CHAPTER VIII

Some Compounds With Hallucinogenic Activity

A. FANCHAMPS

A. Introduction

Although "delusional insanity" has been reported among the manifestations of convulsive ergotism (BARGER, 1931), none of the naturally occurring ergot alkaloids have typical hallucinogenic properties; such properties are confined to a number of semisynthetic derivatives of lysergic acid, the prototype of which is LSD. This substance is the most potent and, by far, the most extensively tested hallucinogen derived from ergot.

This chapter will consequently be centered on LSD. Unlike all other modern drugs, this compound has been assayed in man before an extended pharmacologic testing was performed in animals. Furthermore, its most specific and only interesting activity, the psychotomimetic one, cannot be studied directly in laboratory animals. This is one reason why this chapter is dealing only with human pharmacology. The other reason stems from the fact that all relevant data on animal pharmacology are included anyhow in other parts of this book.

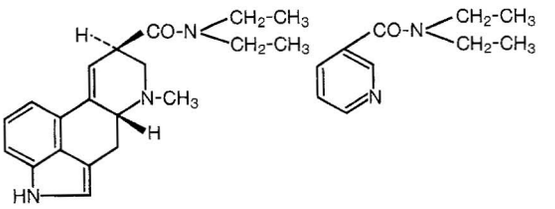
B. Discovery of LSD

LSD[1] was prepared for the first time in 1938 by ALBERT HOFMANN as part of a systematic chemical and pharmacologic investigation of partially synthetic amides of lysergic acid in the Sandoz Research Laboratories (STOLL and HOFMANN, 1943). The diethylamide was synthesized in the hope of obtaining an analeptic, in view of a structural relationship with nikethamide (Fig. 1).

A pharmacologic screening performed by ROTHLIN (quoted by STOLL and HOFMANN, 1943) revealed a marked uterotonic effect on the rabbit uterus in vitro and in situ as well as an excitatory action in these animals; in dogs and cats the substance produced cataleptic phenomena, reminiscent of the action of bulbocapnin (ROTHLIN, quoted by STOLL, 1947; ROTHLIN, 1957). Work on LSD then fell in abeyance for a number of years.

The discovery of its psychotropic effect was partly due to chance, when 5 years later, in April 1943, HOFMANN decided to prepare a fresh quantity of LSD. In the course of this work, he experienced a remarkable state of intoxication, which he described as follows (HOFMANN, quoted by STOLL, 1947; HOFMANN, 1970a):

[1] *d*-Lysergic acid diethylamide. Lysergide (INN rec.), Delysid, LSD25, d-LSD, (No. 73b in Chapter II, "Chemical Background").



LSD Nikethamide

Fig. 1. Structural relationship between LSD and nikethamide

"Last Friday, April 16, 1943, I was forced to stop my work in the laboratory in the middle of the afternoon and to go home, as I was seized by a peculiar restlessness associated with a sensation of mild dizziness. On arriving home, I lay down and sank into a kind of drunkenness which was not unpleasant and which was characterized by extreme activity of imagination. As I lay in a dazed condition with my eyes closed (I experienced daylight as disagreeably bright) there surged upon me an uninterrupted stream of fantastic images of extraordinary plasticity and vividness and accompanied by an intense, kaleidoscope-like play of colours. This condition gradually passed off after about two hours."

The nature and course of this extraordinary disturbance led him to suspect that he had been intoxicated by the substance with which he had been working that afternoon: He had separated the two isomers formed by this synthesis, the diethylamides of the lysergic and isolysergic acids, and prepared the crystalline water-soluble salt of lysergic acid diethylamide with tartaric acid.

Chance made then way to a planned investigation, which led to the actual discovery. In order to clarify the question, HOFMANN decided to perform some self-experiments, starting with what he thought to be a subthreshold oral dose: 0.25 mg. Forty minutes after having ingested the substance, he noted in his laboratory journal (HOFMANN, 1970b):

"17.00, onset of dizziness, anxiety, visual disturbances, paralysis, urge to laugh."

At this point, the laboratory notes were discontinued; the last words had been written only with great difficulty. A supplementary note was entered 2 days later:

"Went home by bicycle. From 18.00 to 20.00, very severe crisis (see special report)."

From this special report, extracts of which have been published in various scientific papers (STOLL, 1947; HOFMANN 1970a), we learn that while cycling home with his laboratory assistant, HOFMANN realized that the symptoms were much stronger than the first time.

"I had great difficulty in speaking coherently, my field of vision swayed before me, and objects appeared distorted like images in curved mirrors. I had the impression of being unable to move from the spot, although my assistant told me afterwards that we had cycled at a good pace ... Once I was at home a physician was called.

By the time the doctor arrived, the peak of the crisis had already passed. As far as I remember, the following were the most outstanding symptoms: vertigo, visual disturbances; the faces of those around me appeared as grotesque, coloured masks; marked motoric unrest, alternating with paralysis; an intermittent heavy feeling in the head, limbs and the entire body, as if they were filled with lead; dry, constricted sensation in the throat; feeling of

choking; clear recognition of my condition, in which state I sometimes observed, in the manner of an independent, neutral observer, that I shouted half insanely or babbled incoherent words. Occasionally I felt as if I were out of my body.

The doctor found a rather weak pulse but an otherwise normal circulation ... Six hours after ingestion of the LSD my condition had already improved considerably. Only the visual disturbances were still pronounced. Everything seemed to sway and the proportions were distorted like the reflections in the surface of moving water. Moreover, all objects appeared in unpleasant, constantly changing colours, the predominant shades being sickly green and blue. When I closed my eyes, an unending series of colourful, very realistic and fantastic images surged in upon me. A remarkable feature was the manner in which all acoustic perceptions (e.g. the noise of a passing car) were transformed into optical effects, every sound evoking a corresponding coloured hallucination constantly changing in shape and colour like pictures in a kaleidoscope. At about one o'clock I fell asleep and awoke next morning feeling perfectly well."

This was the first planned human experiment with LSD. Subsequent, more prudent trials have revealed that the dose chosen by HOFMANN was about five times the average effective amount.

C. Effects of LSD in Man

Effective doses range from 0.5 to 2.0 μg per kg of body weight, either given orally or intravenously. Enteral absorption is fairly complete. Effects usually set in 30–40 min after ingestion and reach a maximum within 90 min. The intensity of the reaction may then show wave-like variations for a further 2–3 h and then begin to decline progressively; most subjects have largely recovered 8–12 h after the start of the experiment. Certain individuals may experience bouts of after-effects, such as strange feelings, mood disturbances, or hallucination, days or even weeks after the drug intake (ROSENTHAL, 1964; HOROWITZ, 1969).

1. Somatic Actions

Autonomic and neurologic disturbances usually become manifest before the effects on mind and perception. In the majority of cases, they are of a mild nature. *Autonomic changes* reflect a stimulation of both branches of the autonomic nervous system. Sympathetic stimulation is evidenced in most subjects by a pupillary dilatation and moderate increases in heart rate and blood pressure; other, inconstant signs are piloerection, a slight blood-sugar elevation, and, rarely, some increase in body temperature. Respiration is generally unchanged. Other symptoms point to a parasympathetic stimulation: Sweating and salivation are frequent; nausea may occur; vomiting is exceptional; an increase in diuresis is occasionally noted; flushing of the face is more frequent than paleness. Sympathicotonia usually predominates, but there are great individual variations and a marked parasympathicotonia with bradycardia and hypotension may be observed in some subjects. Headache and dizziness have sometimes been reported.

The most consistent *neurologic effect* is an exaggeration of the patellar (ISBELL et al., 1956) and other tendon reflexes. Other, less constant signs are a slight unsteadiness of gait, ataxia, a positive Romberg's sign, and mild tremor.

Figs. 2 and 3. Drawings executed during an LSD session (100 μg orally) by painter O. JANECEK. The artist represented hallucinations he was experiencing. In Figure 2, "A politician", the disproportionate right hand and the hollow head are remarkable. The face in Figure 3 has an additional eye and is surrounded by two oversized left hands. (Reproduced with permission of J. ROUBICEK, 1961)

2. Psychic Actions

The characteristic psychic and perceptual effects of LSD have been excellently described by W.A. STOLL (1947) in the very first clinical paper on the new drug, so that later investigators, such as BECKER (1949), CONDRAU (1949), RINKEL et al. (1952), LIDDELL and WEIL-MALHERBE (1953), ABRAMSON et al. (1955d), BERCEL et al. (1956a), and many others could do little more than confirm these observations (while often completing the investigational method with psychologic or psychometric tests, performing laboratory tests, EEG's etc., and expanding the material to various categories of mentally ill subjects).

a) Psychologic Effects in Mentally Normal Subjects

In mentally normal subjects, the most important changes concern perception, mood, relationship to the environment, and ego integrity.

Fig. 3

α) Perception

Most prominent are *visual* phenomena. They usually start as prolonged afterimages, then rapidly proceed to illusions and, especially in a dark room, to elementary hallucinations. Finally, formed hallucinations occur in many subjects. Objects, including faces, appear distorted; sizes and distances are misjudged; objects seem to approach or to recede. Perception of colors is altered, yellow and red appearing with particular frequency; in general, colors are perceived brighter than normal, but they may also appear drab and greyish during depressed phases. Elementary hallucinations may start with flickering, glittering points, flashes of light, colored waves, strips, spots, circles, spirals, whirls, and may gradually turn into well-defined objects, animals, human beings (Figs. 2 and 3), or whole sceneries.

Optic sensations may be triggered or modified by auditory stimuli (HOFMANN, quoted by STOLL, 1947; BERCEL et al., 1956a) or by pressure on the eye balls. LSD may also induce visual experiences in blind subjects (KRILL et al., 1963), even after enucleation of both eyeballs (ALEMA, 1952), provided there is a history of previous visual activity.

Acoustic phenomena often consist in hyperacousis; slight noises are perceived very loud, reverberating, filling the space. Acoustic illusions are frequently mentioned, but true acoustic and especially verbal hallucinations are rare (BENEDETTI, 1951; SAVAGE, 1952).

Olfactory and *gustatory* distortions or illusions are less prominent.

Tactile illusions are relatively frequent. On touch, objects including the own

body may feel different (harder, or softer, rougher, smoother etc.) from usual. DE SHON et al. (1952) describe "a rather vivid experience in a subject of his trousers being wet from urine."

β) Alterations of Body Image

Alterations of body image form an important part of the LSD syndrome (ARNOLD and HOFF, 1953b). The whole body or part of it is felt to be altered in size, shape, consistency, or to be strange in some way. A limb may be said to be "like detached" from the rest of the body or completely missing (BERCEL et al., 1956a). The body may be perceived either as increased (LIEBERT et al., 1958) or, more often, as reduced in size. The subject feels as if he were transformed into a child; SANDISON et al. (1954) mention a woman 29 years old who became a girl of 5 or 6; she felt that her clothes were huge and hanging loosely about her, and her hand appeared small compared to the doctor's hand grasping hers. Door handles may appear out of reach as they would be to a small child. Such experiences are especially conspicuous in neurotic individuals, where they are usually associated with the reliving of repressed personal memories of childhood.

γ) Time Sense

Time sense is frequently impaired, aberrations occurring both in the direction of acceleration or slowing down even to a feeling of complete arrest of time passage (BECKER, 1949; ARONSON and KLEE, 1960).

