), who briefly reported that a parenteral dose of 5—10 mg is active and revealed the following details in a letter to the author: "My clinical studies involved a total of 9 subjects, 4 males and 5 females, within the age range of 33 to 65 years. All were healthy volunteers, all with considerable experience with drugs that can alter one's state of consciousness. The parenteral route of administration was in all cases by inhalation of the fused free base suspended on *Tanacetum vulgare* in cigarette form. The onset of action occurs in less than 60 seconds, reaches a plateau in the 2nd to 3rd minute, and is largely dissipated at 20 minutes, although there may be some lingering awareness for the remainder of an hour. Centrally, there is the loss of some reality sense, some eyes-closed imagery and a general feeling of being enclosed and isolated in a sensory sense. Peripherally, there have been occasional tremors noted, and occasional mydriasis. These effects are from 6 to 10 mg of the free base. I have personally conducted no oral experiments and do not know its effects via this route".

5-OH-DMT is mostly found to act briefly, altering the perception of colours and sometimes of space, when given in intramuscular doses of 10—15 mg (Isbell, quoted by Turner and Merlis (1959) and by Wassén and Holmstedt (1963)) and in intravenous doses of 4—16 mg (Fabing and Hawkins, 1956) or 12—16 mg (Bonhour et al., 1967). In schizophrenics intravenous amounts up to 20 mg, given by bolus injection (e.g. 10 mg within 1 min) or by infusion (e.g. 20 mg in 77 min), produced neither visual disturbances nor the psychological changes seen after DMT administration (Turner and Merlis, 1959). Many secondary sources doubt the hallucinogenic capacity of 5-OH-DMT following peripheral administration and then point to its poor lipid solubility at physiological pH and its consequent inability to enter the central nervous system readily (Holmstedt and Lindgren, 1967; Luchins et al., 1978; Glennon et al., 1979). Experiments with laboratory animals

have demonstrated that in contrast with the lipid soluble DMT (Cohen and Vogel, 1972) and 5-MeO-DMT (Sanders and Bush, 1967), 5-OH-DMT does not cross the blood-brain barrier in appreciable amounts (Sanders and Bush, 1967; Luchins et al., 1978; Glennon et al., 1979). This suggests that the reported effects of 5-OH-DMT may well be somatic symptoms of intoxication rather than signs of true hallucinogenic activity. According to Isbell (1967), it is difficult to say whether 5-OH-DMT is a hallucinogen or not because of its powerful and dangerous cardiovascular effects; for this reason, it is not possible to push the dose in man and it would be difficult to differentiate whether psychotic reactions were due to central effects or to cardiovascular actions.

Oral experiments with *Anadenanthera* alkaloids have failed to demonstrate hallucinogen-like effects, although the tested amounts were much higher than parenterally active doses. DMT was ineffective in a normal subject who took this compounds in very small quantities up to 250 mg (Szára, 1967) as well as in schizophrenics who received single doses up to 350 mg (Turner and Merlis, 1959). 5-OH-DMT was without effect when ingested in doses up to 50 mg by a healthy individual (Hofmann, 1963) or in doses up to 100 mg totally (Isbell, quoted by Wassén and Holmstedt, 1963). This inefficacy of oral dosing is likely to be principally due to extensive first-pass metabolism. The physicochemical properties of *Anadenanthera* alkaloids, in particular those of DMT and 5-MeO-DMT (Glennon et al., 1979), exclude a defective absorption, and chemical evidence for inactivation by the gastric juice has not been found. DMT and 5-OH-DMT are almost completely metabolized in man when given parenterally; the urinary recovery of unchanged drug was 1—6% of an injected dose of 5-OH-DMT (Sanders-Bush et al., 1976) and as low as about 0.07% in the case of DMT (Kaplan et al., 1974). The structurally related neurotransmitter 5-hydroxytryptamine (5-HT) is promptly degraded by intestinal and hepatic monoamine oxidase (MAO) when taken orally (Douglas, 1980). Although *Anadenanthera* alkaloids have a dimethylated amino-group, there is experimental evidence that they are inactivated in a similar way. MAO-inhibition prolongs the half-life of DMT in rats (Wang Lu and Domino, 1976) and other animal experiments have shown that 5-MeO-DMT and 5-OH-DMT are deaminated by MAO and, just as with 5-HT, preferentially by MAO-A (Squires, 1975). In a human subject, MAO-inhibition was found to double the urinary excretion of endogenous DMT (Oon et al., 1977). Not only MAO, however, but also hepatic microsomal enzymes may be capable of oxidating the dimethylated amino-group of *Anadenanthera* alkaloids (Fish et al., 1955). The deamination of 5-HT leads mainly to 5-hydroxyindole acetic acid, which is the principal urinary metabolite (Douglas, 1980). Intravenously given 5-OH-DMT was found to be excreted for 68—74% in the form of 5-hydroxyindole acetic acid (Sanders-Bush et al., 1976), whereas in an early study on DMT the urinary excretion of indole acetic acid, free and in alkali-labile form, accounted for only one-third of the intramuscular dose

(Szára, 1956). This implicates that deamination is a major metabolic pathway for these compounds, but not the only one, especially not in the case of DMT. This alkaloid was reported to be 6-hydroxylated to the extent of about 5—20% of the administered dose (Gillin and Wyatt, 1977).

The assumption that the active constituents of *Anadenanthera* are likely to undergo extensive first-pass metabolism by intestinal and hepatic MAO and by hepatic microsomal enzymes, may explain why this genus is most often taken nasally. The nasal route certainly can provide the advantage of by-passing the gut wall and the liver. A recent study on propranolol has demonstrated that for this high-clearance drug the nasal route is superior to the oral one and as effective as the intravenous route (Hussain et al., 1980). It is less easy to presume that the rectal taking of *Anadenanthera* will be advantageous. Since it is likely that the availability of enzymes in the gut wall decreases in the direction jejunum, caecum, colon, rectum (de Boer et al., 1982), it may be speculated that inactivation by intestinal MAO is avoided by rectal application. There is considerable doubt, however, that rectal administration usually provides the advantage of adequately by-passing hepatic inactivation. It is true that, while the upper rectal vein drains into the hepatic circulation, the inferior and probably also the middle rectal veins pass directly into the systemic circulation. A complicating anatomical factor, however, is the presence of anastomoses between the rectal veins (de Boer, 1980) and rectal dosage forms do not remain in the lower parts of the rectum, but move upward into a higher region (Moolenaar and Schoonen, 1980). Studies on the degree of enema penetration indicate that penetration as far as the ascending colon may be achieved and that, depending on the enema volume, penetration at least as far as the descending colon is likely (Lima and Jusko, 1980), so a large enema cannot be expected to provide a substantial by-pass of the liver (Quevauviller and Jund, 1951). A recent study on lidocaine has shown that in principle the use of a micro-enema can result in partial avoidance of a hepatic first-pass effect (de Boer et al., 1979). However, in various other experiments with 5-methoxypsoralen (Stolk, 1982), paracetamol (Moolenaar et al., 1979), promethazine (Moolenaar et al., 1981), propranolol and salicylamide (de Boer, 1980), the systemic availability of a micro-enema did not surpass that of an oral dosage form. It certainly cannot be concluded from these experimental findings that high-clearance drugs will generally show higher systemic availability when administered rectally. An extensive search of the medical literature has not yielded experimental data on the rectal application of an *Anadenanthera* alkaloid. In the author, single rectal doses up to 125 mg of DMT in 15 ml water were without any discernible effect. The enemas contained up to 185 mg of DMT bioxalate (Schuchardt, Munich), and were taken with the aid of a syringe and a special adaptor, developed for the rectal application of Valium® injection fluid (Anonymous, 1981). The most likely explanation for the inactivity is that first-pass elimination was not completely avoided. Further experiments in more than one volunteer would be needed, of course,

especially with higher doses, to ascertain whether or not any avoidance is possible. So long as such testing has not been done, it can neither be excluded nor concluded safely that *Anadenanthera* alkaloids produce systemic effects, when orally inactive amounts are taken in the form of an enema.

