Clin. Pharmacol. Ther. 6, 183-255 (1965). LSD 1310/LAE/OL/BOL/PSI

D-Lysergic acid diethylamide (LSD): A review of its present status

This is a review of an important but controversial subject, written by one of the important figures involved in the controversy. It was not possible to get a review in depth by someone who was not also involved in the controversy. With this in mind, this review was accepted for publication because it was written by an authority actively engaged in the problem and because it was thought important to bring details of the subject to the attention of a large readership. Correspondence is invited.

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I am attempting a comprehensive review of the present status of D-lysergic diethylamide (LSD). Since Albert Hofmann[198-202] first experienced what LSD can do to normal subjects in April of 1943, it has had an astonishing development. By the end of 1950, 6 reports were published. The number of reports for each year until the end of 1957 was 10, 14, 18, 29, 97, 118, 86, and since then about 100 reports per year have appeared.

LSD quickly became involved in several controversies. The first one was whether the experience was a model of schizophrenia. The majority of investigators concluded it was a useful model. The second controversy concerned its clinical use for treating certain classes of psychiatric conditions. The third controversy centers around its psychedelic properties and the legal controls surrounding its use. These three aspects of the use of LSD are still being debated. I hope to present enough information in this review so that each reader can draw his own conclusions.

Received for publication Aug. 20, 1964.

Sources of lysergic acid diethylamide

D-Lysergic acid diethylamide is one of four stereoisomeric alkaloids which can be synthesized from lysergic acid, but it is the only one which has very powerful properties for altering animals' behavior. Its unusual ability to produce model psychoses in man has led it to its present pre-eminent position as a compound which is used to study not only man's aberrant psychological states, but to restore aberrant man to normal. It has enormous appeal to scientists, artists, and theologians as one of the finest scalpels for dissecting the psyche or soul of man.

D-Lysergic acid diethylamide (LSD hereafter) is the culmination of over a century of research into the chemistry of ergot alkaloids. According to Stoll,[370] research on

ergot began around 1850 A.D. with John Stearns' publication, "Account of the Pulvis Parturiens, A Remedy for Quickening Child-Birth." But only seventy-five years later was the first ergot preparation, ergotinine, crystallized, and another forty-five years were needed to prove that the action of ergot on uterine muscle was due to these multiring alkaloids.

There are two main sources of LSD; ergot, known as a poison or toxin for many centuries, and the morning glory plant.

Ergot. Ergot is the rhizomorph of *Claviceps purpurea,* the parasitic fungus which grows in the heads of members of the grass (Gramineae) family. Rye is the principal plant, but enough is found in wheat to worry agriculturists. The fungus destroys the ovaries of the grain and instead of a normal kernel of grain one finds a brownish violet, horn-shaped mass protruding from the head of the grain.

If through careless agriculture or unusual sets of circumstances appreciable amounts of ergot got into the grain and then into the flour or feed, ergotism could and frequently did break out in major epidemics. The major epidemic in France in 994 A.D. killed about 40,000 people, and the epidemic in 1129 A.D. in the Cambrai region killed about 1,200. The epidemics disappeared when strict legislation controlled the quantity of ergot permissible in bread grains.

There are two clinical forms of ergotism, gangrenous and convulsive. Gangrenous ergotism starts with a tingling in the fingers, vomiting, and diarrhea, followed a few days later by gangrene in the fingers and toes. In severe cases dry gangrene of the entire limbs can develop, leading to complete separation. The convulsive form starts the same way but is followed by painful contractions of the muscles of the extremities leading finally to epilepsy-like convulsions. Severe changes in the brain also occur and many of the diseased patients become delirious or psychotic.

Ergotism is extremely rare because of public health nutritional controls, but the discovery that ergot alkaloids are present in the morning glory has produced a new unexpected source, and it is likely physicians now and then will see patients who have ergotism due to their consumption of morning glory seeds. Ergotism also may assume one of two forms in cattle.[353] The classical or gangrenous form is due to chronic poisoning. The tips of the ears, the end of the tail, and the feet become gangrenous. Pregnant animals may abort. The acute form results from the consumption of large quantities in a short period of time. Outstanding symptoms are nervousness, excitability, and incoordination. The animals walk or run with a swaying motion. Farmers have been advised not to feed grain containing more than one to three ergot sclerotium per 1,000 kernels. Later work suggests even this may be toxic.[382] There is no cure for ergotism in livestock.

Morning glory. The psychological studies of Osmond[286] and the chemical investigations of Hofman,[198] corroborated by Taber, Heacock, and Mahon[375] and Genest,[137] are only the culmination of research begun in the distant past in the Central Americans by unknown Indians. Francisco Hermandez in 1570 was the first non-Indian to describe ololiuqui, the narcotic of the Aztecs. Ololiuqui was correctly identified as a member of Convolvulaceae in 1854. This was finally proved by Schultes.[345]

Ololiuqui is *Rivea corymbosa* (*Ipomoea sidaefolia* [HBK]), Choisy, *Turbina corymbosa* (L.) Raf. The plant is a large woody vine with broadly cordate leaves 5 to 9 cm. long with many long white or whitish flowers. The seeds are roundish and rather woody.

Rivea is found in the East Indies, Africa, South and Middle America, and in the West Indies. Only Rivea *corymbosa* is native to the New World.

R. Corymbosa contains two active fractions: (a) a glucoside first isolated by Cook and Kieland,[96] its structure is unknown; and (b) ergot alkaloids,[199-202] identified as ergine (iso-lysergic acid amide),

isoergine (lysergic acid amide), chanoclavine, clymoclavin, and lysergol. Of these, D-lysergic acid amide is the most powerful hallucinogen, having 10 per cent the activity of D-LSD. The amide is also present in ergot growing on some grasses.

Taber and Heacock[374] corroborated Hofmann's findings and demonstrated that the presence of these ergot alkaloids in ololiuqui seeds was not caused by surface contamination by chemicals or spores of fungi. They extracted *Rivea corymbosa* seeds obtained from the Atkins Garden and Research Laboratory, Cienfuegos, Cuba. Using the Vining and Taber[387] method, they found between 20 and 25 mcg. of total alkaloid per seed expressed as ergometrine equivalents (seeds weighed fresh about 20 mg. each, one lot 17 mg., another 25 mg.). The ergot alkaloids were located in the embryo but not in the coat in the resinous layer beneath the coat, or in the membrane located centrally. Both the hypocotyl and cotyledon portions of the seed had alkaloids.

They isolated 52 fungi from the fragmented seeds. These were present in the seed coat, most frequently about the hilum, but not in the embryo. Claviceps species, the previously known source, were not found. Taber and Heacock concluded that the seeds, rather than the contaminant, were the sources of the alkaloid.

Taber, Heacock, and Mahon[375] found ergine and lysergic acid amide in the leaf and stem but not in the root of *Rivea corymbosa* grown in a greenhouse. The amount increased with age until about 0.012 per cent and 0.027 per cent concentration per dry weight of stem and leaf was reached in 9 months. There was no increase in the amount of alkaloid per plant above that found in the seed until the plant was well beyond the cotyledonous stage. The stem and leaves had less total alkaloid than the seed, but, since only one seed per flower is formed, there was as much in the leaf and stem of a plant as in the seeds. Taber, Vining, and Heacock[376] found these alkaloids in a number of commercially available varieties of morning glory. These are members of the convolvulaceous family, as is ololiuqui. The following varieties had these alkaloids in the seeds, per cent fresh weight:

0.04 and higher
Pearly Gates (California)
Ipomoea rubro – Caerulea praecox
Rivea corymbosa – Cuba

0.02 to 0.039
Heavenly Blue (California)
Convolvulus Tricolor Royal Marine
Ipomoea Pearly Gates

0.01 to 0.019
Convolvulus Royal Blue
Convolvulus Mauritanicus
Ipomoea Hybrida Darling
Convolvulus Tricolor Cambridge Blue
Convolvulus Lavender Rosette
Ipomoea Scarlet O'Hara

None of a large number of nonconvolvulaceous seeds contained these alkaloids, including mustard, rape, beans, sweet pea, hemp seed, buckwheat, grapefruit, safflower, sunflower, marigold, poppy, etc. The morning glory Pearly Gates was grown in a greenhouse. The distribution of alkaloids between leaf, stem, and root was the same as that for ololiuqui.

The composition of the alkaloids of Pearly Gates differed from that of ololiuqui. Ololiuqui contained relatively more lysergic acid amide.

Isoergine and chanoclavine made up 34 per cent of Pearly Gates. These authors suggested this could account for the lack of reference in the literature to the psychotomimetric properties of morning glory seeds.

In view of the literature reviewed by Schultes,[345] it is not surprising that Osmond found activity in the ololiuqui seeds. There is not much evidence that the Indians were poorer than white men at introspection and at discovering plants which contained hallucinogenic substances. What was surprising were the failures by Isbell[210] and by Kinross-Wright[229] to find any activity. Presumably Isbell used addicts who perhaps are physiologically different and

would not be expected to respond in the same way. It has been found that alcoholics require over twice as much LSD in order to achieve the psychedelic experience. They were probably also not adept at introspection. In general, such subjects are not the best type of volunteers to use.

Kinross-Wright used 8 male subjects (no further description was given) who were given crushed seeds ranging in weight from 0.25 to 2.25 grams (the latter equaled 125 seeds). Apart from emesis in 2 cases and later mild gastrointestinal discomfort, there were no observable changes objectively or subjectively. Kinross-Wright also prepared ethereal extracts and alcoholic extracts of the seeds. But, since the ergot alkaloids would probably be present as salts, very little would be taken out by the ether or alcohol. The salt would first have to be split by alkali. Thus Vining and Taber[387] treated ololiuqui seeds with 10 per cent ammonium hydroxide before extracting with ether. Taber and Heacock[374] extracted the seeds three times with alkaline ether in order to get out the alkaloids.

Ethanol would remove some of the glucoside, but even here Cook and Kieland[96] first de-fatted the pulverized seeds. The self-experiments by Kinross-Wright were also negative even though he consumed up to 50 seeds (1 Gm.). He concluded that the evidence against *Rivea Corymbosa* having any psychopharmacologic activity was incontrovertible and he further suggested that those who believed *Rivea corymbosa* was psychologically active had overidentified with the ololiuqui legend. Finally, Kinross-Wright resurrects the old hypothesis so uncritically accepted by Safford that ololiuqui was made from Datura species, even though this had been finally overthrown by Schultes and even though the belladonna psychoses are quite different from the accounts of the ololiuqui-induced reactions.

Ololiuqui was used extensively as an ingredient of magical ointments and potions, as an anesthetic agent or analgesic agent. Most of the early writers about ololiuqui described these medicinal properties. I agree with Schultes' conclusion that further investigation of this interesting plant may reveal unusual analgesic chemicals.

Solms[360] compared the psychological activity of LSD, lysergic acid monoethylamide (LAE), and lysergic acid amide (LA). The experimental subjects were chiefly male physicians and chemists. About 0.1 to 1.0 mg. of LA was required to produce the typical LA effect; i.e., it seemed to have only one-tenth the activity of LSD. It was, however, comparable to LAE in dosage requirement. In contrast to LAE, LA produced a greater degree of indifference, a decrease in psychomotor activity, and a desire to sleep more strongly than LAE. Finally, sleep was produced after 30 minutes to one hour. If not awakened, subjects slept about 2 hours. With higher doses autonomic changes developed, such as emesis, diarrhea, and dizziness but there were no hallucinatory changes. Sometimes the subject was irritable and depressed. Thus, removing the ethyl groups decreased the hallucinogenic power of the ergot alkaloid, decreased the psychomotor activity, and sedated the subjects. It is, of course, possible that anything which removed the intensity of visual changes should allow the natural relaxing or sedative power of the ergot alkaloids to appear. It may well be it is the intensity, variety, and excitement of the visual and other perceptual changes which are responsible for the wakefulness induced in subjects by LSD.

This account of LA's effect by Solms differs in some degree from the reports of Osmond and Schultes. It is possible that the other constituents of ololiuqui alter the experience. The chief other constituent is the glucoside already discussed.

Rivea corymbosa (ololiuqui) is one of the semitropical varieties of the huge morning glory plant. After Hofmann's incredible discovery in 1960, it became apparent to many investigators and many curious nonprofessonals that the native morning glory might be as good a hallucinogen. The use

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of two varieties aptly called "Heavenly Blue" and "Pearly Gates" is expanding. "Wedding Bells," the richest,[137] is described by Cohen,[89] * who wrote, "A feed and seed store is an odd place to purchase dreams." The successful "blastoffs into inner space" started a wave of new morning glory seed purchases. Federal agents seized a hundred pounds of the seeds in a raid in Harlem. Psychotherapists, cut off from their supplies of the established hallucinogenic drugs by the recent Food and Drugs regulations, also dabbled with the black seeds of the twined vine. The "beat" group gave it a play. Columnists began mentioning it in the press, and everyone who could read had become aware of the fascinating possibility that the colorful flowers under their sill might have attractions other than visual beauty.

A horticultural magazine of a few years ago says: "The Morning Glory is one of the most popular plants for screening unsightly objects." This statement now takes on meanings well beyond the intended at that time.

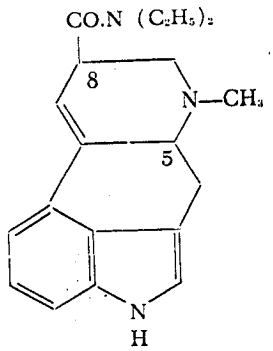
"The ingestion of large numbers of morning glory seeds by the adventurous is not recommended. Their action is variable and can be disastrous. Even should the desired mystical state be achieved, definite adverse effects might occur if the individual is not protected and suitable counter-measures are not available. The price of morning glory could be too high."

Chemistry

D-Lysergic acid diethylamide has the structure shown in the next column.

Carbons 5 and 8 are asymmetric and 4 isomeric, optically active isomers are possible and are known. These are D- and L-lysergic acid diethylamide and D- and L-isolysergic acid diethylamide.[370-371]

D-LSD crystallizes from benzene in pointed prisms. Its melting point is 83 and



its optical rotation $[\alpha]_D^{20}$ + 30°. It is usually stabilized in solution as the tartrate salt.

Pharmacology

According to Rothlin[314-316] and Hofmann[200] LSD is quickly absorbed. In the blood of the rat it was neither bound nor destroyed. In homogenates of the liver or muscle it lost 50 per cent of its activity in a few minutes. During the next 17 hours there was little additional change. In brain homogenates LSD activity was reduced to 42 per cent after 10 minutes and to 20 per cent in 17 hours. The decrease was the same at 3° and 38° C.

The distribution in blood and organs in mice and rats has been studied by direct assay and by radioactive tracer studies. The half-life (50 per cent disappearance) in blood was 7 to 10 minutes by tracer studies and 35 minutes by direct assay. The maximum level was reached in 10 to 15 minutes in most organs, in 30 minutes in the liver. The amount in various organs in decreasing order was gut, liver, kidney, adrenals, lung, spleen, heart, muscle, skin, and brain. Axelrod, Brady, Witkop, and Evarts[31] found the same general distribution. They calculated the brain to have 0.0003 μg per gram (0.3 μg per human brain).

After 12 hours 70 per cent of the radioactivity was in the gut. Only 7 to 8 per cent of the radioactivity was excreted in 12 hours. Only 10 to 20 per cent reached sys-

*From Cohen, S.: What Price Morning Glory, Mind 2:217-220, 1964.

temic circulation in the rat when given intraperitoneally.[53] LSD passed quickly from the blood, built up very quickly in the organs and brain, and was excreted quickly into bile.

Most of the LSD undergoes chemical change. Paper chromatography showed that bile contained three different radioactive substances. One of the derivatives of LSD was 2-oxy LSD.[30, 129] This substance in doses of 300 mcg. did not alter spontaneous cortical activity and had no psychological effect. Axelrod and co-workers[31] found that the half-life in cat blood was 130 minutes, and in monkeys 100 minutes.

The following review of the pharmacophysiologic effects is taken from Rothlin's[314-316] excellent account. On the peripheral body LSD had a direct effect. In vitro and in vivo it contracted the rabbit uterus but was a bit less active than ergometrine. It caused vasoconstriction in perfused blood vessels of rat kidney, rabbit ear, and in the cat spine. In the intact animal there was a decrease in blood pressure. LSD selectively antagonized serotonin on isolated rat uterus, smooth muscles of guinea pig gut, blood vessels, and bronchial muscles in vivo. It expanded the chromatophores of the female guppy. Long pretreatment with serotonin inhibited this.

LSD increased the amplitude of the heart of *Venus mercenaria* without altering its sensitivity to acetylcholine. It mimicked the action of serotonin on the heart of *Venus mercenaria,* but in contrast to serotonin its effect was not decreased by washing the heart. LSD produced both sympathetic and parasympathetic effects. Rinkel, Hyde, Solomon, and Hoagland[312] studied the effect of 1 or 0.5 mcg. per kilogram. Under LSD the pulse rate was 90 per minute compared to 84 for the controls; the pulse rate was also more stable. There was no effect on blood pressure but under LSD a dynamic interview increased the pressure a bit more. LSD did not alter the blood pressure response to noradrenaline, but the systolic response to adrenaline under LSD was less. Sankar and co-workers[331] reported that chronic treatment with LSD increased the response to adrenaline.

Respiration may be elevated or lowered. Rinkel and colleagues[308, 309, 312] found it was more variable. Very high doses in animals caused inhibition and paralysis. Mydriasis is the most common feature. Rinkel and co-workers measured pupil size increases from 3 to 5.25 mm. This is one of the most useful physiologic changes and is an excellent measure of the response to LSD.

The most sensitive measure of activity in animals is the marked pyretogenic effect in rabbits.[316] Doses as low as 0.5 to 1 mcg. per kilogram raised the temperature of rabbits. The pyretogenic response in rabbits and the psychic response in humans run a paralleled time course.

LSD has an interesting effect on pain. Kast[224] studied the analgesic effects of LSD. He compared 2 mg. of dihydromorphinone HCl (Dilaudid), 100 meperidine HCl against 100 mcg. of LSD. The first hour after the drug was given there were no differences. During the second hour Dilaudid was better than meperidine or LSD. During the third hour LSD was better than both. With Dilaudid and meperidine, analgesia began to wear off during the third hour but it still remained low for LSD. With meperidine the patients were free of pain 5.7 20 minute periods; with Dilaudid, 81.4; and with LSD, 95.6 or 32 hours. Since this study was made on 50 gravely ill subjects suffering intense pain, the results are very impressive.

Biochemistry

Sankar and associates[330, 332] studied the effect of LSD in rats on some parameters of biochemical change. They gave the rats 500 mcg. of LSD (intraperitoneally) per day for 2 consecutive days. LSD decreased feed intake, decreased urea excretion, increased ammonia excretion, and decreased the excretion of creatinine, keto acid, phosphate, sodium, potassium, and total amines. The decrease in keto acids and urea excre-

tion was marked. The effect on phosphate excretion will be described.

Neurophysiologic effects of LSD

Effect on spontaneous cerebral activity. In his review, Evarts[114] summarized many animal studies. LSD decreased the amplitude of spontaneous activity in rabbits but did not block the response to activation. In curarized rabbits, small doses (1 to 5 mcg. per kilogram) decreased the amplitude and increased frequency.[304] Doses in micrograms per kilogram caused a continuous alert pattern, and 20 to 60 mcg. caused the reappearance of slow waves. Frenquel blocked these effects.[302, 303, 305] They concluded that LSD stimulated the mesodiencephalic activating system.

The electroencephalographic patterns of cats were also activated by LSD when given orally or into the brain ventricles.[55, 110, 152] LSD abolished barbiturate spindles, i.e., countered barbiturate depression.

Changes in human cortical activity have been slight. Rinkel and co-workers[310] reported that LSD increased alpha frequency slightly. Gastaut and co-workers[134] found that 40 to 60 mcg. of LSD suppressed alpha activity and increased frequency in 9 out of 10 subjects. In 6 out of 12 subjects beta activity was increased. In 7 of 12 cases photic stimulation augmented occipitally evoked potentials, and in 5 the responses radiated to the frontal region. They suggested that LSD reduced the filtering of impulses through nervous centers by increasing neuron excitability. Schwarz, Bickford, and Rome[346] found minimal changes in 13 subjects given 50 mcg. of LSD. In 7 they observed some reduction in the alpha rhythm.

Pfeiffer, Jenny, Murphree, and Goldstein[295] and Goldstein, Murphree, and Pfeiffer[144] used a quantitative analysis of EEG changes. This method provides a measure of the electrical energy output measured at the scalp. Normal subjects have organized but variable activity. When they took LSD there was a reduction in the mean energy accompanied by a reduction in EEG variability. In this, LSD resembled amphetamine. When LSD was given to chronic schizophrenic patients, there was no change in energy content. Instead there was an increase in variability, which was at its maximum in 1½ hours.

Effect on spontaneous activity in the deep areas of the brain. Monroe and associates[278] used depth electrodes for measuring electrical activity in the brain. They had found that in chronic schizophrenic patients[163] the deep electrodes placed in the hippocampal, amygdaloid, and septal areas of the brain picked up marked pathologic activity even when none appeared in the skull electrograms. LSD given to their subjects activated this schizophrenia-like activity in these areas. Paroxysmal activity in the hippocampal, amygdaloid, and septal regions appeared. This correlated with the increase in psychotic behavior.

Monroe and Heath[277] compared the activity of several LSD analogues in monkeys and cats. LSD had the most marked activity. DAM and LPD had moderate EEG activity and had about 10 per cent of LSD's psychological activity. MLD-4 and LSM had minimal activity on the EEG and 20 to 40 per cent of LSD's psychological activity. L-LSD, BOL, and UML had no EEG or psychological effect. In sharp contrast, ALD-52 is as active psychologically as LSD. Perhaps this is due to a slower release of LSD from its acetyl derivative.

Effect on synaptic transmission. Marrazzi and Hart[260-262] found that intracarotid administration of LSD reduced amplitude of the postsynaptic component of the transcallosal response. Marrazzi[253-259] showed that all the hallucinogens cause some inhibition of this synapse but there are no quantitative relationships. Marrazzi suggested that hallucinations resulted from some disturbance in normal neuronal patterns of activity because of this kind of synaptic inhibition.

Evarts and co-workers[115] found that LSD also inhibited synaptic transmission in the visual system of the cat. Intracarotid ad-

ministration of 30 mcg. per kilogram decreased the geniculate postsynaptic response 80 per cent. The transmission within the retina and between geniculate radiation fibers and cortical cells was very resistant to LSD inhibition.

Purpura[298-301] found that LSD facilitated the primary cortical responses to auditory and visual stimulation and altered the recovery rate. Higher doses depressed the auditorily evoked potential but still facilitated the visually evoked ones. Purpura believed LSD inhibited synapses at apical dendrites, resulting in a cortical aroused pattern.

Effect on electroretinograms. Apter and Pfeiffer[23, 24] found that LSD initiated spontaneous action potentials in the retinas of anesthetized cats. Large spikes appeared in the visual cortex of the cats after LSD; they disappeared when the optic nerves were severed. Apter and Pfeiffer concluded that LSD hallucinations are not due entirely to central activity, but also depend upon the retinal changes.

Comparison of activity of some ergot alkaloids

A large number of derivatives of LSD have been synthesized by Sandoz Pharmaceuticals.[315] They may be divided into five main groups.

Group 1. These are the 4 isomers of LSD. Of these, only D-LSD is active psychologically.

Group 2. In these compounds the double

Table I. *Comparative activity of some lysergic acid alkaloids*

Full name	*Code*	*Toxicity in rabbits (intravenous)*	*Pyretogenic effect*	*Antiserotonin effect*	*Psychological effect in man*	*EEG activation*
Group 1						
D-Lysergic acid diethylamide	D-LSD-25	100	100	100	100	Marked
L-Lysergic acid diethylamide	L-LSD	1.8	0	0	0	None
D-Iso-lysergic acid diethylamide	D-iso-LSD	3.7	0	0	0	
Group 3						
D-L-Methyl lysergic acid diethylamide	MLD-41	5.6	5	370	40	Minimal
D-L-Acetyl lysergic acid diethylamide	ALD-52	19	13	200	100	None
D-2-Brom lysergic acid diethylamide	BOL-148	5	5	103	0	None
4-L-Methyl-2-brom lysergic acid diethylamide	MBL-61	2	0	533	0	
Group 4						
D-Lysergic acid amide					10	
D-Lysergic acid ethyl amide	LAE-32	34	17	12	5	AL
D-Lysergic acid dimethylamide	DAM-57	78	43	23	10	Moderate
D-Lysergic acid pyrrolidide	LPD-824	73	10	5	10	Moderate
D-Lysergic acid morpholide	LSM-775	43	10	2	20	Minimal
Group 5						
D-L-Methyl lysergic acid monoethylamide	MLA-74	3.2	0	835	5	
D-L-Acetyl lysergic acid monoethylamide	ALA-10	6	1	39	5	
D-L-Methyl lysergic acid pyrroliddide	MPD-75	4	0	130	7	

bond between carbons 9 and 10 is saturated to give dihydro-D-lysergic acid diethylamide or lumi-D-lysergic acid diethylamide. Both are psychologically inactive.

Group 3. These are compounds where substitution is made on the indole nucleus. One of these, D-L-acetyl lysergic acid diethylamide, is as active psychologically as LSD, probably because the substituent group is easily hydrolyzed.

Group 4. These are monosubstitution compounds of the amine nitrogen.

Group 5. These are disubstitution derivatives of the amide nitrogen.

A comparison of some of the common alkaloids which have been investigated is shown in Table I.[6, 74, 199, 360]

Of the three pharmacologic indices, the pyretogenic activity in rabbits correlated best with psychotomimetic activity.

Toxicology of LSD

The toxicology of LSD has been reviewed by Rothlin and Cerletti[317] and Rothlin.[315] The intravenous acute LD_{50} varies with the species. It is 46 mg. per kilogram for the mouse, 16.5 mg. per kilogram for the rat, and 0.3 mg. per kilogram for the rabbit. An elephant died after being given 297 mg. of LSD,[395] a dose considered 99 times too large by Harwood[159] for producing an LSD experience in elephants. If the LD_{50} for elephants weighing roughly 5,000 kilograms is about 300 mg. (0.15 mg. per kilogram), there is an interesting relationship between total body weight and acute toxicity, which decreases from 46 mg. per kilogram for the smallest mammal tested to 0.15 mg. per kilogram for the largest land mammal. By interpolation one could assume the LD_{50} for man is 0.2 mg. per kilogram, or 14,000 mcg. This may be too low since some subjects have been given 1 mg. safely. But the data suggest that doses larger than this might be dangerous. In chronic experiments, rats tolerated 2.5 mg. per kilogram intravenously daily for 30 days. The rats showed increased reflex responses, mydriasis, piloerection, and growth was slowed. There was no cumulative effect. The animals had the same LD_{50} as untreated animals. No tolerance for toxicity developed.

LSD is so powerful that doses given to humans are a very small fraction of the hypothetical toxic dose. From a physiologic point of view, it is not a toxin for the human body when recommended doses are used. It has been given in doses of 100 mcg. per day for many months with no harmful effects.

The increasing use of morning glory seeds will lead to some toxic effects. This toxicity is due not only to the lysergic acid amide which is present but the seeds also contain substantial quantities of other ergot alkaloids. Subjects who consume many hundred seeds several days in a row run the risk of poisoning themselves with ergot and they may manifest symptoms of ergotism. A couple of subjects did consume too many seeds and for 48 hours one suffered pronounced vasoconstriction and coldness of the hands. This might have been a prelude to gangrenous ergotism. The seeds probably also contain other substances which have not been investigated.

Complications of LSD use. The complications which may follow the use of LSD must be differentiated sharply from its toxicology. As I have shown, LSD does not produce a toxic state in humans because man is not toxic physically. But there are two kinds of complications following LSD therapy: (1) the reaction may be too intense and (2) the reaction may be too long. While under the influence of LSD, subjects may carry out decisions which they normally would not and which they may regret. The experience alters one's judgment, and this may lead to thoughtless acts which endanger the subject or others. If the reaction lasts too long, it is no different from having schizophrenia, and the person is affected in much the same way.

The basic rules for using LSD are, therefore: (1) keep the reaction under control and (2) do not let it operate too long. When accidents do happen, it is safe to assume these cautionary measures have not

been followed. There is a high correlation between the number of harmful complications in subjects and the degree of incompetence of the therapists giving the LSD. The most incompetent can be the subject who administers it to himself; in these instances there have been many accidents.

The most thorough studies of the complications were compiled by Cohen[86] and Cohen and Ditman.[90, 91] Cohen[86] collected the results of LSD complications from 44 investigators (out of 62 queried). This group gave about 5,000 subjects either LSD or mescaline 25,000 times. Each subject was given 25 to 1,500 mcg. one to eighty times.

There were no serious physical side effects. The most common problems during the LSD experience were unmanageability or panic and severe physical complaints. Cohen found that with few exceptions therapists who wish to prove hallucinogenic agents are of no value for psychiatric explorations have unhappy reactions with it. In a small series of studies, four analysts had adverse reactions with 100 mcg. of LSD.

The most common prolonged reaction was short-lived depression. Five out of 5,000 subjects (25,000 experiences) attempted suicide. Four completed suicide many months after an LSD session. Considering that LSD has usually been given to the most hopeless psychiatric cases including addicts, alcoholics, psychopaths, and others with personality problems, as well as those with depressions, this is a remarkably low suicide rate. It is likely that LSD decreased the rate since in such a group of subjects I would expect a higher mortality rate by suicide.