δ) Mood Changes

Mood changes are prominent during the LSD experience; there is usually an alternation between euphoric and depressive episodes, with a certain prevalence of the former. The subject may be delighted by the beauty of his hallucinatory experiences. Euphoria may also take the form of a shallow elation with silly smiling and giggling, or unmotivated, uncontrolled laughter. Certain individuals become disinhibited or frankly hypomanic, with an increased urge for action. This, coupled with the mental aberrations, may make the subject dangerous to himself or to others. A man, for instance, jumped out of a window, having complete faith that he could fly (COHEN, 1967), while another tried to walk on the sea (COHEN, 1966). On the other hand, cases of homicide have also been reported (KNUDSEN, 1964). In spite of the disinhibition, sexual stimulation rarely occurs (ANDERSON and RAWNSLEY, 1954).

Emotional indifference is sometimes reported, but dysphoria is more frequent. The experience may be felt as unbearingly flat and dull; depression may take the form of a quiet sadness or be of a more agitated nature. Suicide is a potential danger (COHEN and DITMAN, 1962) and a further reason for the unadvisability of LSD experiments outside strict medical and psychologic supervision.

Tension, anxiety, or a frank panic may develop at the height of the reaction. The hallucinatory experience can be extremely frightening. The feeling of becoming

insane is very anguishing to some subjects, especially if they have doubts about the reversibility of their abnormal condition (FROSCH et al., 1965; COHEN, 1966).

ε) Consciousness

Consciousness is maintained, orientation usually remains intact, and the vast majority of subjects remain aware that their uncommon experience is caused by the drug; however, this insight may be lost, especially after high doses. Memory is not impaired, the individual is usually able to remember every detail.

ζ) Ego Integrity

Ego integrity is often disturbed by feelings of depersonalization and derealization—often related to distortions of the body image—or of division of the personality, which may closely mimic schizophrenic symptoms (DE SHON et al., 1952; LANGS and BARR, 1968; YOUNG, 1974). On the whole, however, most experts feel that there are more differences than similarities between the clinical pictures of most types of schizophrenia and the LSD intoxication (ROUBICEK, 1958a, b; LANGS and BARR, 1968).

η) Psychologic and Psychometric Tests

In order to explore more in depth the effects of the LSD intoxication on mental functioning, thought patterns, mood, personality, and psychomotor performance, a large array of psychological and psychometric tests have been applied. Discussion of the results is not possible in the frame of this chapter, but Table 1 will facilitate reference to the original papers. In this connection, it must be pointed out that filling out questionnaires, concentrating on a mental or physical task, or submitting to other test procedures may considerably weaken the LSD experience (the most vivid effects are usually obtained in a dark and quiet surrounding).

b) Psychologic Effects in Mental Patients

Psychotic patients, especially schizophrenics, are more resistant to the psychologic and hallucinogenic (though not necessarily to the somatic) effects of LSD than mentally normal or neurotic individuals (STOLL, 1947, 1952; CONDRAU, 1949; BECKER, 1949; BUSCH and JOHNSON, 1950; FORRER and GOLDNER, 1951; RINKEL et al., 1952; HOCH et al., 1952; ARNOLD and HOFF, 1953a, and many others). With sufficiently high doses, however, an increase in psychomotor activity and verbal exteriorization may be obtained even in stuporous schizophrenics, and patients with mania may become greatly excited. LSD often accentuates the preexisting emotional state, so that melancholic patients become still more depressed and manic patients still more euphoric (CONDRAU, 1949; SLOANE and LOVETT DOUST, 1954). Psychiatric patients are usually able to distinguish between the drug-induced and their usual hallucinations.

In *neurotic patients*, especially when applied in connection with analytic psychotherapy, LSD may produce very conspicuous disinhibiting effects, and thus greatly

Table 1. Psychologic and psychometric tests under LSD

Test	In normal subjects	In mental patients[a]
Mental state, mood		
Questionnaires	ABRAMSON et al. (1955d, e) ABRAMSON (1960a) JARVIK et al. (1955a) KORNETSKY et al. (1957) BRENGELMANN (1958) LEBOVITS et al. (1960a) LINTON and LANGS (1962)	ISBELL et al. (1956) PAUK and SHAGASS (1961)
Clyde mood scale	LEBOVITS et al. (1960b, 1962)	
Powick rating scale	SANDISON (1959b)	SANDISON (1959b)
Anxiety tests	MCGLOTHLIN et al. (1967)	
Personality		
MMPI	KORNETSKY and HUMPHRIES (1957) KLEE and WEINTRAUB (1959) LEBOVITS et al. (1960a, 1962)	BELLEVILLE (1956) UNGERLEIDER et al. (1968a)
Perceptual reaction	BRENGELMANN (1958)	
Personality, attitude, and value test battery	MCGLOTHLIN et al. (1967)	
Aesthetic sensitivity test battery	MCGLOTHLIN et al. (1967)	
Thinking process		
Thematic aperception (TAT)	LEBOVITS et al. (1962)	SANGUINETI et al. (1956)
Projective test battery	MCGLOTHLIN et al. (1967)	
Concrete-abstract thinking, proverb interpretation	DESHON et al. (1952) COHEN et al. (1962)	
Rorschach	DESHON et al. (1952) RINKEL et al. (1952) STOLL (1952) GASTAUT et al. (1953) DELAY et al. (1954) SLOANE and LOVETT DOUST (1954) LEVINE et al. (1955b) BERCEL et al. (1956b) HURST et al. (1956) TALLAFERRO (1956) VON FELSINGER et al. (1956) LEBOVITS et al. (1960b, 1962) PIERCE (1961) AXELROD and KESSEL (1972)	BENEDETTI (1951) SMORTO et al. (1955) ISBELL et al. (1956) SANGUINETI et al. (1956) TALLAFERRO (1956) ZIOLKO (1959)
Goldstein-Scheerer sorting		ISBELL et al. (1956)
Raven progressive matrices	KRUS et al. (1961)	
Color pyramid	LIENERT (1961)	
Four pictures	VAN LENNEP (1960)	VAN LENNEP (1960)
Thurstone hand test	ABRAMSON et al. (1955c)	

Table 1 (continued)

Test	In normal subjects	In mental patients[a]
Zucker		SMORTO et al. (1955)
Word association	WEINTRAUB et al. (1959, 1960)	
Associational fluency (Guilford)	MCGLOTHLIN et al. (1969)	MCGLOTHLIN et al. (1969)
Creativity test battery	MCGLOTHLIN et al. (1967)	
Porteus maze	ARONSON and KLEE (1960) MCGLOTHLIN et al. (1969)	MCGLOTHLIN et al. (1969)
Spatial orientation map test	MCGLOTHLIN et al. (1969)	MCGLOTHLIN et al. (1969)
Intelligence		
IQ (Shipley-Hartford)	COHEN et al. (1958) MCGLOTHLIN et al. (1969)	MCGLOTHLIN et al. (1969)
Wechsler-Bellevue	LEVINE et al. (1955a)	ISBELL et al. (1956)
Digit symbol	KORNETSKY et al. (1957)	
Cattell	GASTAUT et al. (1953)	
IST-Amthauer	LIENERT (1956, 1959)	
Memory and learning		
Memory	BERCEL et al. (1956a) SILVERSTEIN and KLEE (1958a, 1960a)	
Recall and recognition test battery	JARVIK et al. (1955c) ARONSON et al. (1962)	
Picture recognition	BARENDREGT (1960)	BARENDREGT (1960)
Figure reconstruction	BRENGELMANN (1958) BRENGELMANN et al. (1958a) BARENDREGT (1960)	BARENDREGT (1960)
Learning	ARONSON et al. (1962)	
Drawing task		
Bender-Gestalt	ABRAMSON et al. (1955f) BERLIN et al. (1955) TALLAFERRO (1956) BAMBAREN VIGIL (1957)	TALLAFERRO (1956) BAMBAREN VIGIL (1957) PAUK and SHAGASS (1961)
Draw a tree, draw a person	BERLIN et al. (1955) SILVERSTEIN and KLEE (1958b) PIERCE (1961) MCGLOTHLIN et al. (1967)	GOMIRATO et al. (1958)
Three tree	VAN LENNEP (1960)	VAN LENNEP (1960)
Mirror-image drawing	ORSINI and BENDA (1960)	
Minnesota percepto-diagnostic (MPDT)	MCGLOTHLIN et al. (1969)	MCGLOTHLIN et al. (1969)
Spontaneous drawing and painting	MATEFI (1952) BERLIN et al. (1955) RINKEL (1956) ROUBICEK (1956, 1958a, b, 1961)	SAURI and DE ONORATO (1955) ROUBICEK (1958a, b, 1961) MACHOVER and LIEBERT (1960) LEUNER (1962, 1963a)

Table 1 (continued)

Test	In normal subjects	In mental patients[a]
	TONINI and MONTANARI (1955a) VON MERING et al. (1957) MACHOVER and LIEBERT (1960)	MACCAGNANI et al. (1964)
Attention		
Attention and concentration test battery	JARVIK et al. (1955b)	
Düker calculation	LIENERT (1956, 1958, 1959)	WAPNER and KRUS (1960)
Counting backwards	COHEN et al. (1962)	
Adding (Kraepelin, Birren, Pauli)	HURST et al. (1956) KORNETSKY et al. (1957) KRUS et al. (1961) PIERCE (1961)	
Arithmetic problems	JARVIK et al. (1955d)	
Number square	HORACKOVA et al. (1958)	
Lahy	GASTAUT et al. (1953)	
Stroop color-word	WAPNER and KRUS (1960) KRUS et al. (1961)	
Trail making	MCGLOTHLIN et al. (1969)	MCGLOTHLIN et al. (1969)
Estimation of quantities	BRENGELMANN (1958)	
Psychomotor functions		
Tapping	LANDIS and CLAUSEN (1954) SLOANE and LOVETT DOUST (1954) BERCEL et al. (1956a) HURST et al. (1956) BARENDREGT (1960) KRUS et al. (1961)	BARENDREGT (1960)
Reaction time	ABRAMSON et al. (1955b) ORSINI and BENDA (1959) ROSENBAUM et al. (1959) EDWARDS and COHEN (1961)	WIKLER et al. (1965a)
Purdue pegboard	LANDIS and CLAUSEN (1954)	
Rotatory pursuit	ABRAMSON et al. (1955a) KORNETSKY et al. (1957) ROSENBAUM et al. (1959)	
Dual pursuit	SILVERSTEIN and KLEE (1960b)	
Steadiness	ABRAMSON et al. (1955a) KRUS et al. (1961)	
Speed of copying	KORNETSKY et al. (1957)	
Handwriting	STOLL (1947) BERCEL et al. (1956a) HIRSCH et al. (1956) HURST et al. (1956) KRUS et al. (1961)	THURING (1960)
Language		PRIORI (1957) FINK et al. (1960)

Table 1 (continued)

Test	In normal subjects	In mental patients[a]
Visual functions		
Flicker fusion	LANDIS and CLAUSEN (1954) HURST et al. (1956) TAKASHINA (1960)	
Visual threshold	CARLSON (1958) TAKASHINA (1960)	
Retinal function, ERG	KRILL et al. (1960)	
Color detection	EDWARDS and COHEN (1961)	
Tachistoscopic discrimination	KORNETSKY et al. (1957)	
Figural after-effects	SMITH (1960)	
Embedded figures (Witkin)	MCGLOTHLIN et al. (1969)	MCGLOTHLIN et al. (1969)
Part-whole relationship	KRUS and WAPNER (1959)	
Size constancy	EDWARDS and COHEN (1961)	
After-image duration	BRENGELMANN (1958)	
Apparent horizontal	WAPNER and KRUS (1959)	
Apparent eye level	KRUS et al. (1966)	
Various physiologic functions		
Patellar reflex	WIKLER et al. (1965b)	ISBELL et al. (1956) WIKLER et al. (1965b)
Galvanic skin response	FISHER and CLEVELAND (1959) MCGLOTHLIN et al. (1967)	
Warmth detection	EDWARDS and COHEN (1961)	
Tactual threshold	KORNETSKY et al. (1957)	
Two-point discrimination	EDWARDS and COHEN (1961)	
Weight discrimination	ROSENBAUM et al. (1959)	
Audiometric threshold	HENKIN et al. (1967)	
Subjective time	BOARDMAN et al. (1957) ARONSON et al. (1959) BENDA and ORSINI (1959) ORSINI and BENDA (1959)	

[a] Including psychotics, psychoneurotics, and former drug addicts.

facilitate release and abreaction of repressed material, while enhancing contact and transference. These properties of LSD have been widely exploited as an adjunct to psychotherapy and psychoanalysis (see D, 1).