The reported use of plant ashes as ingredients for paricá snuffs and clysters (Barbosa Rodrigues, 1875; Horwitz, 1921; Natterer, quoted by Wassén, 1965) deserves some comment here. Schultes (1967b) believes that plant ashes are added to snuffs to help keep the finely pulverised particles from absorbing humidity from the excessively wet atmosphere and lumping so that the material could not be used as a snuff. From the pharmacological view these admixtures are interesting, because, due to their alkaline nature (Rivier, 1981), they can enlarge the non-ionized proportion of an alkaloid. This might facilitate the absorption from nasal and rectal preparations, which do not meet with the enormous absorbing surface at a rather high physiological pH that oral dosage forms encounter. In contrast with DMT and 5-MeO-DMT, 5-OH-DMT is poorly lipid soluble at pH 7.4 (Glennon et al., 1979), so the last alkaloid might profit in a more substantial way if vegetable ashes indeed have a beneficial effect on absorption.

Maikoa and the like

Ethnological and botanical data

Many South American tribes, especially in western South America, ingested preparations from tree *Daturas* in a ritual context (Safford, 1922; Cooper, 1949; Lockwood, 1979; Plowman, 1981). Among the Jivaro, headhunters of eastern Ecuador and Peru, the rectal route of administration was employed as well (Wassén, 1972b; Emboden, 1979a). It is said that a decoction of a tree *Datura* was drunk or taken as an enema through a straw by Jivaro warriors desiring to gain power and foretell the future (Steward and Métraux, 1948). Karsten (1935) tells that a *Datura* preparation called maikoa was given in the form of a clyster during the initiation ceremony, if the novice could not continue drinking this intoxicating liquid; "The oldest men of the family or tribe arrange themselves in two parallel rows facing each other. Each man holds a pininga containing a small quantity of maikoa. The novice must now go from the one to the other in due order and take a sip from each pininga, starting with the oldest member of the family. Generally it is easy for him to do this with the first ones, but frequently it is impossible for him to drink from the clay vessels of the last men in the rows. Their contents are then given him in the form of a clyster...It is considered absolutely necessary, it should be understood, that the novice should receive something from the clay vessel of each man".

Tree *Daturas*, all of which are native to South America, have usually been regarded as the *Brugmansia* section of the genus *Datura*, but on morphological and biological grounds this section is now treated as a distinct genus (Lockwood, 1979). There is usually no danger of confusing *Brugmansia*

with any other hallucinogen, but when the older literature offers an indentification of the plants used, the statement is usually not supported by a voucher specimen (Schultes and Hofmann, 1980b). According to Karsten (1935), the maikoa drink was simply prepared by squeezing the juice from the bark of the stem of *Datura arborea*. There has been a tendency in the past, however, to apply this binomial to any white-flowered tree *Datura* (Bristol et al., 1969), so it is uncertain how frequently the plant actually did represent *Brugmansia arborea*. Other authors have attributed maikoa preparations to *Datura candida* (Emboden, 1979a) and to *Brugmansia suavolens* (Lockwood, 1979).

Herbaceous *Datura* species have been widely employed by the aboriginal inhabitants of North and Middle America (Safford, 1922; Schultes and Hofmann, 1980a,b). The ethnological record on their rectal administration is less impressive than the data on *Brugmansia* enemas. In the initiatory ritual of the Algonquin Indians, a tribe of the eastern United States, the youths were kept intoxicated for 18 or 20 days by means of wysoccan liquid (Beverly, 1705) which is believed to have had the root of *D. stramonium* as its chief ingredient (Safford, 1922; Schultes and Hofmann, 1980b). Emboden (1979a) points out that such a prolonged state of intoxication would be more easily maintained through enemas than through oral fluids. Furthermore the ancient Aztecs of Mexico are known to have taken *Datura* rectally for medicinal purposes. An authoritative early account on Aztec medicinal plants states that tlapatl leaves were applied in the form of suppositories to relieve fever (Hernandez, 1790). Tlapatl has been identified as *D. stramonium* (Safford, 1922), but it referred more probably to *D. inoxia* (= *D. meteloides*) (Schultes, pers. commun.).

Chemical and pharmacological data

As far as is known, all *Brugmansia* species and hybrids contain tropane alkaloids (Hoppe, 1975; Schultes and Hofmann, 1980b), so there does not seem to be any serious uncertainty about the active principles, even though information on the species utilized is often inconclusive. In most cases, scopolamine, also called hyoscine, has been isolated as the predominant alkaloid (Evans et al., 1965; Shah and Saoji, 1966; Bristol et al., 1969; Leary, 1970). Aerial parts of white-flowered *Brugmansia* trees, referred to as *Datura aborea* from India (Shah and Saoji, 1966) and as *Datura candida* and its Sibundoy cultivars from Colombia (Bristol et al., 1969), contained about 0.1—0.3% of scopolamine, whereas up to about 1% of this alkaloid could be found in the red-flowered *Brugmansia sanguinea* (Evans et al., 1965). The structurally related atropine and/or its laevo-isomer hyoscyamine may also be present (Evans et al., 1965; Shah and Saoji, 1966; Bristol et al., 1969; Leary, 1970). It should be noted that the distinction between these two compounds can be affected by racemisation upon extraction (List and Hörhammer, 1972) and by inseparability on the paper chromatogram (Evans et al., 1965; Shah and

Saoji, 1966; Bristol et al., 1969). Various other minor *Brugmansia* alkaloids have been isolated, including aposcopolamine, norscopolamine, norhyoscyamine, noratropine, pseudotropine, tropine, oscine and meteloidine (Bristol et al., 1969; Leary, 1970). The active principles in herbaceous *Datura* species are also tropane alkaloids (Hoppe, 1975). Main components are hyoscyamine in *D. stramonium* and scopolamine in other species, such as *D. metel* (Wade, 1977; Schultes and Hofmann, 1980b).

The central toxicity of the tree *Daturas* (Anonymous, 1976; Belton and Gibbons, 1979) and their pure alkaloids (Longo, 1966; Shader and Greenblatt, 1971) is commonly known. As the following discussion focuses on scopolamine and atropine, it should be noted that hyoscyamine is the pharmacologically active laevo-isomer of the racemic atropine, of which the dextro-isomer is practically inactive (Shader and Greenblatt, 1971; Wade, 1977).