Cohen also reported several prolonged reactions to LSD. These are extremely interesting from a theoretical point of view. Hoch and Malitz (Cohen's respondents) reported that LSD was given to a normal twin (the other was schizophrenic) of a pair of identical twins. Two days later the reaction recurred and the subject had to be treated in hospital for 5 days. Cohen reported there were 8 prolonged reactions but 7 were in patients undergoing psychotherapy at the same time. No subjects became addicted to LSD.

Cohen concluded that the following precautions must be followed: (1) proper screening of subjects, prepsychotics are a contraindication; (2) adequate observation and control during the experience; (3) adequate supervision after LSD.

Had these simple rules been observed, many of the complications could have been avoided. In a further report, Cohen and Ditman[90] concluded that LSD-25 used properly was an important instrument for investigating problems in the study of the mind. These authors[91] then reviewed a series of prolonged psychotic reactions.

Case 1. This subject developed schizophrenic psychosis 10 days after an LSD experience and required several admissions to the hospital.

Case 2. A secretary took LSD 200 to 300 times over a three-year period in doses of 25 to 400 mcg.; i.e., she averaged one session every 4 days. She also took other hallucinogens.

Case 3. A chronically depressed person had made a suicidal attempt and had been treated with electroconvulsive therapy (ECT). He had 8 sessions of LSD therapy and remained psychotic for 2 years.

Case 4. A boy, aged 10, by accident ingested a sugar cube containing 100 mcg. of LSD. He was abnormal for one month.

Case 5. A hypnotist had 25 therapeutic sessions with LSD. He remained psychotic for 7 months. In addition, one subject remained depressed and in 2 pre-existing psychopathic traits were released.

The remarkable fact about all the LSD complications are that they are extremely rare. They have occurred among those who are emotionally labile, hysterical, or paranoid. In the majority of cases the subjects have obtained LSD from improper sources and many have dabbled in other drug use, such as peyote, marijuana, amphetamine, barbiturates, and narcotics.

Reasons for complications.

During the experience. If any complica-

tions arise during the experience, they are probably caused by the inexperience or incompetence of the therapist. Complications may arise because the experience produces great confusion, deep depression, paranoid ideation, or pan-anxiety. The therapist must be able to anticipate these changes and take proper remedial action. These reactions do not come abruptly and in nearly every case the subject has indicated in many ways what will probably happen.

Prolonged experiences. Cohen and Ditman[90, 91] recommended that LSD not be given to prepsychotic individuals. This is very important. These patients have the biochemical abnormality present in schizophrenia but it has not been fully expressed clinically. The LSD may intensify the biochemical abnormality and the experience may drive them into schizophrenia. Both factors operating simultaneously may send the subject into schizophrenia for a long time.

There are three lines of evidence for viewing schizophrenia as a contraindication.

A. Subjects with schizophrenia have had very prolonged reactions to LSD.[91] I have seen one case in Saskatchewan. The subject was a clinical psychologist who was able to acquire a small supply of LSD from my research stock. At his home he took LSD three times over a period of one week with no supervision. After the last dose of LSD he was unable to fall asleep and after many hours of wakefulness his wife finally sought help. He was admitted to the University Hospital. On admission he was clearly a paranoid schizophrenic. He was treated with nicotinic acid, 3 Gm. per day, and a series of ECT. After he recovered it became clear that the subject had been on the edge of schizophrenia for some weeks before. The use of LSD, against regulations, was merely an illustration of his psychotic judgment, and the injudicious self-abuse with LSD merely forced him deeper into psychosis. The subject continued to take nicotinic acid for 12 months after discharge and remained well. One year later the schizophrenia recurred but the man had not precipitated this one with LSD.

B. I have already referred to Hoch and Malitz's identical twin pair in which the normal member suffered a reactivation of the LSD experience. This suggests that the twin had latent in him the biochemical potential for becoming schizophrenic. The study of Anastasopoulos and Photiades[21] almost proves this. These investigators gave LSD 97 times to relatives of 21 schizophrenic patients. The relatives were parents, siblings, uncles, and aunts. Each was given 0.5 to 1 mcg. per kilogram. Out of 21 families in only one were both parents and siblings normal LSD reactors. In all other cases at least one parent of a schizophrenic patient had an abnormal LSD reaction. These reactions included: (1) paranoid features, ideas of reference; (2)deliria; (3) strong feelings of unreality which they could not delineate from reality and which caused them anxiety; and (4) severe depression.

Visual and auditory hallucinations were common, leading finally to complete inability to understand what was going on. Reassurance was rarely accepted. The acute phase of the intoxication lasted a few days to 6 weeks. Persistent insomnia was very common.

Two examples from these families illustrate the relationship of abnormal reactors to schizophrenic members.

In one family the father reacted abnormally to LSD while his wife and brother reacted normally. They had 4 children. One son reacted normally, one son and one daughter reacted abnormally, and one daughter was schizophrenic. In the second family one woman married twice. She reacted abnormally but had one sister who reacted normally to LSD. She had 3 children: one daughter who reacted normally to LSD, one son who reacted abnormally to LSD, and one daughter who was schizophrenic. She married a second time to a man who reacted normally to LSD. There

were 2 daughters. Of these, one was schizophrenic and the other reacted abnormally to LSD. The second husband had had a previous marriage, with one son who had reacted normally.

The frequency of abnormal reactions to LSD was very high and supports the view that these families had a powerful potential for becoming schizophrenic and that LSD triggered the transient schizophrenia in them. Cohen and Ditman found about 10 from several thousand cases. But Anastasopoulos and Photiades found that more than one third of their 97 subjects reacted this way; i.e., members of families where there is one schizophrenic individual have a 0.33 or better chance of becoming temporarily schizophrenic under LSD. The expected incidence in Saskatchewan is 10 out of 1,000 or 0.1; i.e., being a sibling or parent of a schizophrenic increases the likelihood of having a schizophrenic reaction about 33 times.

C. As a consequence of my interest in the biochemistry of LSD, we found that about 20 per cent of the subjects excreted high Rf mauve staining substances in the urine after LSD when it was not present before. This paper chromatographic technique is described by Irvine[208] and Hoffer and Mahon,[188] and the clinical implications of this findings have been described by Hoffer and Osmond.[192, 193, 195] The still unknown substance is not an LSD derivative but appears to come ultimately from one of the amino acids. Very large numbers of patients have been tested over the past 5 years. Table II gives the frequency with which it appeared.

The presence of this mauve factor cuts across all diagnostic groups, but it is clearly related to the schizophrenics. When subjects with schizophrenia recover, it vanishes; if they relapse it reappears first. This also occurs with nonschizophrenics who recover or relapse. There are many similarities between all subjects who have the mauve factor in all groups. These factors are their clinical description, the results of psychological tests, EEG changes, the response to treatment, etc. Hoffer and Osmond[195] therefore concluded that the mauve test could be a diagnostic test for a syndrome they called malvaria. A malvarian is any human who excretes the mauve factor in the urine. It is completely an operational definition.

Table II. *Frequency of the presence of the mauve factor in the urine of various groups of patients*

Group	*No.*	*Per cent with factor*
Schizophrenia		
A. Not treated	200	75
B. Treated—recovered	50	0
C. Treated—not recovered	300	50
Neurosis, personality problems, etc.	250	20
Physically ill, mentally normal	100	10
Normal	100	5

I have examined the relationship between malvaria and the prolonged responses to LSD. If all malvarians are indeed biochemical schizophrenics (not recognized clinically), then the prolonged responses of schizophrenics already reported would lead to the prediction that malvarians would also suffer prolonged reactions. In Saskatchewan we have given LSD to 1,000 subjects—a total of 2,000 treatments or more (2 per subject). Only a small proportion of this group had the urine tested, but so far no subject free of malvaria has had a prolonged reaction, whereas 4 out of 20 malvarians had reactions lasting a week or more. None of the malvarians was clinically schizophrenic. The frequency therefore is 20 per cent, which is close to that found by Anastasopoulos and Photiades[21] for relatives of schizophrenics. The probability of having a prolonged reaction if one has malvaria is 0.20; this is somewhat lower than that for relatives of schizophrenics but much higher than the expected incidence for normal subjects. Because there are so many

variables involved, the only safe conclusion is that malvarians and schizophrenic relatives have a much greater chance of having prolonged reactions.

Suggested rules for LSD therapy. (1) Treat in the hospital. (2) Observe constantly (even to bathroom) until out of the experience. (3) Terminate if panic or severe psychotomimetic reactions occur with nicotinic acid, if it is decided to continue psychotherapy, and tranquilizers, if the session is to be terminated. (4) Discharge only if completely recovered. (5) Contraindications include (a) acute schizophrenia, (b) malvaria, (c) severe depression.

Relation of dose of LSD to psychological activity

One could determine the dose-response relationship for each parameter of LSD's activity. For many of the parameters there will be a more or less linear relationship, but with larger doses Wilders law[398] would come into play. I will consider only the dose-hallucinogenic response.

Minimal recognizable dose. The minimal effective dose is about 25 mcg. per adult subject. Stoll[367-369] used 20 to 30 mcg. orally. A few years ago I completed several double-blind recognition trials with 5 normal volunteers. Fifteen micrograms per subject was not recognized reliably against placebo but most subjects were able to detect 25 mcg. quantities.

Optimum psychotomimetic or psychedelic dose. This varies between about 100 mcg. to 1,000 mcg., depending upon the variables described. For nonalcoholics it varies from 100 to 200 mcg. For alcoholics it usually ranges from 100 to 500 mcg.

Relationship between minimal recognizable dose and optimal dose. Abramson and associates[14] studied the dose response of 31 nonpsychotic volunteers. The doses were 0, 1 to 25, 26 to 50, 51 to 75, 76 to 100, and 101 mcg. or more. They divided the symptoms into neurotic, i.e., nervousness, anxiety, inner trembling, tachycardia, feeling hot or cold; and psychotic, i.e., hallucinations, depersonalization, feelings of unreality, confusion, delusions, and uncommunicativeness. The correlation between psychotic and perceptual changes and dose was about 0.90 but there was no correlation with neurotic symptoms. They suggested that neurotic symptoms were a function of personality and situation. De-Maar and colleagues[102] found that subjects could distinguish between 25, 50, and 100 mcg. doses of LSD. There was a linear relationship between the dose and number of symptoms.

It has already been stated that in the dose range I use for treating patients, there was no linear response between the intensity of the experience and the dose, but there is little doubt that toxic (physiologic) changes do have a clear relationship to dose.[172] Recently Klee and co-workers[231] used the dose range of 70 to 1,120 mcg. per 70 kilograms subjects to study the dose response. They found that physiologic changes were most intense at the highest dose, and even some hypertension was measured. The time of onset of symptoms became shorter, perceptual changes were more intense, but reactions such as paranoia and depression were not dose related.

Maximum clinical dose. The largest dose recorded is 1.5 mg. (1,500 mcg.) per adult. This seems to be the upper limit for a safe dose and should not be exceeded. This applies only to doses given to subjects who have not developed tolerance.

Effect on normal subjects

Lysergic acid diethylamide is a remarkably potent chemical for producing different psychological states. It is impossible to describe what a typical experience is, for the experience depends upon a large number of variables. This explains why psychiatrists who have worked a great deal with LSD seem unable to comprehend each other's work. This will become clear after I have listed the major variables which have been studied; there may be others still to be examined.

Variables which influence the LSD reaction.

Factors within the subject.

PERSONALITY. There are no generally acceptable definitions of personality, yet most of us know what is meant. It is not a static thing yet there is something constant about any one of us by means of which we are recognized by our friends and enemies. It has to do with the physical body, its rate of reactivity, with our manner of speech, with our way of reacting to people, to situations, stress, anxieties, and misfortunes. Only a superb novelist can describe a personality for us, and it may take him many years and many hundreds of pages to do it. All these intangible factors also influence the LSD reaction. Sometimes they are predictable; very often they are not. Thus it can be assumed safely that a taciturn, quiet, reflective person will tend to have an experience which he will not share readily with his observers. A voluble, introspective, extroverted subject will be more likely to spend many hours describing his experiences to friends. But these predictions may be completely erroneous.

There is one way of predicting and that is to use the results of one experience for predicting the response to another. The general type of reaction tends to be repeated.

PHYSICAL TYPE. Sheldon[347] described three main somatotypes of man and presented evidence that there was some correlation between physical type and personality.

There has been no study relating somatotypes to the LSD reaction. It would be valuable for this to be done.

EDUCATION. A subject with a Ph.D. in psychology will not have the same kind of experience as the subject who has been barely able to graduate from public school. Not only will the experiences be different, they will be described in different terms and will have a different impact.

VOCATION. A writer accustomed to sharing his ideas with others will not respond the same way as a psychiatrist accustomed to hearing and interpreting. This fact has not been fully grasped by many and accounts for the unhappiness of some over the LSD descriptions written by some authors. The many accounts of the LSD experience fall into two groups. The first are those by research psychiatrists and psychologists. These are descriptions of the experience given to them by their subjects and their tests, which they abstract. The stories are generally dull, uninteresting, and do not even partially describe the experience. The second group of accounts was written by subjects who were novelists or very literate subjects and so able to describe the experience. The account by Aldous Huxley, *Doors to Perception*, is the best example of the second group. There are a few scientists with the creativity of novelists who have given extremely vivid and accurate reports of their response to LSD. There are several who have described their reaction to mescaline: Ellis,[111] Mitchell,[275] Kluver,[232] and one who has described LSD, Humphry Osmond.[285] The exciting, vivid, and fascinating accounts are written by the second group. Their experiences, true for them, do not necessarily represent the kind of experience the rest of humanity might have. This may lead many to disappointment and frustration because they do not have the same experiences as those described in the literature.

Yet one's avocation is no guarantee it will determine the experience. There are several reports of philosophers who found nothing in their response to LSD which quickened or altered their philosophy. There have been Zen mystics who suffered only tension and pain from LSD even though the experience has been compared to Zen mysticism.[106]

AGE. The majority of subjects have been over age 18. The few young people to whom I have given LSD seem to react as do adults and the very old. Education and avocation are probably much more important variables.

HEALTH. The state of health is an important variable. A subject indisposed with a cold will not react the same way as the perfectly healthy individual. Perhaps even more important is the presence of psychiatric disease. There is a large amount of literature in which schizophrenic patients have been given LSD and the response compared to that of normal subjects. There are predictably major differences. It is probably equally true that persons with depressions, anxiety neuroses, or epilepsy, for example, will not react as if they are normal subjects.

REASONS FOR TAKING LSD. The set or expectations of subjects are extremely important factors. The alcoholic who hopes the experience will increase his self-understanding which will help him stay sober will not react the same way as the alcoholic forced to take LSD by pressure from his wife and family before he is convinced he is an alcoholic. The volunteer who takes LSD for pay to help a research psychologist will respond differently than a volunteer forced by a sense of duty to participate because his profession, his director, or his colleagues expect him to.

The subject's preconceptions, whether right or wrong, will also influence the experience. If he suspects it is a truth drug, he will have one kind of response; if he expects he will reawaken his early life memories, he will have another. Set or expectations depend among other factors upon the therapist and the information he conveys to the subject.

HIS EXPERIENCE WITH HALLUCINOGENS. The first LSD experience is the least representative for any person even though it may be the most vivid, startling, and dramatic. For in most cases there is a degree of anxiety, suspense, etc., which adds something to the intensity of the reaction. It is like opening night in the theatre or the first glimpse of the atomic explosion. Thereafter the reaction may be as rewarding or as fearful but is seldom as memorable or as intense. From then on, each experience has a life of its own and in essence it differs from the one before and from those which will follow.

Subjects develop tolerance to LSD very quickly. The first time it is taken, 100 mcg. will produce an intense experience in most normal subjects. But there must be a few days' rest before the session is repeated, for if the same quantity is taken the second day the experience is much weaker by comparison. The third day there may be no reaction at all. If there is an interval of 3 to 5 days, the experience can regain some of its original intensity. I have given subjects 300 mcg. on one day with the usual reaction. The second day there was hardly any reaction to 100 mcg., and for up to a week 100 mcg. each day produced so little reaction the subject was practically unaware he had taken the LSD.

Familiarity with other drugs which produce psychological changes is also relevant. Alcoholics and drug addicts seem better able to cope with the LSD experience than normal subjects. I have had more difficulty with anxiety and panic in normal subjects than in patients who have had long experience with drugs. Perhaps the often-repeated experience of being inebriated or toxic and of having had delirium tremens trains these subjects for LSD. Perhaps this is why alcoholics need more LSD than normal subjects in order to have the full reactions. The series of many hundred alcoholics in Saskatchewan suggests that 300 mcg. the first time is equivalent to 100 mcg. for most normal subjects.

PREVIOUS PSYCHIATRIC TREATMENT. Since psychiatric treatment produces a set or state of mind in subjects which depends upon the therapist's orientation and skill, it is not surprising that sophisticated subjects (psychiatrically) will respond differently than naïve subjects. Subjects who have been psychoanalyzed rarely have a psychedelic experience. Ditman and associates[104] reported that few subjects who had had analytic orientation were benefited. I have made similar observations. It may be merely coincidence, but out of several thousand subjects given LSD in Saskatche-

wan, only about 5 previously had psychoanalysis. Everyone had a uniformly bad time of it, although they were treated the same way as the others and by therapists with very strong psychological interest and orientation. Yet nationally known psychoanalysts such as Professor H. Abramson and Dr. R. Carrier have treated patients with low and high doses of LSD very successfully using analytic psychotherapy. Perhaps the conclusion must be that subjects who have had analysis should be given LSD only by psychoanalysts.

PREMEDICATION. The many drugs which influence the LSD reaction will be described. It is important that subjects about to be given LSD should not be tranquilized or heavily sedated, for this may prevent the experience from developing its normal intensity.

CIRCADIEN RHYTHM. The time of day can be quite important. In general, experiences in the evening and night are more intense, or the same intensity of experience can be produced by less LSD.

RELATION TO MEALS. For many years we gave our subjects LSD at 9:00 A.M. and did not allow them breakfast. A couple of years ago Dr. R. Laidlaw* informed me that LSD given after a full breakfast made the induction period much easier. The usual introductory tension, pain, and anxiety were much less troublesome. Since then I have given my subjects breakfast before LSD. I have fully corroborated Dr. Laidlaw's observations. There is a much smoother and more pleasant induction into the full experience. Nausea is very rare and retching and vomiting nearly nonexistent. On an empty stomach they are fairly common.

Factors within the therapist. In any LSD experience there is one key person, the psychiatrist, psychiatric nurse, social worker, or friend. This is the person who takes responsibility for the session and on whom the subject depends throughout the experience. This person plays a powerful role in determining the kind of reaction the subject will have. Some of the factors within the therapist are:

HIS EXPERIENCE WITH HALLUCINOGENIC DRUGS. The best therapist is one who, having himself once taken LSD, is able to sense what kind of reaction his patient will have and when. If he has had a psychedelic reaction, he is more apt to understand similar reactions in his subjects. If he has had a psychotomimetic experience, he will find it very difficult to understand how LSD can be used in therapy.

If the therapist has not taken LSD, he can learn nearly as much about it by carefully observing many subjects reacting to LSD. But this knowledge of the reactions of LSD depends also on the therapist's objectives in acquiring experience. If he has run an experimental program to study LSD's ability to model schizophrenia, he will not see it in the same way as a therapist studying LSD's value in enhancing creativity among artists, for example.

HIS OBJECTIVES. The psychologist who expects his subject to perform psychological tests under LSD is quite disinterested in the subject's early memories. In fact, the numerous perceptual changes which are so fascinating to many are merely a curse to the tester, as they interfere and even ruin the best planned protocols. The therapist who treats will be interested in those factors he believes are relevant to the problem and will dampen down other facets of the experience. He may even use drugs to reduce perceptual changes. The psychiatrist who uses LSD to produce a model of delirium tremens will not be surprised if the subjects have something like delirium tremens and continue to drink thereafter.

OTHER FACTORS NEED NOT BE DESCRIBED. These include the subject's personality, avocation, education, and orientation. I have no doubt that a Jungian analyst would be delighted with the archetypes produced by LSD, nor would Freud's disciples lack early memories of Oedipal conflict.

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The setting. Like any play which must have actors and directors (producers), there must also be a stage and a setting. The setting for LSD is equally as important to the experience as are the props and sets of the theatre to the over-all performance. It is true that badly arranged settings may allow some subjects their experience, but this would be unusual. In general, all the factors of space, color, sound, and humidity, which increase comfort, tend to lead to pleasant or psychedelic experiences; whereas noisy, unpleasant, uncomfortable rooms do the reverse.

PHYSICAL SETTING. Some investigators have designed spaces which increase the chances of having good experiences. Very little is known about these problems. Perhaps when enough architects have taken LSD in various surroundings they will be able to design proper spaces for psychedelic treatment.

NUMBER OF PEOPLE PRESENT. The number of other people present has a profound effect upon the LSD response.[76] There are no hard and fast rules about the optimum number. This depends upon the familiarity and trust between subject and observers. The objective of the session is also important. If the objective is therapy, then an optimum number is 2 to 4 in the room. If the objective is communication of emotion or ideas between skillful LSD subjects, 5 or 6 may be tolerable. In any event it is best for all observers to be present in the room before the subject develops the experience. They may then come and go without unduly disturbing him. A stranger coming into the room has a profoundly harmful effect on the experience. The most harmful kind of setting is one where strangers, visitors, and other curious people pop in and out.

VISUAL AND AUDITORY AIDS. Photographs, paintings, colorful drapes, and rugs help the subject gain a good experience. Music can also be very helpful. I have seen subjects stuck in a psychotomimetic experience pass within seconds into the psychedelic experience when especially meaningful (to them) music was played. But these props must be looked upon as aids and not as objectives of the experience. Some subjects find music intolerable and visual aids repulsive, and their wishes and feelings must be honored. They find music extremely distracting and it prevents them from fully experiencing other components of the reaction. Terrill[377] concluded: "Any attempt to impose a structured test or interview radically altered the experience."

The effect of LSD on normal subjects. From the first accidental experience Albert Hofmann[198-202] had in 1943 with LSD, there has grown an enormous amount of literature on how normal subjects react, ranging from accounts of those who experienced nothing to those who had the most fantastic changes. There may be about 100 reports which describe how normal subjects react. Papers, review articles, novels, and books have appeared.

There is no limit to what normal people may experience when they have taken LSD. It would be inappropriate to review every paper and describe in detail all the changes which can and have taken place. In a study which was completed in 1952, Stefaniuk and Osmond[365] gave 17 normal subjects 100 or 200 mcg. of LSD. One subject took LSD twice. A verbatim record was made of the entire session and self-accounts were received the following day. I will outline the kinds of changes normal subjects have described, without referring in detail to each individual report from the literature. But this description, which will be dull, descriptive, and informative, will not tell anyone what an LSD experience is. In order to learn this, each one will need to take LSD. Of course, if he has been schizophrenic or has had any toxic or organic psychoses, he will have some approximation of what might happen—at least in the psychotomimetic experience.

The changes will be described under the major headings: perception, thought, mood, and activity.

Perceptual changes. Perception concerns all afferent impulses to the brain and in-

cludes visual, auditory, touch, taste, smell, kinesthetic, somatic, body image, and sense of time passing.

VISUAL CHANGES. These are the most vivid perceptual changes for most normal subjects, especially the first time LSD is taken. They occur whether the eyes are open or closed. Stefaniuk and Osmond[365] classified these visual changes. I will follow their classifications, but will elaborate as needed using material from the literature and drawing upon my familiarity with many hundreds of subjects and case records.

Eyes open.

1. Blurring of vision. This is very common but it is not present all the time and tends to come and go. It was present in 7 subjects out of 18.[365] (Hereafter, all numbers refer to the number of subjects who reported these changes out of 18.) Along with blurring of vision, 2 had vision they decribed as distorted, queer, or funny; 4 had a shifting, fluttering vision; and 2 complained of difficulty in focusing. Blurring of vision could be caused by the marked mydriasis which is noted as the experience develops.

2. Imagery filling the visual world. Stefaniuk and Osmond ran these experiments in a large, comfortably furnished living room. Their subjects therefore had experiences which were determined by the visual and spatial aspects of this room. Normal subjects having LSD in other rooms or outdoors would similarly have their experiences shaped by the environment.

Imagery filling the visual world refers to things seen in the dimensional space within the subject's field of vision. Eleven (out of 18) subjects had these visual changes. The following images were described: the space full of patterns and objects, weird patterns, a lacework pattern over everything, stuff growing all over the room, ribbons streaming all over the room, several layers of patterns superimposed, air full of little circular things, a rainbow effect, glass balloons filling the air, a gray lacework over everything, fog or smoke filling everything, and so on. The imagery was usually in front of the subject but could also appear in the periphery of vision. Two subjects noted that, as they moved, objects had a veil which followed closely.

3. Changes in three dimensional space. Space was very commonly distorted during the LSD experience. Space became smaller and larger in pulsations. Two subjects noted that the room changed in size and shape. Perspective was altered in 2 more. For 7 the floor and walls moved. The rug was particularly active and moved for 6, while for 4 there were changes only in pattern. Distortion of space also affected the regularity of angles which appeared too acute or too broad. Some of the changes may be very disturbing, as, for example, when the walls close in on one.[389]

Many subjects talk about new dimensions of the experience. These should not be confused with spatial coordinates. They are attempts to describe new worlds of reality and there is no limit to the number of new dimensions of the experience which are described.

Objective tests have confirmed subjective statements that space perception is changed. Weckowicz[392] studied the effect of 35 mcg. of LSD on constancy of perception. He used a double-blind, Latin-square crossover design. LSD increased the variability of performance of each individual in judging the size of objects. With a larger dose, 125 mcg., Edwards and Cohen[107] found size constancy was decreased when the standard object was 30 cm. away but not when it was 180 cm. away. The Mueller-Lyer illusion was increased. Objects appear to fluctuate in distance from the observer. Six subjects noted this. Perhaps the normal minor adjustments of distance vision are exaggerated by LSD.

Interesting changes appear in faces and in pictures. Five subjects reported that faces were flat (two dimensional) and very

frequently two dimensional pictures in photographs, paintings, and on drapery became three dimensional and alive.

Very interesting effects were produced when the subject walked or drove. Objects passing by became large too quickly and subjects had the impression the objects exploded into their field of vision.

Long corridors became interminably long. This was very disconcerting to some subjects.

4. Changes in faces. These are very common and lead to many unusual and bizarre associations. Eight subjects described changes in the shape of faces. Three noted changes in the shape of eyes, which became slanted, oriental, etc. This gave many faces an oriental cast and allowed subjects who had taken LSD to associate the faces changed with changes in age or disease. Four noted changes in eyebrows which appeared animal-like, tufted, etc. Sometimes the face became very young, then there was an overcorrection and the face appeared very old.

Eyes commonly became very piercing and frightening. It was not unusual for subjects to see three eyes as drawn by the Cubist School of Art. There were two eyes facing to one side in a profile view with one eye facing the viewer directly. I have seen similar drawings by paranoid schizophrenics. It may be due to a prolonged afterimage effect as the head is turned.

Shadows and areas of light produced unusual facial changes. Dark areas became accentuated; the shaven beard grew hair. Colors were altered and skin often developed a marked greenish hue. Many times certain prominent features were accentuated and the subject saw caricatures of faces. Ten subjects at one time or another observed these caricatures, which ranged from animal- or birdlike faces to old men, old geezers resembling W. C. Fields—the comedian, a fox, and one face even appeared like a snake. The same changes were observed in one's face seen in the mirror; often subjects saw their father or mother there. The mirror exercise was useful for exploring the subject's associations with his parents.

The extremities also were changed. Six subjects noted changes in size; to 3 the hands seemed to wither away. Seven saw hair or fur growing on their hands. Very common was an unusual change in the size of one's hands or feet. They appeared to pulsate by getting larger or smaller or they were seen as growing closer and then receding. Occasionally subjects saw their limbs float off in space. There were changes in surface, texture, color, shape, etc.

5. Changes in objects. Objects developed unusual movements as did faces and limbs, but of course the associations were different. They changed in shape and size and pulsated regularly. Objects appeared endowed with life. I saw a wall clock pulsate regularly and glow with an interesting purple hue. Parallel lines or patterns often became distorted. They developed wavelike forms and seemed to move or ripple as if covered with a layer of water. There were similar changes in pictures. Van Gogh's paintings seem particularly appropriate for eliciting interesting visual changes, but any other artistic work may be just as effective. It was not unusual for subjects to find themselves within the picture which became their world. Pictures were extremely useful props for assisting in the production of the psychedelic experience.

6. Colors and colored objects. Twelve subjects reported changes in shading or in hue and 7 saw colors change from one to another. Five subjects saw the colors of objects project beyond the border of the colored surface. Unusual colors of familiar objects made them grotesque, e.g., purplish green hues on faces, or dazzlingly beautiful. Four subjects saw brilliant colors filling the air.

Objective tests supported these findings. Edwards and Cohen[107] reported that there was no effect in color detection; but Hartman and Hollister[158] reported that LSD increased color experiences when a variety of stimuli was used. Hue discrimination

was reduced more by psilocybin than by LSD or mescaline. The latter two produced more color imagery. Abramson and coworkers[11, 13] reported that LSD enhanced color perception.

Halos are areas of color or light which are seen to surround living objects, especially heads, and sometimes inanimate objects. Very few normal people see halos all the time. Some schizophrenic patients see halos and it is not uncommon with LSD subjects. Four of this series saw colored halos around the heads of the observers.