Reliving of traumatic childhood experiences is usually accompanied by a regression of the body image to a size corresponding to the relived age. Certain authors even claim that patients under LSD have been able to relive their own birth (LEWIS and SLOANE, 1958; SANDISON, 1960).

The psychologic effects of LSD in neurotic subjects have been analyzed in depth by LEUNER in his book *Die experimentelle Psychose* (1962).

3. Effects of LSD on the Human EEG

The first investigators found no LSD-induced changes in the electroencephalogram (FORRER and GOLDNER, 1951). With refined evaluation methods, however, the following effects were observed rather consistently:

1. An accelerated and decreased amplitude of the alpha-rhythm (RINKEL et al., 1952; GASTAUT et al., 1953; ROUBICEK, 1958a; BENTE et al., 1958).
2. An increase in β-activity (GASTAUT et al., 1953), which may become dominant (ROUBICEK, 1958a).
3. In patients with drug-induced slow background rhythm, e.g., during a combined treatment with chlorpromazine and reserpine, LSD increases the frequency and decreases the amplitude (BENTE et al., 1958).
4. In epileptics, slow rhythms are accelerated, but spike activity may be increased (BENTE et al., 1958).
5. Blocking of the α-activity by a visual stimulus is preserved (ROUBICEK, 1958a) and may be prolonged (BERCEL et al., 1956a), which might correlate with the frequently observed persistence of after-images.
6. Evoked potentials due to flicker light are increased (GASTAUT et al., 1953).
7. In the quantified EEG, one observes a decrease in electrical energy with an associated reduction in variability; the tracings becoming strikingly similar to those of chronic schizophrenic patients (PFEIFFER et al., 1965).

On the whole, the effects of LSD on the EEG appear to result from an increased neuronal activity.

The effect of LSD on the depth EEG of patients with convulsive and/or psychotic disorders has been investigated by SCHWARZ et al. (1956); in epileptics, they observed a pronounced quieting effect on the spike and sharp-wave foci, whereas chronic schizophrenics responded with an increase in paroxysmal activity. MONROE et al. (1957) attempted to correlate, in schizophrenic patients with implanted electrodes, the behavioral effects of LSD with EEG modification; paroxysmal activity in the hippocampal, amygdaloid, and septal regions seemed to be associated with overt expressions of disturbed psychotic behavior.

In patients with exposed cerebral cortex, PURPURA et al. (1957) observed that, if perfused locally into a small cortical artery, LSD inhibits the dendritic activity evoked by electrical stimulation of the cortical surface.

4. Clinical Laboratory Investigations

a) Liver Function Tests

Liver function tests, which may be pathologic in schizophrenia, revealed only a mild and transient disturbance under LSD. Quick's hippuric acid excretion test as well as the Hijmans van den Berg and Takata-Ara reactions remain negative (FISCHER et al., 1951; BELSANTI, 1955), whereas the more sensitive cinnamonic acid test of Snapper and Saltzmann revealed a slight dysfunction (FISCHER et al., 1951). After i.v. LSD in schizophrenic patients, SANGUINETI et al. (1956) found no change in bilirubinemia but an increase of the albumin-globulin quotient and some disturbances in tests for serum lability. Curiously enough, liver functions

have hardly been tested in more recent studies. According to BROWN (1972), SGOT is unchanged and liver functions unaffected by LSD.

b) Carbohydrate Metabolism

Besides an occasional slight elevation of blood sugar (LIDDELL and WEIL-MALHERBE, 1953), LSD may produce an increase in the plasma concentration of hexosemonophosphate (MAYER-GROSS et al., 1952, 1953); the authors conclude that LSD impairs glycogen mobilization by blocking its metabolism at the level of hexosemonophosphate, but their corroborating in vitro findings were not confirmed by others (BAIN, 1957).

ARNOLD (1955) observed that high oral or intravenous doses of glutamic acid or succinic acid may interrupt or retard the LSD reaction 3–5 h; from this he inferred that the effect of LSD on brain function might be connected to a derangement in the citric acid cycle.

c) Adrenaline Metabolism

The fact that signs of adrenergic stimulation usually precede the mental symptoms points to a possible involvement of the adrenaline system in the mechanism of LSD psychosis (RINKEL et al., 1955). LIDDELL and WEIL-MALHERBE (1953) reported that following LSD, plasma adrenaline first rises, then drops below the starting level, then rises again, but such changes could not be confirmed by MANGER et al. (1956). An increased urinary excretion of adrenaline and noradrenaline was found after LSD in manic-depressive but not in schizophrenic patients (ELMADJIAN et al., 1957).

HOFFER and his group, who from 1954 on investigated this problem in a number of studies (quoted by HOFFER, 1965), thought to have identified adrenochrome and adrenolutin as probable mediators of certain mental effects of LSD as well as possible pathogenic factors in schizophrenia. The main evidence on which they base their theory is as follows: Adrenaline is metabolized into adrenochrome, which in turn is converted into (1) dihydroxyindole or (2) trihydroxyindole, pathway 1 being preferred. LSD (but not the nonpsychomimetic BOL148, No. 37a in Chapter II) increases the in vitro conversion of adrenaline into adrenolutin as well as the blood levels of adrenochrome and adrenolutin. When adrenochrome is injected into a schizophrenic patient or to an LSD pretreated subject, the adrenochrome blood level remains elevated much longer than in controls (or after treatment with BOL148). This could be interpreted as resulting from a block of the main metabolic pathway, leading to an accumulation of adrenochrome and to an increased formation of adrenolutin (pathway 2). According to these authors, adrenochrome and adrenolutin induce psychologic changes and hallucinations (HOFFER et al., 1954; OSMOND, 1956), a finding which could not be confirmed, however, by RINKEL et al. (1955), using a stabilized form of adrenochrome nor by the surgical experience with adrenochrome used as an hemostatic; since native adrenochrome is unstable, the psychotic effects observed by HOFFER were possibly caused by a degradation product.

d) Phosphate Excretion

In schizophrenic patients, urinary phosphate excretion is low compared to normal controls but increases after ACTH. LSD produces identical phenomena in normal subjects: Low urinary output of phosphate and increase after ACTH (HOAGLAND et al., 1955); the authors suggest that LSD acts on enzyme systems to facilitate the binding of phosphate, which is reversible by adrenocorticoids; in schizophrenic patients, an endogenous derivative of adrenaline metabolism would have a similar phosphorylation facilitating effect.

e) Enzymatic Systems

Studies on the effect of LSD in various enzymes in man, in animal models, or in vitro have been unrewarding, as far as the psychotomimetic mechanism is concerned. CLARK et al. (1954, 1956) found a slight inhibition of the succinic dehydrogenase system in rat brain homogenates, no effect on lactic dehydrogenase, and a slight activation of malic dehydrogenase as well as a stimulation of cytochrome C oxidase and of alkaline phosphatase. However, the centrally inactive levorotatory isomer l-LSD (No. 61) has identical effects on malic dehydrogenase and alkaline phosphatase. Among the brain cholinesterases, only pseudocholinesterase is consistently inhibited by LSD (THOMPSON et al., 1955); the same authors found no effect on true cholinesterase and tributyrinase, whereas FOLDES et al. (1959) observed a definite inhibition. Inhibition of human serum cholinesterase (FRIED and ANTOPOL, 1956; ZSIGMOND et al., 1959; EVANS, 1960) and pseudocholinesterase (THOMPSON et al., 1955; ZEHNDER and CERLETTI, 1956) has been regularly demonstrated with LSD concentrations of the order of magnitude of 10^{-6} M but with lower concentrations such as 6×10^{-9} M FRIED and ANTOPOL (1957) found a potentiation of serum pseudocholinesterase. The relevance of these alterations in cholinesterase activity for the psychotomimetic effect is doubtful, since similar inhibitions were demonstrated with the nonpsychotomimetic compounds BOL 148 (No. 37a) (ZEHNDER and CERLETTI, 1956; FOLDES et al., 1959; ZSIGMOND et al., 1959; EVANS, 1960), l-LSD and d-iso-LSD (No. 93c) (ZSIGMOND et al., 1960).

Mono-amino-oxidase is not affected by LSD (CERLETTI, 1956), and the same applies to 5-hydroxytryptophane decarboxylase, dopa decarboxylase, glutamic acid decarboxylase, and amino acid oxidase (CERLETTI, 1958). On the other hand, LSD was found to inhibit glutamic dehydrogenase (SIVA SANKAR et al., 1961).

More recently, an increase of serum creatine phosphokinase (CPK) activity has been observed following ingestion of LSD or of street drugs believed to be LSD (HARDING, 1974; MELTZER, 1975); this was possibly an indirect effect of the psychotic reaction rather than a direct effect of LSD, since experiments in rats failed to show any alteration in CPK activity after i.p. or i.m. injection of LSD (MELTZER, 1975). Increased CPK has also been found in some individuals with spontaneous psychoses (MELTZER, 1968, 1975).

f) Cerebral Circulation and Metabolism

Cerebral circulation and metabolism have been investigated in normal subjects and schizophrenics at the height of the effect of i.v. LSD by SOKOLOFF et al.

(1957). Cerebral blood flow (nitrous oxide method), cerebral vascular resistance, cerebral oxygen consumption, and glucose utilization remained practically unchanged.

5. Tolerance to LSD Effect

If LSD is given daily, tolerance develops very quickly but disappears after a few days off the drug. ABRAMSON et al. (1956) used their questionnaire method to demonstrate such tolerance in normal volunteers receiving fixed or increasing oral doses for 3–6 days. The same was observed by ISBELL et al. (1956, 1961) in former morphine addicts. CHOLDEN et al. (1955) gave daily intramuscular injections to schizophrenics; tolerance was already evident on day 2 and complete on day 3 of drug administration, and a period of 4 to 6 days free of LSD was necessary to reinstate the original reaction.

