CHAPTER THREE

SOME FACTORS TO BE TAKEN INTO CONSIDERATION IN THE MULTIDISCIPLINARY APPROACH TO RITUAL INTOXICATING PLANTS

3.1. Some botanical considerations

In the multidisciplinary approach to native ritual plants, botany forms the crucial hinge between field observations and laboratory results. By providing the scientific identity of the ritual plant, botany opens the way to chemical and pharmacological studies. It goes without saying that careful botanical recording requires the collection of a herbarium voucher specimen. Any field report which does not indicate voucher specimen numbers, does not live up to modern scientific standards and may therefore be open to question. Especially in the early days, many explorers failed to do this, which usually makes it impossible to check the validity of their botanical information. However, a voucher specimen in itself is not the ultimate proof of reliability. Indigenous informants may deliberately supply wrong material, because they do not want to disclose the botanical source of their sacred drug, or because they like to pull the investigator's leg. It is, of course, not the responsibility of the natives, but that of the botanist to collect accurate data.

Original data may be obtained not only by going out into the field but also by studying already collected material. The Amerindian collections of many ethnographical museums comprise paraphernalia for ritual drug-taking, and sometimes the drug itself or its vegetal source is also present. Such materials have often been gathered by travellers who merely recorded ethnological data because they lacked specific botanical interest or training. In such cases, botanical examination may still reveal the identity of the drug source, especially if it can be backed up by the results of chemical analysis. For instance, the Museum for Ethnology in Vienna possesses well preserved paricá seeds of the Brazilian Maué Indians, who are said to have used these seeds as an enema and snuff ingredient. The seeds certainly look like Anadenanthera seeds, and this botanical impression is corroborated by the recent isolation of the Anadenanthera alkaloid bufotenin (vide 1.3). This example clearly illustrates the importance of museum material as a tool to extend our ethnobotanical knowledge on native ritual practices.

Botanical reviews on hallucinogens tend to offer relatively much information about the western hemisphere. This is hardly surprising in the case of proven hallucinogens, for nowhere in the world has the aboriginal use of truly hallucinogenic plants been more varied and extensive than in Middle and South America.

The same tendency, however, is also seen with alleged hallucinogenic plants which have not been properly evaluated by additional field studies, phytochemical analysis, and pharmacological experiments. This appears to be due not only to cultural and botanical differences between the western and the eastern hemisphere, but also to a scientific predilection for the New World. Appendix F clearly illustrates this point by providing an ethnobotanical view of ritual plants and reputed botanical intoxicants of New Guinea natives. It must be emphasized that the table has been compiled without regard to pharmacological validity and that New Guinea sorcerers commonly try to obtain a magical 'heat' or power which is unfolded or augmented by the chewing of spicy plants like ginger (Sterly 1970; Glick 1972; Wolff-Eggert 1977). In other words, certain plants in the table, such as cinnamon, curry and stinging nettles are most probably valued for their 'heating' properties rather than for specific effects on the central nervous system. Other plants, however, may ultimately be proven to have profound psychoactive effects. An interesting candidate would seem to be the Elaeagnus species, which is ritually smoked by the Gimi of the Highlands (Glick 1967). The genus Elaeagnus is rich in beta-carbolines like tetrahydroharman (Hegnauer 1966; Allen and Holmstedt 1980), and such alkaloids are not likely to be pyrolyzed during smoking (Holmstedt, pers. commun. 1983). Nothing appears to be known at present about the effects of tetrahydroharman in man, but central neurochemical changes have been observed after intraperitoneal administration to mice (Buckholtz 1979). While these data are far from sufficient to draw any conclusion, they are interesting enough to warrant closer examination.

A last specific point which should be outlined here, is a tendency in the ethnological and botanical literature to disregard pharmacological definitions of certain terms. For instance, the pharmacological literature associates systemic oral therapy with gastrointestinal absorption. Consequently it is somewhat a misnomer from the pharmacological point of view to denote coca chewing as oral administration, as this practice involves significant buccal absorption (vide 2.1.7.2). A more notable example is the custom to designate hallucinogenic plants as narcotic plants. In pharmacological parlance, the term 'narcotic' does not refer to hallucinogens, but to stupifying agents in general and to morphine-like analgesics in particular (Jaffe and Martin 1980).