7. Illusions and hallucinations. The basis for illusions has already been described. Formal hallucinations are common. Usually the subject is aware they are hallucinations but occasionally during moments of panic they may develop a frightening reality. There is no point attempting a description of hallucinations. They are described by Ellis,[111] Kluver,[232] Huxley,[207] and many others. Our subjects saw animals, explosions, people, Balinese dancers, dancing nymphs, etc. One of my subjects found a rectangular grid before him. At each intersection he saw a nude dancing woman who danced in rhythm with music then playing. He found this more interesting than a television program his friends were watching.

8. Changes in intensity of light. Often the first change was a sudden awareness that there was more light about, or the room or world became darker. There was often a fluctuation between these light changes.

9. Visual perseveration. This was quite common. Eight subjects perseverated images, 7 noted afterimages. Rapid movement of objects produced interesting afterimages. The moving hand sometimes appeared like a number of hands standing still. A ball flying through the air appeared to be an arc of several balls stopped in flight. Color afterimages also were very frequent.

10. Qualitative changes in objects. There were striking changes in the qualitative judgment of things seen. Objects which normally carry no emotional connotation became extraordinarily distressing or overwhelmingly beautiful. One subject, a psychologist, spent 2 hours absorbed in a small speck on the wall of my office. He had never seen anything as beautiful. He watched it pulsate, change in shape and color, and it had a pronounced impact upon him. This property of LSD allows one to use visual aids for altering a psychotomimetic to a psychedelic experience. As an example, certain flowers which have cuplike forms, such as roses, became alive. The petals seemed to breathe by opening and closing. Many subjects found this very valuable and those who had any mystical orientation found many significant associations to this. On the other hand, the writhing, pulsating flower became repulsive and might be thrown away by the subject.

In line with these findings, Kelm, Jensen, and Ramsay[227] found that 200 mcg. of LSD decreased the magnitude of the figural aftereffect in alcoholic subjects. Kelm[226] developed a very accurate and sensitive method for measuring figural aftereffects. Alcoholics under LSD resembled schizophrenics not given LSD.

Eyes closed.

When the eyes are closed rich visual changes occur. Seven subjects saw brilliantly colored lights and objects. Geometrical patterns, formless shapes, colors, and forms became visible. Eight subjects saw a succession of formed scenes. Religious scenes were common, as were animal scenes, palaces, cathedrals, and jewels.

Blind people do not have vivid visual perceptual changes. Alema[20] gave 50 mcg. of LSD to a man blind since enucleation of the first eye. There was only a slight change in the colors he was aware of normally. Rinkel[307] gave a blind physicist LSD twice. This man, blind since birth, had no visual experience on either occasion.

Recently I gave 100 mcg. of LSD to an intelligent university student blind since birth. This subject was completely independent and could get along anywhere

with no help. Auditory acuity was keenly developed and she could accurately judge the size of rooms, objects in them, and distance from speakers, whether they were sitting or standing, by sound only.

She had a psychedelic reaction to LSD. There was only one transient visual response when she had a sensation of light but otherwise there was no visual reaction. The entire psychedelic experience took place in the field of sound. The room pulsated, became larger and smaller. The ceiling came down to her. She had the out-of-the-body experience which commonly develops with the psychedelic reactions.

In order to simulate blindness I gave LSD to 3 normal subjects who were blindfolded. The first subject was given 200 mcg. For 2 hours while the blindfold was on, there were no visual reactions. When the blindfold was removed, the subject became violently seasick. This he later explained was due to the violent motion he saw all about him. The other 2 subjects' reaction was not entirely suppressed by blindfolding. The reaction was there but it was less intense visually.[183]

Cohen and Edwards[92] combined sensory deprivation with the effect of 125 mcg. of LSD. Sensory deprivation consisted of sitting in a soft armchair in a lightproof, sound-attenuated cubicle for 2 hours. This was a double-blind experiment. After 2 hours the subjects were asked whether they had been given LSD. Of the 10 subjects given LSD without sensory deprivation, all correctly concluded they had been given LSD. Of the 10 subjects given LSD with sensory deprivation, 6 concluded they had been given nothing or a placebo. Another believed he had been given a smaller dose of LSD. But, shortly after deprivation was terminated, all 7 soon noted the onset of the typical visual changes. In one case the reaction came on in the middle of a sentence. This is very similar to the reaction of my one subject blindfolded for 2 hours.

These findings can be easily reconciled with the hypothesis that LSD changes the brain in such a way that, when it is given, visual stimuli are altered. Thus, subjects who are blindfolded or placed in isolation will have fewer visual stimuli, and so will have moderate or no changes. Only when the visual stimuli are operating in a normal manner will the typical visual experience develop.

AUDITORY CHANGES. To most normal subjects the auditory world is less stimulating than the visual world and consequently there are fewer changes under LSD. For the blind, auditory changes are most important. The example of a psychedelic experience in the blind girl demonstrates that it is not dependent upon vision. The changes which are possible and which take place are increased sensitivity to sound or decreased sensitivity, inability to localize the source of sound, confusion or inability to comprehend sounds, and finally auditory hallucinations. There are also qualitative changes in judging sound.

1. Increased auditory acuity. This was very common at one time or another with LSD. Six subjects reported it. They became aware of background noises which observers were not hearing. Perhaps there was a decreased ability to select appropriate sounds from the background noise.

2. Decreased auditory acuity. This was much less common. It did not appear in any of the 18 subjects.

3. Inability to localize source of sound. This also was very rare and if it did occur it did so only at the height of confusion. One subject was so confused. It can be very frightening. Some subjects confused their own voice with the observer's voice and were surprised when they realized it was their own voice. Five of the subjects reported a pulsation of sound so that the speaker seemed first near then far. The blind subject felt that the room was alternately getting smaller and larger because the echoes from sound seemed to pulsate in this manner.

4. Inability to comprehend sounds. This was noted during LSD confusions. If there were 3 or more people present, and the

conversation general, the subject became even more confused by the babble (to him) of words.

5. Hallucinations. These were rare but did occur. Any auditory hallucination which occurs in delirium or schizophrenia will be heard and includes music, voices, unusual sounds, etc.

6. Qualitative changes. Very often sounds which normally have no particular esthetic appeal were heard in a most unusual manner. Subjects who were indifferent to music were enthralled by it. One of our subjects, a physicist, was overwhelmed by the beauty of music being played on an old scratchy record player. After a while he exclaimed, "I wish they could play it as beautifully as I now hear it." The background noise from the record did not reduce his appreciation of the music. This property of the experience is very useful for bringing out the psychedelic reaction. Carefully selected music can be very powerful in altering the subject's mood and associations. One subject, an intellectual, cold physician, who was an alcoholic, did not have any emotional reaction to 300 mcg. of LSD for about 2½ hours. When "Ave Maria" was played, he seemed startled, then in a few minutes became transfixed with emotion and began to cry. The song had suddenly taken him to his youth when he had been very happy. The music triggered off an emotional catharsis which completely altered a psychotomimetic to a psychedelic experience.

7. Mixed sensation of sound. Six subjects experienced visual phenomena when certain sounds were made. In one case the telephone rang and the subject saw ripples of waves each time it rang. Another subject saw flashes of light emitted from a glass each time it was struck by a fork.

TASTE CHANGES. There were very few changes. Taste was altered so foods were flat (4 subjects) or peculiar new tastes appeared. More important than actual taste changes were tactile changes in the mouth. Foods felt coarse, gritty, etc., and this markedly altered the sensation of taste. In my own case, coffee tasted extremely sour. If food tasted bitter, some naïve subjects became paranoid and suspected the food had been altered.

OLFACTORY CHANGES. The sense of smell was not altered very much. Only 2 subjects reported any change. However, we normally live in a rather odor-free environment and this may explain the paucity of changes. The usual office is so free of odor one might compare it to a sensory deprivation experience in the field of odor. When subjects were exposed to strong odors, they had pronounced reactions and found them pleasant or quite unpleasant.

TACTILE CHANGES. These were more frequent than olfactory or taste changes. Seven subjects reported them. Cloth changed its texture and became coarse, dry, unreal, different, very fine, velvety, etc. There was hyperacuity to one's own clothes which was sometimes painful. Small pieces of sculpture produced extraordinary tactile sensations. The skin felt grimy and dirty and some subjects washed their hands excessively trying to get it off. Eight subjects complained of localized anesthesia.

There were changes in awareness of temperature. Six subjects felt too warm, one too cool, and one alternated. Often subjects felt so cold they covered up on a hot day and became extraordinarily sensitive to a slight draft. Some subjects (4) complained of feeling sweaty.

Edwards and Cohen[107] reported that subjects were less able to discriminate on the two-point test.

KINESTHETIC CHANGES. Kinesthetic changes are those which concern one's awareness of the relationship of the body to gravity. Many changes occurred. There were pressure-weight sensations. Subjects felt filled up, clogged up, heavyheaded, lightheaded, and empty; 10 felt lightheaded.

There were shaking or vibration phenomena in 9 subjects. These were independent of other changes. Some subjects felt they could not walk, eat, or smoke, but usually when urged to do so they had little difficulty, to their own surprise.

An important change was a decreased awareness of limb position combined with a curious limpness. Subjects sat in an armchair with one limb in an unusual or even dangerous position and could transiently injure their arms by pressure. Observers must be aware of this and ask their subjects to move about when this happens. One subject noted his arm was so light it floated up to the ceiling of its own accord. He seemed catatonic. Many subjects felt dizzy or foggy and tingling of the extremities was not rare (3 subjects).

CHANGES IN BODY IMAGE. The visual changes have been described. There remains a most peculiar change which may be termed an "out-of-the-body experience." Subjects became so unaware of their body they felt they were free of it and were floating off in space. The in-and-out-of-the-body experience alternated. This out experience was reported only in the psychedelic reaction and was used by subjects for time, travel, exploring the world, etc. It is curious how frequently the real person identified himself with what has "gone out" and how seldom with the body which had been left. Occasionally the out-person saw himself sitting in the chair.

SOMATIC CHANGES. These do not clearly separate from kinesthetic changes, but they include bodily sensations which are distinctly unpleasant. They are most common during the early phases of the LSD reaction. They include nausea (8 subjects) and very rarely vomiting. Since I have started to give LSD after a full breakfast, the changes are very rare. Other changes are tension in one's muscles—which became very painful, headache, neckache, etc.

SENSE OF TIME PASSING. Subjective time became completely altered. It stopped, became slow, became very fast, or even ran backward. These changes are extraordinary to most of us conditioned by the clock to a uniform rate of time passing. The changes were so remarkable that there were no words available with which to describe them; subjects used phrases which seemed grossly exaggerated to the observers.

Subjects exclaimed after several hours that only minutes had gone by. Sometimes time seemed to stop. In my own case, while I was watching the electric wall clock the second hand stopped moving. Time was more often accelerated and after a moment's experience subjects reported thousands of years had passed. Sometimes time had no beginning or end. I heard a high note being sung. I still do not remember its beginning or end and while listening I might have reported it was running on forever.

One of Dr. Osmond's subjects picked up a cup of tea to drink. He then was astonished to find that it was reversed and he sipped from the cup before he picked it up, as if a film had been run backward.

Objective time is also altered. Aronson[28] found that 1 or 2 mcg. per kilogram of LSD caused subjects to estimate time intervals as having elapsed sooner. On the other hand, Boardman and co-workers[51] found that LSD did not make 4 subjects overestimate one second of time but their temporal frames of reference were altered. Kenna and Sedman[228] found that 8 out of 29 subjects given LSD reported altered time experiences when doses of 40 to 200 mcg. were used. At higher doses (70 to 400 mcg.) an additional 12 subjects observed the time changes.

Edwards and Cohen[107] found that the reaction time was increased when 125 mcg. was used. With lower doses no changes were noted,[11] but verbal reaction time was increased and also the time required to name colors.

Thought changes.

PROCESS. By process I refer to the act or process of thinking. This has nothing to do with the content or subject matter being thought about. Process refers to the act of putting together logical sequences of words or phrases so that a coherent account of one's thought becomes possible. Examples of changes in process are blocking—when the mind seems wiped clear of all thought for a moment, skidding, jumping about, er-

ratic responses, and finally inability to construct sentences.

The following process changes can take place: (1) concentration span becomes shortened (8 subjects); (2) interposed thoughts (2); (3) mind wandering (3); (4) wavelike changes in thought (3); (5) unable to control thought (6); (6) memory changes (5).

Jarvik and associates[221] found that 100 mcg. of LSD significantly impaired performance on arithmetic but 50 mcg. did not. Jarvik, Abramson, and Hirsch[220] further reported that LSD decreased performance on tests of attention and concentration. The higher dose significantly impaired recognition and recall of various stimuli. LSD had a deleterious effect upon recall and recognition of various kinds of visual and auditory stimuli.

CONTENT. This has to do with the subject matter of thought and includes ideas of reference, delusions, associations, bizarre ideas, etc. These are very common under LSD. The predominant thought content depends upon personality, life's experience, education, kind of LSD experience, and so on. Stefaniuk and Osmond's subjects had the following changes: feeling of influence, 2 subjects; feelings of unusual significance attributed to random events, 6; unusual associations to objects and events, 11; paranoid ideas, 10; lack of motivation, 6 subjects.

Judgment depends upon normal perception, normal thought process, as well as content. Judgment of changes in reality is often impaired. Seven subjects felt they had awakened from an unusual or different reality. Seven described different forms of reality, 9 were depersonalized, 2 subjects felt they were dual beings, and 2 experienced déjà vu phenomena.

MENTAL TESTING. Stefaniuk and Osmond tried to complete a number of mental tests. They discussed the dilemma facing the tester. When the best clinical doses, 100 mcg. or more, are used, subjects are unable to cooperate because of the intensity of perceptual and other changes. And when lower doses are used, one is testing experiences not typical of LSD. Nevertheless many tests have been given and most investigators report many kinds of impairments.

1. General comprehension tests. In response to the Wechsler-Bellevue question about the addressed and stamped envelope being found, one subject described what he had previously done to a letter mailed to him; another could not answer. In response to the "fire in theatre" question, one subject replied he would "head for the door, if it was hot enough he could make it." Another replied he would shout. A third subject stated she wished the observer would not talk about it.

2. Proverbs. Associations aroused by proverbs were not related to the task but were drawn from personal elements within the subject, i.e., they depended upon the LSD experience. Proverbs were answered in a concrete manner. Subjects rephrased the initial wording, repeated the qualitative indicators; e.g., all that glitters is not gold was responded to by "nice and shiny."

3. Problems. Mental problem solving becomes very difficult under LSD. One subject attempted to solve the pail-water problem and failed. After a while he stated the fire was too small for the water and suggested the examiner put out the fire by putting his foot on it. Persistent discussion by the examiner finally caused the subject to become annoyed. He stated the problem was "silly as hell." When this subject was given 1 Gm. of nicotinic acid, he was able to solve this problem in a normal manner in a few minutes.

4. Comprehension and similarities. These tests were very difficult to score. Replies were inappropriate; e.g., when asked why people require a license to get married, one subject replied there would be no marriages in the experiment. When asked why shoes were made of leather, he replied, "because they were down here on the floor and were green." Another asked should they be made of something else. Similarly

bizarre responses were given to the similarities test.

5. Digit span. Silverstein and Klee[351] found that 2 mcg. per kilogram of LSD definitely impaired digit span memory. One of Stefaniuk and Osmond's subjects was able to recall a sequence of seven digits. He showed the least response to LSD.

6. Word association test. Four subjects given this test showed a marked variability of response. One subject found the test annoying and foolish because it interfered with perceptual changes. Another was able to repeat only the stimulus word. He appeared very confused. A third subject who showed no thought disturbance was able to answer appropriately. The fourth subject gave clang associations; e.g., to laugh he replied seraph, to seraph he replied giraffe.

Thus, with 200 mcg., the word associations test was seldom completed and merely proved the gross impairment observed clinically. Weintraub and co-workers,[393, 394] using less LSD, 2 mcg. per kilogram, gave WAT to 50 subjects. LSD did not produce schizophrenia-like responses but it did abolish the differential response to traumatic and nontraumatic stimuli. Subjects had more errors, fewer popular responses, and reacted more slowly. On retesting, comparison normal subjects were able to correct previous pathologic responses but under LSD they repeated the previous pathologic responses.

7. Numerical test subtraction. One of the most useful tests was the minus seven test. The subject is asked to subtract 7 from 100, and so on. Most subjects cooperated but few were able to complete it normally.

8. Learning. Aronson and others[29] found that LSD impaired the learning of paired words when 30 pairs were used, but not when 22 pairs of words were used. Memory, which is basic to learning, was also impaired.[351] They also found performance on the Dual Pursuit test impaired.[352]

However, other types of learning may be unimpaired and may be much improved. If this were not so, the psychedelic experience would help no one. A large number of alcoholic subjects learn concepts and ideas in a few moments that they had not grasped for years. These are termed flashes of inspiration or insight but they seem to me to be the acquisition of new concepts. One subject, a brilliant physician alcoholic, prided himself on the fact he took no drugs. Under LSD he vividly learned alcohol is a chemical and, by his old definition, a drug. Other subjects learned understanding, tolerance, compassion, the meaning of psychotic fear, etc. I would suspect that learning in tasks which are trivial for the subject would be impaired, e.g., psychological learning tests, whereas matters of great importance to the subject might be learned even more quickly. Memory after the event is usually extremely good and insights learned are never forgotten even if they are not always used. This is one of the main differences between the LSD experience and barbiturate abreactions.

9. Performance tests. Aronson and Klee[27] tested 28 subjects on the Porteous maize test with 75 mcg. against 34 comparison subjects. LSD decreased performance and produced a 2 year deficit. In this way it resembled chlorpromazine. LSD decreased the capability of subjects to carry out well-planned and adaptive behavior.

Abramson and colleagues[12] reported 100 mcg. of LSD impaired performance on the Thurstone hand test. Performance was also impaired on the Minnesota Paper Form Board test at 100 mcg. The Bender-Gestalt test[18] was performed less well. LSD impaired performance on a pursuit rotor test and on a modified Dunlap steadiness test.[10] Impairment was slight and was countered on subsequent tests by a practice effect.

10. Intellectual function. Levine and coworkers[237] concluded that LSD reduced intellectual function. There is little doubt their conclusions are sound. But it is possible that, if all tests were repeated on sophisticated subjects, i.e., subjects who have taken LSD so often they are no longer surprised at anything which can happen, different conclusions would follow. I have

seen sophisticated subjects perform so well that no observer unaware they had taken LSD could be certain something was wrong. Some subjects have recorded their experiences on paper while they were happening and their literary effort could not be excelled for clarity, interest, and composition. But unfortunately few of these gifted individuals are about.

Linton, Langs, and Paul,[243] using a questionnaire, tested the recall of a series of normal subjects. They were tested during the reaction and the following day. The retrospective accounts agreed with the drug day accounts ($r = 0.90$). Of the 74 items, 26 were stable, 18 were dropped the following day, 8 were added, and 6 were both added or dropped. Had the questionnaire been given again several weeks later, there would have been additional changes. In general, the more vivid, perceptual, concrete changes were not forgotten. A test designed primarily to evaluate these changes would show the recall was good. Hoffer and Osmond,[189] using the HOD test, found the scores from subjects given LSD one week before were similar to those achieved by a smaller group of subjects who had taken LSD several years before.

Memory of the LSD experience does not differ much from memory of any memorable event. Some will remember details for many years; others will only remember highlights.

11. The Rorschach test. This is one of the least useful tests. Subjects do not like it, are not able to complete all the cards, and often refuse to be diverted by dull cards from their more interesting experiences. Cards were rejected as too dull, too fluid, too alive, or too silly. Cards pulsated and the blots took on grotesque shapes. Some subjects complained that colors came and went. Subjects saw women, bears, puppies, cows, bats, flowers, and crabs. Associations to the imagery were often bizarre. Only card number 6 produced a sexual phantasy in one subject. He described the middle area as a penis.

In general when visual changes were minimal, subjects found the cards dull and when visual changes were present the cards were more interesting.

Changes in mood. Any change in mood can occur.

EUPHORIA. This was noted in half of Stefaniuk and Osmond's[365] subjects. Euphoria was often the first indication that LSD was beginning to work and was usually uncontrollable. It ranged from very slight to tears and came in waves. Often there were no precipitating events and then the subjects felt silly because they could not help giggling or even laughing uproariously. Some rolled on the floor in uncontrollable laughter.

TRANSCENDENTAL. Many subjects found themselves in a remarkable state wherein they were completely relaxed, intensely interested, and supremely happy though nothing was apparent to the observer. These experiences which transcended anything the subjects had ever experienced before were described usually after the moment had passed or the following day.

FLAT. Six subjects felt flat, i.e., they felt no emotion whatever. This was very marked in the first volunteer I gave LSD pretreated with penicillamine.[187]

FEAR. Five subjects were very fearful. This is quite common in the psychotomimetic experience. Some were very anxious; some felt alone and cut off from the world.

Many subjects used safety mechanisms such as visual objects or ideas when they became too fearful. One subject looked at distant objects which were visually stable and this steadied him. Another found that looking at the observer's green shirt helped reduce the fear. Several used the corner of the room (where three lines intersect) to steady them. These intersecting points seldom moved about visually. Other subjects kept talking constantly. One subject found that a cup held in his hand gave a sense of security and stability.

When subjects who are fearful have no safety mechanism, it should be given to them by the therapist, who can use reas-

surance, e.g.: You have taken LSD, it will not last long; visual props, music, etc.

Activity changes. When the reaction is run by qualified, competent therapists, there is little activity. But when the experience is uncontrolled, activity may be impulsive and foolish. In some cases unskilled therapists stimulate bizarre behavior. Many years ago one of our subjects, during the height of the experience, stated, "I am going to take off my clothes." The young psychiatrist jestingly replied, "Why don't you," whereupon she proceeded to disrobe. When the nurse and psychiatrist attempted to persuade her not to unclothe, she became hostile and violent and the experience had to be terminated with intravenous nicotinic acid. It is because of the possibility of these impulsive acts that subjects must be under continuous and careful observation.

Creativity. The main roots of creativity come from one's emotional, perceptual, and thought processes. Because the processes are altered so strikingly by LSD, it has been suggested frequently that LSD should improve creativity. Many artists have been schizophrenic and this seems to have made them more creative, e.g., Vincent Van Gogh and Blake. Wasson and Wasson[390] suggested that early mankind created the idea of God as a result of taking hallucinogenic mushrooms. There are two chief possibilities: (1) that creativity will be enhanced during the experience and (2) that a permanent enhancement will remain after the experience.

It is impossible to test proposition one, for even if creativity were enhanced during the height of the LSD experience, the effect on sensation and on eye-hand coordination would effectively prevent its expression. Berlin and co-workers[47] gave four nationally known artists 50 mcg. of LSD or 400 to 700 mg. of mescaline. As would be expected, most were reluctant to draw at the height of the experience. The authors concluded that the drawings which each made indicated greater esthetic value according to a panel of artists. Some of the drawings were published and to me seemed remarkably like those produced by some schizophrenic patients. But quality in art is as difficult to objectify as improvement in psychiatry.

Tonini and Montanari[381] gave one artist 60 mcg. of LSD. He could not draw at the height of the experience but he could paint as the experience began to wane. The painting did not contain any new elements of creativity. They were very similar to the artistic productions of schizophrenic patients. Silverstein and Klee[351] used the draw-a-person test as a measure of body image changes. Under LSD, subjects, not surprisingly, drew less well.

Even though it has not been proved that LSD does improve creativity, there is little doubt it improves recognition of creativity in the observer. Many of our subjects who had no interest in music or art before LSD was taken found to their surprise that the experience greatly enhanced their appreciation of the arts thereafter.

It is my opinion that LSD does not enhance creativity by putting into the subject something he does not have before. A noncreative person will not thereafter become more creative, nor will the gifted artist become more gifted. The main effect of the LSD experience comes from the alteration of old interests or the production of new interests which then inspire the creative person to enter fields which previously did not interest him. Or, as Savage[337] puts it, "the transcendental state may open up avenues to creativity, but it is not creativity itself."

Psychotomimetic reaction to LSD

The first detailed clinical accounts appeared in European psychiatric journals.[37, 95, 100, 139, 269, 270, 272, 313, 350, 367, 368, 369, 396] They looked upon the reaction as an exogenous or toxic one. The reports carry clinical descriptions of the LSD experience which have not been surpassed. The large number of studies since then merely elaborated what these scientists had found. This is another example where no-blind, purely

subjective studies of Hofmann in 1945 were confirmed by no-blind studies on subjects by clinicians. Only much later were double-blind studies used. They have added nothing to our knowledge of LSD.[241, 242]

LSD was first studied in North America by Rinkel[306] in 1949 and reported at the Annual Meeting of American Psychiatric Association in 1950. The studies by Rinkel and co-workers,[310] DeShon and associates,[103] and Hoch and others[177, 178] may be the classical American studies with LSD. They corroborated the earlier European reports but went further; they were impressed with the similarity between the LSD experience and, if one may call it so, the schizophrenic experience.

This work prepared the ground for the concept of the model psychosis, the experimental psychosis which so resembled schizophrenia in many ways. The workers suggested that studies of the LSD psychoses would yield very valuable data which could be applied toward a solution of the problems of schizophrenia, and of course they were right. The early European workers were more impressed with LSD's similarity to exogenous psychosis and did not believe it could offer too much to the student of schizophrenia. The controversy still lingers on and even now a psychiatrist will question the validity of the model psychosis, e.g., Hollister,[205] who believes the term "model psychosis" is misleading. This argument is intellectually stimulating but scientifically of little interest. There are too many ambiguities both in the definitions of schizophrenia and in the production of the LSD experience for it to have much significance. The experience can be employed to model (not to ape or reproduce identically) neuroses, psychopathy, behavioral disorders, depression, schizophrenia, and even toxic psychoses such as delirium tremens. Some may find the differences between the model and the syndrome modeled more rewarding, others will find the similarities more useful. Both aspects are important.

DeShon, Rinkel, and Solomon[103] gave LSD 17 times to 15 normal subjects using between 20 and 90 mcg. They divided the time course of the reaction into four phases. This is a useful classification which fits the nearly one thousand LSD experiences I have studied. These states are: (1) the prodromal state, which terminates when the full experience is developed; (2) the height of the experience; (3) the termination of the height until evening; and (4) the aftermath. I will call these stages the (1) prodromal, (2) the experience, (3) the recovery, and (4) the aftermath.

Prodromal phase. The prodromal phase generally is unpleasant. It is characterized by a gradual development of sympathetic excitation. The best indicator is the dilation of pupil size. There may be nausea, seldom retching, but hardly ever vomiting. The symptoms are sharply reduced in intensity and frequency if LSD is given after a substantial breakfast. There may be severe pain, as if muscles are cramped, which comes and goes in waves. At the end of this stage the changes are less intense and less troublesome in the psychotomimetic experience and may be completely absent in the psychedelic experience.

The time when symptoms first appear depends upon the method of administration more than it does the dose. Hoch[172] found that 100 to 250 mcg. given orally produced symptoms in 30 to 45 minutes. The intramuscular route produced an initial response in 15 to 20 minutes. The intravenous routes caused symptoms in several minutes and the intrathecal route caused symptoms almost immediately. This last route sometimes produced toxic changes, and Hoch did not recommend its general use.

There is of course a remarkable variation in the timing of the phases. The time required to initiate symptoms does not depend linearly on the dose, except of course when doses too small are used the subject may never get out of the prodromal stage. As a rule, 100 mcg. or more in normal subjects will produce a prodromal phase of about one hour but it may vary from 20 minutes to 2 hours.

The experience. There is no evidence that the duration of the peak experience is markedly influenced by either the dose or the method of administration. I have found that when the full experience is reached, it will last approximately 1 to 4 hours whether 100 mcg. or 1,000 mcg. is used. It seems as if the LSD triggers off a series of biochemical and psychological reactions which are programmed to run down in a given number of hours. There is a remarkable variation between subjects within any diagnostic class and between classes of subjects. Alcoholics may have peak experiences as short as ½ hour and normal subjects as long as 6 or more hours. Pseudoneurotic schizophrenics may have an experience which lasts all day or conversely they may fail to react. The duration of this stage depends upon so many variables that it cannot be predicted accurately. The psychedelic peak in our studies occurs between 10 A.M. and 12 noon when LSD is given at 9:00 A.M. It is my rule that if the initial quantity of LSD has not taken the subject into stage two by 10:00 or so, a booster dose is given.

Thus, an alcoholic may be given 300 mcg. and between 10:00 and 10:30 it may be followed by another 200 to 300 mcg. or more.

Stage three. Recovery begins when the symptoms begin to wane. It is certain when the subject experiences the first wave of normality. Thereafter he will experience waves of experience followed by waves of normality the rest of the day. With each cycle the waves of normality become longer and the waves of abnormality become shorter. Late in the afternoon (2 to 9 hours after taking the drug) only residual symptoms are left. When LSD is used for treating patients, someone (nurse or doctor) is present with them continually for 7 hours from the beginning. Thereafter our guard is relaxed, although nurses regularly check the subject until he is asleep, usually after being heavily sedated. The experience at the end of stage three may be reactivated momentarily by fatigue or unusual events. The subject should be warned this may happen so he will not be frightened.

Stage four. For most subjects this is very mild and is gone by noon of the day following the experience. It consists of some fatigue and tension. Stage four may, however, continue all day. By the second day nearly everyone is normal. Rarely reactions will last up to one week and I know of one case in which the reactions lasted one year. The toxic effects will be discussed later.

There is an interesting state of relaxation in many that may last several days to several months. The subjects find themselves in an unusual state of ease in which they find it difficult to become irritable or hostile. Invariably they eventually regain their normal state of reactivity or irritability.

