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HALLUCINOGENIC AGENTS

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also contains the hallucinogen 3,4-methylenedioxyamphetamine (Bocher and Naranjo, 1969). Ibogaine has been placed in the same category as LSD and other hallucinogens by the U.S. Food and Drug Administration (Farnsworth, 1968).

There appear to be no detailed reports in the literature regarding the psychic effects of ibogaine in man, and the only iboga alkaloid to be so studied is the related ibogaline (Schmid, 1967). Oral doses of 0.1-1.2 mg./kg. of ibogaline hydrochloride produced a state of intoxication and mild sedation without any pronounced productive symptomatology and in the absence of profound changes in mental state usually associated with hallucinogenic drugs. In only 5 of 12 subjects were psychic changes observed, with visual hallucinations and changes in perception of a relatively minor nature. The contrast between this report and the cultic use of *Tabernanthe iboga* suggests that one of the other alkaloidal constituents of the plant may be the active hallucinogen or that the doses of 10-105 mg. used by Schmid are inadequate. *Tabernanthe iboga* can contain up to 6 per cent of iboga alkaloids and it is clear that the West African native can ingest very high oral doses of these compounds if the root is chewed for a sufficiently long time.

The iboga alkaloids are long overdue for a detailed examination of their psychic effects in man. It is interesting that simplification of the iboga structure to give the hexahydroazepino[4,5-b]indoles (for example, 4.42) enhances the tryptamine-like properties, at least as far as tremorogenic activity is concerned, but also enhances the sedative effects. Thus, these compounds have chlorpromazine-like properties in both man and animals (Hester, Tang, Keasling, and Veldkamp, 1968).

IV. LYSERGIC ACID DERIVATIVES

1. OLOLIUQUI

Constitution

The history of the Mexican magical drug ololiuqui is bedevilled by controversy (Hoffer and Osmond, 1967). Though correctly placed in the *Convolvulaceae* as early as 1854 and identified as *Rivea corymbosa* in 1897, the erroneous but dogmatic view of Safford (1915) that ololiuqui was a species of *Datura* prevailed for no better reason than that 'it is not known that any of the *Convolvulaceae* are narcotic, though many of the *Solanaceae* are'. Schultes (1941) finally settled the botanical issue, but doubts were revived by the inability of

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Kinross-Wright (1959) to repeat the self-experiments of Osmond (1955) with the seeds of *Rivea corymbosa*. Hofmann's subsequent isolation from ololiuqui of derivatives of lysergic acid (Hofmann and Tschertter, 1960), previously found only in fungi, was met with a state of disbelief bordering on accusations of scientific fraud. Nevertheless, it is now accepted that both *Rivea corymbosa* and *Ipomoea*

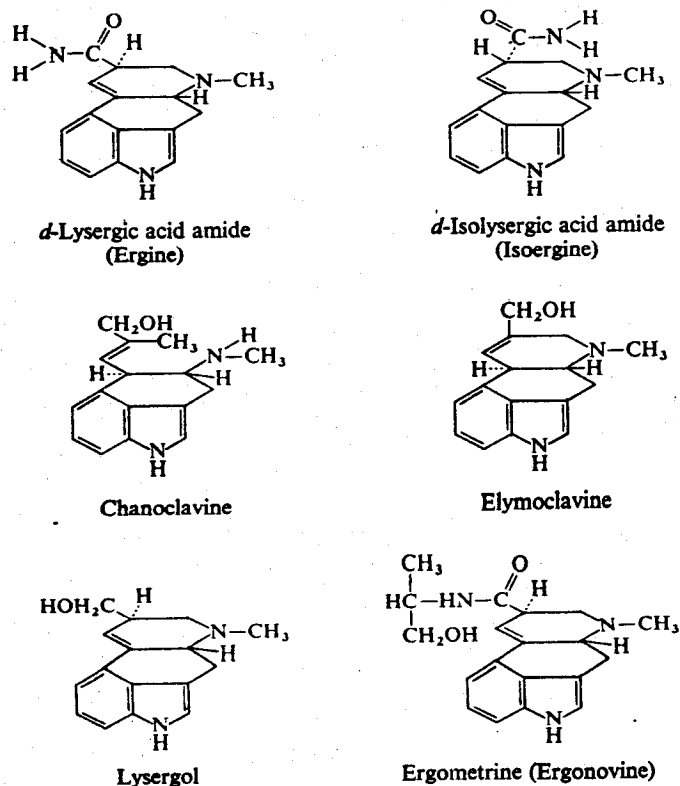


Fig. 4.3.—Derivatives of lysergic acid found in *Rivea corymbosa* (ololiuqui) and *Ipomoea violacea* (badoh negro).

violaceae, from which are prepared the magical drugs ololiuqui and badoh negro respectively, contain a number of indoles related to the ergot alkaloids (Fig. 4.3).