6. Inhibitors of LSD Reaction

The acute LSD reaction can be aborted by sedatives and tranquilizers. By far the most widely applied antidote is intramuscular or intravenous chlorpromazine. Within a few minutes of an injection of 25–100 mg, most autonomic and psychic disturbances are completely abolished (SCHWARZ et al., 1955; HOCH, 1956a, b; ISBELL and LOGAN, 1957; LESSE, 1958; SANDISON, 1968); the same applies to the EEG alterations (SCHWARZ et al., 1956; MONROE et al., 1957). Oral chlorpromazine is much less effective (ISBELL, 1959; ABRAMSON et al., 1960b); nevertheless, in connection with the therapeutic use of LSD in psychoneurotic patients, MARTIN (1957) terminated the experience by giving one to three oral doses of 50 mg chlorpromazine. A preventive effect on the LSD psychosis may be observed if chlorpromazine is applied orally before the hallucinogen, either in a single dose of 50–100 mg 30 min prior to LSD (ISBELL and LOGAN, 1957) or in repeated daily doses of 200–600 mg (GIBERTI and GREGORETTI, 1955).

Reserpine applied parenterally is definitely less effective than chlorpromazine as an antagonist (HOCH, 1956b; MONROE et al., 1957), and pretreatment may even potentiate the LSD-reaction (ISBELL and LOGAN, 1957; ISBELL, 1959).

On the other hand, strong sedation by intravenous amobarbital (500 mg or more) is a very efficient method to stop the LSD reaction and put the subject eventually to sleep (HOCH, 1956a; HOFFER, 1965).

Among the minor tranquilizers, azacyclonol attracted much interest following reports by FABING (1955) that a pretreatment with oral daily doses of 10–30 mg given for 2–7 days was able to almost block completely the psychic reaction to 100 μg LSD. According to BROWN et al. (1956), 100 mg of i.v. azacyclonol injected at the height of the LSD reaction promptly relieves the symptoms. However, this striking antagonistic effect of azacyclonol could not be confirmed by CLARK (1956), HOCH (1956b), ISBELL and LOGAN (1957); MONROE et al. (1957) observed no effect on the behavioral changes and only a doubtful effect on the LSD-induced alterations of the EEG.

Hydroxyzine, another minor tranquilizer, was tested as a pretreatment by LOEB and GIBERTI (1959) as well as by PIERCE (1961) in a self-experiment; the subsequent LSD experience was attenuated, especially regarding the mood disturbances, but

the perceptive alterations were not suppressed; the LSD-induced EEG changes were not modified.

More recently, diazepam, 5–15 mg i.v., 10 mg i.m., 10–50 mg orally, has been described as a very potent antidote of the acute LSD experience (EDITORIAL, 1971); even after oral application, hallucinations, euphoria, panic, and terror disappear in about half an hour (LEVY, 1971).

In cases of prolonged psychotic reactions following abuse of LSD, lithium therapy (achieving blood levels ranging from 0.5 to 1.2 mEq/l) proved more effective than phenothiazines in normalizing the psychic state (HOROWITZ, 1975); the author concludes that, at least in certain individuals, the LSD-induced psychotic reaction is closer to manic-depressive illness than to schizophrenia.

Other attempts at counteracting the effects of LSD were connected with theories on the biochemical mechanism of action. ARNOLD (1955), suspecting a derangement in the carbohydrate metabolism, observed that glutamic acid, 20 g i.v. or 100 g orally, or succinic acid, 10 g i.v., interrupted or retarded the LSD reaction for several hours. In the hands of HOCH (1956b), however, these two substances didn't prove very effective.

Nicotinic acid has been tested by AGNEW and HOFER (1955); they found that in subjects pretreated with 3 g nicotinic acid per day for 3 days, the LSD reaction was modified, exhibiting less visual disturbances but more feeling of unreality and confusion about self-identity. When 200 mg nicotinic acid were injected i.v. at the height of the LSD experience, all the disturbances except affect were markedly reduced within a few minutes. HOFFER (1965) as well as O'REILLY and REICH (1962) used nicotinic acid routinely during LSD therapy to mitigate or terminate the reaction. In a double-blind study by MILLER et al. (1957), nicotinic acid did not alter the pattern of the response to LSD, except for a reduced anxiety.

Also steroid hormones have been used in conjunction with LSD. ABRAMSON and SKLAROFSKY (1960) pretreated normal subjects with 40–165 mg of prednisone per day for 3–7 days; anxiety was reduced, but the other LSD effects were not modified. According to CLARK and CLARK (1956), premedication of schizophrenic patients with cortisone had no observable effect upon their sensitivity to LSD. KRUS et al. (1961), using a battery of tests in a double-blind study in normal subjects, observed that 600 mg progesterone given 1 h before LSD decreased the sensory-motor, perceptual, and conceptual disturbances.

A clear attenuation or even suppression of the LSD reaction was observed by GROF and DYTRYCH (1965) in patients pretreated for several weeks with the MAO-inhibitor nialamide, 150–500 mg per day parenterally and orally; the protective effect lasted as long as 2 weeks after cessation of the drug. This action might be related to an interference with the metabolism of brain serotonin.

Serotonin itself was also tried (POLONI, 1955), but since it does not cross the blood-brain barrier, it is not surprising that no clear-cut modificaton of the LSD experience could be observed. The precursor 5-hydroxytryptophan (25 mg i.v.), which increases the concentration of serotonin in the brain, did not markedly alter the reaction to i.v. LSD, although the psychologic tests suggest a slight alleviation (BRENGELMANN et al., 1958b).

Finally, small daily doses of propranolol, a beta-adrenoceptor blocking agent, have been found effective in relieving delayed anxiety reactions after high doses

of LSD in subjects who had responded poorly to chlorpromazine and diazepam (LINKEN, 1971).

7. Side-Effects and Complications

As long as LSD is administered under professional supervision, the incidence of side-effects and complications seems to be relatively low. In 1960, COHEN reported the results of an inquiry among 44 LSD researchers covering 5000 individuals who had undergone one or more LSD sessions for experimental or therapeutic purposes and combined these data with a survey of the literature. He estimated the rate of major complications per thousand patients undergoing therapy as follows: 1.2 attempted suicide; 0.4 completed suicide; 1.8 experienced a psychotic reaction over 48 h. The corresponding figures per thousand normal experimental subjects were: O attempted or completed suicide and 0.8 psychotic reactions persisting longer than 2 days. COHEN concluded that LSD induced only very few toxic or psychologic complications.

This reassuring picture changed dramatically with the advent of illicit and unsupervised use, as noted by the same author 2 years later (COHEN and DITMAN, 1962). The complications most frequently encountered are:

1. Acute panic reactions (FROSCH et al., 1965; COHEN, 1966)
2. Acute paranoid state with acting-out behavior (COHEN, 1966)
3. Confusion state with disorganized behavior (COHEN, 1971)
4. Depression, which may lead to suicide attempts (COHEN, 1966; UNGERLEIDER et al., 1966)
5. Late recurrence of symptoms such as depersonalization and perceptual distortions, which may occur intermittently for weeks or months (FROSCH et al., 1965)
6. Chronic anxiety reactions (COHEN, 1966; UNGERLEIDER et al., 1966)
7. Prolonged psychotic episodes (COHEN and DITMAN, 1962), not only after repeated intake, but also after a single ingestion, chiefly in individuals with underlying schizophrenia (FROSCH et al., 1965).

Since the total number of illicit LSD intakes cannot be determined, the proportion of them leading to complications is unknown, but the magnitude of the problem is illustrated by a survey performed in 1966–1967 in Los Angeles County by UNGERLEIDER et al. (1968b): On the basis of a questionnaire filled out by 1584 professionals (psychiatrists, psychiatric residents, internists, general practitioners, psychologists), the total number of adverse reactions to LSD occuring in this area during an 18-month period was estimated at 4100.

Dealing with illicit use, however, the causal relationship between LSD and the reported reactions is obscured by the fact that black market LSD is of questionable purity and very often contains unknown contaminants, and even more because most subjects have been taking other drugs as well, ranging from barbiturates to amphetamine, marijuana, mescaline, or heroin (COHEN and DITMAN, 1962).

On the other hand, the relative safety of LSD when used therapeutically under adequate supervision in a hospital setting was again stressed in 1969 by DENSON: Among 411 LSD sessions in 237 patients, 87% were entirely uncomplicated, and

only 4% led to major complications, such as confusion, violence, or depression, scores which compare favorably with those of many widely used medicaments.

Whereas the LSD-induced complications encompass a large array of mental and psychologic disorders, somatic side-effects are rather exceptional. In a review covering the LSD complications published up to 1967, SCHWARZ (1968) found only slight indices of suspicion regarding definite physical effects from LSD. Convulsions have been produced in rare instances (COHEN, 1966, 1971). Slight alterations of the electrocardiogram with T-wave flattening and depression of the S-T segment have been observed by TENENBAUM (1961). Acute overdosage leads to a complex toxic symptomatology, which may include extreme hyperthermia (FRIEDMAN and HIRSCH, 1971), emesis, collapse, coma, respiratory arrest, platelet dysfunction, and mild generalized bleeding (KLOCK et al., 1974).

LSD intoxication in children has occured following accidental intake, which is favored by the fact that black market LSD is often deposited on sugar cubes (COHEN, 1966). Transient or prolonged psychotic reactions resembling those of adults usually ensue, but notable differences may also be observed. MILMAN (1967) describes the case of 5-year-old girl who ingested 100 μg LSD and developed, besides a prolonged psychotic reaction, signs of organic brain dysfunction which persisted for several months, with impaired visual-motor function and EEG abnormalities (diffuse high voltage, slowing, dysrhythmia) opposite to those produced by LSD in adults; a similar discrepancy betwenn LSD-induced EEG changes in children and adults was reported by SCHIEFER et al. (1972). A striking case of intoxication in a 2-year-old boy who ingested the huge amount of 180 μg/kg LSD has been described by SAMUELSSON (1974): After an initial phase of extreme excitability with ataxia and mydriasis, the child, without loosing consciousness, went into a state of total catatonia which lasted for about 4 h. Laboratory investigations as well as ECG and EEG remained normal; recovery was uneventful and there were no lasting sequelae.

The possible genetic effects of LSD including chromosomal anomalies are dicussed in detail by GRIFFITH et al. in Chapter XII.

8. Illicit Use and Addiction

Whereas for nearly 15 years, LSD had been used exclusively for scientific or therapeutic purposes by and under the supervision of responsible researchers and clinicians, unsupervised use and abuse of LSD and other hallucinogens quickly developed in the early 1960's, first in the United States and then spreading to Europe and the rest of the world. LUDWIG and LEVINE (1965a) refer to "abuse" when hallucinogens are taken by individuals who have procured them through illicit channels and/or taken them in medically unsupervised or socially unsanctioned settings.

This unfortunate development started with enthusiastic reports of novelists such as Aldous HUXLEY (1954, 1956) on mescaline and of some psychologists of Harvard Universtity (LEARY and ALPERT, 1963; LEARY, 1964) ascribing to LSD mind expanding, creativity-enhancing properties and describing it, as COHEN puts it in a critical review article (1971), "as a solution to all of one's personal problems and a solution the world's woes if it were universally utilized". A sensational,

wide-spread publicity disseminated by the mass media ensued, which triggered the formation of subcultural groups of LSD devotees, some led by psychologists (e.g., the IFIF or International Foundation for Internal Freedom), others formed among students, intellectuals, beatniks, or hippies, many involving a mystique or religious component. Simultaneously, individual use burgeoned among the same categories of people, also including many unstable, emotionally disturbed, unadapted, frustrated persons, neurotics, psychopaths, drug addicts (LUDWIG and LEVINE, 1965a) and permanent dropouts from society (LOURIA, 1968). In 1971, COHEN estimated that 5–10% of all college students in the United States had tried LSD at least once, and that perhaps 1% were regular users. A detailed analysis of the psychologic background of this "epidemy" and of the motives for using LSD has been published by FREEDMAN (1968).