Ketchum et al. (1973) have demonstrated that parenteral scopolamine and atropine produce a virtually identical syndrome of delirium, when allowances are made for differences in time of action and potency. The delirium lasts for 6—8 h with scopolamine and for 10—12 h with atropine. The intramuscular dose of atropine necessary to produce hallucinations in half the subjects was estimated to be about 0.15—0.17 mg/kg (about 11 mg/70 kg), whereas intramuscular scopolamine was found to be 7.5, 8 and 11 times as potent in this respect, dependent on the test employed (mean 8.8 times; about 1.3 mg/70 kg). In a cross-over study by Mirakhur (1978) on peripheral activity of tropane alkaloids, the ratio of equivalent intramuscular to oral doses of atropine appeared to be 1 : 2 and that of scopolamine about 1 : 5—6. If these ratios also apply to central activity, the difference in central potency of both alkaloids would be reduced from 8.8 times parenterally to 3.2 times orally. Unfortunately, a cross-over study comparing central effects after ingestion and injection does not seem to be available. It is known only that oral doses up to 10 mg of atropine sulphate or up to 3 mg of scopolamine HBr do not induce delirium, whereas 4.5 mg of scopolamine HBr orally causes illusions and hallucinations in half the subjects (Ostfeld et al., 1959; Ostfeld et al., 1960). It may well be that scopolamine and atropine undergo substantial first-pass metabolism, which would explain why the activity of these alkaloids is route-dependent. Neither their physicochemical properties (Windholz, 1976) nor the rapid appearance of peak plasma levels after oral administration (Beermann et al., 1971; Chandrasekaran et al., 1978) are suggestive of a faulty absorption. Furthermore the observed activity ratios correspond rather well with reported urinary recoveries of non-metabolized drug, viz. 30—50% and 70—95%, respectively, for oral and intravenous atropine (Beermann et al., 1971), in contrast with only 4—5% and about 10% for oral and parenteral scopolamine, respectively (Chandrasekaran et al., 1978).

Naturally occurring tropane alkaloids have been found to produce delirium with various routes of administration (Shader and Greenblatt, 1971),

including inhalation (Bergman et al., 1980) and topical application into the eye (Freund and Marin, 1970) or on the skin behind the ear (Osterholm and Camoriano, 1982). Furthermore, scopolamine (Tonndorf et al., 1953) and atropine (Hyde et al., 1953) have been shown to produce systemic effects when taken nasally. Reports on their activity following rectal administration appear to consist merely of various uncontrolled studies, in which rectal multiple drug preparations (containing inter alia one or more natural tropane alkaloids) were rated to be useful as premedication for children (Chayen and Sarnat, 1973; Lindahl et al., 1981) or for the facilitation of delivery (Weinstock, 1934; Rittmeyer, 1935; Lehmann, 1952).

The preceding data suggest that *Burgmansia* alkaloids might easily produce systemic effects when given in the form of an enema. However, to prove this point beyond any doubt, well-designed studies on their rectal administration to man are still desirable, especially since a report on the mydriatic activity of atropine suppositories in the rat mentions a surprisingly large difference between equivalent intravenous and rectal doses of atropine, viz. 0.02 mg/kg vs. 0.5 mg/kg (Tardos et al., 1959).

Alcoholic beverages

Ethnological, botanical and chemical data

Before the conquest, distillation was unknown in the New World, but Mesoamerican Indians were familiar with a variety of alcoholic drinks prepared by fermenting agave, maize, honey (Furst and Coe, 1977) or numerous fruits such as pineapple (Schultes, pers. commun). Consequently the alcoholic content was only about 3—6% (Erosa Barbachano, 1976). Among the ancient Aztecs, getting drunk without incurring the wrath of society was a privilege of old age; drunkards could receive severe punishments, ranging from public disgrace to death by stoning or beating (Ross, 1978). Wilder drinking habits prevailed among the Huastecs of the Mexican northern Gulf Coast, who were considered barbarian by the Aztecs (Wasson, 1980). According to the early chronicler Sahagún (1961), the Huastecs "always went about as if drunk".

Several early records speak of rectal administration in connection with their inebriating practices (Bourke, 1892; Nordenskiöld, 1930; Furst and Coe, 1977; Robicsek, 1978). The conquistador Diaz del Castillo (1916) gives the following account, clearly from his European point of view: "About drunkards I do not know what to say, so many obscenities take place among them; I wish to note only one here which we found in the province of Panuco; they make an injection by the anus with some (hollow) canes and distend the intestines with wine, and this is done among them in the same way as among us an enema is applied". An anonymous companion of Cortés (El Conquistador Anonymo, 1941) states: "(they) worship figures showing different forms of pleasure between a man and a woman and figures of human beings with their legs lifted different ways...the men are great

sodomites, cowards, and — bored drinking wine with their mouths — lie down and, extending their legs, have the wine poured into their anus through a tube until the body is full". A similar description can be found in yet another anonymous early record (Relación Anonima Segunda, 1963). The "wine" in these reports most likely refers to fermented sap of Agave species, commonly known as pulque (Von Winning, 1972; Furst and Coe, 1977). Some caution in accepting the term at face value may be in order, however, since the Spaniards lacked experience with and a vocabulary for hallucinogenic drinks (Wasson, 1980).

There is circumstantial evidence that other Middle American peoples besides the Huastecs may have known of ritual alcoholic clysters. First the worshipped human figures with lifted legs, mentioned by El Conquistador Anonymo (1941), are reminiscent of certain rather poly-interpretable pre-Hispanic clay figurines from the central Veracruz region in Mexico. Evidence for a relationship between these so-called "bed figures" and the alcoholic beverage pulque has been reviewed by Von Winning (1972). A definite explanation for their peculiar raised leg position cannot be offered, but perhaps it is concomitant with the Huastec way of taking intoxicating enemas (Von Winning, 1972; Furst and Coe, 1977). Second there are at least two enema scenes on classic Maya pottery (see the section below), in which dots or small circles are depicted at the mouth of an enema jug which in all probability contains the enema. This is thought to indicate the presence of a fermented beverage, probably balche (Furst and Coe, 1977; Robicsek, 1978), in the same way as in Aztec codices dots above pottery signify the presence of pulque (Ross, 1978). Balche has been described as a mild intoxicant, concocted of fermented honey and water, to which was added the bark or root of the balche tree *Lonchocarpus violaceus* (= *L. longistylus*) (Roys, 1943, 1976; Goncalves de Lima et al., 1977). This admixture has been reported to contain antibacterial longistylines (Delle Monache et al., 1977), but it is not known to contain any hallucinogenic principle. According to 16th century sources, there were other intoxicating beverages as well: their base seems to have been honey, together with maize or the root of an agave, but roots of unidentified plants were added (Roys, 1943). Hellmuth (pers. commun.) believes that in the classic period the upper class of the Maya used to drink excessive amounts of alcohol: "On the basis of 12 years analysis of over 5,000 polychrome funerary vase paintings in private collections, I have found several scores of unpublished paintings that show the Maya engaged fervently in drinking rituals. Gestures and positions on some of the vases suggest possible intoxication. The offering and receiving of cups of liquid from the same jug later used to fill the enema syringes is clearly a major focus of Classic period vase painters of the Peten region. The murals of the Drunkards of Cholula are immediately brought to mind. However, the traditional archaeologists view is that the Maya were pacific and conservative. Also, other scholars — who are unfamiliar with the abundant paintings in private collections — have not seen the drinking and enema scenes, so they have not yet discussed drinking among the Classic Maya".