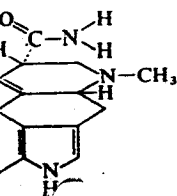
d-Lysergic acid amide (ergine) is the major constituent of the seeds of both *Rivea corymbosa* and *Ipomoea violacea*, together with smaller amounts of *d*-isolysergic acid amide (isoergine), chanoclavine, elymoclavine, and the *N*-(1-hydroxyethyl)amides of lysergic and

isolysergic acid. The ergot alkaloids are also found in the ergot of *Claviceps purpurea* (Taber, 1963). The ergot alkaloids are also found in the ergot of *Claviceps purpurea* (Taber, 1963). The ergot alkaloids are also found in the ergot of *Claviceps purpurea* (Taber, 1963).

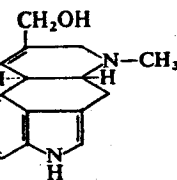
Pharmacology

The first ergot alkaloid to be isolated was ergometrine (about 1900) down with a dose of 1 mg. It is a powerful hypnagogic and produces feelings of drowsiness rapidly. The hangover results in the ololiuqui alkaloid (Isbell and Lubin, 1960) even in doses of 1 mg. It is used to induce the detachment of the placenta from the uterine wall.

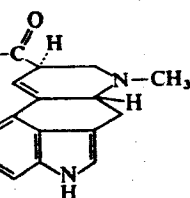
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isolysergic acids. Lysergol is found in *Rivea* but not in *Ipomoea*, while ergometrine (ergonovine) is present in the latter but not the former (Hofmann and Tschertter, 1960; Hofmann, 1961b, 1964; Hofmann and Cerletti, 1961; Gröger, 1963). The alkaloids are present in the embryo but not in the seed coat of these species and have not arisen by fungal contamination (Taber and Heacock, 1962), but they are also found in some vegetative tissues such as the leaves and stems (Taber, Heacock, and Mahon, 1963; Taber, Vining, and Heacock, 1963). The total alkaloid content of *Rivea* seeds is about 0.012 per cent, rather less than that (0.06 per cent) in *Ipomoea*, which may explain the reputedly greater potency of badoh negro over that of ololiuqui. The constituents of these convolvulaceous plants were not new even in 1960; the isomeric lysergic acid amides had previously been obtained as cleavage products by hydrolysis of the ergot alkaloids (Smith and Timmis, 1932, 1936), while chanoclavine (Hofmann, Brunner, Kobel, and Brack, 1957) and elymoclavine (Abe, Yamano, Kozu, and Kusumoto, 1955) had been isolated from ergot. Lysergol, ergometrine, and the isomeric amides had also been synthesized in the laboratories of the Sandoz group (Stoll, Hofmann, and Schlientz, 1949).

Pharmacology

The first carefully controlled experiments with ololiuqui were those of Osmond (1955). Self-administration of 60–100 *Rivea* seeds (about 1 mg. of total alkaloid), which were pulverized and washed down with water, produced anergia and irritable apathy combined with a degree of heightened visual perception and an increase in hypnagogic phenomena, eventually leading after about 4 hours to feelings of calm, alertness, and relaxed well-being. Effects appeared rapidly (within 20 minutes) but were of short duration and left no hangover. Kinross-Wright (1959) was unable to reproduce these results in volunteers, possibly because of inadequate preparation of the ololiuqui seeds with subsequent poor absorption of the active alkaloids. Nevertheless, two recent studies in former opiate addicts (Isbell and Gorodetzky, 1966) and normal subjects (Heim, Heimann, and Lukacs, 1968) suggest that ololiuqui is not a true hallucinogen even in doses as high as 5 mg. of total alkaloids and does not produce the typical alterations in perception and consciousness associated with mescaline and LSD. Drowsiness, apathy, and mental detachment seem to be the major effects of either crude extracts of ololiuqui or of synthetic alkaloid mixtures, both of which contain a strong sedative component in their central actions. Heim and his colleagues concluded that the heavy intoxication with

reduced consciousness and autonomic side-effects produced by large doses of ololiuqui was similar to that encountered in toxic psychoses resulting from the action of drugs like ibogaine and scopolamine.

It is clear that the pharmacologically active constituents of ololiuqui are the isomeric lysergic acid amides. Intramuscular doses of 0.5 mg., or larger oral doses, of *d*-lysergic acid amide produce apathy, decreased motor activity, and tiredness, culminating in a clouding of consciousness (Solms, 1956; Hofmann, 1963b). Oral doses of 2 mg. of isolysergic acid amide are reported to produce a feeling of mental emptiness and total detachment from the outside world. Heim and his colleagues suggest that the overall effects of ololiuqui are due to these two compounds, the *d*-lysergic acid amide giving intoxication with strong autonomic side-effects and the *d*-isolysergic acid amide producing some euphoria, synaesthesia, and altered time experience. Certainly elymoclavine, lysergol, chanoclavine, and ergometrine produce no psychic changes in man (Isbell and Gorodetzky, 1966; Hofmann, 1968), though the first two do produce central excitation in animals (Yui and Takeo, 1958). Moreover, the time-course of absorption and distribution of *d*-isolysergic acid amide in rat brain exactly paralleled the course of behavioural aberrations produced by intraperitoneal doses of 5 mg./kg. (Vogel, Carapellotti, Evans, and Der Marderosian, 1972).