LSD is not physically addicting, and an abstinence syndrome is not identifiable (COHEN, 1971; BROWN, 1972), but a psychologic dependence may be encountered (LUDWIG and LEVINE, 1965a). In a series of LSD users mentioned by SANDISON (1968), nearly three-fourths of all persons who had had LSD expressed an interest in taking it again, and more than half of the regular users showed signs of habituation. Mentions of individuals having taken LSD several hundreds of times are not exceptional in the literature (FROSCH et al., 1965; SANDISON, 1968; MCGLOTHLIN and ARNOLD, 1971). Furthermore, the dose of LSD taken under illicit conditions is often much higher than the 0.5–2.0 or 3.0 μg/kg of body weight, which are regarded as reasonable by responsible researchers and therapists; COHEN (1966) mentions a man who repeatedly took up to 4000 μg at a time, and in his 1971 article, the same author cites one instance where 10 mg was swallowed without a fatal result. The deleterious effects of such chronic use and overdosage may further be aggravated by the fact that many of these individuals are taking not only LSD but indulge in multiple drugs, including other hallucinogens, stimulants, sedatives, and narcotics (COHEN and DITMAN,, 1962; LUDWIG and LEVINE, 1965a; LEUNER, 1971a; TRUBE-BECKER, 1975). Fortunately, according to a follow-up survey of 247 LSD takers, the drug seems to become less attractive with continuous use, so that its abuse becomes self-limiting (MCGLOTHLIN and ARNOLD, 1971).

Up to the early 1960's, Sandoz Ltd. was the sole producer of LSD; it did not introduce the drug commercially and restricted its free-of-charge distribution to carefully selected investigators and experienced therapists. When abuse became evident, in 1965, Sandoz further drastically strengthened its distribution policy for LSD and the related hallucinogen psilocybin; from then on, shipments were made to investigators only if they could produce an official authorization from the health authority of their own country. In the United States, selection of and distribution to the investigators were entirely farmed out to the National Institute of Mental Health. Following these measures, the output of LSD from Sandoz dropped to negligible amounts. Thus, the huge quantities of LSD appearing in illicit trade and use do not originate from a diversion of "legal" LSD but are prepared illegally from lysergic acid (which is now freely available on the fine chemical market), a procedure which does not require particular skill, especially if is not attempted to obtain a completely pure substance. Combined with the above-mentioned lay-press publicity, this easy access to LSD paved the way to the development of abuse. In turn, abuse and misuse imposed severe legal and

administrative restrictions which greatly impeded or even sterilized further research with hallucinogenic drugs, since, as LOURIA (1968) puts it, "it is now far easier to obtain LSD for illicit use than for legitimate and important medical experiments."

D. Clinical Applications of LSD

In addition to its use as an experimental tool to produce transient "model psychoses"—in the hope of reproducing at will and studying the psychodynamic, physical, and biochemical anomalies which characterize and perhaps cause spontaneous psychoses—LSD has been widely used for therapeutic purposes. In the frame of this review, only a short account of the main fields of application can be given.

1. Adjuvant to Psychotherapy

The first attempt to use LSD during sessions of psychotherapy in order to reduce repression and permit recall of traumatic experiences was made as early as 1950 by BUSCH and JOHNSON, but 4 years elapsed before the next reports appeared in the literature (FREDERKING, 1953/54; SANDISON, 1954; SANDISON et al., 1954). From then on, the method has been applied by an increasing number of psychotherapists, until the advent of illicit use and the ensuing legal restrictions drastically limited the access of serious clinicians to this drug. Among the people who have gathered the largest experience with LSD as an aid to psychotherapy, one may cite SANDISON and his co-workers (SANDISON 1954, 1959a, 1960; SANDISON and WHITELAW, 1957; SANDISON et al., 1954), MARTIN (1957, 1962), LING and BUCKMAN (1960, 1963), BIERER and BROWNE (1960) in England; ABRAMSON (1955, 1956a, b, 1957, 1960b), SAVAGE (1957, 1961), EISNER and COHEN (1958), COHEN and EISNER (1959), CHANDLER and HARTMAN (1960) in the United States; LEWIS and SLOANE (1958), BAKER (1964) in Canada; WHITAKER (1964) in Australia; LEUNER and HOLFELD (1962), LEUNER (1963a, b, 1971b) in Germany; BAROLIN (1961) in Austria; VAN RHIJN (1960), ARENDSEN HEIN (1963) in Holland; GEERT-JÖRGENSEN et al. (1964) in Denmark,; STEVENIN and BENOIT (1962) in France; ALHADEFF (1963) in Switzerland; GIBERTI et al. (1956) in Italy; ROJO SIERRA (1959) in Spain; FONTANA (1961) and PÉREZ MORALES (1963a, b) in Argentina.

Besides individual psychotherapy, LSD has also been used to facilitate group therapy, e.g., by FONTANA and ALVAREZ DE TOLEDO (1960), ROJO SIERRA (1960), TENENBAUM (1961), SPENCER (1963), PÉREZ MORALES (1963c), EISNER (1964), and HOFFER (1965).

This combined use of psychotherapy and hallucinogens is sometimes referred to as "psycholytic therapy," according to LEUNER's proposal (LEUNER and HOLFELD, 1962). Obsessive-compulsive neuroses, anxiety neuroses, sexual neuroses and deviations, character disorders, and psychopathy are considered the best subjects. LSD is usually applied in small or medium doses for a series of psychotherapeutic or psychoanalytic sessions. It acts by removing the blocks to insight, relieving emotionally charged memories, intensifying affectual responses, and increasing the

transference relationship to the therapist; the latter lends support and later interprets. Abreactions may occur and ego defenses may be reduced. According to most authors, the psychotherapeutic process may thus be considerably shortened, and cases resistant to conventional methods can be made amenable to therapy.

The true value of LSD in facilitating psychotherapy, however, has been questioned by some investigators. In a controlled study, ROBINSON et al. (1963) found no difference in the outcome of treatment of neurotic patients undergoing either plain or drug-assisted psychotherapy (with oral LSD or i.v. methamphetamine/hexobarbital being applied to induce abreaction). More recently, SOSKIN (1973) compared LSD and a placebo in two parallel series of patients undergoing psychotherapy; as measured by a battery of rating scales, both groups improved moderately, but the LSD patients didn't do better than the placebo patients, neither after five drug-assisted sessions, nor after a 18-month followup. The author hypothesizes that the impressive improvement rates reported by earlier investigators were due to the heightened therapist motivation and involvement, to the unusual amount of time and attention provided to the patient, and to the tacit permission given to the patient to express otherwise unacceptable thoughts and feelings.

2. Psychedelic Therapy

The term "psychedelic"—which means mind-manifesting—has been proposed by OSMOND (1958) for substances such as LSD which, besides mimicking mental illness, are supposed to "enrich the mind and enlarge the vision." It has subsequently been used to designate a therapeutic method developed in Canada and the USA; after a period of psychologic preparation, a high dose of LSD is given for one single session (or at the utmost for a limited number of sessions), the effect often being reinforced by the therapist's attitude, a religious atmosphere, an esthetic surrounding, music (BONNY and PAHNKE, 1972), or even hypnosis (LUDWIG and LEVINE, 1965b), etc. The aim is to produce an overwhelming, "transcendental" experience with ego-dissolving, expansion of consciousness, sense of harmony, or, according to COHEN's formulation (1971), "a psychological death-rebirth experience with the opportunity for a new beginning."

a) Alcoholism

This method has been applied primarily in the treatment of alcoholism. At first, enthusiastic reports were published by SMITH (1958), CHWELOS et al. (1959), SAVAGE (1962), JENSEN and RAMSAY (1963), KURLAND et al. (1967, 1968, 1971), and others. However, on the basis of their literature review, ABUZZAHAB and ANDERSON (1971) concluded that the overall effectiveness remains disappointing. As a matter of fact, none of the controlled studies in which psychedelic therapy has been compared to a no-drug treatment performed under similar circumstances was able to show a significant superiority in the LSD-treated patients (e.g., SMART et al., 1966; VAN DUSEN et al., 1967; JOHNSON, 1969; LUDWIG et al., 1969; DENSON and SYDIAHA, 1970; BOWEN et al., 1970). In their book devoted to a fair appraisal of the therapeutic efficacy of LSD in alcoholism, LUDWIG et al. (1970) conclude that "the various LSD procedures used do not offer any more for the treatment of alcoholism

than an intensive milieu therapy program, and the latter, at best, is quite ineffective in deterring drinking."

b) Narcotic Addicts

The psychedelic method has also been applied on a more limited scale to the treatment of narcotic addicts. Two controlled studies (LUDWIG and LEVINE, 1965b; SAVAGE and MCCABE, 1973) have been performed; they are in favor of the LSD-treated groups.

3. Use in Psychoses

The activating effect of LSD on psychotic symptomatology has been used by some psychiatrists for a therapeutic purpose. Basing on the usual observation that acute schizophrenic phases with abundant productive symptoms show a high tendency to spontaneous remission, JOST (1957) performed a series of LSD sessions in patients with slowly developing, nonproductive forms of the illness; in a number of cases, symptoms were markedly enhanced, and JOST claims that the evolution towards remission was accelerated. SANDISON and WHITELAW (1957) followed an analogous reasoning, but they aborted the acute LSD reaction by a chlorpromazine injection; they report encouraging results in seven out of 14 psychotic patients resistant to orthodox therapy. PERILLO and GARCIA DE LA VILLA (1963) succeeded in activating, by means of LSD, cases of schizophrenic dementia and treated them subsequently with thioridazine.

Somewhat similar experiences were made by ITIL et al. (1969) in therapy-resistant chronic schizophrenics, characterized by a hypersynchronous EEG with predominant alpha activity, who were given a series of i.v. LSD injections; as soon as an acceleration and desynchronization of the EEG, accompanied by an activation of the psychotic symptomatology, became apparent, the hallucinogenic drug was stopped; conventional psychotropic drugs were then reinstated, and proved more effective than before the LSD course.

ABRAMSON et al. (1958a) followed a different approach. They used LSD to enhance communication between a schizophrenic patient and a nonpsychotic "stablemate" during group therapy.

Other investigators, such as LESSE (1959), WIJSENBEEK and LANDAU (1960), had negative results, and most experts consider that LSD is contraindicated in compensated schizophrenics or patients with schizoid personality because of the possibility of precipitation into a psychosis (COHEN, 1960; BAROLIN, 1961).

4. Therapeutic Use in Children

LSD has been used in conjunction with psychoanalysis in psychotic children by ROJAS BERMUDEZ (1960); communication with the therapist was facilitated, and in spite of the high dosage (50–300 μg), no side effects were encountered. FONTANA (1961) notes a progress when associating LSD to psychotherapy in children with character disorder.