Two other groups of investigators studied the reaction of patients to LSD. These studies foreshadowed the psychedelic use of LSD later on. Busch and Johnson[71] and Forrer and Goldner[123] suggested the experience could be used for gaining access more readily into problems of chronic schizophrenic patients and for shortening psychotherapy. But they observed psychotomimetic changes only.

The psychedelic experience

*Psychedelics (Hallucinogens)**

Give me a button of wild peyote
To munch in my den at night,
That I may set my id afloat
In the country of queer delight.

So hol it's off to the land of dreams
With never a stop or stay,
Where psychiatrists meet with fairy queens
To sing a roundelay.

Give me a flagon of mescaline
To wash o'er my mundane mind,
That I may feel lie a schizophrene
Of the catatonic kind.

So hey! let in the visions of light
To banish banality,
Then will I surely catch a sight
Of the Real Reality.

*From Hanley, F. W.: Psychedelics, J.A.M.A. 90:686, 1964.

Give me a chalice of lysergic
To quaff when day is done,
That I may get a perceptual kick
From my diencephalon.

So ho! let all resistance down
For a transcendental glance
Past the superego's frosty frown
At the cosmic underpants.

Give me a pinch of psilocybin
To sprinkle in my beer,
That my psychopathic next-of-kin
May not seem quite so queer.

So hey! it's off for the visions bizarre,
Past the ego boundary,
For a snort at the psychedelic bar
Of the new psychiatry.

Natural phenomena are usually known or perceived long before they are named, but seldom does the phenomenon get detailed study and examination by scientists, philosophers, and others until it has been given a name. For the possession of a name gives to the phenomenon a kind of reality or solidity it did not have before. In his now classic paper, Osmond[289] showed that many investigators working with LSD had become aware that the experience did not always model schizophrenia as it is generally known. On the contrary, many subjects had unusually vivid, insightful, and happy experiences from which they derived a good deal of understanding about themselves, others, and about their relation to the cosmos. Osmond summarized the potential uses of this kind of experience as follows: (1) to aid psychotherapy and to its variant psychoanalysis, (2) to educate those who work in psychiatry and psychology to understand the strange ways of the mind, (3) to explore the normal mind under unusual circumstances, and (4) to examine the social, religious, and philosophical implications of these agents. Osmond was aware that none of the potentials had much chance of being realized until the experience which would make them possible was drawn to the attention of the scientific world under a new name. This would then educate the people working with LSD that it was something more than a psychotomimetic, a device for making people mad. Osmond coined the word psychedelic, which he defined, "A psychedelic compound is one like LSD, or mescaline which enriches the mind and enlarges the vision. It is this kind of experience which provides the greatest possibility for examining those areas most interesting to psychiatry and which has provided men down the ages with experiences they have considered valuable above all others."*

Osmond pointed out that this interest in chemically produced new states of mind is not new. It has been sought and studied since before the origin of history and has played a notable part in the evolution of religion, art, philosophy, and science. The Wassons[390] make a persuasive case for the origin of all religions in the mental states produced by the hallucinogenic mushrooms. Man has not been deterred by the greatest obstacles in his search for these mystical states. To some the experiences came easily, but others had to undergo prolonged and severe mortifications of the spirit and flesh before the desirable visions were achieved. So difficult has it been to achieve these states that man has considered it almost immoral if they come with little effort. In fact, one of the greatest criticisms of the psychedelic experience is that it comes too easily, as if only what is attainable with extreme difficulty is valuable. The experience is debased, so they say, unless the price is high. An example of this attitude is seen in Dean Peerman's[293] book review of *The Joyous Cosmology: Adventures in the Chemistry of Consciousness.* His title, "Instant Mysticism," is designed to create an atmosphere of hostility and brings to the mind the ersatz or instant coffee of many decades ago. Peerman is evidently disturbed by his misconceptions: (1) that hallucinogenic drugs are not natural, i.e., are artificial, which is odd since they are synthesized by Nature (in fact,

*From Osmond, H.: A review of the clinical effects of psychotomimetic agents, Ann. New York Acad. Sc. 66: 418-434, 1957.

starvation and flagellation seem less natural ways of getting instant mysticism); (2) that these instant (chemically induced) experiences will allow men to escape from their inner self, from moral judgment, and from time—from those things which the Christian who wishes to do God's will must be concerned. Peerman represents the immediate, thoughtless reaction of the ignorant. For, contrary to his fears, it is precisely these matters which are brought forcefully to the attention of the individual and society by these psychedelic experiences. They have directly led to some of the most beneficial movements in society: religion, Alcoholics Anonymous, and recently Synanon[251]—a new and promising society which may do for the drug addict what A.A. has done for the alcoholic. Osmond anticipated these objections when he wrote: "While we are learning, we may hope that dogmatic religion and authoritarian science will keep away from each other's throats. We need not put out the visionary's eyes because we do not share his vision. We need not shout down the voice of the mystic because we cannot hear it, or force our rationalizations on him for our own reassurances. Few of us can accept or understand the mind that emerges from these studies, Kant once said of Swedenborg, "Philosophy is often much embarrassed when she encounters certain facts she dare not doubt yet will not believe for fear of ridicule.

"In a few years, I expect, the psychedelics will seem as crude as our ways of using them. Whether we employ them for good or ill, whether we use them with skill and deftness or with blundering ineptitude depends not a little on the courage, intelligence and humanity of many of us working in the field today.

"I believe that the psychedelics provide a chance perhaps only a slender one for homo faber, the cunning ruthless, foolhardy, pleasure-greedy toolmaker to emerge into that other creature whose presence we have so rashly presumed, homo sapiens, the wise, the understanding, the compassionate, in whose fourfold vision, art, politics, science and religion are one. Surely we must seize the chance."*

Since Osmond's delineation of the psychedelic experience, there has been an extraordinary development in this field. The subject has been described in poetry, in learned journals, in the lay press, and there is the *Psychedelic Journal.* Even within such a brief period of time, there are three stages of psychedelic research. The first consists of Osmond's early work followed by research we carried out in Saskatchewan, which was largely exploratory but which led to our large therapeutic trials using LSD as a component in the treatment. The second stage was developed by the group at the International Foundation for Advanced Study, Menlo Park, California. Professor Harman and his colleagues[153-155] have been their most able advocates. This work expanded the use of the psychedelic concept into the broad group of behavioral problems and neuroses. The main catalyst has been A. Hubbard, a pioneer in using LSD.

The present stage is typified by the careful studies and researches of Unger.[385] The first two stages were carried out in relative freedom from harsh criticism, since the vast majority of people were unaware the studies were being done. Most psychiatrists were either ignorant of the investigations or, if they had heard of LSD, considered it only a drug used by research psychiatrists for making people mad. But stage three was marked by the tremendous upheaval and turmoil which followed the Harvard University enterprises of R. Alpert and T. Leary in 1962. One result of this massive use of LSD on large numbers of volunteers was a remarkable dissemination of LSD's uses and abuses until it is hardly likely any literate citizen has not heard something about it. The controversy according to *Pageant Magazine* (1963) "rocked the academic, medical and psycho-

*From Osmond, H.: A review of the clinical effects of psychotomimetic agents, Ann. New York Acad. Sc. 66: 418-434, 1957.

logical professions—as well as the governments of the U.S.A. and Mexico." Feature articles were also published in *Confidential, Cosmopolitan, Esquire, Fate, Ladies Home Journal, Life, Look, MacLeans, Medical Tribune, Medical World, News, Playboy, The Reporter, Saga, Saturday Evening Post, Time, Toronto Star Weekly,* and cautionary editorials appeared in the *Journal of American Medical Association* and the *Archives of General Psychiatry.*[148, 149]

As a result of the widespread interest in psychedelic drugs in the mass media, several things predictably followed:

A. There was public demand supported by professionals for the introduction of strict legal controls. The advice of the professionals fell into two groups: those of research psychiatrists who were very familiar with LSD, its uses and evils (Cohen[84-94] and our group in Saskatchewan under my direction, who recommended controls so that the drugs would be freely available to physicians skillful in the use of LSD); and those professionals, i.e., Grinker,[148, 149] whose criticisms, if accepted, could have led to the suppression of these chemicals.

B. Strict legal controls were instituted in the United States and of course in Canada. For a while it seemed as if LSD would join thalidomide as a banned drug in Canada but fortunately, as a result of advice given freely to Canada's government by organized medical societies, LSD was placed in a restricted category and it is now available to phychiatrists who have university appointments and are on the Minister of Health's list.

It was in this atmosphere of fear and mistrust that Unger[386] became vocal in his support of the psychedelic concept.

Stage one of psychedelic research. Following Osmond's[287, 289] review, we began an intensive study of the psychedelic experience. Before this we had used LSD as a treatment in a psychotomimetic way. We hoped that a frightful experience which modeled the worst in natural delirium tremens could persuade our alcoholic patients not to drink anymore and so avoid delirium tremens. But by 1957 it was apparent that even though many of our patients were helped by LSD, it was not its psychotomimetic activity which was responsible. In spite of our best efforts to produce such an experience, some of our subjects escaped into a psychedelic experience. Our psychiatrists were more at ease working with the psychedelic experience because it was possible to establish a therapeutic relationship and use psychotherapy.

As a result of our using LSD as a psychedelic drug, some in our group developed the hypothesis that if a therapist who had had much self-experience with LSD were to take it at the same time as the patient, the patient would be guided more easily and effectively through the unpleasant first stages to stages five and six. The results of treatment would therefore be much better. This type of therapy was described by Blewett and Chwelos.[50] The first part of the hypothesis is of course very difficult to prove or disprove. But the expected corollary, i.e., better results, remains unproved. A small series of alcoholics was intensively treated by the technique of Blewett and Chwelos, and the recovery rates were no better than those achieved when the therapist did not take LSD at the same time.

Stage two of psychedelic research. In stage one of LSD research, no special effort was made to control the environment of the patient undergoing therapy. Hospital rooms or psychiatrists' offices were used and there were many environmental distractions which interfered with the patient's experience. The first to take these factors into account were MacLean, MacDonald, Bryne, and Hubbard,[249] who prepared specially designed settings and aids. They used comfortably furnished rooms, free of distractions. Visual aids to comfort and enlarge the experience were used, which included photographs of members of the family, reproductions of works of art, and music. Further modifications were made by

the International Foundation for Advanced Study, which builds treatment rooms that would enhance the psychedelic experience.[153-155, 337, 342, 348, 349]

Stage three of psychedelic research. In stages one and two, double-blind comparison studies were not used for evaluating the efficacy of psychedelic therapy. Theoretically it is impossible to run comparison groups for testing the psychedelic treatment. There is a good deal of evidence which suggests that it is the experience itself and not the drug which is the therapeutic factor, provided that the experience is long enough. Mescaline and LSD produce experiences within 6 to 18 hours and both seem equally effective. We preferred LSD because of its shorter duration of activity. There is some evidence that the short experiences induced by psilocybin or dimethyltryptamine are not as effective, perhaps because that experience is too short and is not so firmly impressed in the memory or in consciousness. Any drug which produces a psychedelic experience should therefore be as effective as LSD. If intravenous amphetamine, for example, were selected as the control drug, and if the entire therapeutic session were run as if a psychedelic experience resulted, then there would be no comparison possible. One would merely have a comparison of two sets of psychedelic experiences.

If the comparison drug produced no experience, it would soon become known to both subject and observers and no double-blind study would be possible.

Stages one and two investigators were aware of these matters but the difficulties did not deter them from doing what they could. Those who demand double-blind studies are simply ignorant of the nature of these experiences. But stages one and two investigators studied a large variety of variables which may more or less be controlled.

Stage three investigators have profited from these studies and have begun large-scale trials, particularly at Spring Grove State Hospital.

Comparison of LSD with other nonergot hallucinogens

It is generally agreed that the experiences produced by all the known hallucinogens are quite similar. The variability of response to one compound is just as wide as the variability of response between drugs. Mescaline, LSD, and psilocybin produce extremely similar experiences.[101, 179, 206] The most convincing studies were those by Isbell[211] and Abramson,[7] who reported that their subjects could not distinguish between LSD and psylocybin. The general view is that these drugs trigger or activate a process, the content of which depends on all the variables other than drug already described. Isbell[211] hypothesized that some common biochemical mechanism was activated. Cross-tolerance between some of the compounds supports this.[15, 33, 34, 214]

LSD has also been compared with Amytal Sodium interviews,[58] with[1] anticholinergic hallucinogens,[235, 290, 291] with taraxein,[266] and with some tryptophan derivatives.[280]

The LSD experience has become the standard, and most compounds which have any activity which resembles that of LSD are compared against it.

Effect of LSD on schizophrenic patients

There are two diseases which so alter men that they do not react to LSD in the normal manner. One is schizophrenia, where the range of clinical reactivity is much wider than that in normal subjects, both in the effective dose and in the degree of response. Some schizophrenics react to normal doses and experience a reaction which varies from very slight to the most severe psychotic experience. Others, when given very large doses, show the same range of reactivity to LSD. The other is alcoholism, which will be discussed.

A large number of investigators have studied the effect of LSD on schizophrenic patients.[39, 40, 78, 81, 82, 95, 123, 139, 145, 146, 169, 170-175, 177-180, 225, 234, 240, 250, 282, 294, 306, 310, 319, 336, 341, 355, 366, 367, 368, 388]

There is hardly any agreement in this large number of studies, with respect to the following questions: (1) Do schizophrenics react in the same way as normals? (2) Are they more resistant in terms of dose? (3) Do they develop tolerance more quickly?

The reason for this divergence of opinion probably lies in the numerous variables which influence the LSD effect in normal volunteers plus several new ones unique to schizophrenia.

The observers' conclusions about this depend upon the stage of the disease, upon the kind of perceptual changes which develop, and the presence of thought disorder. Other variables have already been listed and discussed.

Stages of schizophrenia.

Malvaria. The malvaria concept was discussed under the heading, Complications of LSD. I stated that subjects who are malvarian are more apt to have prolonged reactions. Some time after I began to test alcoholics for malvaria, it occurred to me that very few of the malvarians had psychedelic experiences. I therefore examined all the records of alcoholics whose urine had been tested and who were given LSD as treatment.

About half of the nonmalvarians reached a psychedelic experience. The patients more often made positive statements than negative statements, but this is not surprising since the statements merely confirm that the subject was enjoying the session. For the whole group the means for positive and negative statements were the same, five each. But a few had psychedelic experiences even though most of the statements were negative, and a few had many positive statements and enjoyed the experience but did not approach a psychedelic experience.

The difference would be much more striking if I had included a very large series of normal subjects. So far in my studies no normal adult has had malvaria but about half of them had psychedelic experiences. If this group were added to the nonmalvarian group, the differences between malvaria and nonmalvaria would be significant beyond $P < 0.01$.

The malvarians, however, did not differ in any respect when compared with nonmalvarians who had the usual psychotomimetic experiences; e.g., their perceptual changes and changes in thought and mood were within the normal range. These patients were not schizophrenic and suffered no thought disorder so they had no difficulty in describing the experiences to the observer during the session or after recovering from the LSD the following day. Most of the alcoholics were given at least 200 mcg. of LSD and most often 300 mcg. There was no difference in the intensity of the reaction between the malvarians and nonmalvarians.

Malvarians have the same biochemical abnormality as the majority of schizophrenic patients. It is not unreasonable to assume that nonschizophrenic malvarians represent an early or subclinical form of schizophrenia.

Pseudoneurotic schizophrenia. This diagnostic term developed by Hoch and Polatin[181] is a very useful one. It includes a group of patients who are schizophrenic but whose symptoms are primarily neurotic. One could describe them as patients who have the symptoms of neurosis and the signs of schizophrenia.

Many of these individuals have never had typical schizophrenia, many have recovered from the florid symptomatology and remain chronically ill, and many have become alcoholic because while drunk the extremely distressing symptoms of schizophrenia were temporarily masked by the intoxication. They often develop typical schizophrenia after joining Alcoholics Anonymous. I have several patients who have gone through this sequence many times. These subjects should not be given LSD. In my opinion this is an absolute contraindication, for there is the grave risk of being jolted into a florid schizophrenic psychosis in which the patient may remain up to several years. Hoch, Cattell,

and Pennes[177, 178] found that with as little as 60 mcg. of LSD, subjects with well-preserved pseudoneurotic schizophrenia showed an intense emotional reaction.

These patients react to normal quantities of LSD, have a reaction which ranges from the usual to a very psychotic reaction, and are apt to have prolonged reactions. Since there is no thought process disorder, the subjects can describe their experience during or after LSD, unless of course an acute schizophrenic reaction is precipitated in which a thought process disorder does develop.

If there are impelling reasons for giving LSD to subjects with pseudoneurotic schizophrenia, the therapist should be prepared to treat the prolonged reaction vigorously with nicotinic acid, 3 Gm. per day, and/or tranquilizers. Occasionally a series of ECT will be required. It is hazardous to assume that the patient is suffering merely a prolonged reaction which will subside in a few days.

Acute florid schizophrenia. Patients with florid schizophrenia may or may not react to normal doses of LSD. It may be very difficult to determine this because if thought process disorder is present the subjects will not be able to give a coherent account of their experience. Also, there may be an accentuation of the symptoms already present. If, in the waxing and waning of symptoms, they have had some previously just as strong, they may not distinguish the LSD effect. On the other hand, the symptoms may be entirely different and easily distinguishable from those present before LSD was given. A patient having only auditory hallucinations will have no difficulty distinguishing and reporting visual perceptual changes. But a patient hearing voices may not note an increase or decrease in auditory perceptual acuity.

Subjects with acute schizophrenia will not have a prolonged reaction to LSD. Since they presumably are already as schizophrenic as they can be, it may not be possible to prolong it, that is, the natural disease will outlast the reaction. But there can be no certainty on this question, since it would be impossible to distinguish which reaction is present.

Chronic schizophrenia. Most studies of the effect of LSD were carried out on patients with chronic schizophrenia. It is generally agreed that they have an increased tolerance for LSD and require more than normal subjects in order to have the expected reaction. However, if thought disorder is severe, it may not be possible to determine whether the LSD changes are present since the ability to describe will be impaired.

Recovered schizophrenics. There are some patients who have completely recovered from the disease. They have no symptoms, no signs can be elicited, and the urine test is negative for the mauve factor. However, there are personality problems which may be explored under LSD and there are alcoholics who have not yet stopped drinking. It is my policy not to deny these individuals an LSD

Table III. *The effect of LSD on various stages of schizophrenia*

Stage of schizophrenia	*Dose range*	*Perceptual changes*	*Thought content*	*Disorder process*	*Ability to describe*	*Probability (P) of violent or prolonged reactions*
Malvaria	Normal	Yes	Normal	Normal	Normal	0.20
Pseudoneurotic	Normal	Yes	Abnormal	Normal	Normal	0.20
Acute florid	Normal	Yes	Abnormal	Abnormal	Reduced	?
Chronic	Increased tolerance	Reduced	Abnormal	Abnormal	Reduced	?
Recovered	Normal	Yes	Normal	Normal	Normal	0.01

psychedelic session. But they will have taken nicotinic acid or nicotinamide, 3 Gm. per day, before and will continue to take it afterward for several years.

A summary of the five stages of schizophrenia and their response to LSD is shown in Table III.

The use of LSD in psychotherapy

The field of psychotherapy is broad and complex and, unless its limits are defined more narrowly, it is impossible to consider how LSD has been used by those who believe they are practicing psychotherapy. I will restrict the term "psychotherapy" to the verbal interchange which takes place between a trained therapist, i.e., a physician or psychologist, and a subject who knows he is a patient and hopes the exchange will help him be relieved of certain troublesome symptoms and signs. This definition excludes chemical abreactions used only to obtain information, it excludes the use of LSD by other people who are interested in the psychedelic uses of the experience, and of course it excludes cultic uses by any groups that use LSD as a cult or as a sacrament in their religion. I do not mean to imply these are less desirable, inferior, or evil uses, but simply that in my opinion they do not constitute psychotherapy. In fact, the results as measured by permanent beneficial changes induced in the users may be even better than when psychotherapy as I have defined it is practiced.

When a patient receives psychotherapy alone, it is often difficult to determine whether the improvement which may take place is due to the specific action of the verbal exchanges or to a host of other variables to which humans are prone, such as natural physiologic recoveries, changes in the marital state, changes in familial relationships, and all the other factors which influence behavior. But when a chemical is used as an integral portion of the therapy, another variable is added to the complexity of factors already operating. The chemical may act by the nature of the experience which is produced or it may act by a direct chemical effect on the physiologic or biochemical reactions of the body and thus initiate a series of corrective biochemical changes which lead to the response. This applies equally well to tranquilizers, Amytal interviews, etc., as it does to LSD. The evidence that LSD does influence bodily processes has been reviewed. It is possible any one of these or some combination might initiate the changes leading to recovery.

Schmiege[344] divided the methods of working with LSD into two groups: (1) as a psychoadjuvant, (2) as a psychedelic. The first method, suggested by Busch and Johnson[71] for LSD, was quickly adopted by many therapists, including conventional psychotherapists and psychoanalysts such as Abramson.[2-6, 8] LSD is used to facilitate therapy and is given frequently in small doses beginning with 25 mcg. The dose is generally increased to about 150 mcg. The main emphasis is upon a thorough exploration of the psyche repeatedly, much as one might use Amytal Sodium interviews. The second method is quite different. Large doses, 200 mcg. or more, are given a few times or only once and the main emphasis is given to the intense psychedelic experience which follows. During the height of the experience, which may last several hours, there may be no verbal exchanges whatever between the subject and therapist. Elsewhere, Hoffer[185] suggested that in this method psychotherapy is an adjuvant to the psychedelic experience. The advantage of this way of looking at it is that it dethrones "psychotherapy" from its position as emperor of all the therapies and places it where it belongs as one of the less effective therapies used by physicians and psychiatrists.

Psychoadjuvant use of LSD. Busch and Johnson[71] found that patients were able to talk about their problems more easily during delirious states. They looked upon LSD as another delirient and so studied LSD's action on various psychiatric conditions. The authors used what would now

be considered very minor doses, 30 mcg. for women and 40 mcg. for men. In twenty-one psychotic patients the psychoses were activated, but some subjects seemed more interested in their fellowman. Eight more were given these quantities of LSD as a psychoadjuvant. The 3 with schizophrenia were not benefited. Two of the remaining 5 with neuroses were improved sufficiently, requiring no further treatment. They concluded: (1) LSD may offer a method for gaining access to those who are chronically withdrawn; (2) it may serve as a new tool for shortening psychotherapy.

Guttmann and Maclay[150] suggested that the mescaline experience might be a valuable aid to psychotherapy. Since then perhaps 200 reports have appeared which deal with the use of LSD in various groups of psychiatric patients.

The first suggestion that hallucinogenic drugs might be used to facilitate psychotherapy came from Guttmann and Maclay,[150] who had worked with mescaline. By the end of 1954 the groundwork for using LSD as an adjuvant to psychotherapy had been completed. The pioneers in this research[22, 43, 71, 123, 124, 125, 225, 324-329, 338, 396] established LSD's use as an aid to psychotherapy. Their findings have been enlarged and expanded until LSD has achieved a definite role in psychotherapy.

Abramson,[2-6, 8] in an interesting series of studies, demonstrated how LSD can be used as an aid to psychoanalytic psychotherapy. He started with small doses of LSD and in subsequent sessions increased the dose gradually. Abramson found it very effective in removing blocks in the analysis, in increasing tolerance to anxiety, and in intensifying the transference phenomenon.

Anderson and Rawnsley[22] treated 19 patients with 10 to 600 mcg. of LSD. Of this group, 6 were improved. The authors did not draw any conclusions about the effectiveness of LSD.

Chandler and Hartman[75] treated 110 patients with LSD. The group included 44 neurotics, 36 with personality disorders, 22 sociopaths, and 8 others. Each patient had an average of 6.2 (1 to 26) or 30 hours of psychoanalytic therapy each. The subjects were prepared by several sessions of psychotherapy beforehand. The interval between LSD sessions was 2 weeks. These investigators routinely started with 50 mcg. and increased the dose by 25 mcg. each session until they reached 150 mcg. After 4 to 5 hours the sessions were terminated. If the subjects remained anxious they were given chlorpromazine; if depressed, methylphenidate.

Out of this group 24 were markedly improved, 26 were considerably improved, and the rest did not improve. Only 2 subjects withdrew from therapy and subsequently made good life adjustment. In only 3 cases was there no facilitation of psychotherapy. In most instances there was a profound penetration and an accelerated psychotherapeutic effect.

Cohen and others[86, 90-94, 108] studied not only the therapeutic potential of LSD but the complications and side effects. The side effects have been discussed earlier. Eisner and Cohen[108] treated 22 subjects. The initial dose was 25 mcg. and it was increased by 25 mcg. to 125 mcg. over a follow-up period of 6 to 17 months. Sixteen in the group were improved.

Feld, Goodman, and Guido[119] gave 18 subjects 52 treatments with LSD (range 1 to 8 sessions). LSD brought into focus the repressed emotional attitudes, conflicts, etc., of the patients and activated them so they could be used in psychotherapy. An intense transference developed.

Fontana[122] found LSD most effective for facilitating individual psychotherapy after the patient had been in psychotherapy up to 6 months. Frederking[124, 125] based his conclusions on 200 treatments with LSD or mescaline and recommended doses lower than 100 mcg. He used an analytic approach and sought a psychocathartic effect. The LSD was given when it was desirable to shorten therapy, reactivate a stalled treatment, and to dissolve affect or memory blocks. Hoch[176] also believed that

LSD could be used as an adjunct to psychotherapy.

Sandison's group has been particularly active in developing the therapeutic uses of LSD. Sandison[325] and Sandison, Spencer, and Whitelaw[328] described in some detail their results with 36 neurotic patients. Their approach was Jungian psychotherapy. Out of the 36, only one did not complete the therapy. All had failed to respond to earlier treatments. The subjects suffered such extreme tension that leukotomy was indicated. The duration of illness for 9 was for 0 to 2 years; 7, 3 to 5 years; 12, 6 to 10 years; and 8, over 10 years. The dose varied from 25 to 400 mcg. The number of sessions varied with the individual. Of the total group, 14 recovered, 1 was much improved, 6 were moderately improved, and 2 not at all. The rest were still under treatment.

Sandison and Whitelaw[329] reported what had happened to the original 36 patients 2 years later. The results were: recovered 4, greatly improved 8, moderately improved 7, not improved 11, and unknown 6. For a group of patients with intractable neurosis the results are very good. In 1954, 21 were improved and 2 years later 19 still remained improved.

Before treatment with LSD, 27 out of the 36 had required treatment in mental hospitals. Sandison and Whitelaw also reported the results of an enlarged series of 94. Of these, 21 recovered, 20 were greatly improved, 20 were moderately improved, i.e., 65 per cent were improved. None had responded to earlier therapies.

Sandison[327] defined LSD psychotherapy as the relationship between therapist and patient during which the patient is given LSD. It produced a deepening of the patient's emotional tone, changed his thinking, and relieved emotionally charged memories.

Savage[338] treated 15 patients with LSD. Of these, 2 with involutional psychosis recovered, 4 with schizophrenic depressions were not benefited, but 5 with schizoid depressions were improved. He used 20 to 100 mcg. LSD per day for one month. Savage[337, 339] discussed some of the problems involved in using LSD. Savage,[337] Terrill[377] and Jackson[216] described the therapeutic effects of LSD.

Whitaker[397] treated 100 successive nonpsychotic subjects with LSD as an adjuvant. He used 100 to 250 mcg. of LSD and routinely gave subjects 200 mg. of nicotinic acid orally to reduce perceptual changes and so facilitate psychotherapy. Each patient averaged 3.28 treatments. Out of the 100 subjects, 47 were recovered, 18 improved, and 35 failed to improve. Of a group of neurotics treated by other methods before LSD was started, 12 were recovered, 30 improved, and 58 were failures.

The recovery rate was closely related to chronicity, as shown in Table IV.

The majority of patients who were improved did not have a relapse.

Leuner,[236] using methods developed by Sandison, treated 54 subjects. Previously 22 had been treated unsuccessfully with ECT psychoanalysis and continuous narcosis. Of this group, 19 recovered or were much improved and 17 were improved. The best results were found with subjects with character neuroses, of whom 10 out of 12 were in the recovered or much improved group.

In his discussion Leuner referred to 500 cases reported at the European Symposium on Psychotherapy and LSD held at Göttingen, Germany, November, 1960.

Psychedelic use of LSD. This has been developed primarily for the treatment of addicts, alcoholics, and those with person-

Table IV. *Relation of duration of illness and the response to LSD**

Duration of illness (years)	*No.*	*Recovery (%)*
0 to 2	8	75
3 to 5	32	50
6 to 10	25	40
11 to 20	24	45
Over 21	11	37

*From Whitaker, L. H.: Lysergic acid diethylamide in psychotherapy, M. J. Australia 1:36-41, 1964.

ality problems. A description of LSD therapy of alcoholics will give the reader a good account of the psychedelic use of LSD. The Native American Church of North America used peyote, which contains mescaline, in a similar way.[365]

The use of LSD for the psychedelic treatment of alcoholism is described in a series of 10 clinical reports beginning with those of Smith.[357, 358] A summary of his data is given in Table V.

Smith[357] treated 24 of the most difficult alcoholics who were then available. All but 4 had tried and failed Alcoholics Anonymous. Eight had delirium tremens at least once; only 2 had not had some complications arising from alcoholism. The average period of uncontrolled drinking was 12.1 years. Of the 20 nonpsychotic alcoholics, 11 were improved; of the 4 psychotic volunteers, 3 were no better after treatment. Corroborative studies[79, 108, 223, 249, 283, 284, 340, 349, 357] are shown in Table VI.