It is possible that other constituents of ololiuqui may possess central actions. Thus, glucosides have been isolated which are five times as potent as central stimulants as the crude alkaloid extracts of *Rivea corymbosa* (Cook and Kieland, 1962; Perezamador, Jiminez, Herren, and Flores, 1964). However, Hoffer and Osmond (1967) report that they produced only sedative and narcotic effects upon self-administration at doses of 5 mg. (p.o.).

The derivatives of lysergic acid present in ololiuqui are widely distributed throughout the *Ipomoea* and other convolvulaceous species (Der Marderosian, 1967). Their presence in the seeds of ornamental Morning Glories has led to considerable self-experimentation with these potential hallucinogens which bear no legal restriction on their use. Though there has been no systematic psychopharmacological investigation of these plants, several cases of morning glory seed intoxication have been reported in the United States (Cohen, 1964; Ingram, 1964; Fink, Goldman, and Lyons, 1966; Whelan, Bennett, and Moeller, 1968). One was serious enough to provoke suicide and several required hospitalization; the danger has been underlined that latent psychoses can be activated by excessive ingestion of the seeds. The subjects reported autonomic effects such as nausea, flushed skin, extremely dilated pupils, low

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blood-pressure, and increased pulse-rate, following ingestion of 150–300 seeds. Hallucinations and visions were occasionally present, but the chief psychic changes were apathy and concern with the reality of people and objects. The unpleasant nature of the psychic changes produced by Morning Glory seeds makes it unlikely that they will be used widely as intoxicants, particularly since Der

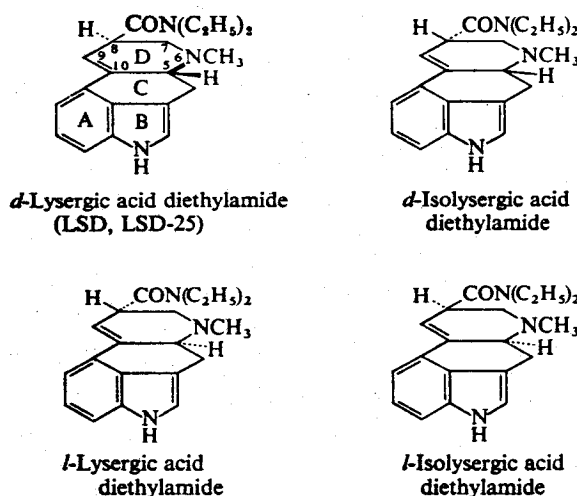


Fig. 4.4.—The four stereoisomers of lysergic acid diethylamide. Only LSD produces psychic effects in man.

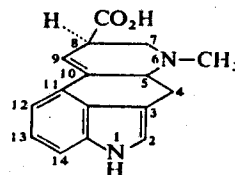
Marderosian has pointed out the possibility of ergot poisoning if large doses are taken. Five-hundred seeds of certain ornamental *Ipomoea* varieties contain as much as 1 mg. of ergometrine, which is usually considered to be an effective oxytocic in doses as low as 0.2–0.5 mg.

2. LYSERGIC ACID DIETHYLAMIDE

Structure-Activity Relationships

d-Lysergic acid diethylamide (LSD, LSD-25) does not occur in nature. It was produced synthetically by a process analogous to that used to prepare ergometrine and other amide derivatives of lysergic acid (Stoll and Hofmann, 1943). The original synthesis used hydrazine to cleave ergot alkaloids to lysergic acid hydrazide, which was treated with nitrous acid to give an azide followed by acylation of

Table 4.3.—COMPARATIVE HALLUCINOGENIC POTENCIES IN MAN OF DERIVATIVES OF D-LYSERGIC ACID*



Compound	Dose equivalent to 1 µg/kg. (p.o.) of LSD	Potency relative to LSD = 100	LSD-like Psychic Effects	Quicker (Q), or Slower (S) Onset than LSD	Longer (L) or Shorter (S) Duration than LSD
AMIDES					
Diethylamide (LSD)	1.0	100	—	—	—
<i>l</i> -lysergic acid diethylamide	> 70	0	No	—	—
<i>d</i> -isolysergic acid diethylamide	> 50	0	No	—	—
Dimethylamide†	10	10	Yes	Q	S
Monoethylamide	20	5	Yes	Q	S
Pyrrolidide	10	10	Yes	—	S
Morpholide	9	11	Yes	—	S
1-and-2-SUBSTITUTED COMPOUNDS					
1-methyl, diethylamide	3	33	Yes	S	S
1-acetyl, diethylamide	1	100	Yes	—	—
2-bromo, diethylamide	> 86	< 2	Partial	—	S
1-methyl-2-bromo, diethylamide	> 175	< 1	No	—	—
1-methyl, monoethylamide	25	4	Yes	Q	S
1-acetyl, monoethylamide	15	7	Yes	Q	S
1-methyl, pyrrolidide	> 20	< 5	Partial	Q	S
MISCELLANEOUS					
<i>d</i> -2,3-dihydrolysergic acid diethylamide	8	12.5	Yes	S	L
<i>d</i> -9,10-dihydrolysergic acid diethylamide	> 50	0	No	—	—