Pharmacological data

Ethyl alcohol is a reversible general central nervous system (CNS) depressant, and its acute ingestion can lead to an inebriation characterized by stupour (Ritchie, 1980; Eckardt et al., 1981). Hallucinations may be expected only after chronic administration, in particular as signs of a withdrawal syndrome (Thompson, 1978). They occur usually after a prolonged drinking bout (Eckardt et al., 1981) but are sometimes experienced while the alcoholic is severely intoxicated (Jaffe, 1980). Isbell et al. (1955) studied withdrawal symptoms in well-nourished, healthy volunteers, who were given different amounts of 95% alcohol: sudden abstinence induced hallucinations in most of the subjects who had been drinking 383—489 ml for 48—87 days but in none of the subjects who had been taking 266—346 ml daily for 7—34 days.

Taken orally, alcohol can be readily absorbed from the gastrointestinal tract. Since most absorption occurs in the small intestine, the absorption rate depends on the rate of gastric emptying, which in its turn is determined by factors like the properties of the beverage and the presence of food in the stomach (Wilkinson et al., 1977; Ritchie, 1980; Eckardt et al., 1981). The author is not aware of experimental data on the absorption of alcohol from an enema but, in view of the oral absorption characteristics and physicochemical properties of this substance (Offerhaus, 1979), a good and rapid absorption should be possible, if it be rectally administered. It must be noted that a clyster with an alcoholic content as high as 20% was found to be quite irritating to the rectal tissue (Moolenaar, pers. commun.).

Alcohol is known to affect the actions of many other drugs. Direct interactions occur at the pharmacodynamic level, e.g. when alcohol enhances the deleterious effects of another CNS depressant on performances and skills. Indirect interactions involve the pharmacokinetic level, e.g. when alcohol increases the absorption rate of a drug by enhancing its gastric solubility or the gastrointestinal blood flow (D'Arcy and Merkus, 1981). In the present context, it is interesting that, in an experiment by Moolenaar (pers. commun.), the presence of alcohol enhanced the absorption rate of the drug sodium salicylate from an enema. As to classical New World hallucinogens, the medical literature contains some undetailed claims that the drinking of alcohol potentiates the action of tree *Daturas* (Anonymous, 1976) and of *Psilocybe* mushrooms (Benjamin, 1979; Young et al., 1982). Well-documented clinical studies on this subject do not seem to be available. It has been shown only that atropine taken together with alcohol can impair attention more strongly than either substance alone (Linnoila, 1973).

Tobacco

Ethnological and botanical data

Neither botanists nor pharmacologists consider tobacco to be a true

hallucinogen, but it may be conceptually and functionally indistinguishable from hallucinogens in American Indian ritual practices (Wilbert, 1972). The references to its indigenous ritual use are numerous and there are ethnological reports on its induction of trance-like states analogous to those induced by hallucinogens (Castiglioni, 1943; Spinden, 1950; Wilbert, 1972; Janiger and Dobkin de Rios, 1976; Siegel et al., 1977; Robicsek, 1978). Several recent secondary sources state that tobacco was taken rectally in the western hemisphere (Schultes, 1981), in particular on the South American continent (Schultes, 1972; Furst, 1976; Furst and Coe, 1977), but neither the purpose nor other details are clearly mentioned. The main ways in which South American Indians have used tobacco are smoking, snuffing, chewing, drinking, eating and licking (Stahl, 1925; Cooper, 1949; Hartmann, 1981). As to the rectal route, a pre-Hispanic Bolivian grave was found to contain both tobacco fragments and small syringes (see the section on guayusa), and early accounts on Surinam (Fermin, 1775) and Brazil (Spix and Martius, 1831) touch lightly on tobacco enemas. These data, however, can hardly be considered as substantial evidence for the non-medical rectal use of tobacco by South American natives. Schultes and Wilbert (pers. commun.) are not aware of any detailed primary reference on this subject.

Decisive data are equally hard to find for Middle and North America. Several early sources on Middle America describe the rectal administration of tobacco, but only as a medicinal cure. The famous Aztec herbal known as the Badianus Codex recommends clysters prepared from tobacco and various other ingredients as a sure remedy for rumbling of the abdomen (Cruz and Badianus, 1940). Emboden (1979a) claims that a tobacco enema mentioned in the Badianus Codex was designed to produce inebriation, but according to the original text purgation was intended. The 16th century physician Monardes (1574) includes the use of clysters among the various methods of applying tobacco as a medicine and the Relación de Texcoco says that the Spaniards used the herb to clear malaria, "taking it as a suppository because it purged them" (Pomar, 1941). Drawing from an early French account (Charlevoix, 1744), several references indicate that the Indians of eastern Canada revived those nearly drowned by forcing tobacco smoke up the rectum. Then the victim was hung up by his feet to a tree so that he could cast up the water he had swallowed (Brooks, 1937, 1941; Van Wart, 1948; Gorter, 1953). In past centuries, resuscitation of drowned people by a rectal tobacco fumigation was practised in Europe as well (Brooks, 1937, 1938, 1941; Gorter 1953).

Furst (1976) suggests that the ritual enemas of the ancient Maya (see the section on Maya enema scenes) might have had tobacco as an ingredient. In one enema scene, a Maya dancer in a jaguar outfit and with an enema syringe sticking out from his belt carries on his back the typical enema jug, so often seen in these paintings. Sticking out of the jug are pointed sticks which might be cigars or blood-letting daggers (Hellmuth, 1978). In another enema scene, stylized smoke comes out of the syringes (Coe, 1978). According to

Hellmuth (pers. commun.), the cigar symbol: viz. smoke, would be appropriate, if the enema liquid contained the same tobacco that they smoked; alternatively, the smoke could symbolize pungency. A pungent clyster would, of course, be more suited for cleansing than for intoxication.

The two principal tobacco or *Nicotiana* species which have been employed ritually in the western hemisphere, are *N. tabacum* and *N. rustica.* At the time of the Spanish invasion, the first species was known in Central and South America and much of the West Indies, and the second one in North America and Mexico (Schultes, 1967b, pers. commun.). Although the literature sometimes warns that there is no certain information to prove the existence of *N. tabacum* in pre-Hispanic Mexico (Spinden, 1950), this species is frequently implicated to have occurred there (Setchell, 1921; Castiglioni, 1943; Schultes, 1981). Long after the conquest, *N. tabacum,* which comprises most varieties of commercially grown tobacco, was introduced from the Old World to the North American continent (Schultes, 1967b).

Chemical and pharmacological data

The principal *Nicotiana* alkaloid is nicotine as it may account for about 95% of the total alkaloid content of tobacco (Wenusch, 1940; Rotenberg, 1982). The amount in the leaf of *N. tabacum* varies widely from 0.6% to 9% (Hoppe, 1975; Schultes, 1981), but in commercial cigarette tobacco it seldom exceeds 3% (Siegel et al., 1977; Robicsek, 1978). *N. rustica* usually has a higher nicotine content, which was found to range from 4.5% to 8.6% in African samples and from 1.89 ± 0.02% to the surprising figure of 18.76 ± 2.6% in west Mexican samples (Siegel et al., 1977). Minor constituents include many other pyridine alkaloids such as anabasine, anatabine, 2,3'-dipyridyl, myosmine, nicotelline, nicotyrine and nornicotine (Wenusch, 1940; Hoppe, 1975; List and Hörhammer, 1977). In addition, very small amounts of the beta-carboline alkaloids harman and norharman have been isolated from commerical tobaccos and their smoke; the amounts in the smoke are about 0.01—0.02 mg per cigarette which is some 40—100 times greater than that in the tobacco leaf, indicating that pyrosynthesis occurs in the leaves during burning (Janiger and Dobkin de Rios, 1976).