One of the best controlled studies was completed by Jensen.[222, 223] Treatment was carried out on a male admission ward where 10 alcoholic patients comprised part of a group of 40 psychotic patients. The alcoholics had their own dormitory. After physical examination and treatment of the complications of alcoholism, the subjects were started on a series of A. A. meetings, three per week. These were not compulsory, but all were strongly encouraged to attend. They also were given 2 hours of group psychotherapy and were encouraged to form a group, which they did. Toward the end of the period of hospitalization (mean, 2 months), the men were given the LSD treatment and received 200 mcg. During the session the therapist remained

Table V. *Results of treatment with LSD*

Group	*No.*	*Much improved*	*Improved*	*No change*
Character disorder	8	4	3	1
Psychopathy	12	2	2	8
Borderline and actual psychosis	4	0	1	3
Total	24	6	6	12

Table VI. *Results of treating alcoholics with LSD as a main treatment variable*

Investigator	*No.*	*Follow-up period (months)*	*Much improved*	*Results improved*	*No change*
Osmond*	2	9	1		1
Smith[357]	24	2 to 36	6	6	12
Chwelos[79]	16	2 to 9	10	5	1
MacLean[249]	61	3 to 18	30	16	15
Jensen[223]	58	6 to 18	34	7	17
O'Reilly[284]	33	2 to 22	7	10	16
Sherwood[349]	3	5	3		
Eisner[108]	2		1		1
Savage[340]	20		10		10
O'Reilly[283]	68	2 to 34	26		
Total LSD			128	44	73
Comparison controls, LSD Jensen[223]	80	6 to 18	11	7	62

*Original series of two, 1953.

7 to 8 hours with the patient. They were encouraged to bring their own records and family photographs. The therapist then worked with the patient using psychotherapy to bring out repressed memories, abreactions, new insights, and new understanding.

Another group received the same therapy, but for several reasons they were not given LSD and left the hospital early. This group was considered unfit to take LSD because of physical reasons or because of refusing to take the LSD.

A third comparison group consisted of alcoholic patients admitted during the same period. They received individual therapy from other psychiatrists.

Jensen's criterium for those who were much improved was complete abstinence after discharge or after a brief drinking bout shortly after discharge.

Studies by Belden and Hitchen,[38] using similar methods, corroborated these results. Belden and co-workers used about 300 mcg. of LSD and found that the treatment was unusually effective for psychopathic or character disorder alcoholics. Schizoaffective patients were not benefited. Their results were estimated conservatively as follows: one-third total abstinence over prolonged periods with improvement in socioeconomic mobility, one-third failures, and one-third no longer heard from.

So far there have been no therapeutic studies in which LSD has been used as a psychedelic agent where similar success rates were not found. It is odd that there have been no negative papers. But no negative report can be accepted as valid, when it does appear, unless methods similar to the ones described here are used. Psychiatric scientists must learn to repeat other people's work using methods which, if not identical, must be as close to them as possible. Where there are differences in methodology, the onus of proof is on them to show that the difference in technique was unimportant.

Ditman, Hayman, and Whittlesey[104, 105] examined the duration of claims for improvement made by subjects who had been given LSD. The authors gave the subjects 100 mcg. of LSD-25 orally in a *permissive* and *nontreatment*° setting in order to compare the experience with delirium tremens. They stated that subjects received no psychotherapy during the LSD experience. Questionnaires were sent to the subjects about 6 months to 1½ years after the last LSD experience; of those who responded, 27 were alcoholics. Of this group of 27, 18 subjects said they were better, that they were in more comfortable circumstances, earning more money, and had decreased or stopped drinking.

Inasmuch as this group had not been given LSD as therapy or in a therapeutic setting and had received only 100 mcg. of LSD, which we have found is relatively ineffectual for most alcoholics, this is indeed a surprising result.

However, a second questionnaire 2 years later was answered by only 16. Four of the other 11 had died, 3 of drinking. Of this group of 16, 11 still claimed periods of abstinence ranging from 1 to 1½ years and 12 claimed lasting benefit. The authors stated that this indicated fewer claims, but a Chi-square analysis of their own reported data does not support this contention. Thus, in the first questionnaire, 18 out of 27 claimed improvement; in the second questionnaire, 11 out of 16. Chi-square is less than 0.5. The results are practically identical. However, none had maintained sobriety. I interpret this to mean that, although nearly two-thirds of the group maintained they were improved at the time of the second questionnaire, 3½ years after having had received an ineffectual dose of LSD none had been continuously sober that entire period.

Psychopaths and behavioral problems. The treatments already outlined in detail have been used successfully for treating many patients with these problems.

Drug addicts. Isbell and co-workers[212]

°Emphasis is mine, not the authors'.

found that addicts reacted normally to LSD. I have given LSD to 2 addicts who reacted in much the same way as alcoholics. A direct result of LSD therapy was the development of Synanon, the new self-help organization developed by addicts for addicts. It seems to be as effective for addicts as A. A. for alcoholics.

Homosexuality. Ball and Armstrong[35] treated 10 homosexual patients with LSD; 2 were much improved. Martin[267] treated one homosexual with 8 LSD sessions. Six years later the subject was still normal. I have treated 3 homosexual men with LSD. One was also schizophrenic and alcoholic. He was treated with nicotinamide for the schizophrenia and later with LSD for the alcoholism and homosexuality. The subject is now well, 3 months later. Of the other 2, one is well.

Adolescent behavioral problems in boys. Cameron[72] treated 8 severely disturbed boys, aged 14 to 18, with LSD; 4 were much improved. I have treated 2 boys with behavioral problems. Of these, one has been well 5 years since treatment.

Criminal psychopaths. Arendsen-Hein[25] treated 21 severe criminal psychopaths with LSD. All were considered hopeless, with a history of 5 to 20 court sentences each. Treatment consisted of sessions with LSD (50 to 450 mcg.) every week or two for 10 to 20 weeks. Between LSD sessions they were given group therapy. Of the 21, 12 were clinically improved and 2 much improved. One was a chronic alcoholic who remained sober after treatment. The advantages of using LSD were: (1) there was no fear of the procedure; (2) motivation was activated; (3) past experiences were relived; (4) much therapy time was saved; and (5) the internalizing of conflicts was promoted.

The few studies with these behavioral problems are very encouraging. Well-conceived, large clinical studies are essential so that the indications and uses of LSD may be worked out.

Group psychotherapy and LSD. A good deal of skill and much experience are required to run LSD groups. Over the past eight years we have run many groups. In my opinion they are no better for the patient than are individual sessions. The main advantage is for the therapist, who can give the experience to 2 or more subjects and so conserve time. There are many disadvantages, the chief being that it is difficult to observe more than one patient accurately, and subtle clues to change, which are so valuable in individual sessions, are missed.

However, groups may be very advantageous for studying group interactions. It is advisable for every member of the group who will take LSD to have had one or more individual sessions so that the severe disorganization of the first experience is avoided. As a rule there should be one nonlysergized observer for each 2 subjects who have taken LSD. I have not had any experience with groups larger than 4. It is probable they would break down into several smaller groups.

Slater, Morimoto, and Hyde[354] studied the effect of group interaction on the LSD reaction. Subjects who took LSD in groups had more manic or schizoaffective reactions. The group did not reduce symptoms such as unreality, indifference, changes in body image, and the other severe psychotic symptoms. However, anxiety, depression, inappropriate behavior, underactivity, hallucinations, thinking, and speech disturbances were reduced.

Several times I have observed groups of 2 which had to be separated. One subject would develop great anxiety or panic which would often induce panic in the other. There was a kind of reverberation of affect which was not controlled until the subjects were taken to separate rooms, when anxiety in each quickly subsided.

Spencer[361] combined permissive group therapy with LSD. He found the chief value was that it mobilized repressed experiences. Ten very different patients with hopeless prognoses comprised the group. They had failed every previous treatment. The group included psychopaths, hysterics,

phobics, and recurrent depressions. Of the 10 subjects, 3 were so improved they no longer needed therapy, 4 were helped, and 3 were not helped.

Recently Cheek[76] used the Bales technique for measuring the effect of LSD on group interactions. LSD was given to a 4 person group of reformatory inmates. At times only one group member was given LSD, sometimes all 4. LSD had a marked effect on group interactions, total interaction rates, signs of tension, tension release, and overt hostility. In some cases marked behavioral changes were detected by the interaction technique, even when subjective accounts showed little change.

Autistic children and LSD

Freedman, Ebin, and Wilson[126] administered 100 mcg. of LSD to 12 autistic children whose age varied from 6 to 12 years. The results were similar to those of adult schizophrenics; none was improved.

Bender and co-workers[41, 42] used LSD for treating autistic children, using an entirely new concept in LSD therapy. A group of 50 autistic children was given daily doses of LSD starting with 25 mcg. and increasing the amount until daily doses of 150 mcg. were given. Treatment continued from 2 to 12 months. No previous treatment had helped any of them. UML was also used as another treatment.

Autistic children. There were no serious side effects. All showed some response. The children became "gay, happy, laughing frequently." Nearly all were more alert, interested in other people. Some showed appropriate facial emotion for the first time; many were able to understand and follow directions more readily. Some of the quieter, less aggressive children became quieter and more normal. There were no sleeping problems and vocabularies of several improved.

Verbal children. These were schizophrenic children, aged 6 to 12 years. Their illness had been less chronic and the children had attended public school. All could talk and all were improved. None was a management problem on the ward. Their interpersonal relationships improved, they developed insight, lost their hallucinations, and generally were much better. Psychological tests before and during therapy confirmed the clinical evaluations.

When half the children were taken off medication for 4 weeks, there was evidence of regression within a short time. Reserpine or imipramine for 4 weeks had no beneficial effect. When LSD was resumed, the children again responded.

These striking results are probably not due to the LSD experience, for UML, which does not produce an experience, was just about as good.

Both LSD and UML increased the uptake of inorganic phosphate by red blood corpuscles, thus normalizing phosphate metabolism.

Rapid personality change and LSD

The claims of many authors that the psychedelic experience could produce a permanent change in patients have been rejected by many psychiatrists whose orientation is psychoanalytic. It is basic to their belief to assume that each person has a stable personality which is altered with great difficulty. People become sick because their personality has been warped or not allowed to develop because of pathologic relationships with their parents. The only sure way of changing these twisted personalities is by a thorough analysis of many years' duration, during which all the roots of the pathologic personality are uncovered and treated. Any other treatment, psychotherapy, or drug therapy is considered merely symptomatic treatment which leaves the patient superficially better. Obviously these psychiatrists cannot accept rapid, permanent personality changes. Another group are psychologists, who have accepted the hypothesis that personality is a stable attribute to man.

This reluctance to believe that people can be permanently altered in a short time seems strange. History is replete with these sudden transformations. Religions and

mass self-help movements, e.g., Alcoholics Anonymous, originated from these changes. William James described many of them in *The Varieties of Religious Experience.*[217] Unger[384, 385] has given a lucid account of the issue of rapid personality change. Maslow[268] has described this phenomenon as "peak" experiences, and Sargant[335] tried to abstract those factors which make man susceptible to these rapid changes. According to Sargant, a state of increased excitation in the subject's persuasion is essential. He includes psychoanalysis as one of the conversion techniques, together with religious conversations, etc.

Three techniques have been used for demonstrating permanent personality changes: (1) clinical descriptions, which include subjective statements by patients and clinical evaluation by the therapists (these have already been discussed); (2) more objective questionnaires; and (3) psychological tests.

McGlothlin and colleagues[246-248] used questionnaires which subjects completed some time after experiencing the LSD reaction. In the first study McGlothlin was given access to a large volume of Janiger's[218] unpublished data. The therapy groups claimed more lasting benefit than nontherapy groups. From the latter, artists claimed the best response. Of the four nontherapy groups, the physician-psychologist group claimed the fewest benefits, however, the interval between the session and testing was longest. Increasing this interval tends to decrease the claims of benefit.

In the second study McGlothlin and others gave 15 subjects 200 mcg. of LSD. There were 14 comparison subjects. All were again tested one week later with Cattell's anxiety measures. There was no change in the comparison group but the treated subjects showed a drop in dogmatism and an increase in constructive responses. A comparison was made of the claims or expressions of opinion about the experience between Ditman's[104] subjects, Janiger's,[218] and their own. These are given in Table VII.

Table VII. *Comparison of personality changes*

	Group		
	Ditman N = 74 (%)	*Janiger N = 194 (%)*	*McGlothlin N = 15 (%)*
Experience described as:			
1. Pleasant	72	66	60
2. Upsetting	18		20
3. Would like to repeat	66	74	87
4. An experience of great beauty	66		67
5. Greatest thing that ever happened to me	49		60
Aftereffects:			
1. Enhanced understanding	54	61	67
2. Reduced anxiety and tension	34		53
3. Better relations with others	37	41	40

Modifiers of the LSD experience

Factors which modify the LSD experience may conveniently be classified into reducers and activators. Reducers are factors which decrease the intensity of the experience or which decrease the duration of action. Activators, on the contrary, intensify the experience or prolong it. Although the factors may be environmental, psychological, or physical, the physical factors only will be discussed, as the other two variables have already been described.

Reducers.

Sedatives and tranquilizers. Amytal Sodium has been used for decreasing the intensity of the experience, which it does rather well whether given intravenously or orally.[172] I have routinely used about 500 mg. of Amytal Sodium to ensure deep sleep after the LSD experience. But much larger quantities may be required. One

normal subject did not fall asleep until he had been given 1.2 Gm., but then slept 30 hours or so.

The nonstimulant tranquilizers have been studied most intensively and seem to be the best antidotes for the LSD reaction. The experience can be quickly terminated by intramuscular or intravenous chlorpromazine. Pretreatment with chlorpromazine for several days will completely protect the subject against LSD.[57, 78, 97, 140, 171, 172, 209, 213, 244, 329, 346] The minimum intramuscular dose is 50 mg. Other phenothiazines with properties similar to those of chlorpromazine should work just as well.

Murphree[279] studied the effect of chlorpromazine on the ability of volunteers to detect small quantities of LSD. Eighteen subjects were given 0, 5, 10, 15, and 20 mcg. The 20 mcg. dose was the threshold. When 25 mg. of chlorpromazine was given at the same time, recognition was not blocked. When 30 mg. was given 30 minutes before the LSD, recognition was blocked and so was mydriasis.

Reserpine does not seem as effective. Giberti and Gregoretti[140] pretreated subjects with about 10 mg. each day for several days. The subjects did not react to the LSD. But Isbell,[209] Isbell and Logan,[213] and Elder, Gogerty, and Dille[109] found that pretreatment with reserpine potentiated the effect.

Frenquel (α-C4-piperidyl benzhydrol HCl), a mild antipsychotic substance, has a marked effect in controlling the LSD reaction, according to Fabing,[116-118] who found, using double-blind studies, that 10 to 30 mg. daily for one week blocked the LSD reaction almost completely in 5 out of 6 normal subjects when given 100 mcg. of LSD. Brown, Braun, and Feldman[66, 67] reported that 100 mg. of Frenquel intravenously at the height of the LSD reaction promptly relieved the symptoms in 4 out of 5 subjects. Indirect support was found by Rinaldi and Himwich,[166, 303-305] who reported that Frenquel corrected electroencephalographic changes produced in rabbits by LSD. The antagonism was specific for the EEG changes since mydriasis was unaltered.

On the other hand, Isbell,[209] Clark,[80] and Isbell and Logan[213] found Frenquel no better than placebo. There the matter rests.

Substances which modify glucose metabolism.

GLUCOSE. Mayer-Gross, McAdam, and Walker[270-271] reported that LSD blocked the breakdown of hexomonophosphate and so interfered with the utilization of glucose. This was not confirmed by Bain.[32]

Nevertheless, based on this idea, they gave glucose to a few subjects reacting to LSD and felt there was a slight decrease in symptoms. Smith[357] repeated this experiment once by giving 100 Gm. of glucose orally to an alcoholic, diabetic subject at the height of the LSD experience. The blood glucose was elevated about 200 mg. per 100 ml., but there was no significant effect on the experience. However, the experience is very difficult to quantify. In any event, the striking effect of chlorpromazine and the equally vivid decrement of symptoms which follow 400 mg. of intravenous nicotinic acid were not observed.

GLUTAMIC ACID AND SUCCINIC ACID. Hoff and Arnold[182] and Arnold and Hofmann[26] reported that 20 Gm. of glutamic acid intravenously, 100 Gm. orally, and 10 Gm. of intravenous succinic acid interrupted or retarded the LSD reaction 3 to 5 hours. This reaction seems similar to the antidotal action of succinic acid or the mescaline experience.

NICOTINIC ACID. Agnew and Hoffer[19, 185] pretreated normal volunteers with 3 Gm. per day for 3 days and then gave 100 mcg. of LSD. Another group of 5 volunteers was given 200 mg. of nicotinic acid intravenously at the height of the experience. There were striking differences between nicotinized and normal subjects given the LSD. Difficulties in power of expression were mild when subjects were pretreated with nicotinic acid. Visual disturbances which are striking normally were rare and appeared as the major symptoms in only

one out of 5. Finally, there was a marked increase in feelings of unreality and in confusion about self-identity. A different type of model psychosis was produced which seemed more like schizophrenia. When the nicotinic acid was given intravenously at the height of the experience, there was a striking reduction in all the disturbances except affect. This occurred within a few minutes after the injection and was maintained the rest of the day. Since then, I[186] have used nicotinic acid when needed during LSD therapy to reduce confusion and decrease perceptual changes and so allow the psychedelic experience to emerge more readily. O'Reilly and Reich[284] routinely terminate their LSD therapy session with alcoholics by giving them nicotinic acid. Ruiz-Ogara and co-workers[319] also found that nicotinic acid was very effective in reversing much of the LSD experience. Whitaker[397] also used nicotinic acid to reduce the perceptual component of the experience and so improve the psychotherapeutic interchange. Miller, Williams, and Murphree[274] and Bertino, Klee, and Weintraub[48] also found that nicotinic acid modified the experience, but in their hands they saw chiefly a decrease in anxiety. The latter group reported that out of 8 subjects given nicotinic acid, 3 reported lasting and substantial improvement. Out of 44 other subjects given saline, nicotinamide, histamine, thiamine, and pyridoxine, none reported similar subjective improvement (Chi square > 10.0 $0.005 > P > 0.001$). The remarkable conclusion of the authors was that the effect must have been nonspecific (whatever that is), perhaps due to the flush. Their 4 subjects given histamine reported no subjective improvement, even though histamine produces just as marked a flush as nicotinic acid.

LSD congeners. The best antagonist to LSD, according to Abramson, is LSD itself. Subjects who take LSD everyday acquire tolerance to it very rapidly so that pretreatment for several days with LSD effectively prevents any further reaction. But LSD given at the height of an experience will not wash it out. It may either intensify, prolong, or do both.

Tolerance to LSD develops very quickly.[6, 9, 15, 212, 214] Cholden, Kurland, and Savage[78] found the same tolerance developed in chronic schizophrenic patients. A free period of 4 to 6 days is required before the full LSD experience can again develop.

Abramson and associates[17] found, in addition, that both MLD-41 and BOL-148 also developed cross-tolerance and prevented LSD from acting, but BOL-148 was only one-third as effective. Ginzel and Mayer-Gross[141] gave 6 volunteers 2 to 3 mg. of BOL-148 by mouth for 1 to 2 days, then LSD. If given for 2 days there was no effect; if given one day the LSD effect was reduced at the height of the LSD experience; intravenous BOL-148 had no effect.

Other substances. Yamada and Takumi[406] found that histamine infusions produced a marked but transient decrease in the LSD reaction in 7 out of 9 subjects.

Serotonin has some effect on the LSD experience but it is not a reducer or an activator. Poloni[296] reported that 5 mg. of serotonin given intravenously accelerated the rate of onset of 50 mcg. of LSD. If given at the height of the experience, it was accentuated but the duration of the effect was shortened. Brengelmann, Pare, and Sandler[59] pretreated subjects with 25 mg. of DL 5-hydroxytryptophan, a precursor of serotonin. Then they gave 60 mcg. of LSD intravenously. There was no effect clinically but some of the psychological tests suggested the experience was reduced slightly.

Elder and co-workers[109] reported that Dibenzyline decreased the LSD response in cats. Bertino and colleagues[49] found that it blocked mydriasis and other peripheral effects but did not block the psychological effects.

Bergen and others[45, 46] found that steroid hormones suppressed the effect of LSD on rats. Abramson and Sklarofsky[16] gave a large series of LSD sessions (25 to 50 mcg.) to 5 sophisticated subjects pretreated with 40 to 165 mg. of prednisone

per day for 3 to 7 days. This reduced or eliminated anxiety but did not alter any other part of the experience. It had a specific effect on mood. Krus and co-workers,[233] in a double-blind study, gave 12 subjects progesterone (600 mg.) one hour after they had received 75 mcg. of LSD. The authors noted a slight decrease in the LSD reaction.

Substances which have no effect. Phenoxybenzamine,[279] cortisone,[81] atropine and scopolamine,[109, 274] saline,[48] nicotinamide, thiamine, and pyridoxine,[48] have no effect on the LSD experience. I had observed by 1954 that nicotinamide did not block the LSD reaction and have not recommended its use.

METHYLENE BLUE AND DIPARCOL. Fischer,[120] while working in my laboratory, reported that pretreatment of subjects with methylene reduced the intensity of 50 mcg. of LSD about 40 per cent. This was based upon one subject to whom I had given this combination of drugs. When the experiment was completed, I concluded that there was no significant effect of the methylene blue on the LSD except that the intramuscular injections caused intense pain.

Activators. The main activators are sympathomimetic compounds. Bradley and Elkes[54] found that dl-amphetamine produced an alerting response in the cat, i.e., low amplitude and diffuse, fast waves. This was similar to the alert reaction produced by LSD. According to Elkes[110] the LSD alerting depends on environmental stimulation, whereas amphetamine produces an alert state less dependent on the environment.

It is not surprising amphetamine can potentiate the effect of LSD. It is well known that the amphetamines will extend the duration of the LSD experience and they are frequently used in therapy for this purpose.

Benadryl. There is a report by Elder and associates[109] that Benadryl given before LSD increased the reaction of cats to LSD.

How does LSD act?

Biochemical. One would expect a substance as active psychologically as LSD would also be very active biochemically. It does have an effect on a large number of reactions and thus exerts some influence on many cells, tissues, and organs of the body. However, not one of the reactions has been accepted as a primary cause of LSD activity. Everyone of these properties of LSD is shared with other very similar substances in one degree or another even though LSD is the most active. It seems likely the unique activity of LSD depends upon a combination of properties which interfere with two or more biochemical systems. This would decrease the probability that other similar compounds would share similar properties and increase the likelihood that a minor alteration in the molecule would produce a major change in its properties.

LSD must somehow interfere in the transmission of stimuli from one cell to another, either at the synapse or at the terminal boutons. Either effect could lead to an over-all marked change in brain function. For, in a system so complex as the brain, a very slight change at synapses repeated in sequence becomes a major change in the final result. LSD could influence the cell by blocking energy production, by altering cell membrane permeability, by reducing the blood supply to local or general areas of the brain, or by increasing permeability of the blood-brain barrier and so allowing toxic substances to enter. It could alter synaptic transmission by being a competitive inhibitor or by facilitating the direct action of some neurohormones such as serotonin, noradrenalin or adrenaline, or histamine. These are direct effects.

An indirect effect is one in which LSD produces a major change in some other biochemical system resulting in an increase or decrease beyond normal limits of other essential substances. There are at least two systems which are so altered: the acetylcholine system, which controls the

parasympathetic nervous system; and the noradrenalin, adrenaline, adrenochrome system, which forms part of the sympathetic nervous system.

Direct action.

Effect on brain cells. Woolley,[401-402] Woolley and Shaw,[405] and Miura and colleagues[276] reported that the normal pulsating rhythmical movements of oligodendroglia in pure culture was altered by LSD. With five micrograms per milliliter in the medium, LSD first caused a relaxation and vacuolization of the cells that eventually subsided and was succeeded by a strong contraction. The contraction was augmented by serotonin. However, the initial relaxation and vacuolization were prevented by serotonin. With one hundred micrograms of LSD the reaction was much stronger. Woolley and Shaw referred to the fact that brain is poorly vascularized compared to other organs, and that this defect in structure may be compensated by the slow pulsations of the oligodendroglia, which act as numerous, small stirring pumps. This would accelerate the exchange of chemicals between cells and blood. LSD, by interfering in the rhythmical movements of these cells, could alter their metabolism by impeding the uptake of oxygen and other essential nutrients and by a reduction in removal of the end products of metabolism, which are toxic if not removed.

Geiger[135, 136] also found marked changes in brain cells grown in pure culture. She observed mixed cultures and subcultures of neurons and glia with time lapse, phase contrast microcinemaphotography. LSD, at a concentration of 0.0002 to 0.001 μg per milliliter, was added. Within 15 to 20 minutes granules, which were concentrated around the nucleus, became dispersed in the cytoplasm of the neuron. The body of the neuron contracted and the processes of the axonal endings and dendrites often retracted. The movement of the terminal boutons on the cell body at the synapse slowed. The rate of movement of the nucleus became larger and irregular in shape. Similar changes were observed when cells were stimulated by Metrazol, electric current, etc. With LSD, Nissl substance decreased in the nucleus. With prolonged exposure to 0.001 μg per milliliter, chromatolysis occurred. The oligodendroglia contracted, then gradually expanded, and remained in this expanded state several hours. A lower concentration, 0.0002 μg per milliliter, also caused similar changes. When LSD was washed out, the observed effects were reversed in one-half hour.

The effect of LSD on the neurons depended upon the kind of neuron and where it had come from. Thus, Nissl substance from cerebellar cortex neurons was changed more rapidly than that from cerebral cortex neurons.

Serotonin was also very active in altering neuron behavior. Geiger[135, 136] often observed extrusion of cellular material into the environment from contracted oligodendroglia. She suggested that the rhythmical pumping movement of these cells and the rhythmical contractions of the neuron could control transfer of nutrients and metabolic end products. Adrenaline and noradrenalin were also very active. Most toxic of all was adrenochrome. At a concentration of 0.001 μg per milliliter it induced more rapid and drastic changes in neurons than did adrenaline or noradrenalin. Within 24 hours the neurons were killed.

The concentrations of LSD which affect neuron and oligodendroglia actively are very low, between 0.2 μg to 1 μg per liter. If we assume the brain has a volume of about 1 L., then only 1 mcg. free in the brain could produce marked changes.

The changes in physical activity of these cells must reflect major biochemical changes within the cell. These have been reviewed by Bain.[32] Mayer-Gross and coworkers[270, 271] found that 4×10^{-9}M LSD produced a 30 per cent stimulation of oxidation of glucose and a 40 per cent inhibition of the utilization of hexosemonophosphate. The data, which in any event were incomprehensible, were disproved.[32, 82, 238] However, Geronimus, Abramson, and Ingraham[138] found that guinea pig brain ho-

mogenates were inhibited in the use of oxygen by LSD (also BOL-148, L-LSD-25, D-iso-LSD-25, and D-LAE-32, even in absence of electrical stimulation). Lewis and McIlwain[238] did find that 5×10^{-5}M LSD inhibited glucose oxidations and lactate production 40 per cent in electrically stimulated guinea pig brain slices. This is a more natural model, since in the brain neurons are actively firing all the time. Clark and co-workers[80-82] found succinic acid dehydrogenase from the brain was inhibited 23 per cent by 1 mM. LSD while cytochrome oxidase was stimulated. Rudolph and Olsen[318] investigated the metabolism of glucose 1-C^{14} and glucose 6-C^{14} in prostate slices of dogs. Total radioactivity in CO_2 from glucose 1-C^{14} was considerably higher than from glucose 6-C^{14}. With 5×10^{-4}M LSD in system, labeled carbon in CO_2 was markedly increased with glucose 6-C^{14} but not with glucose 1-C^{14}.

Sankar and Bender[330] found LSD enhanced glucose oxidation by cerebral homogenates but depressed oxidation of cerebellar homogenates. Oxidation of citrate, succinate, and gamma aminobutyric acid was increased by both cerebral and cerebellar tissue, but oxidation of noradrenalin and serotonin was inhibited by both. LSD activated glutamic acid decarboxylase in cerebral tissue but inhibited it in cerebellar tissue.

Greig and Gibbons[147] found that LSD decreased the penetration of radioactive C^{14} glucose into the mouse brain. They suggested the LSD inhibition of cholinesterase produced a relative lack of glucose.

LSD also markedly alters excretion patterns of phosphate in urine, perhaps because of some inhibition of one of the phosphorylation reactions. Hoagland and co-workers[168] compared the excretion of inorganic phosphate in the urine of 12 normal men before and after taking LSD. After taking LSD (0.5 to 1.0 mcg. per kilogram) there was a marked reduction in urinary phosphate excretion for 6 hours after LSD was taken. The injection of ACTH during the LSD reaction increased phosphate excretions. In these studies the LSD-induced biochemical changes were remarkably like those found in schizophrenic patients not given LSD. Hoffer and Osmond[191] reported similar findings in normal subjects given adrenolutin and in schizophrenics not given anything. Similar findings were reported by Hollister.[203, 204, 206] LSD produced similar changes in phosphate excretions in guinea pigs.[44]

The number 4 position of the indole seems to be related to psychotomimetic activity. The more thoroughly it is tied up in the chemical structure, the more active is the compound. Mescaline, which could be indolized, could not form a 4 indole derivative.[73] Psilocybin simply has a phosphate group on position 4, while LSD has number 4 carbon incorporated into two rings. The respective doses are 500 mg. of mescaline, 10 to 20 mg. of psilocybin, and 0.1 mg. of LSD. This suggests that the body does not have enzymes which can split readily this linkage and that number 4 carbon plays a major role in the configuration of psychotomimetic activity.