BENDER et al. (1962, 1963) and BENDER (1968) applied a different concept in treating schizophrenic children, 6–12 years old, with LSD; the drug was given daily for 2 months or longer in progressively increasing doses of 25–150 μg; no psychotherapy was attempted. Autistic children became less introverted and plastic, more aware and responsive, contact improved, and there was some increase in verbal communication. Intelligent, verbal schizophrenics in the same age group showed an improved behavior, changes in fantasy and bizarre ideation to more insightful and reality-oriented, though often anxious and depressive attitudes, improved maturity and organization. The improvement was confirmed by Rorschach, Bender-Gestalt, and Human Figure Drawing tests. When taken off medication the patients deteriorated and responded again when LSD was resumed. There were no serious side effects. Since BENDER obtained nearly identical results with methysergide, the beneficial effect she observed with LSD was probably not connected to the hallucinogenic action of the latter.

FREEDMAN et al. (1962) also tried LSD in autistic schizophrenic children, not in daily doses like the above authors, but on one single or, at the most, on two occasions, the dose ranging from 50–200 μg. Some reaction was observed, but the hoped-for change from muteness to speech did not occur.

5. Use in Terminal Cancer Patients

KAST (1963) included LSD in his investigations on the analgesic properties of some narcotic compounds in patients suffering from intolerable pain, mostly due to terminal cancer. After a single dose of 100 μg LSD, pain and distress were often relieved for 18 h or longer, and appeared to be reduced for 2 or 3 weeks, the patient becoming indifferent to the pain experience. In addition, depression and apprehension concerning approaching death were lessened. In more recent publications, this author analyzed the psychologic mechanism of the LSD analgesia (KAST and COLLINS, 1964; KAST, 1966) and reported the incidence of adverse reactions in his series of 128 cases: panic episode in 5.5%, mild anxiety in 33%, no adverse somatic effects (KAST, 1967).

A useful pain-relieving and psychologic action in a few patients was also reported by COHEN (1965), who concludes that LSD "may one day provide a technique for altering the meaning—and lessening the dread—of dying"; he doesn't seem, however, to have pursued this line, since no mention is made of this potential use of LSD in his more recent reviews (e.g., COHEN, 1971).

The approach of KURLAND and his group was somewhat different. These investigators (KURLAND et al., 1968, 1973; PAHNKE et al., 1969; GROF et al., 1973) didn't look primarily for an analgesic effect but applied LSD in the frame of a psychedelic therapy, with the aim of alleviating the psychologic stress of the dying patient. After intense preparatory psychotherapy, one session with a high dose of 200–500 μg LSD was conducted and possibly repeated after some time if need arose. For the following days or weeks, the patients exhibited a decrease of their emotional distress, depression, anxiety, insomnia, and psychologic isolation, coupled with a better acceptance and less fear of death; emerging mystical or religious feelings reoriented their philosophy of life, they felt detached from the wordly values. Though analgesia was not the main goal, previously excruciating

pain completely disappeared for days or weeks in several patients, even those in whom the organic lesion seemed to make pain inevitable. In most cases, a certain amount of pain persisted but was no longer the primary focus of the patient's attention.

The latest statistics of these authors include 60 cases, of which 29% improved dramatically and 42% moderately, whereas 23% remained unchanged and 6% became worse (GROF et al., 1973). The LSD session appeared to be rather fatiguing for these debilitated patients. Recently, the KURLAND group tended to replace LSD by i.m. dipropyltryptamine or DPT, a shorter acting and therefore less stressful hallucinogen, which has the added advantage of being uncontaminated by adverse lay publicity.

E. LSD Analogues Tested in Man

A large series of chemical analogues of LSD, some natural but most of them semisynthetic, were prepared in the Sandoz Research Laboratories (HOFMANN, 1958, 1964) and tested systematically in vitro, in laboratory animals, and in man. The purpose was twofold:

1. To try and establish a structure-activity relationship
2. To correlate the hallucinogenic effect in man with biochemical and/or pharmacologic activities, in order to gain some clues regarding the mechanism of the model psychosis.

1. LSD Isomers

The levorotatory isomer l-LSD (No. 61[2]) is completely devoid of psychotomimetic activity (GERONIMUS et al., 1956; HOFMANN, 1958; MURPHREE et al., 1958; ISBELL et al., 1959a) and modifies neither the cortical nor subcortical EEG in man (MONROE et al., 1957). Also devoid of psychotomimetic activity are the two derivatives of isolysergic acid, d-iso-LSD (No. 93c) (HOFMANN, 1958; ISBELL et al., 1959a) and l-iso-LSD (No. 62) (HOFMANN, 1958). Compared to LSD, these three inactive isomers are extremely weak serotonin antagonists (CERLETTI and DOEPFNER, 1958a) and are not pyretogenic in the rabbit (Sandoz Research Laboratories, 1958, 1959) (Table 2). On the other hand, l-LSD and d-iso-LSD do not differ from LSD regarding cholinesterase inhibition (ZSIGMOND et al., 1960); rat brain alkaline phosphatase and malic dehydrogenase are activated to the same extent by LSD and l-LSD; the only difference was found with respect to lactic dehydrogenase, which is not affected by LSD but slightly inhibited by l-LSD (CLARK et al., 1956).

2. Hydrogenated Derivatives

Dihydrolysergic acid diethylamide (Dihydro-LSD, No. 74b) is hydrogenated in positions C_9 and C_{10}. In oral doses of 100–200 µg, it produces strong autonomic disturbances (nausea, emesis, tachycardia, shiver, polyuria, headache, and paraesthesias) but no psychic alterations (CERLETTI, 1956). Its antiserotonin effect is about 50% of that of LSD (CERLETTI and DOEPFNER, 1958a). It produces a decrease

[2] Numbers refer to structural formulas in Chapter II.

of the body temperature of the rat in all doses up to 10 mg/kg, whereas LSD produces a decrease only in doses lower than 1 mg/kg but an increase in high doses (Sandoz Res. Lab., 1959).

2,3-Dihydrolysergic acid diethylamide (see general formula in the chapter "Chemical Background," Fig. 15) induces LSD-like autonomic and mental changes; its potency is estimated by GORODETZKY and ISBELL (1964) at about 15% of that of LSD. Its activity in inducing hyperthermia in rabbits is only 4% of the LSD activity (Sandoz Res. Lab., 1959).

3. Unsubstituted and Monosubstituted Amide Derivatives

d-lysergic acid amide (LA 111, ergine, No. 18) is not hallucinogenic; in doses up to 1 mg i.v., it produces—besides autonomic disturbances such as hypersalivation, emesis, dizziness and diarrhea—sedation, clouding of consciousness, and finally sleep (SOLMS, 1956a, 1956b; ISBELL, 1962). Its antiserotonin potency on the isolated rat uterus is 4% of that of LSD (CERLETTI and DOEPFNER, 1958a).

d-lysergic acid ethylamide (LAE 32, No. 73h), the first analogue tested in man, exerts LSD-like hallucinogenic effects, but these are definitely weaker than after LSD and require higher doses—such as 0.25–2.0 mg by injection—in order to become manifest; on the other hand, indifference, apathy, confusion, even lethargy are prevalent (SOLMS, 1953, 1956a, 1956b; JARVIK et al., 1955a). Perceptual alterations, depersonalization, anxiety, and paranoid reactions are less frequent than after LSD (VON FELSINGER et al., 1956; GIBERTI and GREGORETTI, 1958). According to TONINI and MONTANARI (1955b), the LSD-like response lasts only for 2–3 h. In schizophrenic and oligophrenic patients, SOLMS (1953) observed a sedation and sleep-inducing effect after parenteral or oral doses of 0.25–1.5 mg one to three times daily. ABRAMSON (1959) and ISBELL et al. (1959a) took into account not only the intensity of the LSD-like action—as established by their questionnaire method and by rating of the clinical grade—but also the dose relation to assess the comparative potencies of LSD and a series of analogues (Table 2); using this technique, they estimate the psychotomimetic potency of LAE 32 compared to LSD at 3% and 5%, respectively.

As far as the antiserotonin activity is concerned, LAE 32 exhibits 12% of the antagonistic effectiveness of LSD on the isolated rat uterus (CERLETTI and DOEPFNER, 1958a) and 20% on the rat paw edema (DOEPFNER and CERLETTI, 1958). The effect on the various enzymes parallels that of LSD, with the exception of lactic dehydrogenase, which is not affected by LSD but stimulated by LAE 32 (CLARK et al., 1954, 1956; ZSIGMOND et al., 1960). The conversion of adrenaline to adrenolutin is increased to a greater extent than by LSD (HOFFER et al., 1959). On the body temperature of the rat, the effect of LAE 32 exactly mimics the dual action of LSD: Decrease with doses below 1 mg/kg, increase above this dosage (CERLETTI, 1956); in the rabbit its pyretogenic effect amounts to 17% of that of LSD (Sandoz Res. Lab., 1958).

4. Disubstituted Amide Derivatives

Lysergic acid dimethylamide (DAM 57, No. 73c) is about 10 times less active than LSD as a psychotomimetic agent. Using the already-mentioned quantitative

methods, ABRAMSON (1959) estimates its potency at 11% and ISBELL et al. (1959a) at 10% of that of LSD. On the other hand, it exhibits 20% of the serotonin antagonism of LSD on the rat uterus (CERLETTI and DOEPFNER, 1958a) and 13% on the rat paw edema (DOEPFNER and CERLETTI, 1958). When applied by intracerebral injection to conscious mice, it does not antagonize the stupor-inducing effect of intracerebral serotonin (HALEY, 1957). In the rabbit, it shows about 40% of the pyretogenic effect of LSD (Sandoz Res. Lab., 1958).

Lysergic acid dibutylamide (LBB66, No. 73e) is devoid of LSD-like mental effects (Sandoz Res. Lab., 1959). Its antiserotonin effect is 30% of that of LSD (CERLETTI and DOEPFNER, 1958a).

5. Cyclic Amide Derivatives

Lysergic acid pyrrolidide (LPD824, No. 73f) exhibits a modest LSD-like psychic effect (MURPHREE et al., 1958), which ABRAMSON (1959) quantifies at 5% and ISBELL et al. (1959a) at 10% of the LSD-activity.

As a serotonin-inhibitor, it shows 5% of the LSD-potency (CERLETTI and DOEPFNER, 1958a). Its dual action on the body temperature of the rat is identical to that of LSD (CERLETTI, 1956); as a pyretogenic in the rabbit, it exhibits 10% of the LSD potency (Sandoz Res. Lab., 1958).

Lysergic acid morpholidide (LSM775, No. 73g) produces LSD-like mental changes of short duration (GOGERTY and DILLE, 1957); both ABRAMSON (1959) and ISBELL et al. (1959a) estimate its potency at 11% of the LSD one. Its serotonin antagonism is only 2% of that of LSD (CERLETTI and DOEPFNER, 1958a), its pyretogenic effect in rabbits 10% (GOGERTY and DILLE, 1957; Sandoz Res. Lab., 1958). Behavior modifications in mice, rabbits, cats, and dogs are similar to those produced by LSD (GOGERTY and DILLE, 1957). LSM775 does not differ from LSD regarding cholinesterase inhibition (ZSIGMOND et al., 1960) but, contrary to LSD, does not increase adrenochrome plasma levels (HOFFER et al., 1959).

6. Ring-Substituted Derivatives

Substitutions in position 1 of the ring complex of lysergic acid do not suppress the psychotomimetic property, whereas the antiserotonin activity may even be increased.