Although practised smokers are tolerant of some of its effects, nicotine is highly toxic and acute poisoning with a dose of 60 mg may cause death within a few minutes due to respiratory failure. It acts on a variety of neuro-effector and chemosensitive sites and has both stimulant and depressant phases of action. The ultimate response of an organ or system is the product of such different and opposing effects. The central nervous system, for instance, is markedly stimulated by nicotine, but depression may follow (Wade, 1977; Rasche González, 1980; Taylor, 1980). Although smoking might contribute to mental changes (Janiger and Dobkin de Rios, 1976), and extreme acute doses of nicotine could produce hallucinations and

catatonia (Siegel et al., 1977), nicotine is not considered to be a hallucinogen from the pharmacological view (Siegel et al., 1977; Wade, 1977; Taylor, 1980). Other constituents in tobacco smoke, such as harman and norharman (Janiger and Dobkin de Rios, 1976), might be hallucinogenic per se, but all of these compounds appear to be present in such small amounts, at least in commercial tobaccos, that any suggestion of endogenous hallucinogens present in tobacco in behaviourally active amounts should be viewed with appropriate caution (Siegel et al., 1977).

Recent pharmacological studies have demonstrated that the smoking (Russell et al., 1980), snuffing (Russell et al., 1981) and chewing (Gritz et al., 1981) of tobacco all can lead to substantial blood levels of nicotine. Similar prospective experiments are not available for the oral and rectal routes of administration. After oral ingestion, the absorption of nicotine is apparently delayed because of slowed gastric emptying, so that vomiting caused by the central effect of the initially absorbed fraction removes much of the tobacco remaining in the stomach (Taylor, 1980). When injected into the rectum, tobacco might sometimes operate as a cathartic (Osol and Farrar, 1955), but in official Western medicine tobacco enemas certainly are considered obsolete because of their toxicity (List and Hörhammer, 1977). Rectal infusions prepared from 15 to 20 g of tobacco (Fabre et al., 1957) or even as low as 2 g (List and Hörhammer, 1977) are said to have caused fatal intoxications, although recovery after 15 g rectally has also been observed (Lewin, 1962). A recent case report describes nausea and confusion followed by hypotension and bradycardia due to unorthodox self-medication with an enema prepared apparently from 5—10 cigarettes (Garcia-Estrada and Fischman, 1977). In view of these data, there can be no doubt that a tobacco clyster can produce systemic effects.

Tobacco is known to affect the pharmacokinetic behaviour of many drugs, but most of these alterations appear to involve stimulation of hepatic drug metabolism by smoking and are caused probably by the polycyclic hydrocarbons present in tobacco smoke (Jusko, 1978; Dawson and Vestal, 1982; Hansten, 1982). The author is not aware of clinical studies on the combined use of non-smoked tobacco and a classical New World hallucinogen.

Peyote

Ethnological and botanical data

The ritual use of peyote among North American and Mexican Indians has been documented extensively (Furst, 1976, 1981; La Barre, 1975, 1981; Schultes and Hofmann, 1980a,b). Peyote is mostly eaten in the form of so-called "mescal-buttons", the dried tops of the cactus, which are most commonly simply taken into the mouth, softened with saliva and swallowed without mastication, but which are occasionally soaked in water to yield an intoxicating fluid (Schultes and Hofmann, 1980b). The Huichols of the

Sierra Madre in western Mexico, who are renowned for their peyote pilgrimages (Furst, 1976), use peyote in a different way. They only leave one-third of the cactus, and use either the fresh ground form or the dried ground form, whereby they masticate very much (Negrín, pers. commun.). The use of a peyote enema among the Huichols has been reported by the ethnographer Knab who was shown an enema syringe by an elderly female shaman in the community of Santa Catarina (Furst and Coe, 1977). In a personal communication to the author, Knab has given the following details: "Old men and women use a mixture of either fresh ground peyote with its juice or dried peyote mixed with water. Among the Huichols an enema is applied through a short piece of deer bone tied to a bladder. The mixture is applied by filling the bladder, tying the bone to it and sitting on the bladder". As it is unclear, whether the enema will be easily retained this way, it is unfortunate that actual use has not been witnessed. At one time, Furst (1976) suggested that the practice probably has a deeper symbolic meaning, as the sacred cactus is equated with and identified as the deer by the Huichols. On reconsideration, he suspects the reported event to have been idiosyncratic and not something to be generalized to Huichol culture, as the practice would be atypical of known Huichol behaviour (Furst, pers. commun.). This view is shared by Negrín (pers. commun.) who seriously questions the truthfulness of the enema story, since the Huichols are very puritanical and would not give such delicate information to a visitor who only stayed for a few weeks. Negrín adds that the Huichols like to reverse things (viz. rectal instead of oral administration) and like to tell scabrous jokes. There are no indications that peyote has ever been taken rectally north of Mexico (Aberle and Stewart, pers. commun.).

Peyote is a vernacular term applied to a number of plants (Bruhn and Bruhn, 1973). For the Huichols, the common source of peyote is unquestionably *Lophophora williamsii* (Furst, 1976, 1981; Knab and Negrín, pers. commun.).

Chemical and pharmacological data

The total alkaloid content of peyote has been estimated to be 3.7% for "dried upper slices of mescal buttons" and 0.41% for fresh peyote heads (Lundström, 1971), but the literature also states that mescaline, the main alkaloid in *Lophophora williamsii*, occurs in peyote to the extent of 6% (Kapadia and Fayez, 1970, 1973). A chemical study on fresh greenhouse-grown peyote revealed an average total alkaloid amount of 0.4%, consisting mainly of mescaline (30%), pellotine (17%), anhalonidine (14%), hordenine (8%), anhalamine (8%), lophophorine (5%), anhalonine (3%), *N*-methyl-mescaline (3%), anhalidine (2%), 3-demethylmescaline (1—5%) and *N*,*N*-dimethyl-4-hydroxy-3-methoxyphenylethylamine (0.5—2%). In total, more than 50 alkaloids have been isolated from peyote (Kapadia and Fayez, 1970, 1973), but Schultes (pers. commun.) may be quite right to wonder how many of these constituents are artifacts.

Mescaline is not the only peyote constituent with pharmacological activity (List and Hörhammer, 1976; Shulgin, 1977). However, the peyote tetrahydroisoquinoline alkaloids pellotine, anhalonidine, lophophorine and anhalonine are not hallucinogenic in man, even at rather high oral doses (Shulgin, 1973, 1979), and neither are the minor phenylethylamine components *N*-acetylmescaline (Charalampous et al., 1966), *N*-methylmescaline (Shulgin, 1973) and 3,4-dimethoxyphenylethylamine (Shulgin et al., 1966). There does not seem to be clinical evidence for hallucinogenic activity of any minor peyote alkaloid in naturally occurring amounts (Shulgin, 1973, 1979). Studies on certain synthetic modifications of the structure of mescaline have been more rewarding in this respect (Shulgin et al., 1969; Nichols, 1981). Consequently mescaline seems to be mainly responsible for the visual hallucinogenic properties of *L. williamsii* (Shulgin, 1979; Schultes and Hofmann, 1980b). This classical hallucinogen is usually ingested in amounts between 300 and 500 mg of the sulfate which are equivalent to 225—375 mg of the hydrochloride (Shulgin, 1979). The average oral dose needed for a minimum response has been estimated at 3.75 mg/kg, i.e. about 260 mg/70 kg (Shulgin et al., 1969). Schultes and Hofmann (1980b) warn that there is an often overlooked difference between peyote intoxication and mescaline intoxication, but so far as the author knows, the influence of minor peyote alkaloids on the effects of mescaline still needs to be properly tested in a clinical setting.