Heacock and Mahon[160] developed a chromatographic technique for measuring all 4 isomers of hydroxyskatoles. The 5, 6, and 7 derivatives were present, but no 4 hydroxyskatole derivatives were found.[161]

Effect on circulation. LSD does not alter circulation of blood through the brain. Sokoloff and associates[359] found that LSD produced no change in blood flow, no change in vascular resistance, no change in oxygen and glucose utilization, and no change in the respiratory quotient. It is of course possible there are localized changes, but there are no known methods for testing this. Perhaps very high doses might alter blood flow through the brain but this would have no bearing when the usual clinical doses are used.

Effect on the blood-brain barrier. LSD might affect the brain by increasing the permeability of the blood-brain barrier. This would allow blood constituents which might be toxic to the brain to enter when normally they could do no harm. It has

been established that many normal constituents of blood are not injurious to brain function because they do not cross into the brain. Thus, when adrenaline is injected intramuscularly, there is an effect on blood pressure, blood sugar, etc., but no strong effect on brain function. When adrenaline is placed directly into the ventricles of the brain, there is very little change in blood pressure and blood sugar but pronounced anesthesia can develop. Melander and Martens[273] and Martens, Vallbo, and Melander[264-266] found that both taraxein and LSD potentiated markedly the psychotomimetic effect of adrenolutin on monkeys or cats. Similar observations were reported for LSD and adrenochrome in man.[184, 194] I have seen several subjects who did not leave phase one of the LSD reaction 2 hours after it was given. One woman given 300 mcg. of LSD merely remained extremely tense and uncomfortable. At 11:00 P.M. she was given 10 mg. of adrenochrome intravenously (from l-adrenaline). Within a minute or so the tension subsided and the usual LSD experience came on with visual changes, emotional reaction, etc. Melander and Martens proposed the hypothesis that LSD increased the permeability of the brain at certain sites to some molecules in the blood which normally did not penetrate. Supporting this contention was their finding that ceruloplasmin, which bound adrenolutin irreversibly, also protected animals against the effect of both taraxein and LSD. I also have found that adrenolutin is irreversibly bound by ceruloplasmin.

Their theory, therefore, simply is that ceruloplasmin, by binding these toxic metabolites, prevents them from entering the brain even though the permeability is increased; thus ceruloplasmin acts as an antidote for LSD and adrenolutin. It also seems to be an excellent treatment for schizophrenia.

Effect of LSD on transmission of stimuli. Marrazzi and his colleagues[253-263] have developed a theory of hallucinogenic activity based upon interference by these compounds with transmission at the synapse. The present theory of transmission of stimuli across a synapse holds that a neurohormone released at a signal diffuses across a narrow gap to the receptor site and stimulates it, so closing the electrical circuit. It is obvious that the function of the brain will depend upon a fine coordination of all the chemical processes which control this transfer of signals.

All synapses must fire in a coordinated manner. An alteration in the time required to cross a synapse in one can disrupt the entire sequence. When a series of synapses is linked in a series as in the brain, a minor inhibition of one repeated at several sites produces a major final change. Marrazzi therefore measured the effect of adding psychoactive compounds to synapses in the transcallosal pathway of lightly anesthetized cat preparations and initiated a test message with a weak electrical stimulus to the visual cortex on one side. He recorded the electrical changes of the invoked response at a symmetrical point on the contralateral cortex. The drugs were injected directly into the cerebral blood supply via the common carotid artery. This produces an ipsilateral concentration on the side of the recording electrodes. After dilution into the general bloodstream, the concentration becomes too low to produce peripheral stimulation. As a result, an uncomplicated central synaptic response can be measured.

Marrazzi measured the inhibition of a large series of psychoactive compounds with potencies ranged from 1 to 10,000. The compounds fell into three groups in terms of activity. Group A, mescaline and noradrenalin had low activity. Group B, gamma aminobutyric acid, adrenaline, and LSD had medium activity. Group C, serotonin and bufotenin had the highest activity in blocking synaptic transmission.

Antagonism of serotonin. Woolley[399-402] and Woolley and Shaw[403-405] first clearly implicated serotonin in the causation of mental disease. Since then, a voluminous literature has accumulated.[61, 112, 113, 292] The evidence marshaled by Woolley, which

links serotonin to mental disease and to the reaction induced by LSD, is substantial.

1. There is a firm relationship between mental illnesses and the excretion of indoles in urine.[362-364]

2. Most of the known psychotomimetics or hallucinogens are indoles.[190, 194, 197] These compounds included ergot hallucinogens, adrenochrome and adrenolution, harmine, tryptamine, ibogaine, mitrogynine, dimethyl- and diethyltryptamine, and psilocybin.

3. Indoles have definite neurophysiologic and biochemical effects on the brain. They depress synaptic transmission, alter spontaneous activity of the brain, inhibit amine oxidase, inhibit cholinesterases, inhibit hexosemonophosphate production, and inhibit glutamic acid decarboxylase.

4. Nicotinic acid, sedatives, and tranquilizers, which are therapeutic for schizophrenia and for toxic psychoses, antagonize many of the effects of indole hallucinogens.

5. Stress increases excretion of some indoles.[68, 252]

6. Actively psychotic patients excrete larger quantities of indoles than patients with quiescent psychosis.[68]

This is the evidence which links indole metabolism to mental disease. Additional evidence links LSD more directly to serotonin metabolism. Woolley and his colleagues noted that many of the psychoactive indoles were very active on uterine muscle in vitro. LSD was one of the most powerful inhibitors.[132]

Woolley therefore suggested that LSD produced its effect on the brain by directly interfering in the activity centrally of serotonin. It could do so by producing too little or too much serotonin at the active sites.

Following Woolley's proposals, Brodie and associates[60-65] developed the hypothesis that serotonin was a neurohormone. The pronounced effect of many psychoactive drugs such as reserpine, amine oxidase inhibitors, etc., has on serotonin metabolism supports this point of view.

The evidence which links serotonin to LSD's activity is:

1. It is readily available in the brain but is distributed in a highly specific manner. It is especially rich in areas of the brain rich in noradrenalin and adrenaline. Monamine oxidase, which destroys serotonin, is present wherever serotonin is localized.

2. It is protected from enzyme inactivation until after it has served its function.

3. Increasing serotonin levels in the brain of dogs by giving them 5-hydroxytryptophan after pretreatment with amine oxidase inhibitors produces gross behavioral changes.[167] This substance is readily converted into serotonin, and inhibiting amine oxidase prevents the serotonin from being destroyed so the concentration can increase.

4. LSD induces small increases in brain serotonin in dogs.[127] Increases were also found in rat brains. Serotonin levels returned to normal in 24 hours. If the rats were pretreated with reserpine, the effect of LSD upon brain serotonin was much more pronounced. Substances such as 1-methyl-*d*-lysergic acid butanolamide (UML) and L-LSD, which are psychologically not active, did not elevate serotonin even though UML is the most potent peripheral ergot antiserotonin. BOL-148 elevated serotonin slightly but much less than either LSD or ALD. Psychotomimetic activity correlated with this ability to elevate brain serotonin in reserpine-treated animals. The elevation of serotonin occurred in the particulate fraction of brain. According to Freedman[128] LSD increased serotonin 117 per cent in rat brain 30 to 120 minutes after treatment, but decreased noradrenalin 21 per cent. Similar changes were found in rabbit brain. ALD, MLD, and psilocybin produced similar changes.

5. LSD is more toxic and produces a more prolonged reaction in man and the rat 2 to 3 days after one dose of reserpine.[127] The majority of subjects suffered marked tremor and akathisia and in each case the experience was less pleasant than that in the control.

6. Sankar and co-workers[334] also found LSD produced an over-all increase in me-

tabolism of serotonin and an increase of serotonin in all parts of the body except the cerebrum.

Sankar and associates[333] gave rabbits radioactive 5-hydroxytryptophan followed 45 minutes later by LSD, BOL, or chlorpromazine. In the brain LSD increased total radioactivity in every region except the cerebrum. BOL and chlorpromazine elevated serotonin less in the same areas. LSD increased serotonin in all parts of the brain except the cerebrum. BOL and chlorpromazine decreased serotonin in all parts of the brain. The specific effects of LSD on serotonin were in the brain stem and in the parts of the brain excluding the cerebrum and cerebellum.

7. Reserpine, which depletes serotonin from its stores without blocking its formation, is a tranquilizer. The depletion of brain serotonin and the central effect of the reserpine persist for about the same length of time.

8. Barbiturate narcosis is potentiated by serotonin and this is inhibited by LSD.

9. LSD is a powerful antagonist to serotonin in many biologic systems. Bunag and Walaszek[69] found that lysergic acid derivatives blocked the arterial pressure response to serotonin, histamine, and adrenaline. LSD was the most active and was followed by BOL and finally UML. LSD and BOL antagonized the pressor-depressor responses to serotonin, weakly and irregularly, and in dogs BOL was a weak inhibitor.[321, 322]

10. When given intraventricularly to cats serotonin produces a state of lethargy from which they can be aroused by large quantities of LSD.

11. LSD and *d*-amphetamine rapidly reversed reserpine-induced depression in mice. The duration of action depended upon the dose. Less active were amphetamine and LAE, while acetylcholine and adrenaline were inactive.[70]

However, there is a good deal of evidence which the LSD-serotonin hypothesis does not account for. The strongest argument against a direct antiserotonin central effect of LSD is brom lysergic acid diethylamide (BOL-148). BOL-148 is as potent a peripheral antiserotonin as LSD. But BOL in doses 200 times as large as the active human doses of LSD has very slight psychological activity. LSD is primarily sympathomimetic in its effect while BOL is primarily parasympathomimetic. Both inhibit the potentiating effect of serotonin to barbiturates in mice. Finally, Haley[151] found that when both serotonin and LSD were placed in the cerebral area of mice, the LSD effect predominated, i.e., there was no antagonism. Neither did serotonin antagonize the action of LSD placed in the ventricles of cats.[56] These and other findings led Costa and co-workers[98] to suggest that one of the main effects of LSD was a stimulation of the central adrenergic receptors. They believed that the central effects of LSD were not dependent upon its antiserotonin action and that LSD's sympathomimetic effects had been ignored by many. It not only is an indole but is also a phenylethylamine derivative.

Antagonism of histamine. There is no clear relationship between histamine and the central activity in the brain. But there is some evidence it may have something to do with the transfer of electrical stimuli. McGeer, Wada, and McGeer[245] found that only one tissue in the brain, the hypothalamus, had much more histamine than the rest of the brain. The next most concentrated areas were the hypothalamic regions, which had little more than the cortical areas. Previously Harris[156, 157] had found that the basal areas of the brain were most concentrated in histamine, being richest in the medial eminence of the hypothalamus and in the anterior pituitary. He suggested that histamine was excreted from the brain and moved down the stalk into the pituitary, thereby initiating stress activity. Sawyer[343] found that histamine placed in the third ventricle of rabbits produced high amplitude spindling from the septal region. If a lesion were created in the septal region, the injection of histamine produced no electrical disturbance. Heath[164] found that the injection of large amounts of hista-

mine into the septal region induced marked behavioral changes in the experimental animals; they became catatonic. The regions also produced slow wave and spiking activity. Heath concluded that histamine probably played a significant role in behavior and might exert this effect by acting on specific parts of the limbic system of the brain. Marrazzi, Hart, and Gilfoil[263] reported that histamine was also a synaptic inhibitor, about as strong as serotonin. An antihistamine, tripelennamine, counteracted this inhibition. Marrazzi and co-workers suggested that histamine had a potential role in the production of some psychosis. Trendelenburg[383] provided evidence that histamine had a direct action on central ganglionic cells of the sympathetic nervous system.

Finally, Bunag and Walaszek[69] suggested lysergic acid derivatives blocked arterial pressure responses to serotonin by preventing the release of histamine. Thus, any theory of action of LSD may have to consider the interrelation of LSD and histamine.

Antagonism to sympathomimetic amines. There is much evidence that LSD can antagonize noradrenalin and adrenaline in the central nervous system and it is paralleled to the evidence that it antagonizes serotonin.

1. There is a much closer relationship between mental disease and adrenaline function. Adrenaline may be the stress or anxiety mediator.
2. Adrenaline can be converted in vitro and in vivo into adrenochrome and a series of indoles which has psychoactive properties, i.e., they are either psychotomimetics or antianxiety compounds.
3. Adrenochrome has definite effects on the electrical activity of the brain and as a very active chemical interferes in the action of many enzyme systems.
4. Substances which antagonize the effect of adrenochrome are also useful agents for countering the effect of LSD and for treating schizophrenia.
5. They are neurohormones and so are readily available in the brain.
6. Increasing levels of these amines in brain ventricles produce anesthesia.
7. Noradrenalin and adrenaline are localized in the same areas of brain as serotonin.
8. Monamine oxidase is one of the enzymes which destroys adrenaline.

Antagonism of serotonin, histamine, and noradrenalin. LSD could block transmission of stimuli in the brain by anyone of the following mechanisms: (1) mimicking an amine, most likely noradrenalin and adrenaline; (2) blocking action of the amine, most likely serotonin; (3) preventing its destruction by enzymes—this is not likely; (4) depleting amines from nerve endings, most likely noradrenalin and adrenaline; (5) interfering with synthesis—there is no evidence for this; (6) interfering with liberation, most likely histamine, serotonin.

Sankar and co-workers[331] made one of the first attempts to unite the activity of LSD with the three substances. Using radioactive tracers, they showed that in rabbits LSD increased the levels of serotonin in all tissues but the cerebrum and decreased the levels of histamine and noradrenalin. Increased levels of serotonin could release noradrenalin, which would cause sympathetic excitation and decrease levels of noradrenalin because of enzymatic destruction. LSD decreased the excretion of the methylated derivatives of noradrenalin.

Sankar and colleagues suggested that LSD increased bound serotonin, released noradrenalin, and prevented its conversion into normetanephrine. LSD also increased blood serotonin levels 170 per cent and decreased histamine levels 26 per cent.

To make matters even more complex, it is possible that if noradrenalin is not methylated to normetanephrine, it may be oxidized into noradrenochrome. Presumably any adrenaline present would also be transformed more quickly into adrenochrome. This will be discussed later.

Indirect activity.

PARASYMPATHETIC NERVOUS SYSTEM. LSD produces definite parasympathetic changes in the subject. These changes include sali-

vation, lacrimation, nausea, retching, and vomiting.[314] Doses of 50 to 100 mcg. per kilogram in anesthetized cats caused bradycardia, resulting from central vagus stimulation, and a fall in blood pressure. The usual doses in man have very slight effects on blood pressure.

It is likely that LSD exerts its parasympathomimetic effect because it is a very strong inhibitor of acetylcholinesterase. Thompson, Tickner, and Webster[378, 379] found that 10^{-6}M LSD inhibited human plasma cholinesterase 50 per cent. True cholinesterase was not inhibited even at 10 times the concentration. Human esterase was inhibited more than that in other species including the monkey. This inhibition probably accounts for the increase in acetylcholine levels in the brain after LSD, first reported by Poloni and Maffezzoni.[297] But very small concentrations of LSD potentiated cholinesterase activity in rat brain.[130, 131, 380] Zsigmond, Foldes, and Foldes[408-411] also reported that LSD inhibited plasma cholinesterase more than red cell or gray matter (true) cholinesterase. Rabbit enzyme was inhibited less than human enzyme. These authors did not find that low concentrations of LSD accelerated hydrolysis of acetylcholine. LSD was a true competitive inhibitor of both enzymes.

LSD is the most powerful esterase inhibitor of the group of ergot alkaloids, approaching eserine in activity. Goldenberg and Goldenberg[143] compared the activity of some of these compounds. Eserine was the strongest inhibitor, followed by LSD, BOL, and LAE. Zehnder and Cerletti[407] also reported BOL was less active than LSD.

Both LSD and BOL are quite selective in the effect on cholinesterase from various mammalian species. Tabachnick and Grelis[373] studied the inhibition of cat, dog, guinea pig, mouse, and human cholinesterase by LSD and BOL. Cat, dog, and guinea pig esterases were not inhibited, but mouse and human esterases were. They concluded that inhibition by LSD or BOL was observed only with enzymes which could hydrolyze imidazole, propionylcholine (dihydromurexine).

Thus so far there is no correlation between LSD's inhibitory effect on esterases. It would have been elegant if LSD had markedly inhibited true cholinesterase in all mammalian species (since they all react behaviorally to LSD) and if BOL had been inactive. But in vitro enzyme studies are still a long way from the brain, where matters may be much different. Goldberger,[142] using histochemical techniques, studied the effect of LSD on rat brain sections. In contrast to the previous enzyme studies, LSD did not inhibit pseudocholinesterase but did markedly inhibit true cholinesterase in the brain sections. There was no effect on noncortical areas. The intensity of the reaction for hydrolyzing acetylcholine was much reduced in LSD-treated cortical areas. Cell bodies positive for esterase in control sections were negative after LSD. Unfortunately BOL was not studied.

In an additional study Nandy and Bourne[281] investigated the distribution of true cholinesterase, pseudocholinesterase, and monamine oxidase in the spinal cord and spinal ganglia of rats before and after they were given LSD. Neurons of the spinal cord gave a strong reaction for true cholinesterase and almost none for monamine oxidase. Neurons of the spinal ganglia gave strong reactions for both. Pseudocholinesterase was present only in blood vessels. LSD strongly inhibited all three reactions.

SYMPATHETIC NERVOUS SYSTEM. Many sympathetic changes are produced by LSD. These include mydriasis, increases in body temperature in some animals, piloerection, and increases in blood sugar. These responses are blocked by ganglionic blocking agents or sympatholytics. Hoagland and co-workers[168] first suggested that LSD might owe its psychotomimetic properties to an interference in adrenaline metabolism. The evidence for this is substantial.

1. After LSD is given to subjects, adrenaline levels in plasma first rise, then later

decrease below the original levels. Eventually they return to normal.[230]

2. The adrenal gland is activated by LSD. The medulla becomes more active, as measured by the increased uptake of radioactive phosphorus and of course by the increase in adrenaline productions. The cortex also becomes more active. Ganong and associates[133] found that LSD in anesthetized dogs produced a light increase in the excretion of 17-hydroxycorticosteroids. Sackler, Weltman, and Owens[320] also found increases in 17-hydroxycorticosteroids and in 17-ketosteroids in rats.

3. LSD potentiates the action of adrenochrome and adrenolutin in man and in lower animals.[273] Occasionally subjects are not able to have a normal LSD reaction and remain in the first phase which is characterized chiefly by sympathetic activity. There is great tension and anxiety. On several occasions I have given 10 mg. of adrenochrome intravenously a couple of hours after the LSD. Within a few minutes after the injection, the typical perceptual changes occurred and there was a marked decrease in tension and anxiety.[185]

4. Ceruloplasmin binds adrenolutin irreversibly.[273] When animals are pretreated with ceruloplasmin, they are protected against the psychotomimetic effects of adrenolutin and LSD. It is difficult to understand how ceruloplasmin can protect against LSD unless it is assumed that LSD increases the production of adrenochrome in the body, which then goes on to adrenolutin; but in the presence of large quantities of ceruloplasmin the adrenolutin will be absorbed as fast as it is formed and so will effectively remove both adrenochrome and adrenolutin from toxic activity.

5. When adrenochrome is injected into the blood the concentration immediately becomes very high. In normal subjects[185, 194] all the injected adrenochrome is removed from the plasma within 30 minutes. Subjects with schizophrenia may still have the adrenochrome circulating at the end of 2 hours. When a normal subject is given 35 mcg. of LSD and then injected with adrenochrome, it is removed much less quickly and is still present at the end of one hour. If 100 mcg. of LSD is given, there will still be circulating adrenochrome at 2 hours. LSD inhibits the removal of adrenochrome from plasma. BOL-148 has no effect on the removal of adrenochrome.

6. Substances which react strongly with adrenochrome in vitro markedly affect the LSD experience. These are ascorbic acid, which bleaches adrenochrome and produces several indoles which are psychoactive, and penicillamine, which produces similar indoles.

Hoffer[184] treated normal subjects with 4 Gm. of ascorbic acid per day for several days, then administered 100 mcg. of LSD. Other subjects were given ascorbic acid at the height of the experience. Ascorbic acid did not alter the perceptual experience, increased tension and anxiety (probably by keeping adrenochrome levels down), but allowed subjects to concentrate better, produced less suspicion and thought disorder, and produced longer periods of euphoria. The next day subjects who had taken ascorbic acid were not as fatigued.

The effect of penicillamine in modifying the LSD experience has been described.[187] Briefly, it decreases markedly the emotional component of the LSD experience. In a normal subject one dl-penicillamine–LSD session produced a schizophrenia-like psychosis of 2 weeks' duration and a state of reduced tension for over one year.

7. Substances which antagonize the effect of adrenochrome and adrenolutin in human subjects also modify the LSD experience. Thus Szatmari, Hoffer, and Schneider[372] found that adrenochrome given intravenously produced a marked increase in EEG changes in some epileptic subjects. When given nicotinic acid intravenously at the height of the electrical disturbance, the EEG became normal in a few minutes and stayed normal. Nicotinic acid also counteracted the adrenochrome and adrenolutin reaction in man and nicotinic acid modified the LSD reaction.[19]

8. LSD increases the conversion of adrenaline into adrenolutin in plasma[165] Sankar and co-workers[331] found that LSD inhibited the conversion of noradrenalin into normetanephrine. I would expect similar findings with adrenaline. Also, the effect of adrenaline on blood pressure of children treated with LSD is markedly increased. Before LSD medication a small dose of adrenaline increased systolic and decreased diastolic pressure 12.5 mm. and 8.9 mm. After giving LSD daily for 6 to 8 weeks, the increase in systolic pressure and decrease in diastolic pressure were 28.4 mm. and 12.9 mm.

9. LSD increases the depletion of ascorbic acid from the adrenal gland by adrenaline. Costa and Zetler[99] found 10 mcg. per kilogram of LSD intraperitoneally increased the ascorbic acid depletion power of adrenaline. LSD alone had no effect, nor did BOL-148 potentiate. They concluded that LSD potentiated the effect of adrenaline. This is consistent with item 8.

Indirect action hypothesis. The entire autonomic nervous system can be involved in an hypothesis which is simple and easily testable. It is possible that the unique psychotomimetic activity of LSD depends upon a combination of direct and indirect factors. LSD, by inhibiting cholinesterase, will increase acetylcholine levels which produce the parasympathetic symptoms. This in turn increases the secretion of noradrenalin and adrenaline from the medulla and from storage sites in brain. LSD also blocks the methoxylating enzymes and so increases the conversion of adrenaline into adrenochrome. The combination of high acetylcholine, high adrenaline secretion, and higher adrenochrome indoles would account for the changes. This simple hypothesis would satisfactorily coordinate (1) the known changes in acetylcholine and adrenaline levels, (2) the activation of the adrenal gland, (3) the potentiation of the effect of adrenochrome by LSD, (4) the protective action of ceruloplasmin, (5) the increased stability of adrenochrome in LSD subjects, (6) the effect of adrenochrome reactive substances on the LSD experience, (7) the effect of adrenochrome antagonizers on the LSD experience, and (8) the decreased formation of normetanephrine. It could also account for the well-known tolerance which develops rapidly to LSD. In some preliminary research I found indirect evidence that LSD increased the permeability of red blood cells. It has already been suggested that it lowers the blood-brain barriers. Erythrocytes absorb large quantities of adrenaline, and hemoglobin readily absorbs adrenochrome irreversibly. These cells probably act as storage depots for adrenochrome. There are few cells which could do so safely since adrenochrome is a potent antimitotic. If we assume LSD allows adrenochrome to leak out of the cells, we can account for the LSD tolerance, for once the storage sites have been depleted no further reaction can take place until they are regenerated, and this may take up to 5 to 7 days. On the third or subsequent days, the slight experience one does have may simply be the action of LSD without adrenochrome. BOL-148, which does not alter adrenochrome tolerance curves, has no effect on permeability.

Nandy and Bourne[281] proposed a similar over-all mechanism of action. They suggested LSD acts by inhibiting the enzymes which control the transfer of impulses across synapses and also by raising the levels of acetylcholine, adrenaline, and adrenochrome in the blood. Inhibition of true cholinesterase and monamine oxidase of the spinal ganglia and dorsal horn could allow entry of a greater stream of impulses to the brain. This would disturb the fine balance in cortical function and so account for the psychological changes.

Based on this hypothesis, I have used LSD to treat a few patients with intractable schizophrenia whose malvaria Hoffer and Osmond[193, 195] did not clear. LSD does increase secretion of the mauve factor.[188, 208] In the few patients so treated the results were encouraging. The subjects were

in the hospital and were getting high doses of nicotinic acid at the same time. Perhaps this is a chemical rationale for Bender, Faretra, and Cobrinik's[41] use of LSD to treat autistic children.

Psychological. I have already given a comprehensive description of what LSD does to perception, to thought, and to mood. But I have not yet described why or how subjects have their unusual ideation and why they act as they do. We need assume only that the thought associations will be influenced by what is seen, heard, etc., and within the framework of the subject's life experiences he will react appropriately. If he is aware the changes are drug induced, he will react emotionally and intellectually but not by activity; e.g., if a voice invites him to join him in heaven he will not kill himself. But if he has no insight and has forgotten the experience is drug induced, he may make a suicidal gesture. It is doubtful he could carry through such an act. This is why it is so reassuring for the subject to be reminded that he has taken a drug, will come out of it soon, or can be brought out if the experience becomes too intense, fearful, etc.

Activity will similarly be a response to perception and thought changes. One of my subjects suddenly ran from the room down a long corridor. When I caught up with him he told me he had seemed so completely cut off from humanity that he was running to catch up with them. The main effort of the therapist should be to ensure there is as little motor reactivity as possible by keeping the subject aware of why he is having the experience.

Clinical. A good deal is known about LSD, its chemistry, pharmacology, clinical changes, and side effects, but hardly anything is known about the psychodynamic factors which arise from the experience and lead to the long-term changes in personality. Over the years I have tried to discover some unitary finding but I have not been able to come up with any. Subjective statements are not helpful because each subject who has been helped has a different explanation, and the same explanations are given by subjects just before discharge who subsequently do not do well. There is an amazing range of reasons, some of which I will list. These were in reply to my query, "Why were you able to keep away from alcohol?" (1) I don't know. (2) I had no further desire to drink. (3) I realized what my drinking was doing to my wife. (4) I realized I was not as bad as I thought. (5) I now find I understand the A. A. program. (6) I saw God. (7) I was revolted with what I saw in myself.

Objectively, there was no conformity of responses. Some patients were treated with permissive psychotherapy. Some abreacted early events, others did not. Several did not talk at all throughout most of the session.

The only clear findings from research with alcoholics was that the best results were associated with strong emotional reactions. When LSD alone was used, Smith[357,358] and O'Reilly and Reich[284] observed that having an emotional reaction improved the results.

The second most important variable is the therapist, who should be eclectic, knowledgeable about LSD, and continuously alert to any clue or comment which he can use to keep before the patient the main problem and his need to do something constructive about it. Sargant's[335] two main points seem pertinent. The state of excitation may be the combination of perceptual and emotional change produced by the LSD. The therapist and setting provide the persuasive elements of the environment.

Each therapist who has used LSD as a psychoadjuvant on a psychedelic patient has tried to explain LSD's effects within his own therapeutic orientation. Abramson uses LSD to facilitate psychoanalysis. LSD for him helps release material quickly which might require a long time but would eventually come without its help.

Barrios[36] developed an interesting, com-

prehensive hypothesis to account for the LSD effect. According to this hypothesis, a highly vivid image will appear when a cognitive stimulus rises to a dominant position in the stimulus preference hierarchy. His evidence is: (1) increasing cognitive stimulation produces hallucinations, e.g., electrical stimulation of certain areas of the brain; (2) reduction of the competing stimuli allows perceptual changes to appear; (3) LSD has an alerting effect on brain by acting at the brain stem level; and (4) LSD suppresses competing sensory stimuli, competing with cognitive stimuli. This raises the latter in the stimulus hierarchy, resulting in the hallucinations.

His hypothesis is that LSD produces a state of hypersuggestibility. This ability to evoke vivid imagery at will sets hallucinogenic therapy above other forms. The underlying process by which suggestibility leads to personality changes is a process of conditioning—cognitive conditioning.

Under LSD, which has increased suggestibility, cognitive conditioning is facilitated. By suppressing stimuli higher in the hierarchy (especially negative images such as the patient's self-concept), LSD facilitates the formation of new healthy images. Thus the patient comes to experience himself in a totally new way. He sees himself as a new and better person and, once the new images are established, new conditioned associations are formed which in turn lead to new behavior.

Belden and Hitchen[38] compared the LSD experience to a powerful dream experience. Alcoholics have two psychopathologic problems: an early encapsulated deprivation syndrome and a power syndrome. These individuals interpret situations including the LSD situation in terms of a power struggle because of their early damaging experiences. The LSD experience, being more powerful than any alcoholic intoxication, can be designed to be corrective in the presence of a benign authority figure, the therapist who may interpret and bring into consciousness the patient's power orientation. Factors which embrace the probability of success in therapy are total involvement in an inescapable situation, the powerful consciousness-changing quality of LSD, and the nonpunitive attitude of the therapist in conjunction with his traditional interpretative functions.

Jackson[210] looks upon the LSD experience as a new beginning. Subjects who are unable to let go, who cling desperately to their old familiar terminology, maintained a death grip on their "cathexis" and "repressions" and clinging to the old could not let go and be intrigued with the new.