3.2. Some chemical considerations

In multidisciplinary studies on ritual plants, chemistry is an important link between the botanical and pharmacological disciplines. It is difficult to speak in scientific terms of the pharmacology of psychoactive plant material until the relevant constituents have been identified and made available for pharmacological studies.

Chemical reports on ritual plants must give careful attention to the investigated material. Voucher specimens are as essential for chemical laboratory data as they are for botanical field data. The material should preferably come from the area where the plant is ritually utilized. For example, suggestions that North American Indians may have taken Acorus calamus in a ritual context, are frequently accompanied by statements that this plant has sedative properties due to its asarone fraction. Unfortunately, such statements are based on studies with samples from India. There is considerable evidence that a substantial asarone fraction cannot be expected in diploid plants of North America, but only in triploid and tetraploid specimens of the Old World (vide 2.1.1.2).

It is well known that the composition of a plant may vary with its parts. In other words, chemical research on ritual plants should include the plant parts used by the natives. Less obvious factors, which may also be relevant, include the method of harvesting and the freshness of the studied sample. For instance, the scopolamine content of a peach flowered Datura candida form varies with leaf age (Griffin 1976), and storage may alter the tryptamine spectrum of Anadenanthera peregrina seeds (Schultes et al. 1977).

Chemists should not limit their research to the botanical sources of ritual dosage forms, but they must also include the ultimate dosage forms, as the original composition may alter during preparation. For example, one step in the preparation of Virola snuffs involves concentration of the exudate to a more viscose liquid. The effect of such a treatment has been assessed in the laboratory for 6-methoxy-tetrahydroharman. This is the major alkaloid in V.cuspidata, which species could possibly serve as a snuff source. Refluxing in water for eight hours results in partial aromatization to 6-methoxy-harmalan and 6-methoxy-harman (vide 2.1.15.2).

The usefulness of chemical results clearly depends on the specificity and sensitivity of the analytical method by which they have been obtained. Illustrative are the paper chromatographical studies on tree Daturas in the sixties. Their failure

to distinguish between l-hyoscyamine and atropine is pharmacologically relevant, since atropine is the racemic mixture of active l-hyoscyamine and practically inactive d-hyoscyamine (vide 1.1.4.2). Chemical data may not only be devalued by inaccuracy of the final assay, but also by the reactivity of the workup procedure. For instance, ecgonine methyl ester is not a genuine Erythroxylum alkaloid, but an artifact arising from prolonged extraction with sulfuric acid or chloroform (Rivier 1981). Similarly, the cannabicyclol-type and cannabielsoin-type cannabinoids reported for Cannabis sativa are artificial (Turner et al. 1980).

3.3. Some pharmacological considerations

In the scientific approach to native ritual drugs, there is a clear-cut distinction between ethnological field observations and pharmacological test results (Alger 1976). All ethnological data on the psychoactivity of indigenous vegetal drugs require careful pharmacological evaluation, whereby due attention must be paid to differences between native and experimental drug administration.

From the pharmacological point of view, the best aid to enter supernatural worlds is an hallucinogenic agent. At present, there appears to be no generally applicable method for detecting hallucinogenic activity except by administering an agent to man and observing its effects. The use of a universal animal model can already be rejected on the ground that there are several classes of hallucinogens which have different effects and different mechanisms of action. Only within a specific class of closely related agents, animal testing may be useful to obtain an impression of the hallucinogenic potency in man. A plausible example is the observed correlation between the human central potency of classical anticholinergic hallucinogens like the Datura alkaloid atropine and the ability to block oxotremorine-induced tremors in laboratory animals. In the majority of cases, however, it is still too early to assess the predictive value of an animal model, or the method has already been found to have insufficient specificity (Brimblecombe and Pinder 1975). In other words, animal testing is not very useful, when a compound does not belong to a group of well established hallucinogens, and even when this is the case, the results may well be inconclusive. If a relationship with an established hallucinogenic class is lacking, animal studies can merely assess the somatic toxicity of the test compound prior to human experiments.