Early experiments on the fate of mescaline in man have yielded divergent results (Patel, 1968). In a less early study, a maximum of radioactivity appeared in the plasma within 3 h after the oral administration of ^{14}C-mescaline to humans; 87% of the dose could be recovered from the urine of the first 24 h, mainly as unchanged mescaline (55—60%) and its inactive metabolite 3,4,5-trimethoxyphenylacetic acid (27—30%) (Charalampous et al., 1966). According to these results, mescaline taken orally is readily absorbed from the gastrointestinal tract without undergoing extensive first-pass metabolism.

The solubility profile of mescaline (Windholz, 1976) and the reported good absorption of this hallucinogen after oral ingestion (Charalampous et al., 1966) suggest that substantial absorption can be possible after rectal application. This is a theoretical view which still awaits experimental confirmation, for in the only rectal experiment known to the author, 200 mg of mescaline in a suppository caused nothing but a dubious mydriasis (Möller, 1935).

Guayusa

Ethnological and botanical data

Indians of the South American Montaña region, such as the Jivaro (Karsten, 1935), are known to have valued *Ilex guayusa* as a ritual stimulant and

emetic (Cooper, 1949; Patiño, 1968; Schultes, 1972). Bundles of *I. guayusa* leaves have been found together with small syringes in a Tiahuanacoid medicine-man's tomb in Highland Bolivia from about 500 A.D. (Wassén, 1972b). This has raised the question of whether guayusa might have been employed as a clyster (Schultes, 1972, 1981; Furst, 1976). It should be added that the grave also contained *Nicotiana* fragments in a skin pouch (Bondeson, 1972; Bruhn et al., 1976) and that small syringes were sometimes also used for nasal application (Veigl, 1785; Métraux, 1949).

Chemical and pharmacological data

I. guayusa leaves from the grave in question were demonstrated to contain caffeine in amounts of 0.1—1%, whereas 1.8% of caffeine was present in a newly collected specimen (Holmstedt and Lindgren, 1972). This well known alkaloid is a CNS stimulant (Stephenson, 1977), which only rarely has been reported to elicit a psychotic reaction, usually after prolonged use of excessive doses (McManamy and Schube, 1936; Shen and D'Souza, 1979). Its physicochemical properties (Windholz, 1976) and its rapid appearance in the blood after oral administration (Grab and Reinstein, 1968; Robertson et al., 1978) suggest that its absorption from rectal dosage forms may well be substantial. Indeed Maier-Lenz et al. (1981), who recently compared the absorption of caffeine and other drugs from a certain multiple drug tablet and suppository called Migräne-Kranit®, did not find a large difference between the serum levels of caffeine following oral and rectal application. A recent case report describes two deaths related to unofficial therapy with voluminous coffee enemas, but these were assumed to be due to electrolyte disturbances; toxicological results in both cases indicated that not enough caffeine had been absorbed to cause a substantial toxic effect (Eisele and Reay, 1980), possibly because of the difficulty to retain the large volumes used.

Banisteriopsis

Ethnological and botanical data

The genus *Banisteriopsis* which comprises many species of tropical vines, is a major ingredient of certain intoxicating drinks taken in South American rituals (Cooper, 1949; Friedberg, 1965; Rivier and Lindgren, 1972; Schultes, 1982). Some recent sources (Furst, 1976; Emboden, 1979a) claim that *Banisteriopsis* may have been taken as a clyster, but they fail to provide an original report on such practices. The comprehensive monograph by Friedberg (1965) on the ritual use of *Banisteriopsis* does not even hint of enemas prepared from this genus. Despite the apparent lack of substantial ethnobotanical data on such dosage forms, the chemistry and still puzzling pharmacology of *Banisteriopsis* preparations is briefly discussed here.

Chemical and pharmacological data

The principal alkaloids in *Banisteriopsis* species used by natives are beta-carbolines, in particular harmine, harmaline and (+)-1,2,3,4-tetrahydroharmine (Deulofeu, 1967; Hoppe, 1975; Allen and Holmstedt, 1980). The well-studied species *B. caapi* was found to contain 0.11—0.83% of alkaloids in the stem, 0.14—0.37% in the branches, 0.28—0.70% in the leaves and 0.64—1.95% in the root. These total percentages consisted primarily of harmine (40–96%) and, to a lesser extent, of tetrahydroharmine (1–44%) and harmaline (0—17%). Small amounts of harmol, 6-methoxytryptamine and an unidentified compound were sometimes also present (Rivier and Lindgren, 1972). More recent analytical work on the same species has revealed the presence of other beta-carbolines as well: harmine-*N*-oxide, harmic acid methyl ester, harmalinic acid, harmic amide, acetyl norharmine and ketotetrahydronorharmine (Hashimoto and Kawanishi, 1975, 1976).

In a study by Pennes and Hoch (1957), harmine was hallucinogenic in mental patients at an intravenous threshold dose of 150—200 mg, which elicited visual hallucinations in 5 of 11 patients. Some other effects of these intravenous doses were also produced by oral amounts higher than 300—400 mg but it is doubtful that indisputable visual hallucinations occurred with oral amounts up to 960 mg. Naranjo (1967) found harmaline (as the HCl salt) to be hallucinogenic in volunteers at dosage levels above 1 mg/kg intravenously (70 mg/70 kg) or 4 mg/kg orally (280 mg/70 kg). In the same study racemic tetrahydroharmine elicited subjective effects similar to those of 100 mg of harmaline, when given up to the amount of 300 mg by mouth to a single volunteer. Harmine, LSD and mescaline have sometimes been stated to produce essentially similar reactions in both normal and psychotic patients (Vargas, 1959), but the volunteers of Naranjo (1967) clearly distinguished the experience with harmaline from an intoxication with mescaline.

It has not been unequivocally established why the psychoactivity of major *Banisteriopsis* constituents is largely route-dependent. Extensive hepatic first-pass metabolism certainly cannot be discarded as an unlikely cause. In rodents, harmine is extensively *O*-demethylated to harmol by hepatic microsomal enzymes (Slotkin et al., 1970; Burke and Tweedie, 1979). *O*-Demethylation is also the major fate of harmaline in rats (Ho et al., 1971). In rats, as well as in man, an intravenous dose of harmine could be recovered to about one-third from the urine, mainly as conjugates of harmol, with only traces of free harmol and unchanged harmine (Slotkin et al., 1970).

There does not seem to be a study on the rectal administration of *Banisteriopsis* alkaloids. Because of recent evidence that rectal application is not a reliable way of adequately avoiding hepatic first-pass metabolism (see the section on paricá and the like), there is no obvious reason to assume that an enema with *Banisteriopsis* alkaloids will be effective, if it contains orally inactive amounts.