Klee[230] believes LSD releases the bonds which inhibit an inhibited person. Ego functions are released from repressive influences and so the ego appears to function better. The LSD experience allows the subject to regress to a more primitive ego state which could be welcome and useful for the well-integrated individual but could not represent a real enhancement of ego function. Klee's thesis does not derive from the majority of therapeutic studies with LSD. In my experience over 12 years with LSD, I have found that well-integrated individuals have the least change after LSD. They have good experiences and enjoy them but their life flows on thereafter remarkably untouched by it. The most remarkable changes are in subjects who have the poorest integrated egos, addicts, alcoholics, neurotics, etc. It seems to be splitting hairs to claim that ego enhancement is only apparent. It is merely an affirmation that only prolonged psychoanalysis can really enhance ego. Finally, since there are no ways of measuring ego except by performance, Klee is on pretty shaky ground.

Sandison[327] gives a straightforward description of what happened. The immediate results of giving LSD were to deepen the patient's emotional tone, change his drinking pattern, sometimes cause a regression to an earlier emotional and intellectual period, and cause a reliving of emotionally charged memories.

Savage[340] believes LSD cures by pro-

ducing a conversion experience or a mystic state. The transcendental state, he believed, could open up avenues to creativity but was not creativity in itself. Savage[339] believed LSD caused reliving of previous experiences, brought out painful and repressed feelings, liberated the unconscious material and so allowed dramatic insights to occur.

Stevenson[366] stated the LSD experience increased the experience of beauty, produced a new appreciation of external reality, an appreciation their percepts are only partial, and an appreciation of the instability of normal perceptions.

My own opinion is that LSD does very quickly what Sargant believes is done by religion, psychoanalysis, brain washing, etc. It allows subjects to extricate themselves quickly from inhibiting attitudes, ideas, complexes, and conditioned habits. Why it does so still remains a mystery. It is my guess that for many years to come each therapist will develop his own hypothesis.

Schmiege[344] summarized the action of LSD as follows: (1) It helps the patient remember and to abreact both recent and childhood traumatic experiences. (2) It increases the transference reaction. (3) It activates the conscious so as to bring forth fantasies and emotional phenomena which may be handled by the therapist. (4) It intensifies affectivity so that excessive intellectualization is less likely. (5) It allows the patient to see better his customary defenses and allows him to alter them.

Some consequences of LSD's introduction to psychiatry

The experiences produced by mescaline and LSD in man have already had an enormous impact on psychiatry. Mescaline was studied about 100 years ago but it did not stir psychiatry as much as Hofmann's accidental discovery about 20 years ago. The past 20 years have witnessed a most remarkable revolution in psychiatry. Its end is not in sight and the impact is now producing ripples and waves of change in society at large. Its uses and abuses are discussed freely on TV and radio, in public addresses. University campuses from the University of Saskatchewan to Harvard University have seen groups of students indulging in self-experiments with peyote, morning glory seeds, etc. Last year, Dr. Glen T. Seaborg, Chairman of the Atomic Energy Commission, in listing fifteen of the most revolutionary discoveries of our present era, included pharmaceuticals that change and maintain personality at any desired level. He was thinking, states Gerald Heard,[162] of mescaline, psilocybin, and particularly LSD. It may become essential to establish legal and moral codes to govern those who use the materials, who should prescribe them, and under what conditions such a drug could be given to a person in a position of high authority when faced with decisions of great importance.

I will list some of the consequences which have followed the use of hallucinogens.

Model psychosis.

Psychological. This has greatly increased understanding of the inner world of psychosis. It has also increased awareness of the impact of the outer world upon patients with perceptual changes.

It also led to the development of the HOD test.[189] This is an objective card sort test based upon the changes in perception present in the LSD experience and in schizophrenia.

Biochemical.

1. This led to the isolation of the mauve factor[188, 208] and to the malveria concept.[193, 195]

2. It also led to the first clear difference in mineral metabolism between schizophrenics and others,[168] i.e., the effect on phosphorus excretion.

3. The adrenochrome metabolite hypothesis of schizophrenia derived from its use.[190]

4. The serotonin hypothesis of mental disease.

5. The serotonin neurohormone hypothesis.

Treatment.

1. Schizophrenia: (A) nicotinic acid,[186, 194, 196] (B) penicillamine,[194] (C) LSD for autism.[41, 42]
2. Alcoholism—with or without LSD.
3. Other conditions.

Teaching.

Psychiatrists. The inner world of the psychotic individual can be seen dimly by working very closely with him. The only way to see it clearly is to have schizophrenia and recover or to undergo the LSD experience.

Psychiatric nurses. Nurses also can learn from the experience and seem to benefit from it. A large number of psychiatric nurses in Saskatchewan have taken LSD. In my opinion they have been much better at nursing schizophrenic patients thereafter.[52]

Psychiatric architecture. Perceptual studies by Osmond[288] led directly to the construction of several new types of hospitals, called Osmond type hospitals. Osmond reported his own clinical experience of changes in spatial perception that were accompanied by changes in perception of the body, which was not only a special but a very important aspect of general perception. The huge corridors and unnecessarily large spaces so often found in mental hospitals were liable to aggravate one of the most harmful and distressing aspects of schizophrenic experiences—uncertainty about the integrity of the self.

Osmond[288] believed that the appreciation of the nature and experiences of the mentally ill person would allow the architect to develop simple rules for constructing hospitals. The use of LSD-25 and mescaline for changing perception means architects can depend less on their imagination and more upon the reality of the altered perceptual world of the schizophrenic.[215, 391]

Religion. Wasson and Wasson[390] presented a persuasive case for the thesis that religion originated from the use of hallucinogenic mushrooms many centuries ago. Certainly the great religions of the world have come from men who had powerful transcendental experiences. Men who have had the direct experiences or revelations do not need witnesses for their faith. But their followers have to accept the evidence of the revelations secondhand. It has occurred to many ministers and others interested in religion that the psychedelic experience could be used to explore the religious matters. It has been used in two ways.

1. A large number of clergy in Canada and England have taken LSD themselves in order to understand psychodynamics better. Others have used the experience to revive their feeling for religion. As an example, Jarman[219] used his experience of being in heaven or hell as the subject of some of his sermons. He reported that in 48 years of preaching he had never seen people more interested and full of questions about a sermon. Many said they would never be the same again.

As far as I know, no religion has yet incorporated LSD into its ceremonies and rituals. Peyote, which contains mescaline, is used as a sacrament by the Native American Church of North America. And psilocybin, in hallucinogenic mushrooms, is used by Indians in the Central Americas but not as regularly as peyote.

Philosophy. I am not aware of any major philosophical developments as a result of the LSD experience. Perhaps this will come later when many of the young people who have taken LSD have matured and developed their philosophies.

Group interaction. LSD has been used to facilitate group interchange and it may prove very valuable in highlighting group processes.

New psychological frontiers. (a) a reexamination of the concept of the stability of personality[121]; (b) personal space; (c) creativity; (d) parapsychology.

Synanon (for drug addicts). Several years ago a small group of alcoholics was given LSD in California. As a result of this experience, one of them developed the new self-help organization now known as Synanon. It is similar to A. A. but the drug

addicts live together in groups. They operate in group principles with a rigid code of conduct.

The results they have obtained in a few years are very impressive.[77, 251]

Easing the terror and pain of death. "I was sorry," he mumbled, "to hear she was so ill."

"It's a matter of a few days now," said Dr. Robert. "Four or five at the most. But she's still perfectly lucid, perfectly conscious of what is happening to her. Yesterday she asked me if we could take the moksha medicine together, the moksha medicine—the dope, as you prefer to call it—hardly upset her at all. All that happened to her was the mental transformation."

In Aldous Huxley's *Island*,*[207] psychedelic drugs were used very carefully, not only to learn about the present world but something of the hereafter. Pain was relieved at the same time.

"Is the pain bad," she asked.

"It would be bad," Lakshimi (Mrs. Robert) explained, "if it were really my pain. But somehow it isn't. The pain's here, but I'm somewhere else. It's like what you discover with the moksha medicine. Nothing really belongs to you, not even your pain."

LSD's powerful analgesic property has been discussed. Kast[224] gave the LSD to a group of patients, many of whom were aware they were dying. In addition to the relief of pain, the patients developed a peculiar disregard for the gravity of the situation. They spoke freely about their impending death with much less depressive effect than one would expect. This new attitude to death lasted for longer periods of time than the analgesic action. It is likely those who have a visionary, psychedelic, or transcendental reaction may equate this with life after death. This may explain their newer, more beneficial frames of mind while dying.

One of my friends who is very familiar with the LSD experience has recently told me quietly he had no fear of death anymore since he had a psychedelic experience with LSD.

*From Huxley, A.: Island, Toronto, 1962, Clarke, Irwin & Co., Ltd.

References

1. Abood, L. G., and Biel, J. H.: Anticholinergic psychotomimetic agents, *in* Pfeiffer, C. C., and Smythies, T. R., editors: International review of neurology, vol. 4, New York, 1962, Academic Press, Inc., pp. 218-274.
2. Abramson, H. A.: LSD: III. As an adjunct to psychotherapy with elimination of fear of homosexuality, J. Psychol. 39:127-155, 1955.
3. Abramson, H. A.: LSD: XIX. As an adjunct to brief psychotherapy with special reference to ego enhancement, J. Psychol. 41:199-229, 1956.
4. Abramson, H. A.: LSD-25: XXII. Effect on transference, J. Psychol. 41:51-98, 1956.
5. Abramson, H. A.: Verbatim recording and transference studies with lysergic acid diethylamide, J. Nerv. & Ment. Dis. 125:444-450, 1957.
6. Abramson, H. A.: The use of LSD in psychotherapy, New York, 1960, Josiah Macy, Jr., Foundation.
7. Abramson, H. A.: Lysergic acid diethylamide (LSD-25): XXXI. Comparison by questionnaire of psychotomimetic activity of congeners of normal subjects and drug addicts, J. Ment. Sc. 106:1120-1123, 1960.
8. Abramson, H. A., Hewitt, M. P., Lennard, H., Turner, W. J., O'Neill, F. J., and Merlis, S.: The stablemate concept of therapy as affected by LSD in schizophrenia, J. Psychol. 45:75-84, 1958.
9. Abramson, H. A., Jarvik, M. E., Gorin, M. H., and Hirsch, M. W.: LSD: XVII. Tolerance development and its relationship to a theory of psychosis, J. Psychol. 41:81-105, 1956.
10. Abramson, H. A., Jarvik, M. E., and Hirsch, M. W.: LSD: VII. Effect upon two measures of motor performance, J. Psychol. 39:455-464, 1955.
11. Abramson, H. A., Jarvik, M. E., and Hirsch, M. W.: LSD-25: X. Effect on reaction time to auditory and visual stimuli, J. Psychol. 40: 39-52, 1955.
12. Abramson, H. A., Jarvik, M. E., Birsch, M. W., and Ewald, A. T.: LSD: V. Effect on spatial relations abilities, J. Psychol. 39: 435-442, 1955.
13. Abramson, H. A., Jarvik, M. E., Kaufman, M. R., Kornetsky, C., Levine, A., and Wagner, M.: LSD: I. Physiological and perceptual responses, J. Psychol. 39:3-60, 1955.
14. Abramson, H. A., Kornetsky, C., Jarvik, M.

E., Kaufman, M. R., and Ferguson, M. W.: LSD: XI. Content analysis of clinical reactions, J. Psychol. 40:53-60, 1955.
15. Abramson, H. A., Rolo, A., Sklarofsky, B., and Stache, J.: Production of cross-tolerance to psychosis producing doses of lysergic acid diethylamide and psilocybin, J. Psychol. 49: 151-154, 1960.
16. Abramson, H. A., and Sklarofsky, B.: Lysergic acid diethylamide (LSD-25) antagonists, Arch, Gen. Psychiat. 2:89-93, 1960.
17. Abramson, H. A., Sklarofsky, B., Baron, M. O., and Fremont-Smith, N.: Lysergic acid diethylamide antagonists, Arch. Neurol. 79: 201-207, 1958.
18. Abramson, H. A., Waxenburg, S. E., Levine, A., Kaufman, M. R., and Kornetsky, C.: LSD: XIII. Effect on Bender-Gestalt test performance, J. Psychol. 40:341-349, 1955.
19. Agnew, N., and Hoffer, A.: Nicotinic acid modified lysergic acid diethylamide psychoses, J. Ment. Sc. 101:12-27, 1955.
20. Alema, G.: Allucinazioni da acido lisergico in cieco senza bulbi oculari, Riv. neurol. 22: 720-733, 1952.
21. Anastasopoulos, G., and Photiades, H.: Effects of LSD-25 on relatives of schizophrenic patients, J. Ment. Sc. 108:95-98, 1962.
22. Anderson, E. W., and Rawnsley, K.: Clinical studies of LSD, Monatsschr. Psychiat. u. Neurol. 128:38-55, 1954.
23. Apter, J. T., and Pfeiffer, C. C.: Effect of hallucinogenic drugs on the electroretinogram, Am. J. Ophth. 42:206-211, 1956.
24. Apter, J. T., and Pfeiffer, C. C.: The effect of the hallucinogenic drugs LSD-25 and mescaline on the electroretinogram, Ann. New York Acad. Sc. 66:508-514, 1957.
25. Arendsen-Hein, G. W.: *in* Crocket, R., Sandison, R. A., and Walk, A., editors: Hallucinogenic drugs and their psychotherapeutic use, Proc. Royal Med. Psychol. A., London, 1963, H. K. Lewis & Co., Ltd., pp. 101-106.
26. Arnold. O. H., and Hofmann, G.: Investigations on the effects of succinic acid in LSD intoxication and schizophrenics, Wien. Ztschr. Nervenh. 11:92-104, 1955.
27. Aronson, H., and Klee, G. D.: Effect of lysergic acid diethylamide (LSD-25) on impulse control, J. Neuv. & Ment. Dis. 131:536-539, 1960.
28. Aronson, H., Silverstein, A. B., and Klee, G. D.: The influence of lysergic acid diethylamide (LSD-25) on subjective time, Arch. Gen. Psychiat. 1:469-472, 1959.
29. Aronson, H., Watermann, C. E., and Klee, G. D.: Effect of lysergic acid diethylamide LSD-25) on learning and retention, J. Clin. & Exper. Psychopath. 23:17-23, 1962.
30. Axelrod, J., Brady, R. O., Witkop, B., and Evarts, E. V.: Metabolism of LSD, Nature 178:143-144, 1956.
31. Axelrod, J., Brady, R. O., Witkop, B., and Evarts, E. V.: The distribution and metabolism of LSD, Ann. New York Acad. Sc. 66: 435-444, 1957.
32. Bain, J. A.: A review of the biochemical effects in vitro of certain psychotomimetic agents, Ann. New York Acad. Sc. 66:459-467, 1957.
33. Balestrieri, A.: *In* Garattini, S., and Ghetti, V., editors: Crossed tolerance between LSD-25 and mescaline. Psychotropic drugs New York, 1957, Elsevier Press, Inc., p. 581.
34. Balestrieri, A., and Fontanari, D.: Acquired and crossed tolerance to mescaline, LSD-25 and BOL-148, Arch. Gen. Psychiat. 1:279-282, 1959.
35. Ball, T. R., and Armstrong, J. J.: The use of LSD-25 (d-lysergic acid diethylamide) in the treatment of the sexual perversions, Canad. Psychiat. A. J. 6:231-235, 1961.
36. Barrios, A. A.: An explanation of the behavioral and therapeutic effects of the hallucinogens, Personal communication, 1963.
37. Becker, A. M.: Psychopathological effects of LSD, Wien. Ztschr. Nervenh. 2:402-439, 1949.
38. Belden, E., and Hitchen, R.: The identification and treatment of an early deprivation syndrome in alcoholics by means of LSD-25, Am. J. Psychiat. 119:985-986, 1963.
39. Belsanti, R.: Modificazioni neuro-psico-biochimiche indotte dalla dietilamide dell' acido lisergico in schizofrenica e frenastenici, Acta neurol. napoli. 7:340-349, 1952.
40. Belsanti, R.: New studies in experimental psychiatry with LSD, Acta neurol. napoli 10: 460, 1955.
41. Bender, L., Faretra, G., and Cobrinik, L.: LSD and UML treatment of hospitalized disturbed children, *in* Wortis, J., editor: Recent advances in biological psychiatry, vol. 5, New York, 1963, Plenum Press, Inc., pp. 84-93.
42. Bender, L., Goldschmidt, L., and Sankar, D. V. S.: Treatment of autistic schizophrenic children with LSD-25 and UML-491, *in* Wortis, J., editor: Recent advances in biological psychiatry, vol. 4, New York, 1962, Plenum Press, Inc., pp. 170-177.
43. Benedetti, G.: Example of the study of the mental structure and of the pharmacodynamic investigation of a case of alcoholic hallucinosis, character neurosis and psychoreactive hallucinosis, Zschr. Psychother. 1:176-192, 1951.
44. Bergen, J. R., and Beisaw, N. E.: LSD and urinary inorganic phosphate excretion, Am. Physiol. Soc. 15:15, 1956.
45. Bergen, J. R., Krus, D. M., and Pincus, G. G.:

Suppression of LSD-25 effects in rats by steroids, Proc. Soc. Exper. Biol. & Med. **105**:254-256, 1960.

46. Bergen, J. R., and Pincus, G. G.: Steroid suppression of LSD induced behavior changes in rats, Fed. Proc. **19**:20, 1960.
47. Berlin, L., Guthrie, T., Weider, A., Goodell, H., and Wolff, H. G.: Studies in human cerebral function: The effects of mescaline and LSD on cerebral processes pertinent to creative activity, J. Nerv. & Ment. Dis. **122**:478-491, 1955.
48. Bertino, J. R., Klee, G. D., and Weintraub, W.: Effect of certain vitamins and histamines on the LSD psychosis, J. Ment. Sc. **105**:1095-1099, 1959.
49. Bertino, J. R., Klee, G. D., Collier, D., and Weintraub, W.: Clinical studies with dibenzyline and lysergic acid diethylamide, J. Clin. & Exper. Psychopath. **21**:293-299, 1960.
50. Blewett, D. B., and Chwelos, N.: Handbook for the therapeutic use of LSD-25. Individual and group procedures, mimeographed, 1959.
51. Boardman, W. K., Goldstone, S., and Lhamon, W. T.: Effects of LSD on the time sense of normals: A preliminary report, Arch. Neurol. & Psychiat. **78**:321-324, 1957.
52. Bolton, W. B.: Schizophrenia produced by LSD-25, Canad. J. Occup. Ther. **281**:55-62, 1961.
53. Boyd, E. S., Rothlin, E., Bonner, J. F., Slater, I. H., and Hodge, H. C.: Preliminary studies of the metabolism of LSD using radio-active carbon-marked molecules, J. Nerv. & Ment. Dis. **122**:470-471, 1955.
54. Bradley, P. B., and Elkes, J.: The effects of some drugs on the electrical activity of the brain, Brain **80**:77-117, 1957.
55. Bradley, P. B., and Hance, A. J.: The effects of intraventricular injections of LSD-25 and 5HT (serotonin) on the electrical activity of the brain of the conscious cat, J. Physiol. **132**: 50-51 (abst.), 1956.
56. Bradley, P. B., and Hance, A. J.: The effects of intraventricular injections of drugs on the electrical activity of the brain of the conscious cat, Electroencephalog. & Clin. Neurophysiol. **8**:699-700, 1956.
57. Bradley, P. B., and Hance, A. J.: The effect of chlorpromazine and methopromazine on the electrical activity of the brain of the cat, Electroencephalog. & Clin. Neurophysiol. **9**:191-215, 1957.
58. Brengelmann, J. C., Laverty, S. G., and Lewis, D.: Differential effects of lysergic acid and Sodium Amytal on immediate memory and expressive movement, J. Ment. Sc. **104**: 144-152, 1958.
59. Brengelmann, J. C., Pare, C. M., and Sandler, M.: Alleviation of the psychological effects of LSD in man by 5-hydroxy-tryptophan, J. Ment. Sc. **104**:1237-1244, 1958.
60. Brodie, B. B.: Serotonin and norepinephrine as antagonistic chemical mediators regulating the central autonomic nervous system. Neuropharmacology, *in* Abramson, H. A., editor: Trans. of the Third Conference, New York, 1957, Josiah Macy, Jr., Foundation, p. 323.
61. Brodie, B. B., and Costa, E.: Some current views on brain monoamines, Psychopharmacol. Serv. Cent. Bull. **2**:1-25, 1962.
62. Brodie, B. B., Pletscher, A., and Shore, P. A.: Evidence that serotonin has a role in brain function, Science **122**:968, 1955.
63. Brodie, B. B., and Shore, P. A.: On a role for serotonin and norepinephrine as chemical mediators in the central autonomic nervous system, *in* Hoagland, H., editor: Hormones, brain function and behavior, New York, 1957, Academic Press, Inc., pp. 161-180.
64. Brodie, B. B., Shore, P. A., and Pletscher, A.: Serotonin-releasing activity limited to rauwolfia with tranquilizing action, Science **123**: 992-993, 1956.
65. Brodie, B. B., Spector, S., and Shore, P. A.: Interaction of drugs with norepinephrine in the brain, Pharmacol. Rev. **11**:548-564, 1959.
66. Brown, B. B., Braun, D. L., and Feldman, R. G.: The pharmacologic activity of (4-piperidyl) benzhydrol hydrochloride (azacyclonol hydrochloride) an ataraxic agent, J. Pharmacol. & Exper. Therap. **118**:153-161, 1956.
67. Brown, B. B., Feldman, R., and Braun, D. L.: Pharmacologic studies of an LSD antagonist, 4-piperidyl diphenyl carbinol hydrochloride, Fed. Proc. **14**:322 (abst.), 1955.
68. Brune, G. G., and Pscheidt, G. R.: Correlations between behaviour and urinary excretion of indole amines and catecholamines in schizophrenic patients as affected by drugs, Fed. Proc. **20**:889-893, 1961.
69. Bunag, R. D., and Walaszek, E. J.: Blockade of depressor responses to serotonin and tryptamine by lysergic acid derivatives in the chicken, Arch. internat pharmacodyn. **135**: 142-151, 1962.
70. Burton, R. M.: The analeptic action of LSD on reserpine-sedated mice, Ann. New York Acad. Sc. **66**:695-697, 1957.
71. Busch, A. K., and Johnson, C.: LSD-25 as an aid in psychotherapy, Dis. Nerv. System **11**:241-243, 1950.
72. Cameron, K.: Some experiences with LSD in the treatment of adolescent boys, *in* Crocket, R., Sandison, R. A., and Walk, A., editors: Hallucinogenic drugs and their psychotherapeutic use, Proc. Royal Med. Psychol. A., London, 1963, H. K. Lewis & Co., Ltd.
73. Cerletti, A.: Synopsis of certain developments

within the field of hallucinogenic drugs, *in* Crocket, R., Sandison, R. A., and Walk, A., editors: Hallucinogenic drugs and their psychotherapeutic use, Proc. Royal Med. Psychol. A., London, 1963, H. K. Lewis & Co., Ltd.

74. Cerletti, A., and Doepfner, W.: Comparative study on the serotonin antagonism of amide derivatives of lysergic acid and of ergot alkaloids, J. Pharmacol. 122:124-136, 1958.
75. Chandler, A. L., and Hartman, M. A.: Lysergic acid diethylamide (LSD-25) as a facilitating agent in psychotherapy, Arch. Gen. Psychiat. 2:286-299, 1960.
76. Cheek, F. E.: Exploratory study of drugs and social interaction, Arch. Gen. Psychiat. 9: 566-574, 1963.
77. Cherkas, M. S.: Synanon: Hope for the narcotic addict, Mind 1:113-115, 1963.
78. Cholden, L. S., Kurland, A., and Savage, C.: Clinical reactions and tolerance to LSD in chronic schizophrenia, J. Nerv. & Ment. Dis. 122:211-221, 1955.
79. Chwelos, N., Blewett, D. B., Smith, C. M., and Hoffer, A.: Use of d-lysergic acid diethylamide in the treatment of alcoholism, Quart. J. Stud. Alcohol 20:577-590, 1959.
80. Clark, D.: Further studies of the psychological effect of Frenquel and a critical review of previous reports, J. Nerv. & Ment. Dis. 123: 557-560, 1956.
81. Clark, L. D., and Clark, L. S.: The effects of cortisone on LSD-25 intoxication in schizophrenic patients, J. Nerv. & Ment. Dis. 123: 561-562, 1956.
82. Clark, L., Fox, R. P., Benington, F., and Morin, R.: Effects of mescaline, lysergic acid diethylamide and related compounds on respiratory enzyme activity of brain homogenates, Fed. Proc. 13:27, 1954.
83. Cline, H. S., and Freeman, H.: Resistance to LSD in schizophrenic patients, Psychiat. Quart. 30:676-683, 1956.
84. Cohen, S.: Notes on the LSD-25 state, J. Wadsworth Gen. Hosp. 3:79-83, 1959.
85. Cohen, S.: Notes on the hallucinogenic state, Internat. Rec. Med. 173:380-387, 1960.
86. Cohen, S.: Lysergic acid diethylamide: Side effects and complications, J. Nerv. & Ment. Dis. 130:30-40, 1960.
87. Cohen, S.: Morning glory seeds—A warning, Mind 1:228, 1963.
88. Cohen, S.: Suicide following morning glory seed ingestion, Am. J. Psychiat. 120:1024-1025, 1964.
89. Cohen, S.: What price morning glory, Mind 2:217-220, 1964.
90. Cohen, S., and Ditman, K. S.: Complications associated with lysergic acid diethylamide (LSD-25), J.A.M.A. 181:161-162, 1962.
91. Cohen, S., and Ditman, K. S.: Prolonged adverse reactions to lysergic acid diethylamide, Arch. Gen. Psychiat. 8:475-480, 1963.
92. Cohen, S., and Edwards, A. E.: The interaction of LSD and sensory deprivation, *in* Wortis, J., editor: Recent advances in biological psychiatry, vol. 6, New York, 1964, Plenum Press, Inc., pp. 139-144.
93. Cohen, S., and Eisner, B.: Use of LSD in a psychotherapeutic setting, Arch. Neurol. 81: 615-619, 1959.
94. Cohen, S., Fichman, D., and Eisner, B. G.: Subjective reports of LSD experiences in a context of psychological test performance, Am. J. Psychiat. 115:30-35, 1958.
95. Condrau, G.: Clinical experience with LSD in mental patients, Acta psychiat. et neurol. 24:9-32, 1949.
96. Cook, W. B., and Kieland, W. E.: Isolation and partial characterization of a glucoside from Rivea corymbosa (1) Hallier Filius, J. Organic Chem. 27:1061-1062, 1962.
97. Cooper, H. A.: Hallucinogenic drugs, Lancet 268:1078-1079, 1955.
98. Costa, E., Gessa, G. L., Hirsch, C., Kuntzman, R., and Brodie, B. B.: On current status of serotonin as a brain neurohormone and in action of reserpine-like drugs, Ann. New York Acad. Sc. 96:118-133, 1962.
99. Costa, E., and Zetler, G.: Effect of epinephrine on adrenal ascorbic acid following premedication with LSD or 5HT, Proc. Soc. Exper. Biol. & Med. 98:249-252, 1958.
100. Delay, J., and Pichot, P.: LSD and psychic disorders in ergotism, Compt. rend. Soc. biol. 145:1609, 1951.
101. Delay, J., Pichot, P., Lemperière, T., Nicolas-Charles, P., and Quentin, A. M.: Les effects psychiques de la psilocybine et les perspectives thérapeutiques, Ann. med. psychol., Par. 117:899-907, 1959.
102. DeMaar, E. W. J., Williams, H. L., Miller, A. I., and Pfeiffer, C. C.: Effects in man of single and combined oral doses of reserpine, iproniazide and d-lysergic acid diethylamide, Clin. Pharmacol. & Therap. 1:23-30, 1960.
103. DeShon, H. J., Rinkel, M., and Solomon, H. C.: Mental changes experimentally produced by LSD, Psychiat. Quart. 26:33-53, 1952.
104. Ditman, K. S., Hayman, M., and Whittlesey, R. B.: Nature and frequency of claims following LSD, J. Nerv. & Ment. Dis. 134:346-352, 1962.
105. Ditman, K. S., and Whittlesey, R. B.: Comparison of the LSD-25 experience and delirium tremens, Arch. Gen. Psychiat. 1:47-57, 1959.
106. Dusen, W. V.: LSD and the enlightenment of Zen Psychologia 4:11-16, 1961.
107. Edwards, A. E., and Cohen, S.: Visual illusion, tactile sensibility and reaction time un-

der LSD-25, Psychopharmacologia 2:297-303, 1961.