1-and-2-SUBSTITUTED COMPOUNDS

1-methyl, diethylamide	3	33	Yes	S	S
1-acetyl, diethylamide	1	100	Yes	—	—
2-bromo, diethylamide	> 86	< 2	Partial	—	S
1-methyl-2-bromo, diethylamide	> 175	< 1	No	—	—
1-methyl, monoethylamide	25	4	Yes	Q	S
1-acetyl, monoethylamide	15	7	Yes	Q	S
1-methyl, pyrrolidide	> 20	< 5	Partial	Q	S

MISCELLANEOUS

<i>d</i> -2,3-dihydrolysergic acid diethylamide	8	12.5	Yes	S	L
<i>d</i> -9,10-dihydrolysergic acid diethylamide	> 50	0	No	—	—
<i>d</i> -9,10-dihydro-10-hydroxylysergic acid diethylamide (Lumilysergic acid diethylamide)	> 50	0	No	—	—
<i>bis</i> -2,2'-(<i>d</i> -lysergic acid diethylamide) disulphide	> 50	0	No	—	—

*Compiled from Isbell, Miner, and Logan, 1959; Gorodetzky and Isbell, 1964; Hofmann, 1968.

†Rothlin (1957b) states that this compound is inactive at doses of 50 µg./kg., and reports similar negative results for the monomethyl, and the mono- and di-propyl and butyl amides of *d*-lysergic acid.

dimethylamine. The method is not stereospecific and requires chromatographic separation of isomeric compounds, but it was used to prepare most of the amides of lysergic acid discussed in this section. The most advantageous procedure for the preparation of LSD is to treat *d*-lysergic acid with sulphur trioxide in dimethylformamide at low temperature followed by reaction with dimethylamine and hydrolysis; the yield is virtually quantitative, the entire reaction takes less than an hour, and the product is a single isomer (Garbrecht, 1959).

Studies of structure-activity relationships have tended to concentrate on the *d*-lysergic acid series, because its diethylamide is the only one of the four possible stereoisomers (Fig. 4.4) which produces profound psychic changes in man (Rothlin, 1957a, b; Isbell, Miner, and Logan, 1959; Hofmann, 1968). However, synthetic difficulties have precluded any route which does not involve the preformed lysergic acid skeleton, and molecular modifications of LSD are limited to manipulation of this skeleton. They include, in addition to variations in the spatial arrangements at C-5 and C-8, variations in the acid amide residue, saturation of the double bonds at C-9/C-10 or C-2/C-3, and substitution of the indole ring system at C-1 and C-2 (Table 4.3).

Of all the possible changes that have been made in the LSD molecule, only two, acetylation or methylation of the indolic imino group, have yielded compounds of comparable potency to the parent hallucinogen (Table 4.3). Their high activity may well be due to the ease with which they are converted to LSD, particularly hydrolysis of the *l*-acetyl derivative. Various attempts to simplify the LSD structure by breaking it down into molecular fragments have, with the exception of the tryptamines, generally led to profoundly deleterious effects on the hallucinogenic activity (Campaigne and Knapp, 1971). One other compound of interest is *d*-2,3-dihydrolysergic acid diethylamide, which is from one-sixth to one-eighth as potent as LSD but with a slower onset and a longer duration of action; it is not known whether this reflects *in vivo* dehydrogenation to LSD (Gorodetzky and Isbell, 1964). The general trend of hallucinogenic activity in man parallels that of sympathetic stimulation in animals (Hofmann, 1968). Those compounds which are most effective in man are also effective in producing mydriasis, piloerection, salivation, hyperthermia, and other signs of excitation in animals. There is little correlation between hallucinogenic potency in man and antagonism to 5-hydroxytryptamine in animals or *in vitro*, where compounds with high anti-5HT activities can be either poor (for example, 2-bromolysergic acid diethylamide) or potent (1-methyllysergic acid diethylamide) hallucinogens.

Table 4.4.—ACTIVITY OF LSD COMPARED TO OTHER HALLUCINOGENS*

Compound	Approx. Effective Dose (p.o.) (Man)†	ED ₅₀ (i.p.) Size Discrimination (Squirrel monkey)‡	ED ₅₀ (i.p.) Production of Swimming Latency (Rats)§	ED ₅₀ (s.c.) Production of Head Twitches (Mice)	Approx. Dose (i.v.) for 1° rise in Rectal Temperature (Rabbits)
LSD	0.0004 (0.1)	0.15	1.9	0.14	0.006
Psilocybin	0.6 (12)	2.9	8.7	4	0.12
DOM**	0.34 (5)	2.9	9.5	—	0.2
Mescaline	27 (400)	82.2	>31	45	344

*All doses are in μ moles/kg.

†Figures in parentheses are total oral doses (mg.) in man.

‡From Uyeno, 1969.

§From Uyeno, 1968, 1971.

||From Corne and Pickering, 1967.

¶From Horita and Hill, 1973; Aldous and others, 1974.