The type and degree of hallucinogenic symptoms depend on individual personality, mental condition, and experimental setting, and they may vary with the dose level (Szára 1961; Faillace and Szára 1968; Stark-Adamec et al. 1981). Perceptual changes are not a reliable criterium, as their origin may be peripheral rather than central, and they may be less prominent than alterations in thought and mood. Nor can these latter symptoms be used indiscriminately as a diagnostic feature, since many non-hallucinogenic drugs are known to affect mood (Schultes and Hofmann 1980b; Grinspoon and Bakalar 1981). A simple and objective criterium for hallucinogenic activity would be cross-tolerance with LSD, but this phenomenon is not observed with hallucinogens in the broader sense (Fanchamps 1978; Jaffe 1980). All in all, the classification of a new compound as a hallucinogen will depend primarily on the integrity and experienced judgement of the clinical investigator and the test subjects. Obviously, observed effects must be carefully recorded to allow comparison with future results on the same compound and with clinical data on other substances which are already recognized as hallucinogens.

Ethnological reports on the trance-inducing effects of tobacco (Wilbert 1972) attest to the fact that a ritual plant may have effects in the native which are more based on cultural preconditioning than on pharmacological activity. Methodologically, the only conclusive way to distinguish between pharmacological and psychological actions is the cross-over double-blind design. Hereby the subject receives the test drug and a dummy drug (placebo) on two different occasions, and neither the subject nor the investigator knows at the time of administration, which drug is being taken. In an experiment by Manno et al. (1974), subjects who had been given placebo cigarettes, but thought that they had received marihuana cigarettes, indicated that they were high and some became actually stimulated. Only after marihuana cigarettes had been smoked in the next testing session, did several subjects question whether they had received marihuana the first time. Hochman and Brill (1971) tested cigarettes with marihuana extracts, varying in strength from 0 mg to 7.5 mg of Δ^9-tetrahydrocannabinol (THC), in regular marihuana users. These volunteers reported the greatest intoxication from the most potent material, but they experienced a higher degree of subjective intoxication from the THC-free extract than from low-potency cigarettes. This might indicate that the THC-free extract contained some other psychoactive constituent, but it may also signify that only the

most potent extract exceeded the threshold level needed for a pharmacological intoxication. A similar pattern has been observed in a recent study on the activity of nasal cocaine in healthy recreational users of this alkaloid. Central stimulation from 0.2 mg/kg, 0.75 mg/kg and 1.5 mg/kg of cocaine HCl was compared with that from 0.2 mg/kg of lidocaine HCl as a placebo. This local anaesthetic induced a more intense 'high' than did the same dose of cocaine HCl, and it was only slightly less psychoactive than 0.75 mg/kg of cocaine HCl (Van Dyke et al. 1982). Such data show that any vegetal drug or constituent which is only mildly psychoactive in uncontrolled studies must be properly compared with a placebo. For potent principles, the placebo-controlled approach is needed to determine the pharmacological threshold level of the drug.

The validity of clinical data is not only enlarged by the inclusion of a placebo in the experimental design, but also by testing a compound in more than one subject. It should be clear that individual experimentation is one thing and that a scientific dose-response study is something else. An experiment in a single individual will seldom, if ever, provide sufficient information. This may be particularly true, when the subject is an experienced user of hallucinogenic drugs. It is well documented that non-hallucinogenic stimuli may precipitate a flashback phenomenon in individuals with a history of LSD-use (Abraham 1983).

Other relevant factors include the influence of concomitant drug use and the mental state of the test subjects. For example, the response to LSD is attenuated by pretreatment with the Rauwolfia alkaloid reserpine and accentuated by pretreatment with the monoamine oxidase inhibitor isocarboxazide (Resnick et al. 1967). It is also known that schizophrenics are less sensitive to the hallucinogenic effects of LSD than normal or neurotic individuals (Fanchamps 1978).