1-Methyl-LSD (MLD41, No. 34b), if given in 1.5–3 times higher doses than LSD to normal or psychotic subjects, produces qualitatively similar mental effects of a somewhat lesser intensity (MALITZ et al., 1960, 1962). ABRAMSON (1959) quantifies the LSD-like potency of MLD41 at 36%, ISBELL et al. (1959a) at 33%. As an antiserotonin, it is 3.7 times more active than LSD on the isolated rat uterus (CERLETTI and DOEPFNER, 1958a) and exhibits 90% of the LSD activity on the rat paw edema (DOEPFNER and CERLETTI, 1958). When given by intracerebral injection to mice, it produces the same hyperexcitability syndrome as LSD and blocks the stuporous effect of intracerebral serotonin (HALEY, 1957). On the body temperature of the rat, it produces a decrease at all doses, and its pyretogenic effect on the rabbit is 5% of that of LSD (Sandoz Res. Lab., 1958, 1959).

1-Acetyl-LSD (ALD 52, No. 36f) is as effective as LSD as a psychotomimetic. MALITZ et al. (1960, 1962) compared the effects of LSD (0.1–2.8 μg/kg) and ALD 52

(0.6–3.3 μg/kg) in a large series of subjects and psychotic patients; they found very similar action profiles, but ALD 52 produced somewhat more distortions of the body image and thinking disturbances. ABRAMSON (1959) rates its relative effectiveness at 91%, ISBELL et al. (1959a) at 100% of LSD.

As a serotonin antagonist, it is 2.1 times more active than LSD on the isolated rat uterus (CERLETTI and DOEPFNER, 1958a), and upon intracerebral injection in mice, it produces the same excitatory syndrome and serotonin inhibition as LSD and MLD 41 (HALEY, 1957). On the other hand, it has only a modest pyretogenic effect in the rabbit, amounting to 13% of the LSD activity (Sandoz Res. Lab., 1958).

1-Hydroxymethyl-LSD (OML 632, No. 36h) retains 66% of the mental activity of LSD (ABRAMSON, 1959) and 60% of its antiserotonin potency on the isolated rat uterus (CERLETTI and DOEPFNER, 1958a).

If, however, the 1-substitution is performed on side-chain modifications of LSD, the psychotomimetic effect remains as modest as with the parent compounds, whereas the antiserotonin potency may be dramatically enhanced.

1-Methyl-lysergic acid ethylamide (MLA 74, No. 34e) is the methylated analogue of LAE 32. According to ISBELL et al. (1959a), its LSD-like activity is 4% of that of LSD (LAE 32: 5%). Contrasting with this, as a serotonin antagonist on the isolated rat uterus, it is 8.3 times stronger than LSD and 70 times stronger than LAE 32 (CERLETTI and DOEPFNER, 1958b), whereas on the rat paw edema, it produces only 60% of the LSD effect (DOEPFNER and CERLETTI, 1958). Unlike LAE 32, MLA 74 is practically devoid of pyretogenic effect in rabbits (Sandoz Res. Lab., 1958).

1-Methyl-lysergic acid pyrrolidide (MPD 75, No. 34d) is the methylated analogue of LPD 824. It has only a partial, short-lasting LSD-like psychic action, which ISBELL et al. (1959a) rate at less than 5% of the effect of LSD (LPD 824: 10%). As a serotonin antagonist on the isolated rat uterus, it is 28 times stronger than LPD 824 and 1.3 times stronger than LSD (CERLETTI and DOEPFNER, 1958b). It is not pyretogenic in the rabbit (Sandoz Res. Lab., 1958).

1-Acetyl-lysergic acid ethylamide (ALA 10, No. 36g), the acetylated analogue of LAE 32, exhibits 7% of the psychotomimetic effect of LSD (ISBELL et al., 1959a). Its antiserotonin potency on the isolated rat uterus is 40% of that of LSD (thus three times stronger than LAE 32), whereas its pyretogenic effect in rabbits is only 1% of the LSD action (Sandoz Res. Lab., 1958).

With a substitution in position 2 of the lysergic acid molecule, the psychotomimetic effect is practically cancelled, though the antiserotonin effect is retained or even reinforced.

2-Bromo-lysergic acid diethylamide (2-bromo-LSD, BOL 148, No. 37a) has been one of the first and most widely investigated analogues of LSD. The first tests in normal volunteers and carcinoid patients failed to demonstrate any LSD-like action up to doses of 2 mg i.v. or 7.5 mg orally (CERLETTI and ROTHLIN, 1955; SNOW et al., 1955; ROTHLIN, 1957; HOFFER et al., 1959; SCHERBEL and HARRISON, 1959) but only some sedation. In a more sophisticated, cross-over study with placebos, LSD, and other drugs, JARVIK et al. (1955a) found after BOL 148 a psychotomimetic effect which was very modest indeed but clearly stronger than after a tap-water placebo. ABRAMSON (1959) ascribes 7% of the LSD activity

to BOL 148 but ISBELL et al. (1959a), using a similar method, find only a partial LSD-like effect, smaller than 2%. When administering BOL 148 in very high doses by intravenous infusion (0.5–5.0 mg/min., total doses of 15–160 mg) in normal subjects or carcinoid patients, SCHNECKLOTH et al. (1957) observed psychic changes, such as drowsiness, anxiety, restlessness, feelings of unreality and depersonalization, but there were no hallucinations; oral daily doses up to 20 mg had no psychic effects. Individual hypersensitivity may occur, however, as exemplified by the case, reported by RICHARDS et al. (1958), of a laboratory technician who ingested 0.5 mg BOL 148 during a vascular headache and experienced a clear-cut, LSD-like reaction with distortion of body image, perceptual changes, and a wave-like alternation of euphoria and anxiety.

The antiserotonin effect of BOL 148 is about 100% of that of LSD on the isolated rat uterus (CERLETTI and DOEPFNER, 1958a) and 30% on the rat paw edema (DOEPFNER and CERLETTI, 1958). Regarding cholinesterase inhibition, it does not differ from LSD (ZSIGMOND et al., 1960). Contrary to LSD, BOL 148 does not increase plasma adrenochrome or the conversion of adrenaline to adrenolutin (HOFFER et al., 1959). It decreases the body temperature of the rat at all doses (ROTHLIN, 1957) and exhibits only 5% of the pyretogenic effect of LSD in the rabbit (Sandoz Res. Lab., 1958).

1-Methyl-2-bromo-LSD (MBL 61, No. 37b) was expected to combine the effects of the two ring substitutions. Actually, the psychotomimetic property seems to be completely lost (ISBELL et al., 1959a), whereas the antiserotonin activity on the isolated rat uterus surpasses that of the 1-methyl (370%) and of the 2-bromo (100%) derivatives and amounts to 530% of the LSD effect (CERLETTI and DOEPFNER, 1958a); on the rat paw edema, however, it is only 26% as active as LSD (DOEPFNER and CERLETTI, 1958). It is not pyretogenic in the rabbit (Sandoz Res. Lab., 1958).

7. Ololiuqui

Ololiuqui, one of the three "magic" plants of the Aztecs, has been identified as corresponding to two varieties of morning glory, *Rivea corymbosa* and *Ipomea violacea,* the seeds of which are still being ingested by some Mexican Indians in religious or therapeutic rituals. In a series of self-experiments, OSMOND (1955) developed apathy and hypnagogic phenomena after the ingestion of seeds of *Rivea corymbosa.*

Having succeeded in identifying the active principles of Ololiuqui, HOFMANN and his colleagues (HOFMANN and TSCHERTER, 1960; HOFMANN and CERLETTI, 1961; HOFMANN, 1961, 1963) were surprised to find out that they consisted of six already-known alkaloids of the ergot group, which had all been either prepared synthetically or extracted from various varieties of *Claviceps* but never from higher plants.

One of them was *d-lysergic acid amide* or LA 111 (No. 18), the autonomic and weak psychotomimetic effects of which—chiefly sedation and reduced consciousness—had already been described (page 591).

The second main component was *d-isolysergic acid amide,* or Iso-LA 819 (No. 18a). After its identification in ololiuqui, trials were performed in man with oral

doses up to 5 mg; they revealed central effects which were not LSD-like (ISBELL, 1962) but chiefly consisted in relaxation, synesthesias, and altered time experience (HEIMANN, 1965; HEIM et al., 1968).

Elymoclavine (No. 6) produces mainly sedation (ISBELL and GORODETZKY, 1966).

Lysergol (No. 79a) has no effect up to 6 mg, but 8 mg produce a slight sedation (HEIM et al., 1968).

Ergometrine (No. 19) is a specific uterotonic and has very little central effects (JARVIK et al., 1955a).

The last component, *Chanoclavine,* is a tricyclic alkaloid, which is devoid of ergot-like activities.

In a cross-over study on six former opiate addicts, ISBELL and GORODETZKY (1966) compared the effects of a crude extract containing the total alkaloids of *Ipomea violacea* (5 mg) to the effects of 5 mg of a synthetic mixture of the six components (LA111 45%, Iso-LA819 25%, elymoclavine 5%, lysergol 5%, ergometrine 10%, and chanoclavine 10%), of 1.5 μg/kg LSD and of a placebo. This study confirmed that the crude extract and the synthetic mixture had practically identical, predominantly sedative properties and produced only slight autonomic changes; this contrasted sharply with the spectacular psychotomimetic and autonomic actions of LSD in the same subjects. In another group of addicts, 6 g of ground seeds of *Ipomea violacea* produced only very little effects.

A similar study was performed by HEIMANN and his colleagues (HEIMANN, 1965; HEIM et al., 1968), comparing the artificial mixture of the six alkaloids with LA111, Iso-LA819, and lysergol. They found that low doses of the mixture (2–3 mg) produced a relaxation resembling the effect of Iso-LA819, whereas high doses (6–7 mg) elicited unpleasant autonomic changes and a reduced consciousness, such as observed after LA111. They concluded that the central action of ololiuqui was primarily due to its content in these two main alkaloids.

8. Discussion

Table 2 provides a synoptic view of the LSD-like activity of the various analogues and helps to analyze the *structure-activity relationship.*

The three stereoisomers of LSD are devoid of psychotomimetic properties. The same applies to 9,10-dihydro-LSD, whereas the 2,3-dihydro analogue exhibits an appreciable potency.