**DOM is 2,5-dimethoxy-4-methylamphetamine.

specific and requires compounds, but it was ergic acid discussed in re for the preparation ar trioxide in dimethyl- reaction with dimethyl- quantitative, the entire duct is a single isomer

have tended to con- its diethylamide is the (ig. 4.4) which produces alin, 1957a, b; Isbell,). However, synthetic does not involve the cular modifications of keleton. They include, ements at C-5 and C-8, on of the double bonds the indole ring system

een made in the LSD on of the indolic imino arable potency to the a activity may well be ed to LSD, particularly s attempts to simplify o molecular fragments s, generally led to pro- nic activity (Campaigne of interest is *d*-2,3- from one-sixth to one- er onset and a longer er this reflects *in vivo* bbell, 1964). The general els th. of sympathetic hose compounds which in producing mydriasis, other signs of excitation hallucinogenic potency amine in animals or *in* activities can be either diethylamide) or potent no gens.

Pharmacology

Since the accidental discovery by Hofmann in 1943 of the extraordinary psychic changes produced by LSD, an extensive literature has built up dealing with its effects in animals and in both normal and mentally ill human subjects. It is beyond the scope of this section to list them all, and readers are directed for comprehensive coverage to the relatively modern books of Hoffer and Osmond (1967) and Efron (1968), and the review of Cohen (1971). The sheer breadth of investigations with LSD is indicated by its binding to DNA (Yielding and Sternglantz, 1968), its lethal effect at 297 mg. (i.m.) in the elephant (West, Pierce, and Thomas, 1962), its production of a nose-up tail-down position in the Siamese fighting fish (Gettner, Rolo, and Abramson, 1964), and the correlation of hallucinogenic potency in lysergic acid derivatives with motility in liver flukes (Beernink, Nelson, and Mansour, 1963). It seems that no stone has been left unturned.

The original dose of LSD taken by Hofmann in 1943 was 250 µg. (Hofmann, 1961a), although the effective oral dose for the production of psychic phenomena in normal subjects is 0.5–1.0 µg./kg. Amounts as low as 0.02 µg./kg. can induce discernible effects in most individuals, and as much as 10 mg. has been ingested without fatal outcome (Cohen, 1971); recent reports (Tijo, Pahnke, and Kurland, 1969) give 50 µg. as a low dose and 450 µg. as a high dose. These doses produce, in varying degrees, the classical changes in mood, thought, and perception described in Chapter 1. LSD is therefore the most potent hallucinogen, and indeed one of the most potent drugs of any type, known to man; the general trend of potency between LSD, psilocybin, DOM, and mescaline is reproduced in a variety of animal behavioural tests (Table 4.4).

In addition to the psychic phenomena, LSD produces hyperflexia, nausea, tremor, muscular weakness, hyperthermia, and, most commonly, mydriasis. Peripheral and autonomic effects are normally insignificant in man at the hallucinogenic dose levels, but animals

Table 4.5.—TOXICITY OF LSD IN VARIOUS SPECIES (after Cohen, 1971)

Animal	Body-weight (kg.)	LD ₅₀ (mg./kg.)	Brain Weight (g.)
Mouse	0.035	46 (i.v.)	0.5
Rat	0.5	16.5 (i.v.)	1.7
Rabbit	3.5	0.3 (i.v.)	85
Man	70	0.2 (p.o.)*	1400
Elephant	4500	0.15 (i.m.)*	3600

*Estimated values.

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usually respond with a syndrome of general excitation including prominent hyperthermia, piloerection, mydriasis, and salivation. Death can result from respiratory failure if high doses of LSD are given to animals but the therapeutic ratio is high, with the LD₅₀ for man being estimated to be about 14 mg. (Hoffer and Osmond, 1967). The degree of toxicity varies widely with the species, the rabbit being particularly sensitive, and seems to correlate rather better with brain than with body weight (Table 4.5).

In chronic experiments, rats tolerated 2.5 mg./kg. (i.v.) daily for 30 days with no development of cumulative effects or of tolerance (Hofmann, 1968). Nevertheless, tachyphylaxis develops rapidly to the psychic effects of LSD in man, with complete tolerance within a few days. Cross-tolerance occurs between all members of the lysergic acid series, and between LSD, mescaline, and psilocybin; both tolerance and cross-tolerance are lost within a few days of discontinuance of the hallucinogenic drug (Brawley and Duffield, 1972). It is interesting to note that mice can be immunized against the effects of intravenous LSD by treatment with a protein derivatized with lysergic acid, suggesting the possible involvement of antibody production in the mechanism of tolerance (Voss and Berger, 1972).

Absorption and Metabolism

LSD is equally effective whatever the route of administration, although it is normally taken by mouth in the form of tablets or aqueous solutions of its tartrate salt. The onset of symptoms varies with the route, oral administration producing effects within 30-90 minutes, intramuscular injection within 10 minutes, and intravenous injection within a few minutes. Three methods have been used to study the distribution of LSD, based respectively on bioassay of its antagonism to the action of serotonin (Lanz, Cerletti, and Rothlin, 1955), radioactive assay of ¹⁴C-labelled LSD (Stoll, Rothlin, Rutschmann, and Schalch, 1955), and spectrofluorometric estimation of its concentration in tissue extracts (Axelrod, Brady, Witkop, and Evarts, 1957). The accuracy of the last can be improved to detect LSD levels in man as low as 1-2 ng./ml. by irradiating half of the extracts with ultraviolet light prior to fluorometric estimation; this treatment catalyzes the hydration of LSD to the non-fluorescent lumi-LSD giving an effective blank (Upshall and Wailing, 1972). The same results are obtained by all three methods of estimation.