Another point of interest is the duration of the experimental administration. When pharmacological data do not relate to acute effects, but to symptoms of prolonged use, they should not be applied to native practices, unless there is substantial ethnological evidence that the frequency and duration of the native use are equal. For instance, alcohol can induce a psychotic syndrome in alcoholics (Jaffe 1980), but it would be absurd to extrapolate this chronic effect to non-alcoholic natives, who indulge in drinking alcoholic beverages during occasional ritual festivities.

Pharmacological data are mostly not obtained by testing the

whole indigenous dosage form via the indigenous route of administration. Most experiments are performed with isolated constituents, which may be taken in another dose and by another route of administration. Such differences between experimental and native drug uses must be given careful consideration.

It must be verified that the amount of active constituent, which is present in the usual native dose, exceeds the threshold level observed in the pharmacological experiment. Obviously, a native dose will be limited by the somatic toxicity of the active constituents, and the dose problem will be especially relevant for trace components, which occur next to a potent major principle. For instance, among the numerous identified constituents of tobacco smoke, there are various compounds with suspected hallucinogenic properties, such as carbon dioxide, myristicin, nitrous oxide, and beta-carbolines, and there are also hydrocarbons and ketones with deliriant effects. However, 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 Nicotiana in behaviourally active amounts must be viewed with appropriate caution (Siegel et al. 1977). Another example is the presence of beta-carbolines in Virola species. Since such compounds have monoamine oxidase inhibiting properties, it is sometimes suggested that they prevent the degradation of hallucinogenic tryptamines, which are the main alkaloids in indigenously utilized Virola species. However, the trace amounts in which the Virola beta-carbolines occur, are unlikely to be of pharmacological importance (vide 2.1.15.2).

It must be checked whether there are pharmacological data on the activity via the native route of administration. The difference between oral ingestion in the aboriginal ritual and parenteral injection in the clinical setting could be of particular importance. Some drugs, such as quaternary ammonium compounds, show a poor absorption from the gastrointestinal tract because of their low lipid solubility. Other drugs are inactivated by the acid gastric juices or undergo elimination by intestinal or hepatic enzymes before they reach the general circulation. This last phenomenon, which is commonly known as first-pass metabolism, is observed with many drugs, including the opium alkaloid morphine (Routledge and Shand 1979). A parenterally active amount will only be effective via the oral route, when the drug is absorbed, and is not degraded prematurely. In general, centrally active compounds can be expected to be absorbed well, since passage into the brain and absorption from the gastrointestinal tract are both processes

which require sufficient lipid solubility. Consequently poor absorption of hallucinogenic principles would not appear to be a general problem, although exceptions might occur. There is substantial evidence to suggest, however, that first-pass inactivation is not uncommon for naturally occurring hallucinogens. Extensive metabolism and route-dependent activity have been reported for the tryptamine derivative dimethyl-tryptamine, for the beta-carbolines harmine and harmaline, and for the tropane alkaloid scopolamine (vide 1.1).

Among the native inhabitants of the western hemisphere, oral ingestion is certainly not the only way to elicit ritual intoxication. Major non-oral ways are rectal application (vide chapter one), snuffing (vide chapter two), and smoking (vide Appendix G). Rectal administration is not generally an adequate method to avoid first-pass metabolism, but nasal administration can undoubtedly provide a bypass, and this may also apply to smoking. As to the last way of administration, the picture is complicated by the possibility that the developing heat may destroy existing components (pyrolysis) and may form new ones (pyrosynthesis). For instance, the beta-carbolines harman and norharman in tobacco smoke are largely formed during smoking (Janiger and Dobkin de Rios 1976), whereas the Δ^9-tetrahydro-cannabinol present in a marihuana cigarette only partially survives the burning process (Ohlsson et al. 1980; Turner 1980). Another Indian practice which may lead to a direct passage into the sytemic circulation is the holding of a chewing quid between the gum and the cheek or lip (Wilbert 1975; Plowman 1981b). This is not a pure method to avoid first-pass metabolism, however, when the juice or the plant material is swallowed (vide 2.1.7).