Whether indigenous *Banisteriopsis* drinks, known as ayahuasca, contain mind-altering concentrations of harmine and other major *Banisteriopsis* alkaloids, is open to serious question. Chemical analysis of such drinks has demonstrated that an average native dose of 200 ml contains only 6—38 mg of harmine, 1—46 mg of tetrahydroharmine, 0—5 mg of harmaline, 0—20 mg of an unidentified *Banisteriopsis* constituent and, due to an admixture of *Psychotria* leaves, 0—32 mg of DMT (Rivier and Lindgren, 1972). The effects and pharmacokinetics of an ayahuasca beverage with harmine and tetrahydroharmine as its main constituents have been recently assessed in two volunteers (Rivier and Holmstedt, 1982). After a dose of 200 ml, plasma levels were determined by a gas chromatographical/mass spectrometric method to be in the range of 0.01 μg harmine and 0.04 μg tetrahydroharmine per ml; unfortunately these data cannot be viewed without caution because of a suboptimal internal standard (Rivier and Holmstedt, pers. commun.). It might be noted that, in a study on pure harmine, fluorometric determination revealed higher plasma levels of 0.3—0.4 μg/ml after a subhallucinogenic intravenous dose of 35- 45 mg of harmine HCl (Slotkin et al., 1970).

The presence of DMT in ayahuasca preparations is quite interesting, for the beta-carbolines in *Banisteriopsis* are known as potent reversible MAO-inhibitors (Udenfriend et al., 1958; Pletscher et al., 1959; Buckholtz and Boggan, 1977), in particular as selective inhibitors of MAO-A (Fowler et al., 1978; Fuller et al., 1981). Since there is evidence that tryptamine derivatives serve as substrates for MAO, especially for MAO-A (see the section on paricá and the like), it is not surprising that the beta-carbolines are often suggested to enhance the effects of the tryptamines (Holmstedt and Lindgren, 1967; Furst, 1976; Emboden, 1979a; Schultes and Hofmann, 1980a,b). It should be noted, however, that inhibition of degradation is not the only reported mechanism of interaction between MAO-inhibitors and DMT. In the sixties, the response to DMT (Sai-Halász, 1963), as well as that to LSD (Resnick et al., 1967), was found to be diminished by pretreatment with a non-selective irreversible MAO-inhibitor, and this phenomenon was attributed to elevation of central 5-HT levels by the MAO-inhibitor. At the moment, there does not seem to be any reference on the simultaneous activity of DMT and major *Banisteriopsis* constituents in an experimental setting, but reports on such combined use are forthcoming (McKenna and Shulgin, pers. commun.). It is to be hoped that these publications will clarify, whether or not the low amounts of these alkaloids found in ayahuasca beverages can be hallucinogenic when taken together.

Pepper

Ethnological and botanical data

Roth (1924) has included *Capsicum* in a review on narcotics and stimulants of the Guiana Indians, because the Makusi of the Rupununi used peppers as

a stimulant and excitant. Although Spix and Martius (1828) once experienced a narcotic-like action of pepper, it is not possible to draw any ethnobotanical conclusion without further field observations (Schultes, 1967a). Roth (1924) also points out that "in the Pomeroon district it is a very common practice for the Indian women to give capsicum enemata to themselves and children". Unfortunately, he fails to indicate whether the intended effect was stimulation or purgation (Heizer, 1944). The latter possibility is strongly supported, of course, by the irritating properties of *Capsicum*. According to an informant, who may or may not have been joking, the Makusi of the Roraima area use *Capsicum* to discipline children by anal insertion of the fruit as severe punishment (Gorinsky, pers. commun.). In the Guianas, pepper juice was widely used as a cure for congestion (Gillin, 1948). The Jivaro of western South America employed *Capsicum* clysters for medicinal purposes, for instance, to try to cure patients from the consequences of a snake-bite (Karsten, 1935). Among the Shuar-Jivaro, the whole *Capsicum* fruit is inserted rectally to distract from the pain of the snake-bite and also the broken fruit is rubbed on the wound itself (Van Asdall, pers. commun.).

Chemical and pharmacological data

Capsicum preparations, at least those used in official western medicine, have strongly irritating properties due to the pungent principle capsaicin (Hoppe, 1975; Wade, 1977). Perhaps it should be noted that reported minor constituents of *Capsicum* include solanine and solanide (List and Hörhammer, 1972) and that solanines are central intoxicants when taken in substantial amounts (Anonymous, 1979).

Maya enema scenes

Ethnological and botanical data

Polychrome vases and bowls of the classic Maya civilization (A.D. 300—900) not only represent artistic masterpieces of pre-Hispanic America, they also provide a rich source of information on this Mesoamerican culture (Coe, 1978; Hellmuth, 1978; Robicsek, 1978). A good example is the recent discovery of enema scenes on classic Maya pottery (Furst, 1976; Furst and Coe, 1977). According to early colonial references, the Maya employed clysters for diarrhoea and chills or for a swollen abdomen (Roys, 1976), and present-day Maya have been reported to take the purgative castor oil as an enema to treat constipation (Steggerda and Korsch, 1943). Yet the Maya enema scenes are revealing, for these paintings, in which deities and animals or humans dressed up in animal costumes, are frequent actors, undoubtedly represent rituals. Characteristic objects are the enema syringe and a specially shaped jug, which is depicted so often together with the syringe that in all probability it contained the enema (Furst, 1976; Furst and Coe, 1977). The

participants in these rituals often wear a special garment, either as a headdress or as a bib, analogous to an oyster bib (Hellmuth, pers. commun.) In one enema scene, a bib-wearer is obviously vomiting, so the bib may well be worn because of vomiting during the ritual (Hellmuth, 1978). It goes without saying that the rectal route of administration can be advantageous over the oral one, if a subject is vomiting or is going to vomit. Coe (1978) supposes that the sign for the enema ritual is a certain spiral hieroglyph and that this glyph represents an anal sphincter muscle.

The discovery of enema rituals on classic Maya pottery has led Maya specialists to believe that the ancient Maya took intoxicating enemas for ritual purposes (Furst and Coe, 1977; Coe, 1978; Hellmuth, 1978; Robicsek, 1978). This idea is quite contrary to the traditional view that the ancient Maya were a contemplative people, being more engaged in astronomical matters than in martial affairs or ecstatic rites (Furst and Coe, 1977). The Maya enema scenes certainly are reminiscent of the intoxicating rituals which have been reviewed above. Hellmuth has lately pointed out to the author that they may represent part of an intoxicating drinking ceremony rather than an isolated event (see his personal communication in the section on alcoholic beverages). A word of caution may be in order, however, especially since the enema syringes portrayed on Maya vases are usually large. If their size is realistic, it suggests an evacuation enema rather than a retention enema, i.e. ritual purification rather than intoxication.