After substitutions in position 1 of the lysergic acid moiety, the psychotomimetic effect is only slightly reduced, the less so with acetyl (ALD52) and somewhat more with hydroxymethyl (OML632) or methyl (MLD41) substitution. Also if applied to the less potent lysergic acid ethylamide or pyrrolidide, the 1-substitution (ALA10, MLA74, MPD75) only slightly affects the psychotomimetic activity of the parent compounds LAE32 and LPD824. In this connection, it is interesting that methysergide (UML491, No. 34a), which is the 1-methyl analogue of the purely uterotonic methylergometrine (d-lysergic acid L-2-butanolamide, No. 73a), may produce in some migraine patients mental changes reminiscent of a slight LSD reaction, such as unworldly feelings, dreamy state (GRAHAM, 1964), or even

Table 2. Psychotomimetic activity and some pharmacodynamic effects of structural analogues of LSD

LSD-like activity in man				Pharmacological properties		
	①	②	③	5-HT inhibition isol. rat uterus[i, j]	Body temp. rat[a, b, d]	Pyretogenic effect rabbit[d, k, l]
	LSD = 100			LSD = 100	LSD ↘↗	LSD = 100
High						
1-Acetyl-LSD (ALD 52)	91	100		210		13
1-Hydroxymethyl-LSD (OML 632)	66			60		
1-Methyl-LSD (MLD 41)	36	33		370	↘	5
Medium						
LA Ethylamide (LAE 32)	3	5		12	↘↗	17
1-Acetyl-LA ethylamide (ALA 10)		7		40		1
1-Methyl-LA ethylamide (MLA 74)		4		830		0
LA dimethylamide (DAM 57)	11	10		20		40
LA pyrrolidide (LPD 824)	5	10		5	↘↗	10
LA morpholidide (LSM 775)	11	11		2		10
2,3-Dihydro-LSD			15[f]			4
Partial						
2-Bromo-LSD (BOL 148)	7	< 2	0[b]	100	↘	5
1-Methyl-LA pyrrolidide (MPD 75)		< 5		130		0
Absent						
LA amide (LA 111)			sed[e, g]	4		
Iso-LA amide (Iso-LA 819)			sed[h]			
l-LSD		0	0[c]	0.05		0
d-Iso-LSD		0	0[c]	0.1		0
l-Iso-LSD			0[c]	0.1		0
9,10-Dihydro-LSD (DH-LSD)			0[a]	50	↘	
1-Methyl-2-bromo-LSD (MBL 61)		< 1		530		0
LA dibutylamide (LBB 66)			0[d]	30		
Lysergol			0[h]			
Elymoclavine			0[g]			1.4

LA stands for d-lysergic acid; sed = sedation

①ABRAMSON (1959). ②ISBELL et al. (1959a). ③[a] CERLETTI, (1956); [b] ROTHLIN (1957); [c] HOFMANN (1958); [d]Sandoz Res. Lab. (1959); [e] SOLMS (1956a, b); [f] GORODETZKY and ISBELL (1964); [g] ISBELL and GORODETZKY (1966); [h] HEIM et al. (1968); [i] CERLETTI and DOEPFNER (1958a); [j] CERLETTI and DOEPFNER (1958b); [k] Sandoz Res. Lab. (1958); [l] Chapter VI

hallucinations (HALE and REED, 1962). According to ABRAMSON (1959), this action amounts to 1% of the effect of LSD.

By substitution in position 2 with a bromine atom, on the other hand, the psychotomimetic effect is nearly (BOL 148) or completely (MBL 61) suppressed.

Alterations of the diethylamide side chain have a profound influence on the central activity. The nonsubstituted amides LA 111 and Iso-LA 819 have sedative properties. The monosubstituted ethyl-analogues LAE 32, ALA 10, MLA 74 are psychotomimetic, but about 10–20 times weaker than the corresponding diethylamides LSD, ALD 52, and MLD 41. Regarding disubstituted amides, the psychotomimetic activity is reduced by shortening of the chains (DAM 57) and by ring closure (LPD 824 and LSM 775) and suppressed by lengthening (LBB 66).

In the ergolene derivatives, lysergol and elymoclavine are devoid of psychotomimetic properties.

Table 2 also enables one to examine the *correlation of the psychotomimetic activity with some pharmacological properties.*

The hypothesis that brain serotonin plays a role in maintaining normal mental processes, and that the hallucinogenic effect of LSD and of other psychotomimetic compounds might be connected with their serotonin antagonism has been proposed by various authors, especially by WOOLLEY (WOOLLEY and SHAW, 1954; WOOLLEY, 1958). However, CERLETTI and ROTHLIN (1955) concluded from the lack of LSD-like activity of BOL 148 that such a correlation is not very likely; according to these authors, it cannot be argued that BOL 148 does not penetrate into the brain, since it produces sedation, which is a central effect, and has been detected in the brain in the same amounts as LSD after intravenous injection to mice. Their conclusion is further supported by the complete absence of parallelism between the psychotomimetic activity and the antiserotonin potency, as evidenced by Table 2; very weak as well as very strong serotonin antagonists may be found side by side in the group of compounds with medium as well as in the group with no LSD-like properties.

No correlation exists with the pattern of body temperature reaction in the rat, since the relatively strong hallucinogenic MLD 41 produces a decrease at all dose levels, contrary to LSD and the moderately active hallucinogens LAE 32 and LPD 824, which produce an increase in high doses.

A weak correlation seems to exist with the pyretogenic effect in the rabbit, although there is no parallelism; none of the mentally active analogues possess a pyretogenic potency comparable to that of LSD, and some (ALA 10, MLA 74) have practically no such effect. The nonpsychotomimetic elymoclavine, on the other hand, has a certain hyperthermic effect.

As far as the enzymatic effects are concerned, no correlation emerges from the few results available; cholinesterase inhibition was found in the active compounds LSD, LAE 32, and LSM 775 as well as in inactive ones such as BOL 148, l-LSD, and d-iso-LSD (ZSIGMOND et al., 1960); also regarding dehydrogenases and alkaline phosphatase, there were no striking differences between LSD, LAE 32, and l-LSD (CLARK et al., 1954, 1956).

A further search for such correlations, especially if taking into account more recent findings concerning the biochemistry of brain functions, might have led to a better understanding of the mechanism involved in psychotomimetic reactions.

This was prevented, however, by the decision of Sandoz Ltd. to stop all supply of, and experimentation with, LSD analogues following the surge of hallucinogen abuse in the early 1960's.

F. Cross-Tolerance

Since tolerance to the autonomic and mental effects of LSD rapidly develops upon daily administration, cross-tolerance with closely related hallucinogenic analogues was to be expected (Table 3).

Actually, subjects receiving MLD41 in increasing doses (100–360 μg) for 5–6 days proved totally resistant to the effects of 80–100 μg LSD (ABRAMSON et al., 1958b). Similarly, a partial resistance to LSD was elicited in former narcotic addicts by a 1-week treatment with 0.5–1 mg per day of the weaker hallucinogen LAE32 (ISBELL et al., 1959b), and schizophrenics who had become resistant to LSD following daily i.m. injections of increasing LSD doses (100–400 μg) were also resistant to LAE32 (CHOLDEN et al., 1955).

Cross-tolerance has also been investigated between LSD and hallucinogens unrelated to ergot; here, the results were more variable.

Resistance to *psilocybin* was observed by ISBELL et al. (1961) in subjects who had become resistant to LSD following daily intake for 6–12 days and by ABRAMSON et al. (1960a) after a 5–12 day pretreatment with MLD41; conversely, a few days pretreatment with psilocybin nearly suppressed the autonomic and psychic reactions to LSD (ABRAMSON et al., 1960a; ISBELL et al., 1961); BALESTRIERI (1960), however, did not observe the development of tolerance with psilocybin and cross-tolerance between psilocybin and LSD.

The results are not quite consistent with *mescaline* either. BALESTRIERI and FONTANARI (1959) observed a total resistance to i.v. mescaline after a few days pretreatment with oral LSD and a reduced LSD response in subjects who had become resistant to mescaline following daily i.v. injections. Similarly, WOLBACH et al. (1962) found that subjects receiving 1.5 μg/kg LSD i.m. daily for 14 days became resistant not only to LSD but also to 5 mg/kg mescaline i.m., and conversely, that a 14 days' pretreatment with mescaline produces a tolerance to mescaline and LSD. CHOLDEN et al. (1955), however, did not find a cross-tolerance to mescaline after the development of tolerance to LSD.

N,N-dimethyltryptamine (DMT) produces psychic disturbances resembling the effects of LSD, except for a shorter onset and duration of action. According to ROSENBERG et al. (1964), subjects rendered tolerant to LSD by daily i.m. injections of 1.5 μg/kg for 13 days exhibited no tolerance to 1 mg/kg DMT i.m.; even a LSD tolerance produced by 3 μg/kg i.m. twice daily for 20 days did not suppress, but only attenuated, the response to a small dose of DMT (0.5 mg/kg).

Although *d-amphetamine* is not hallucinogenic, it has certain effects in common with LSD, such as euphoria, anxiety, elevation of body temperature, and blood pressure increase; as with LSD, direct tolerance develops after daily administration. However, subjects tolerant to d-amphetamine are not cross-tolerant to LSD, and subjects tolerant to LSD are not cross-tolerant to d-amphetamine (ROSENBERG et al., 1963).

Table 3. Cross tolerance between LSD, structural analogues, and other hallucinogens in man

Tolerance produced by	Test for cross tolerance with	Cross tolerance present	Remarks
[a] MLD41	[a] LSD	yes	
[a] LAE32	[a] LSD	yes	partial tolerance
[a] LSD	[a] LAE32	yes	
[a] Psilocybin	[a] LSD	yes	BALESTRIERI: no tolerance
[a] LSD	[a] Psilocybin	yes	
[a] MLD41	[a] Psilocybin	yes	
Mescaline	[a] LSD	yes	
[a] LSD	Mescaline	yes	CHOLDEN: no tolerance
[a] LSD	[a] Dimethyltryptamine	(yes)	slight reduction of response
d-amphetamine	[a] LSD	no	
[a] LSD	d-amphetamine	no	
[a] LSD	JB336	no	
[a] LSD	Tetrahydrocannabinol	no	
[a] BOL148	[a] LSD	yes	BALESTRIERI: no tolerance
[a] Methysergide	[a] LSD	yes	

[a] Substances with indole structure

Finally, subjects who had developed tolerance to LSD did not show cross-tolerance to *JB336* (N-methyl-3-piperidyl benzilate) (BALESTRIERI, 1960) or to *tetrahydrocannabinol* or THC, an active principle of marijuana (ISBELL and JASINSKI, 1969); the latter substance causes mental disturbances very similar to the LSD reaction but does not produce the autonomic changes characteristic of LSD, such as elevation in blood pressure and body temperature, pupillary dilatation, and increased knee jerk. The lack of cross-tolerance between LSD and certain other hallucinogens indicates that different mechanisms of action must be involved.

The matter is further complicated by the fact that a certain, albeit inconstant, resistance to LSD may be obtained by a pretreatment with ergot derivatives which are usually devoid of hallucinogenic properties, such as BOL 148 and methysergide. After *BOL148* given in daily doses of 2–30 mg for periods ranging from 2 days to 5 weeks, the response to LSD was completely abolished (GINZEL and MAYER-GROSS, 1956; TURNER et al., 1959) or attenuated (ABRAMSON et al., 1958b; ISBELL et al., 1959b); only BALESTRIERI and FONTANARI (1959) failed to observe a resistance to LSD after BOL 148 pretreatment. Even more surprising is the finding by BERTINO et al. (1959) that a single oral dose of 32–64 μg/kg BOL 148 applied 1 h before LSD is able to considerably reduce the LSD response; no antagonism was found if BOL 148 was given simultaneously with LSD (ISBELL et al., 1959b) or at the height of the LSD reaction (GINZEL and MAYER-GROSS, 1956). It is interesting to note that in the rabbit a premedication with BOL 148 blocks the pyretogenic effect of LSD given 30 min later (HORITA and GOGERTY, 1958).

With *methysergide,* according to BALESTRIERI (1960), a 5–6 days' oral treatment with 2–4 mg per day markedly reduced the reaction to LSD, but a single dose given 1 h before LSD was without effect.

When considering Table 3, it becomes evident that – with the one exception of mescaline – cross-tolerance with LSD is confined to molecules, hallucinogenic or not, which comprise an indole structure. This suggests the involvement of brain receptors with a particular affinity for the indole nucleus.

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