The substantial influence of drug absorption, distribution and elimination on drug action has long been recognized by pharmacologists, who have even devoted a special part of their discipline, viz. pharmacokinetics, to the investigation of such processes. On analogy, ethnopharmacology deserves a branch called ethnopharmacokinetics, which must be aimed at the fate of indigenous drug constituents in the body. This branch must assess whether adequate concentrations of native drug principles are reached and sustained at their appropriate sites of action. In practice, it is quite laborious or even impossible to perform direct measurements at a specific site of action in the human body. Instead, most pharmacokinetic studies perform measurements in a readily accessible body fluid, such as blood, urine or saliva. Although monitoring at these convenient sites has its limitations, it has proved to be very useful in many

cases (Rowland and Tozer 1980). A good ethnopharmacokinetic example is the recent demonstration of substantial cocaine plasma levels in coca chewers (Holmstedt et al. 1979; Paly et al. 1980), which puts an end to speculations that cocaine might be hydrolyzed in the mouth before it is absorbed (vide 2.1.7.2).

The pharmacological activity of a naturally occurring mixture may be different from that of the most active isolated constituent or fraction. Classical in this respect are the rabbit studies by Hijmans (1961) on the expectorant effects of thyme herb, ipecacuanha root, and Allium cepa. This investigator was able to demonstrate that different fractions derived from the same plant were more secretolytic in combination than alone. An interesting experiment on the difference between a crude hallucinogenic preparation and a pure active constituent has been performed by List et al. (1969), who measured the permeation of l-hyoscyamine through the isolated small intestine of the rat. When an aqueous solution with pure l-hyoscyamine was compared with a fresh extract of Atropa belladonna leaves, the permeation rate was found to be 70-80% higher in the case of the extract. As it is difficult to assess the clinical significance of this in vitro result, it is unfortunate that the experiment was not followed by an in vivo investigation.

The most striking example of superiority of a whole native dosage form over its isolated principles may well be the South American beverage ayahuasca, containing mostly Banisteriopsis beta-carbolines like harmine, together with dimethyltryptamine from Psychotria. Although conclusive clinical evidence has not been published, there is growing evidence to suggest that the beta-carbolines may protect the dimethyltryptamine from first-pass inactivation by monoamine oxidase A enzymes, thus rendering the tryptamine derivative less inactive orally (vide 1.1.3.2).

The activity of a constituent may also be modified by other components of the native dosage form, which do not have a systemic action by themselves. Many South American tribes prepare their intoxicating snuffs by mixing psychoactive vegetal ingredients with lime or plant ash. Such alkaline admixtures may facilitate the absorption of the psychoactive alkaloids through the nasal mucosa (vide 2.2.1).

It is clear from these data that the influence of accompanying substances should not be neglected, but it should not be exaggerated either. Hofmann (1982) gave some pills with pure psilocybin to the famous Mexican curandera Maria Sabina who attested that there was no difference in efficacy between the pills and her own psilocybian mushrooms. In contrast with this

report, some ethnological and botanical publications tend to overemphasize the difference between isolated constituents and whole native dosage forms. This may even reach the point where vegetal constituents are assumed out of hand to act in a synergistical manner. It should always be borne in mind, however, that antagonism may also occur, and in many cases the effects will be additive rather than synergistic. For example, Heimann (1965) showed that a mixture of the ololiuhqui constituents d-lysergic acid amide, d-isolysergic acid amide and lysergol in healthy volunteers merely elicits the combined symptoms of each separate alkaloid.