LSD is rapidly absorbed from the gastrointestinal tract and disappears quickly from the blood to be assimilated into most of the tissues. It is almost completely metabolized in the body, chiefly in the liver, from whence it is secreted in the bile and excreted via the gut, with negligible amounts of unchanged drug being found in the urine

or faeces. The half-life in rodents is less than 10 minutes, but rats and mice show an enormous capacity to deal with LSD and may be considered to be in a state of almost permanent tolerance; in the cat and monkey the half-life is 130 minutes and 100 minutes respectively. In man the rate of disappearance of LSD from plasma as measured by spectrofluorometry gives a half-life of 175 minutes (Aghajanian and Bing, 1964), a value which was later corrected to 109 minutes based upon a more detailed analysis of the pharmacokinetics (Wagner, Aghajanian, and Bing, 1968). Following intravenous injection of $2 \mu\text{g./kg.}$, plasma levels reached 7 ng./ml. within 30 minutes and gradually declined over 8 hours to 2 ng./ml. , paralleling the general pattern of psychic effects. It is therefore likely that LSD is centrally active *per se* and not as an initiator of a sequence of aberrant neurochemical reactions, a possibility that has been suggested on the basis of extrapolation of rodent metabolic data to man.

There is no specific concentration of LSD into the brain, whatever the route of administration. In most species, including man, only 1-1.5 per cent of absorbed drug reaches the brain and is soon detectable in the cerebrospinal fluid; following a typical human dose of 100 $\mu\text{g.}$, only 1 $\mu\text{g.}$ is distributed to the brain. Nevertheless, this is probably sufficient since qualitatively and quantitatively similar behavioural changes are obtained in rats when LSD is given either intravenously or intracerebrally, the effects of the latter route merely appearing earlier (Haley and Rutschmann, 1957). In the rat (Diab, Freedman, and Roth, 1971), LSD, 1.7 $\mu\text{g./kg.}$ intravenously, penetrates the brain within 5 minutes and reaches maximum concentration in 15 minutes, disappearing after approximately 1 hour. Free drug was distributed generally throughout the brain, but LSD was bound specifically to neurons in the cortex, caudate nucleus, mid-brain, and medulla. This specific localization is confirmed by *in vitro* studies of the binding of LSD to subcellular fractions of rat brain (Farrow and Van Vunakis, 1972), and provides evidence for the association of serotonergic neurons and post-synaptic localization of LSD in serotonin granules in the mechanism of action of the hallucinogen (see Chapter 8). However, there was little evidence of bound LSD in studies of its distribution in the brain of squirrel monkeys receiving 2 mg./kg. (i.v.) (Snyder and Revich, 1966), most of the drug being in the supernatant fractions. Thus, 20 minutes after injection, the blood, cerebral cortex, cerebellum, and brain-stem all had approximately equal concentrations, with 1.5 times as much in the thalamus and extrapyramidal system, 2-3 times as much in the hypothalamus and limbic systems, 2-5 times as much in the auditory and visual cortex, 5-7 times as much in the posterior pituitary and pineal, and 10 times as much in the anterior pituitary. These variable

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10 minutes, but rats with LSD and may be tolerant; in the first 100 minutes of LSD from plasma half-life of 175 minutes was later corrected to 68 minutes. Following intravenous injection of 7 ng./ml. within 10 minutes to 2 ng./ml., parallel to the data to man. Therefore likely that LSD is a sequence of events that has been suggested by the data to man. In the brain, whatever the route, including man, only a small amount of LSD is soon after a typical human dose. Nevertheless, this is quantitatively similar to LSD given either intravenously or by the latter route merely (Diab, 1957). In the rat (Diab, 1957), intravenously, penicillin maximum concentration is approximately 1 hour. Free LSD in the brain, but LSD was found in the caudate nucleus, midbrain is confirmed by *in vitro* cellular fractions of rat brain provides evidence for post-synaptic localization of action of the drug. There was little evidence of LSD in the brain of squirrel and Revich, 1966), most of it. Thus, 20 minutes after injection, and brain-stem all contained 1.5 times as much in the brain as much in the auditory cortex, posterior pituitary and anterior pituitary. These variable

concentrations within the brain may explain the psychic phenomena produced by LSD. Thus, the limbic system is involved in emotionality, the hypothalamus with the overall elaboration of emotion, and the anterior pituitary with the stress response. In human subjects with subcortically implanted electrodes, LSD induces paroxysmal E.E.G. activation of the limbic system and, particularly, the posterior hypothalamus. Finally, inhibition of synaptic transmission in visual reflex areas such as the lateral geniculate body could impair perception (Cohen, 1971; Brawley and Duffield, 1972) (*see* Chapter 8).