It is not known which intoxicating enemas the Maya may have taken. Alcohol, tobacco and hallucinogens have all been proposed as possible candidates (Furst, 1976; Furst and Coe, 1977; Hellmuth, 1978; Robicsek, 1978). Maya specialists have no doubt whatsoever that the classic Maya were familiar with alcohol and tobacco (Furst and Coe, 1977; Hellmuth, 1978; Robicsek, 1978). The enema scenes themselves present some evidence to support the suggestion that these intoxicants, in particular alcohol, may have been taken rectally (see the sections on alcoholic beverages and on tobacco). The conjecture that the Maya employed hallucinogenic clysters necessitates a brief glance at some current ideas about possible Maya hallucinogens. Discussions on this subject tend to focus on mushrooms, toad poison and the water lily (Dobkin de Rios, 1974; Robicsek, 1978; Emboden, 1981a).

Data in favour of the hypothesis that the water lily *Nymphaea ampla* was a ritual Maya plant, have been recently surveyed by Emboden (1981a,b). A jaguar with water lily vegetation, either on his head or surrounding him in a cartouche, is a common motif in classic Maya vase paintings (Coe, 1978; Robicsek, 1978), and this so-called Water Lily Jaguar is sometimes present in Maya enema scenes (Hellmuth, pers. commun.). This does, of course, not prove the presence of the water lily in the enema itself. Many scholars, including Furst (pers. commun.), are quite sceptical of the idea that the ancient Maya used the water lily or toad poison as a ritual intoxicant; on the contrary, it is nearly generally accepted that this people knew hallucinogenic mushrooms (Dobkin de Rios, 1974; Robicsek, 1978). The evidence

includes linguistic findings (entries found in early Maya vocabularies relating to inebriating mushrooms), botanical findings (psilocybian mushrooms and *Amanita muscaria* found in the Maya region), and archaeological findings (mushroom-shaped stone objects found at pre-Hispanic Maya sites) (Hopkins, 1974; Furst, 1976; Mayer, 1977; Wasson, 1980). Despite these data, it would be speculative to claim that the ritual Maya enemas were prepared from mushrooms. Maya enema scenes have not yielded evidence for such a conjecture, and the vases showing these scenes originate from the central Maya area, whereas all the evidence for the ritual Maya use of mushrooms is associated with the Highlands (Hopkins, 1974; Furst, 1976; Mayer, 1977; Wasson, 1980).

The Maya flora is known to include *Datura candida* (Hopkins, 1974), but Schultes (pers. commun.) doubts very much that this tree occurred in Central America in ancient times, as all the *Brugmansia* species are South American. Toh-ku, of which the Maya made many medicines for hemorrhoids, had been identified as *Datura inoxia* (Roys, 1976), and ceramics resembling the spiny fruit of *Datura* have been found in the Maya area (Litzinger, 1981). These ceramics, however, may represent the *Ceiba* tree rather than *Datura* (Hellmuth, pers. commun.).

Chemical and pharmacological data

Pharmacological views on alcohol, tobacco and *Daturas* can be found in previous sections.

The truly hallucinogenic nature of *Psilocybe mexicana* and related mushrooms is well documented; both psilocybin which usually is the main active principle, and psilocin which may be present as well, are LSD-like hallucinogens (Schultes and Hofmann, 1980a,b; Beug and Bigwood, 1982; Young et al., 1982). The medium oral dose of psilocybin, which elicits symptoms similar to those induced by about 2 g of dried *Psilocybe mexicana*, is said to be 4—8 mg; doses of 6—20 mg evoke more profound psychic changes than doses up to 4 mg (Delay et al., 1958; Heim et al., 1958; Hofmann, 1963; Berkenbaum, 1969; Schultes and Hofmann, 1980b). Experimental data on the rectal application of *Psilocybe* alkaloids do not seem to be available. The physicochemical properties of psilocybin (Windholz, 1976) are not suggestive of a good and rapid absorption from rectal dosage forms.

The fly agaric *Amanita muscaria* is also generally classified as a hallucinogen. Its major active principles are stated to be ibotenic acid and the more potent muscimol, which is probably not a genuine constituent but an artifact formed during drying or extraction (Eugster, 1967; Wasson, 1967; Furst, 1976; Gray, 1978; Schultes and Hofmann, 1980a,b). Recent analytical work suggests that the muscimol content may decrease with time: fresh material was found to contain 0.15—0.22%, calculated on dry matter, whereas a maximum of 0.02% could be detected in 3—5-year-old samples (Stijve, 1982).

Clinical evidence for hallucinogenic activity is not so impressive as it is in the case of psilocybian mushrooms. Dry *Amanita muscaria* from California did not induce a truly visionary experience when taken by healthy individuals in an oral dose of 12 g/27 kg body wt (McDonald, 1978), and a Dutch volunteer did not experience hallucinations from doses up to five fresh caps (Plomp, 1982). Clinical data on isolated constituents are still scarce. A normal individual who tested *Amanita* components orally experienced lassitude from 20 mg of ibotenic acid, whereas 10—15 mg of muscimol induced visual and auditory disturbances, confusion and disorientation (Waser, 1967). In schizophrenic subjects, oral administration of 7—10 mg of muscimol caused exacerbations of certain psychotic manifestations, but deterioration of hallucinations was not observed (Tamminga et al., 1978). Muscimol has extreme water-solubility, but also a low molecular weight (Eugster, 1967). It is rather difficult to predict from these properties, whether or not muscimol will be absorbed well after rectal application.

Poison from the skin glands of various *Bufo* species has been demonstrated to contain bufotenin (Bonhour et al., 1967; Schultes and Hofmann, 1980b), which has been extensively discussed above (see the section on paricá and the like). Besides bufotenin, steroidal bufogenins and bufotoxins with a similar chemical structure and cardiotoxic action as digitalis or scilla glycosides may be present (List and Hörhammer, 1972; Alger, 1974; Flier et al., 1980).

Early phytochemical data on the genus *Nymphaea* have been reviewed by Hegnauer (1956). According to this survey, *Nymphaea alba* contains the non-alkaloidal compound nymphaline with digitalis-like activity, and a mixture of unstable alkaloids with hypno-sedative effects. More recently, the Old World species *Nymphaea caerulea* has been reported to alter visual and auditory perception in a single individual who twice ingested a decoction of its flower buds (Emboden, 1979b).

Little is known about the chemistry and pharmacology of *Nymphaea ampla*, the water lily of the New World (Schultes and Hofmann, 1980b). Emboden (1979a, 1981a) has claimed that apomorphine-like compounds as well as nupharine and nupharidine were found in the flowers of *N. ampla* and that aporphine could be extracted from its bulbs and roots. So far as the author knows, however, nobody but Díaz (1976) has done any analytical work on *N. ampla*, and this investigator merely isolated an unidentified alkaloid from the leaves. As to the possible psychopharmacology of *N. ampla*, Díaz (1976) first points at the presence of tetraisoquinoline, benzylisoquinoline and aporphine alkaloids in other Nymphaeaceae, and then describes the central dopaminergic activity of apomorphine, which has an aporphine structure. It should not be overlooked, however, that only aporphines like apomorphine and *N*-propylaporphine, which have an intact dopaminergic moiety in their structure, may be expected to have substantial dopaminergic activity (Pinder et al., 1971; Cotzias et al., 1976).

Note added in proof (Received October 27, 1983)

In a later publication, Díaz (1979) states that he has isolated several alkaloids from the submerged parts of *Nymphaea ampla*. He has also carried out several autoexperiences with the intact material and extracts. On one occasion, 7 g of the pulverized dried bulb were ingested and on another, an aqueous extract equivalent to 35 g of the bulb was taken. There were no detectable psychological modifications.

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