The pharmacological view on hallucinogenic drug rituals must not only consider the influence of accompanying ingredients in the aboriginal dosage form, but also the concomitant use of other separate drugs. This is well illustrated by the clinical finding that alcohol adds significantly to the subjective effects of marihuana smoking (Manno et al. 1974). As is the case with single drugs, folkloristic data on combinations should not be accepted without experimental confirmation. In India, the tamarind fruit is reputed to antagonize the effects of bhang (Cannabis), but Hollister (1976) found the fruit to be ineffective in doses up to 180 g, when it was given an hour before, simultaneously, or an hour after administration of Δ^9-tetrahydrocannabinol orally to man.

3.4. Concluding remarks

Many factors which have been discussed here, are so obvious that it may seem superfluous to review them. Nothing is less true, however, for various publications fail to afford them proper attention. Perhaps the most poignant example why they should never be overlooked is the famous case of the reports by Castaneda (1970, 1972). This author described the use and hallucinogenic effects of a smoking mixture consisting of dried mushrooms with the addition of other dried plants as sweeteners. The mushrooms were vaguely suggested to be a Psilocybe species, possibly P.mexicana. There are substantial scientific reasons to believe that these reports are not authentic, but fictional. For instance, there are no voucher specimens, and the suggestion that these mushrooms could have been P.mexicana must be refuted on the basis of their habitat (de Mille 1980). What is more, the smoking mixture is unlikely to have contained sufficient psilocybin to elicit the profound effects described by Castaneda. In addition, psilocybin is said to be largely degraded during smoking in a

pipe, whereby its availability is further reduced by condensation and deposition on the inner surface of the bowl and stem of the pipe (Siegel 1981). In other words, if proper attention had been given immediately to dose and to way of administration, scientific doubts about the authenticity of Castaneda's accounts would have arisen sooner.

On the other hand, it may also be hazardous to dismiss field data too rapidly as being invalid. This might be illustrated by an early claim that the South American Makusi Indians used Capsicum as a stimulant and excitant (Roth 1924). Since the fruits of most Capsicum forms contain the very pungent principle capsaicin (Hegnauer 1973), I was inclined to conclude that a native Capsicum preparation will not produce any psychoactive effect, but merely extreme local irritation. This idea was somewhat unsettled, however, by the following passage in a 19th century account of travels in Brazil by the German scientists Spix and Martius (1828): 'Auf der Tafel des gastfreien Pfarrers von Chapada fanden wir eine kleine Art von spanischem Pfeffer (Malaqueta), welche hier zu Lande, wie in ganz Brasilien, nebst der kleinen grünen sauren Citrone (Limâo acedo) das gemeinste Gewürz ist, und sich in reinlichen Porcellanschaalen schon durch die schönrote Farbe empfiehlt. Ihr Genuss brachte aber, obgleich die Früchte nicht auffallend scharf waren, uns Beiden die übelste Wirkung: plötzliche Kopfschmerzen, Schwindel, Flimmern vor den Augen und alle Zeichen einer narkotisch-scharfen Vergiftung; doch verschwanden diese Symptome alsbald nach dem Einziehen von Essigdampf in die Nase und einigen Löffeln Essigs innerlich genommen. Weder früher, noch später im Verlaufe der Reise, wo wir diess Gewürz mit Vorliebe gebrauchten, erfuhren wir ähnliche Wirkung desselben. Es ist deshalb wahrscheinlich, dass sich bisweilen das sogenannte Capsicin, welches der Frucht die brennende Schärfe ertheilt vorherrschend in derselben entwickeln könne, während in andern Fällen, wie in den unsrigen, das narkotische Alkaloid entschiedener hervortritt, das den säurefähigen Basen in andern Solaneen, dem Atropin, Daturin, Hyoscyamin u.s.w., entspricht. Welche äussere Verhältnisse zu dieser Verschiedenheit disponieren, verdiente eine genaue Untersuchung'. This report does certainly not provide proof that South American Indians could have valued Capsicum for psychoactive properties, as the uncommon reaction to the malaqueta might have been due to infestation with a toxin producing fungus (Hegnauer, pers. commun. 1984). Yet it shows the risk of dismissing such a possibility off-hand.