The lysergic acid nucleus of LSD is not cleaved or degraded *in vivo*, and little oxidation of the substituted amide side-chain occurs. Boyd (1959) found that only 4 per cent of the drug was degraded to carbon dioxide over the course of 12 hours in the rat, while over 80 per cent of the dose appeared in the bile within 3 hours, principally as the glucuronides of 12- (or possibly 13-) hydroxylysergic acid diethylamide and 12-(13?) hydroxyisolysergic acid diethylamide (Slaytor and Wright, 1962; Szára, 1963). Though LSD is metabolized *in vitro* by guinea-pig liver microsomes to its 2-oxo derivative, this metabolite has not been found in other species (Axelrod and others, 1957). The high potency and great rapidity of action of LSD makes it unlikely that its action is due to an active metabolite, and these products undoubtedly represent detoxification routes.

Biochemical Effects

The symptoms produced by LSD are very dependent on the type of person involved, and certain people seem much more resistant to its effects than do others. Schizophrenics have a markedly high threshold of responsiveness to the drug, chronic alcoholics may often require more than ordinary doses, while those individuals who wish to resist its effects consciously or unconsciously may be able to prevent average doses from having the usual impact (Hoffer and Osmond, 1967). These factors, coupled with investigations of the mode of action of LSD, have led to extensive study of its biochemical effects in man and in animals. Unfortunately, many of the results are contradictory and often not self-consistent; for example, LSD is reported to inhibit, to increase, and to have no effect upon the activity of human brain pseudocholinesterase (Giarman and Freedman, 1965; Hofmann, 1968).

Only two biochemical systems are reported to be affected by LSD in man. The drug diminishes excretion of inorganic phosphate and increases the free fatty acid content of the plasma, possibly as a result of non-specific stress (Hollister and Moore, 1965). Injection of adrenocorticoids during the period of action of LSD further

enhances the excretion of phosphate, a pattern also seen in schizophrenics who have received no LSD. The hallucinogen has no significant effect in man on the following parameters: cerebral blood-flow, cerebral vascular resistance, oxygen or glucose utilization, or respiratory quotient; levels of serum or plasma creatinine, urea, sodium chloride, cholesterol, and total lipid; and activities of serum caeruloplasmin or pseudocholinesterase. LSD produces mild hyperglycaemia, possibly as a consequence of an increased metabolic rate resulting from its inhibition of oxidative phosphorylation in the brain coupled with increased oxygen consumption in the whole organism.

Perhaps the most important biochemical findings are those which relate LSD to serotonin-containing systems (Ahlborg, Holmstedt, and Lindgren, 1968; Cohen, 1971; Brawley and Duffield, 1972). These are discussed fully in Chapter 8, and it is sufficient here to indicate that LSD decreases the turnover of serotonin in the brain and thus increases brain levels of the neurotransmitter. The coincidence of peak rise in brain serotonin, plasma half-life of LSD, and termination of psychic or behavioural effects in man and animals, suggests an involvement of this biochemical effect in the mode of action of the drug. LSD thus decreases the availability of serotonin at the points where it acts in the brain, since the increased levels of the neurotransmitter are intracellular and therefore ineffective at the synapses.

Therapeutic Uses of LSD and Adverse Reactions

When the psychic effects of LSD became widely known in the 1950s, the interest of physicians was such that within a decade the drug had an established place in psychotherapy (Hoffer and Osmond, 1967; Freedman, 1968). It was used both as an adjunct to conventional psychotherapy, to induce loosening of unconscious defence mechanisms, and as a highly specialized form of brief intensive psychotherapy, to make the subject aware of new and different avenues for personality change and development. By 1960, LSD had been used in the treatment of every type of mental affliction and character disorder, ranging from acute schizophrenia and drug addiction to alcoholism and homosexuality. Most of these studies have reported promising results, but it is clear that where carefully controlled studies have been performed, be they for mental illness (Hollister, Degan, and Schultz, 1962; Robinson, Davis, Sack, and Morrissey, 1963) or for alcoholism (Hollister, Shelton, and Krieger, 1969; Ludwig, Levine, Stark and Lazar, 1969), there is little difference in the improvement of patients receiving LSD, placebo, or no drug at all. In recent years LSD has fallen from favour and is

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no longer regarded as the panacea for all mental ills; this rejection seems to be based more on a general reaction to the public image of the drug than to scientific evaluation of the available results. Controlled clinical studies of the drug are still required before its place, if any, in psychotherapy can be properly assessed.

LSD is a dangerous drug and should be given to humans only under carefully controlled conditions and with experienced medical supervision. Nevertheless, its use spread during the 1950s from the research laboratory to practising physicians, who dispensed it to themselves, their patients, and their friends and relatives with a casualness that belied its toxic potential. A general attitude arose that LSD was a reasonably safe drug and its use spread further to the general public, when reports of adverse reactions started to appear with regularity. It is difficult to decide whether many of these are due to LSD or to other constituents of the often impure illicit drug samples, but the general consensus of opinion is now that LSD does produce three overlapping categories of adverse reactions—acute reactions, recurrent reactions in which there is a recurrence of symptoms without reingestion of the drug, and prolonged reactions (Meyer, 1969). The incidence of such reactions is unknown, but they account for about 1 per cent of the total psychiatric admissions to U.S. city hospitals.

Acute reactions arise concomitantly with the ingestion of LSD and are short-lived. They include a psychotoxic reaction resembling acute paranoia, in which the subject has grandiose or persecutory illusions, and a panic reaction, which is a response of the subject to the drug-induced symptoms. These effects can appear in both naive and experienced drug users, and can recur several weeks or months later without further ingestion of the drug. The recurrent reactions may last for only a few seconds or for an extended period of time, and occur most frequently in subjects who are particularly susceptible to suggestion. Chlorpromazine is the recommended treatment for those 'bad trips' (Consroe, 1973), although it is not a complete antagonist and can exacerbate the symptoms of other drugs which may be present in illicit samples of LSD or be mistaken for LSD. Usually, the dose is 25–50 mg. intramuscularly, repeated every 30 minutes until the situation is under control. Nicotinic acid is recommended by Hoffer and Osmond (1967), who consider that thrice-daily doses of 1–2 g. of the vitamin are particularly useful for preventing recurrent reactions in potentially susceptible subjects as well as for treating prolonged reactions to LSD. Habitual use of LSD has been reported to produce chronic anxiety or psychotic states, and may arise in persons who were not psychotic prior to the taking of the drug.

LSD and Genetic Damage

The toxicity of LSD may also manifest itself in mutagenic and teratogenic effects, and particularly in the production of chromosomal abnormalities (Dishotsky, Loughman, Mogar, and Lipscomb, 1971; Long, 1972). Suspicions were originally aroused by the report of Cohen and his colleagues (Cohen, Marinello, and Back, 1967) describing a marked increase in chromosomal abnormalities in human leucocytes which had been incubated with LSD in tissue cultures, and they were apparently confirmed in humans who had been regular users of the drug (Cohen, Hirshkorn, and Frosch, 1967). Accusations of teratogenicity in rats (Alexander, Miles, and Gold, 1967), mice (Auerbach and Rudowski, 1967), hamsters (Geber, 1967), and man (Zellweger, McDonald, and Abbo, 1967; Hecht, Beals, Lees, Jolly, and Roberts, 1968; Carakushansky, Neu, and Gardner, 1969) rapidly followed. The frequent lack of scientific objectivity in many of these reports is incredible, particularly where human toxicity has been based upon one or two cases who have ingested not only LSD but also every other psychotropic agent. There have been a tremendous number of conflicting reports during the last five years and it is more instructive to summarize the results than to refer to every individual paper; the reviews by Dishotsky and others (1971) and by Long (1972) should be consulted for over 100 references to the original literature.

Chromosomal breakage after exposure to LSD has been observed in 6 of 9 *in vitro* studies, the damage arising during or after DNA synthesis. With one exception it was the result of concentrations of drug and durations of exposure which cannot be achieved in man with non-lethal doses. The absence of a dose-response relationship, the lack of *in vitro* detoxification mechanisms for LSD, and the similar aberrations produced by such innocuous events as changes in temperature or oxygen pressure or by common substances like aspirin, caffeine, and even water, cast serious doubt upon the relevance of the positive results. A total of 310 human subjects have been examined for chromosomal damage, with the frequency being triple among illicit drug users (184 subjects) compared with those who received chemically pure LSD (126 subjects). Of all the subjects reported to have chromosome damage, only 18 of the 108 were exposed only to pure LSD, and it can be concluded that such damage, when found, is more related to the effects of drug abuse in general than to LSD in particular. Pure LSD ingested in the normal doses does not produce chromosomal aberrations that can be detected by available methods.

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Studies of the teratogenic hazards of LSD in animals indicate a wide variation of individual, strain, and species susceptibility to its effects. The most comprehensive report (Roux, Dupuis, and Aubry, 1970) using rats, hamsters, and mice, indicates that there is no significant increase in abortifacient, teratogenic, or growth-depressing effects. Nevertheless, the overall view seems to be that a slightly higher incidence of such effects can arise if LSD is given at a highly specific time early in gestation, and it is significant that the drug is almost five times as effective at crossing the placental barrier in mice during early than it is during late pregnancy (Idänpään-Heikkilä and Schoolar, 1969). The incidence of early spontaneous abortion also seems to be slightly elevated in human pregnancies, although the incidence appears to be somewhat lower among those exposed to pure LSD (15 per cent) than it is among either the general population (20 per cent) or those exposed to illicit LSD (37 per cent) (McGlothlin, Sparkes, and Arnold, 1970). There are no reports of malformed children born to women who ingested pure LSD either before or during pregnancy, but 6 cases are recorded of malformations associated with exposure to illicit LSD. There is little evidence, therefore, that LSD is teratogenic in man, notwithstanding that the use of any drug during pregnancy requires that its potential benefits significantly outweigh its potential hazards (Dishotsky and others, 1971; Long, 1972).

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Chapter

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Cannabis : plants used stem (hem with the ha that this c fibre or hi. carried out by Boyce (appears to Himalayas including I grows best (Haney and Preparati man for at duced into with Spani earliest rec produce st writings of did not me herb' (*Can. by birds at significance nabis are p 1970). The properties they enjoy nineteenth Roche (184*