108. Eisner, B., and Cohen, S.: Psychotherapy with lysergic acid diethylamide, J. Nerv. & Ment. Dis. 127:528-539, 1958.
109. Elder, J. R., Gogerty, J. H., and Dille, J. M.: Survey of LSD antagonists, Fed. Proc. 16: 293, 1957.
110. Elkes, J.: Effects of psychotomimetic drugs in animals and man, *in* Abramson, H. A., editor: Neuropharmacology, Trans. of the Third Conference, vol. 3, New York, 1957, Josiah Macy, Jr., Foundation, pp. 205-295.
111. Ellis, H.: "Mescal"—A new artificial paradise, Ann. Rep. Smithsonian Institute, 537-548, 1897; Contemporary Rev. 73:130, 1898; Pop. Sc. Monthly 61:52-71, 1902.
112. Erspamer, V.: Pharmacology of indolealkylamines, Pharmacol. Rev. 6:425-487, 1954.
113. Erspamer, V.: Recent research in the field of 5-hydroxy-tryptamine and related indoealkylamines, *in* Jucker, E. editor: Progress in drug research, New York, 1961, Interscience Publishers, Inc., pp. 151-367.
114. Evarts, E. V.: A review of the neurophysiological effects of lysergic acid diethylamide and other psychotomimetic agents, Ann. New York Acad. Sc. 66:479-495, 1957.
115. Evarts, E. V., Landau, W., Freygang, E., and Marshall, W. H.: Some effects of LSD and bufotenine on electrical activity in cat's visual system, Am. J. Physiol. 182:594-598, 1955.
116. Fabing, H. D.: New blocking agent against the development of LSD-25 psychosis, Science 121:208-210, 1955.
117. Fabing, H. D.: Frenquel: A blocking agent against experimental LSD-25 and mescaline psychosis. Preliminary note on its clinical application, Neurology 5:319-328, 1955.
118. Fabing, H. D.: Experimental compound MER-17 (Frenquel): A new blocking agent against the development of LSD-25 psychosis, Psychiat. Res. Rep. 1:140-144, 1955.
119. Feld, M., Goodman, J. R., and Guido, J. A.: Clinical and laboratory observations on LSD-25, J. Nerv. & Ment. Dis. 126:176-183, 1958.
120. Fischer, R.: Factors involved in drug-produced model psychoses, J. Ment. Sc. 100: 623-631, 1954.
121. Fogel, S., and Hoffer, A.: Perceptual changes induced by hypnotic suggestion for the post-hypnotic state, J. Clin. & Exper. Psychopath. 23:24-35, 1962.
122. Fontana, A. E.: El uso clinicao de las drogas alucinogenas, Acta neuropsiquiát. Argent. 7: 94-98, 1961.
123. Forrer, G. R., and Goldner, R. D.: Experimental physiological studies with lysergic acid diethylamide (LSD-25), Arch. Neurol. & Psychiat. 65:581-588, 1951.
124. Frederking, W.: Intoxicant drugs (mescaline and LSD) in psychotherapy, J. Nerv. & Ment. Dis. 121:262-266, 1955.
125. Frederking, W.: Über die Verwendung con Rauschdrogen (Mescaline und Lysergsaure-diathylamid in der Psychotherapie, Psyche. (Stuttg.) 7:342-364, 1953.
126. Freedman, A. M., Ebin, E. V., and Wilson, E. A.: Autistic schizophrenic children, Arch. Gen. Psychiat. 6:203-213, 1962.
127. Freedman, A. M., and Giarman, N. J.: LSD-25 and the status and level of brain serotonin, Ann. New York Acad. Sc. 96:98-107, 1962.
128. Freedman, D. X.: Psychotomimetic drugs and brain biogenic amines, Am. J. Psychiat. 119: 843-850, 1963.
129. Freter, K., Axelrod, J., and Witkop, B.: Studies on the chemical and enzymatic oxidation of lysergic acid diethylamide, J. Am. Chem. Soc. 79:3111, 1957.
130. Fried, G. H., and Antopol, W.: The effects of psychotomimetic compounds on human cholinesterase, Anat. Rec. 125:610-611, 1956.
131. Fried, G. H., and Antopol, W.: Effects of psychotomimetic compounds on human pseudocholinesterase, J. Appl. Physiol. 11:25-28, 1957.
132. Gaddum, J. H.: Antagonism between lysergic acid diethylamide and 5-hydroxytryptamine, J. Physiol. 121:15P, 1953.
133. Ganong, W. F., Goldfeen, A., Halevy, A., Davidson, J. M., and Boryczka, A.: Effect of lysergic acid diethylamide on adrenocortical and adrenal medullary function in the dog, Acta endocrinol. 37:583-588, 1961.
134. Gastaut, H., Ferrer, S., Castells, C., Leserre, N., and Lushnat, K.: Effect of LSD on the mental functions and the EEG, Confinia neurol. 13:102-120, 1953.
135. Geiger, R. S.: Effect of LSD-25 and serotonin on adult cortical brain cells in tissue culture, Fed. Proc. 16:44, 1957.
136. Geiger, R. S.: Effects of LSD-25, serotonin and sera from schizophrenic patients on adult mammalian brain cultures, J. Neuropsychiat. 1:185-199, 1960.
137. Genest, K.: Identification of ergot-type alkaloids in morning glory seeds, Proc. of the Thirteenth Ann. Conference of Superintendents of Laboratories, Food and Drug Directorate, Ottawa, Jan. 13-17, 1964.
138. Geronimus, L. H., Abramson, H. A., and Ingraham, L. J.: LSD-25: XXIII. Comparative effects of LSD-25 and related ergot drugs on brain tissue, respiration and on human behavior, J. Psychol. 42:157-168, 1956.
139. DeGiacomo, U.: Les Catatonies toxiques expérimentales, Acta neurol. napoli 6:5-10, 1951.
140. Giberti, F., and Gregoretti, L.: Prime expe-

rience di antagonismo psicofarmacologico. Psicosi sperimentale da LSD e trattaments un chloropromazina e reserpina, Sistema nerv., Milano 7:301-310, 1955.

141. Ginzel, K. H., and Mayer-Gross, W.: Prevention of psychological effects of d-lysergic acid diethylamide (LSD-25) by its brom derivative (BOL-148), Nature 178:210, 1956.
142. Goldberger, M.: The effects of lysergic acid diethylamide (LSD-25) upon the histochemical reactions for cholinesterase in the central nervous system, Acta anat. 46:185-191, 1961.
143. Goldenberg, H., and Goldenberg, V.: Inhibition of serum cholinesterase by lysergic acid derivatives. Submicro detection of LSD, J. Hillside Hosp. 5:246-257, 1956.
144. Goldstein, L., Murphree, H. B., and Pfeiffer, C. C.: Quantitative electroencephalography in man as a measure of CNS stimulation, Ann. New York Acad. Sc. 107:1045-1056, 1963.
145. Graham, J. D. P., and Khalidi, A. I.: The actions LSD-25. Part 1. General pharmacology, J. Fac. Med. Baghdad 18:1-10, 1954.
146. Graham, J. D. P., and Khalidi, A. I.: The actions of d-LSD (LSD-25). Part 2. Central actions, J. Fac. Med. Baghdad 18:35-49, 1954.
147. Greig, M. E., and Gibbons, A. J.: Effect of various psychotomimetic drugs on rate of appearance of carbon 14 in the brain of mice after administration of C^{14} glucose, Am. J. Physiol. 196:803-806, 1959.
148. Grinker, R. R.: Lysergic acid diethylamide: Editorial, Arch. Gen. Psychiat. 8:425, 1963.
149. Grinker, R. R.: Bootlegged ecstasy, J.A.M.A. 187:768, 1964.
150. Guttmann, E., and Maclay, W. S.: Mescaline and depersonalization, J. Neurol. & Psychopath. 16:193-212, 1936.
151. Haley, T. J.: 5-Hydroxytryptamine antagonism by LSD after intracerebral injection in conscious mice, J. Am. Pharm. A. (Scient. Ed.) 46:428-430, 1957.
152. Haley, T. J., and Rutscamann, J.: Brain concentrations of LSD-25 (Delysid) after intracerebral or intravenous administration in conscious animals, Experientia 13:199-202, 1957.
153. Harman, W. W.: Some aspects of the psychedelic drug controversy, J. Humanistic Psychol., 1963. (In press.)
154. Harman, W. W.: The humanities in an age of science, Main Currents in Modern Thought 18:75-83, 1962.
155. Harman, W. W.: The issue of the consciousness expanding drugs, Main Currents in Modern Thought 20:5-14, 1963.
156. Harris, G. W.: Ciba Foundation Colloquia on Endocrinology 4:106, 1955.
157. Harris, G. W., Jacobsohn, D., and Kahlson, G.: The occurrence of histamine in cerebral regions related to the hypophysis, *in* Wolstenholme, G. E. W., editor: Ciba Foundation Colloquia on Endocrinology, vol. 4, New York, 1952, The Blakiston Company, p. 186.
158. Hartman, A. M., and Hollister, L. E.: Effect of mescaline, lysergic acid diethylamide and psilocybin on color perception, Psychopharmacologia 4:441-451, 1963.
159. Harwood, P. D.: Therapeutic dosage in small and large mammals, Science 139:684-685, 1963.
160. Heacock, R. A., and Mahon, M.: Conjugated hydroxy skatoles in human urine, Canad. J. Biochem. 42:813-819, 1964.
161. Heacock, R. A., Mahon, M., and Hoffer, A.: The presence of some hydroxy skatole conjugates in psychiatric urines, Am. Psychiat. A. J. 121:172-174, 1964.
162. Heard, G.: LSD: The way to Nirvana, Canad. Dimensions 1:11-13, 1964.
163. Heath, R. G.: Studies in schizophrenia, Cambridge, Mass., 1954, Harvard University Press.
164. Heath, R. G.: Discussion, *in* Wortis, J., editor: Recent advances in biological psychiatry, vol. 3, New York, 1961, Grune & Stratton, Inc., pp. 164-165.
165. Heath, R. G., and Leach, B. E.: Multi-disciplinary research in schizophrenia: Changing concepts of psychoanalytic medicine, New York, 1956, Grune & Stratton, Inc., pp. 201-224.
166. Himwich, H. E.: The effect of Frenquel on EEG changes produced by LSD-25 and mescaline, *in* Cholden, L., editor: Lysergic acid diethylamide in experimental psychiatry, New York, 1956, Grune & Stratton, Inc., pp. 19-26.
167. Himwich, W. A., and Costa, E.: Behavioral changes associated with changes in concentrations of brain serotonin, Fed. Proc. 19:838-845, 1960.
168. Hoagland, H., Rinkel, M., and Hyde, R. W.: Adrenocortical function and urinary phosphate excretion, Arch. Neurol. & Psychiat. 73:100-109, 1955.
169. Hoch, P. H.: Experimentally produced psychoses, Am. J. Psychiat. 107:607-611, 1951.
170. Hoch, P. H.: Experimental induction of psychosis, *in* The biology of mental health and disease, New York, 1952, Paul B. Hoeber, Inc., pp. 539-547.
171. Hoch, P. H.: Experimental psychiatry, Am. J. Psychiat. 111:787-790, 1955.
172. Hoch, P. H.: Studies in routes of administration and counteracting drugs, *in* Cholden, L., editor: Lysergic acid diethylamide and mescaline in experimental psychiatry, New York, 1956, Grune & Stratton, Inc.
173. Hoch, P. H.: The production and alleviation of mental abnormalities by drugs. Twentieth

International Physiological Congress, Brussels, 1956 (abstracts of reviews), p. 429.
174. Hoch, P. H.: Remarks on LSD and mescaline, J. Nerv. & Ment. Dis. 125: 442-444, 1957.
175. Hoch, P. H.: Psychosis-producing and psychosis-revealing drugs, Res. Publ., A. Nerv. & Ment. Dis. 36:335-346, 1958.
176. Hoch, P. H.: *In* Abramson, H. A., editor: The use of LSD in psychotherapy, New York, 1960, Josiah Macy, Jr., Foundation, p. 58.
177. Hoch, P. H., Cattell, J. P., and Pennes, H. H.: Effects of mescaline and lysergic acid (d-LSD-25), Am. J. Psychiat. 108:579-584, 1952.
178. Hoch, P. H., Cattell, J. P., and Pennes, H. H.: Effect of drugs: Theoretical considerations from a psychological viewpoint, Am. J. Psychiat. 108:585-589, 1952.
179. Hoch, P. H., Pennes, H. H., and Cattell, J. P.: Psychoses produced by administration of drugs, Res. Publ., A. Nerv. & Ment. Dis. 32:287-296, 1953.
180. Hoch, P. H., Pennes, H. H., and Cattell, J. P.: Psychoses produced by administration of drugs, *in* Rinkel, M., editor: Chemical concepts of psychosis, New York, 1958, McDowell, Obolensky.
181. Hoch, P. H., and Polatin, P.: Pseudoneurotic forms of schizophrenia, Psychiat. Quart. 23: 248-276, 1949.
182. Hoff, H., and Arnold, O. H.: The treatment of schizophrenia, Wien. klin. Wchnschr. 66: 345-352, 1954.
183. Hoffer, A.: Studies with niacin and LSD, *in* Cholden, L., editor: LSD and mescaline in experimental psychiatry, New York, 1956, Grune & Stratton, Inc., pp. 44, 77.
184. Hoffer, A.: Mode of action of ergot hallucinogens. Brain Research Foundation, *in* Gibbs, F. A., editor: Molecules and mental health, New York, 1959, J. B. Lippincott Company, pp. 44-59.
185. Hoffer, A.: *In* Abramson, H. A., editor: The use of LSD in psychotherapy, New York, 1960, Josiah Macy, Jr., Foundation.
186. Hoffer, A.: Niacin therapy in psychiatry, Springfield, Ill., 1962, Charles C Thomas, Publisher.
187. Hoffer, A., and Callbeck, M. J.: Drug-induced schizophrenia, J. Ment. Sc. 106:138-159, 1960.
188. Hoffer, A., and Mahon, M.: The presence of unidentified substances in the urine of psychiatric patients, J. Neuropsychiat. 2:331-362, 1961.
189. Hoffer, A., and Osmond, H.: A card sorting test helpful in making psychiatric diagnosis, J. Neuropsychiat. 2:306-330, 1961.
190. Hoffer, A., Osmond, H.: Paper delivered to the Dementia Precox Committee, New York, 1952, Scottish Rites Masons.
191. Hoffer, A., and Osmond, H.: The adrenochrome model and schizophrenia, J. Nerv. & Ment. Dis. 128:18-35, 1959.
192. Hoffer, A., and Osmond, H.: The relationship between an unknown factor ("US") in urine of subjects and HOD test results, J. Neuropsychiat. 2:363-368, 1961.
193. Hoffer, A., and Osmond, H.: The association between schizophrenia and two objective tests, Canad. M. A. J. 87:641-646, 1962.
194. Hoffer, A., and Osmond, H.: The chemical basis of clinical psychiatry, Springfield, Ill., 1960, Charles C Thomas, Publisher.
195. Hoffer, A., and Osmond, H.: Malvaria: A new psychiatric disease, Acta psychiat. scandinav. 39:335-366, 1963.
196. Hoffer, A., Osmond, H., Callbeck, M. J., and Kahan, I.: Treatment of schizophrenia with nicotinic acid and nicotinamide, J. Clin. & Exper. Psychopath. 18:131-158, 1957.
197. Hoffer, A., Osmond, H., and Smythies, J.: Schizophrenia: A new approach. II. Result of a year's research, J. Ment. Sc. 100:29-45, 1954.
198. Hofmann, A.: Hallucinogenic principles of ololiuqui. International Symposium on the Chemistry of Natural Products, Australia, 1960.
199. Hofmann, A.: Psychotomimetics, chemical, pharmacological and clinical aspects, Indian Prac. 14:195-197, 1961.
200. Hofmann, A.: Die Wirkstoffe der Mexikanischen Zauberdroge "Ololiuqui." Planta Medica, Ztschr. Arzneipflanzenforsch. 9:354-367, 1961.
201. Hofmann, A., and Cerletti, A.: Die Wirkstoffe der Dutten Aztekischen Zauberdroge, Deutsche med. Wchnschr. 18:885-888, 1961.
202. Hofmann, A., and Tscherter, H.: Isolierung von Lysergsaure Alkaloiden aus der Mexikanischen Zauberdroge Ololiuqui (Rivea Corymbosa (L), Hall F.), Experientia 16: 414, 1960.
203. Hollister, L. E.: Biochemical changes after psychotomimetic drugs, Clin. Res. 9:181, 1961.
204. Hollister, L. E.: Clinical, biochemical and psychologic effects of psilocybin, Arch. internat. pharmacodyn. 130:42-52, 1961.
205. Hollister, L. E.: Drug induced psychoses and schizophrenic reactions: A critical comparison, Ann. New York Acad. Sc. 96:80-88, 1962.
206. Hollister, L. E., Prusmack, J. J., Paulsen, J. A., and Rosenquist, N.: Comparison of three *psychotropic* drugs (psilocybin, JB-329 and IT-290) in volunteer subjects, J. Nerv. & Ment. Dis. 131:428-434, 1960.
207. Huxley, A.: Island, Toronto, 1962, Clarke, Irwin & Company, Ltd.
208. Irvine, D.: Apparently non-indolic Ehrlich-

positive substances related to mental illnesses, J. Neuropsychiat. 2:292-305, 1961.
209. Isbell, H.: Effect of chlorpromazine, reserpine and "Frenquel" on LSD reaction, Fed. Proc. 15:442, 1956.
210. Isbell, H.: Personal communication to H. Osmond, 1957.
211. Isbell, H.: Comparison of the reactions induced by psilocybin and LSD-25 in man, Psychopharmacologia 1:29-38, 1959.
212. Isbell, H., Belleville, R. E., Fraser, H. F., Wikler, A., and Logan, C. R.: Studies on LSD. I. Effects in former morphine addicts and development of tolerance during chronic intoxication, Arch. Neurol. & Psychiat. 76: 468-478, 1956.
213. Isbell, H., and Logan, C. R.: Studies on LSD: II. Effects of chlorpromazine, azacyclonol and reserpine on the intensity of the LSD reaction, Arch. Neurol. & Psychiat. 77: 350-358, 1957.
214. Isbell, H., Wolback, A. B., Wikler, A., and Miner, E. J.: Cross-tolerance between LSD and psilocybin, Psychopharmacologia 2:147-159, 1961.
215. Izumi, K.: An analysis for the design of hospital quarters for the neuropsychiatric patient, Ment. Hosp. 8:31-32, 1957.
216. Jackson, D. D.: LSD and the new beginning, J. Nerv. & Ment. Dis. 135:435-439, 1962.
217. James, W.: Varieties of religious experience, New York, 1902, Longmans, Green & Co.
218. Janiger, O.: The use of hallucinogenic agents in psychiatry, California Clinician 55:251-259, 1959.
219. Jarman, R. C.: The most astounding experience of my life: A sermon published in Chapel Bells, South Gate, Calif., Nos. 33 and 34, 1961.
220. Jarvik, M. E., Abramson, H. A., and Hirsch, M. W.: LSD-25: IV. Effect on attention and concentration, J. Psychol. 39:373-383, 1955.
221. Jarvik, M. E., Abramson, H. A., Hirsch, M. W., and Ewald, A. T.: LSD: VIII. Effect on arithmetic test performance, J. Psychol. 39: 465-473, 1955.
222. Jensen, S. E.: A treatment program for alcoholics in a mental hospital, Proc. of Third World Congress of Psychiatry, Montreal 1: 428-431, 1961.
223. Jensen, S. E.: A treatment program for alcoholics in a mental hospital, Quart. J. Stud. Alcohol 23:315-320, 1962.
224. Kast, E. C., and Collins, V. J.: Study of lysergic acid diethylamide as analgesic agent, J. Int. Anesth. Res. Soc. 43:285-291, 1964.
225. Katzenelbogen, S., and Ai Ding Fang: Narcosynthesis effects of Sodium Amytal, methedrine and LSD-25, Dis. Nerv. System 14:85-88, 1953.
226. Kelm, H.: The figural after-effect in schizophrenia patients, J. Nerv. & Ment. Dis. 135: 338-345, 1962.
227. Kelm, H., Jensen, S. E., and Ramsay, R. W.: The figural after-effect and lysergic acid diethylamide, J. Nerv. & Ment. Dis. 137:557-560, 1963.
228. Kenna, J. C., and Sedman, G.: The subjective experience of time during lysergic acid diethylamide (LSD-25) intoxication, Psychopharmacologia 5:280-288, 1964.
229. Kinross-Wright, V. J.: Research on ololiuqui: The Aztec drug, Neuropsychopharmacology, Proc. of the First Internat. Congress of Neuropharmacology, Amsterdam, 1959, pp. 453-456.
230. Klee, G. D.: Lysergic acid diethylamide (LSD-25) and ego functions, Arch. Gen. Psychiat. 8:461-474, 1963.
231. Klee, G. D., Bertino, J., Weintraub, W., and Callaway, E.: The influence of varying dosage on the effects of lysergic acid diethylamide (LSD-25) in humans, J. Nerv. & Ment. Dis. 132:404-409, 1961.
232. Kluver, H.: Mescal: The "divine" plant and its psychological effects, Kegan, Paul, Trench, Trubner & Co., Ltd., 1928.
233. Krus, D. M., Wapner, S., Bergen, J., and Freeman, H.: The influence of progesterone on behavioral changes induced by lysergic acid diethylamide (LSD-25) in normal males, Psychopharmacologia 2:177-184, 1961.
234. Krus, D. M., Wapner, S., Freeman, H., and Casey, T. M.: Differential behavioral responsivity of LSD-25, Arch. Gen. Psychiat. 8:557-563, 1963.
235. Lebovits, B. Z., Visotsky, H. M., and Ostfeld, A. M.: LSD and JB-318: A comparison of two hallucinogens, Arch. Gen. Psychiat. 2: 390-407, 1960.
236. Leuner, H.: Psychotherapy with halucinogens, *in* Crocket, R., Sandison, R. A., and Walk, A., editors: Hallucinogenic drugs and their psychotherapeutic use, Proc. Royal Med. Psychol. A., London, 1963, H. K. Lewis & Co., Ltd.
237. Levine, A., Abramson, H. A., Kaufman, M. R., and Markham, S.: LSD: XVI. The effect on intellectual functioning as measured by the Wechsler-Bellevue intelligence scale, J. Psychol. 40:385-395, 1955.
238. Lewis, J. L., and McIlwain, H.: The action of some ergot derivatives, mescaline and dibenamine on the metabolism of separated mammalian cerebral tissues, Biochem. J. 57:680-684, 1954.
239. Liddell, D. S., and Weil-Malherbe, H.: The effects of methedrine and of lysergic acid on mental processes and on the blood adrenaline level, J. Neurol. Neurosurg. & Psychiat. 16:7-13, 1953.

240. Liebert, R. S., Wapner, S., and Werner, H.: Studies in the effects of LSD-25. Visual perception of verticality in schizophrenic and normal adults, Arch. Neurol. & Psychiat. 77: 193-201, 1957.
241. Linton, H. B., and Langs, R. J.: Placebo reactions in a study of lysergic acid diethylamide (LSD-25), Arch. Gen. Psychiat. 6: 369-383, 1962.
242. Linton, H. B., and Langs, R. J.: Subjective reactions to lysergic acid diethylamide (LSD-25), Arch. Gen. Psychiat. 6:352-368, 1962.
243. Linton, H. B., Langs, R. J., and Paul, I. H.: Retrospective alterations of the LSD-25 experience, J. Nerv. & Ment. Dis. 138:409-423, 1964.
244. MacDonald, J. M., and Galvin, J. A. V.: Experimental psychotic states, Am. J. Psychiat. 112:970-976, 1956.
245. McGeer, P. L., Wada, J. A., and McGeer, E. G.: Correlations between central aromatic amine levels and behavioral tests following administration of psychoactive drugs, *in* Wortis, J., editor: Recent advances in biological psychiatry, vol. 5, New York, 1963, Plenum Press, Inc., pp. 228-236.
246. McGlothlin, W. H.: Long lasting effects of LSD on certain attitudes in normals: An experimental proposal, Los Angeles, Calif., 1962, The Rand Corporation, p. 2575.
247. McGlothlin, W. H.: Hallucinogenic drugs: A perspective with special reference to peyote and cannabis, Los Angeles, Calif., 1964, The Rand Corporation, p. 2937.
248. McGlothlin, W. H., Cohen, S., and McGlothlin, M. S.: Short term effects of LSD on anxiety attitudes and performance, Los Angeles, Calif., 1962, The Rand Corporation, p. 2757. J. Nerv. & Ment. Dis. 139:266-273, 1964.
249. MacLean, J. R., MacDonald, D. C., Byrne, V. P., and Hubbard, A. M.: The use of LSD-25 in the treatment of alcoholism and other psychiatric problems, Quart. J. Stud. Alcohol 22:34-45, 1961.
250. Machover, K., and Liebert, R.: Human figure drawings of schizophrenic and normal adults. Changes following administration of lysergic acid, Arch. Gen. Psychiat. 3:139-152, 1960.
251. Manas Editors: Synanon. A Manas pamphlet, 1963.
252. Mandell, A. J.: Some determinants of indole excretion in man, *in* Wortis, J., editor: Recent advances in biological psychiatry, vol. 5, New York, 1963, Grune & Stratton, Inc., pp. 237-256.
253. Marrazzi, A. S.: Some indications of cerebral humoral mechanisms, Science 118:367-370, 1953.
254. Marrazzi, A. S.: The effects of certain drugs on cerebral synapses, Ann. New York Acad. Sc. 66:496-507, 1957.
255. Marrazzi, A. S.: *In* Fields, W. S., editor: The effect of drugs on neurons and synapses brain mechanisms and drug action, Springfield, Ill., 1957, Charles C Thomas, Publisher, pp. 45-70.
256. Marazzi, A. S.: The effects of certain drugs on cerebral synapses, Ann. New York Acad. Sc. 66:496-507, 1957.
257. Marrazzi, A. S.: A theory of hallucination on a neuropharmacologic basis, *in* Wortis, J., editor: Recent advances in biological psychiatry, New York, 1960, Grune & Stratton, Inc., pp. 333-343.
258. Marrazzi, A. S.: Inhibition as a determinant of synaptic and behavioral patterns, Ann. New York Acad. Sc. 92:990-1003, 1961.
259. Marrazzi, A. S.: Synaptic and behavioral correlates of psychotherapeutic and related drug actions, Ann. New York Acad. Sc. 96:211-226, 1962.
260. Marrazzi, A. S., and Hart, E. R.: Relationship of hallucinogens to adrenergic cerebral neurohumors, Science 121:365-367, 1955.
261. Marrazzi, A. S., and Hart, E. R.: The possible role of inhibitions at adrenergic synapses in the mechanism of hallucinogenic and related drug actions, J. Nerv. & Ment. Dis. 122:453-457, 1955.
262. Marrazzi, A. S., and Hart, E. R.: Evoked cortical responses under the influence of hallucinogens and related drugs, Electroencephalog. & Clin. Neurophysiol. 7:146, 1955.
263. Marrazzi, A. S., Hart, E. R., and Gilfoil, R. M.: A potential histaminogenic (allergic?) mechanism for psychosis, *in* Wortis, J., editor: Recent advances in biological psychiatry, vol. 3, New York, 1961, Grune & Stratton, Inc., pp. 164-165.
264. Martens, S., Vallbo, S., and Melander, B.: An approach to biochemical therapy in schizophrenia, Acta psychiat. et neurol. scandinav. 34:349-360, 1959.
265. Martens, S., Vallbo, S., and Melander, B.: Effects of ceruloplasmin administration to schizophrenics, *in* Masserman, J. H., editor: Biological psychiatry, New York, 1959, Grune & Stratton, Inc.
266. Martens, S., Vallbo, S., Andersen, K., and Malender, B.: A comparison between taraxein and some psychotomimetics, Acta psychiat. et neurol. scandinav. 34:361-368, 1959.
267. Martin, J.: A case of psychopathic personality with homosexuality treated by LSD, *in* Crocket, R., Sandison, R. A., and Walk, A., editors: Hallucinogenic drugs and their psychotherapeutic use, Proc. Royal Med. Psychol. A., London, 1963, H. K. Lewis & Co., Ltd., pp. 112-115.
268. Maslow, A. H.: Recognition of being in the

peak experience, J. Genet. Psychol. 94:43-66, 1959.

269. Mayer-Gross, W.: Experimental psychoses and other mental abnormalities produced by drugs, Brit. M. J. 2:317-321, 1951.
270. Mayer-Gross, W., McAdam, W., and Walker, J. W.: Psychological and biochemical effects of lysergic acid diethylamide, Nature 168:827-828, 1951.
271. Mayer-Gross, W., McAdam, W., and Walker, J. W.: Lysergic acid diethylamide and carbohydrate metabolism, Nervenarzt. 23:30-31, 1952.
272. Mayer-Gross, W., McAdam, W., and Walker, J. W.: Further observations on the effects of LSD, J. Ment. Sc. 99:804-808, 1953.
273. Melander, B., and Martens, S.: The mode of action of taraxein and LSD, Dis. Nerv. System 19:478-479, 1958.
274. Miller, A. I., Williams, H. L., and Murphree, H. B.: Niacin, niacinamide or atropine versus LSD-25: Model psychoses in human volunteers, Fed. Proc. 16:169, 1957.
275. Mitchell, S. Weir: Remarks on the effects of anhalonium lewinii (The Mescal *Button*), Brit. M. J. 2:1625, 1896.
276. Miura, T., Tsujiyama, Y., Makita, K., Nakazwa, T., Sato, K., and Nakahara, A.: The effect of psychotropic substances on nerve and neuroglia cells developed in tissue culture, *in* Garattini, S., and Ghetti, V., editors: Psychotropic drugs, New York, 1957, Elsevier Press, Inc., p. 478.
277. Monroe, R. R., and Heath, R. G.: Effects of lysergic acid and various derivatives in depth and cortical electrograms, J. Neuropsychiat. 3:75-82, 1961.
278. Monroe, R. R., Heath, R. G., Mickle, W. A., and Llewellyn, R. C.: Correlation of rhinencephalicelectrogram with behaviour: A study on humans under the influence of LSD and mescaline, Electroencephalography 9:623-642, 1957.
279. Murphree, H. B.: Quantitative studies in humans on the antagonism of lysergic acid diethylamide by chlorpromazine and phenoxybenzamine, CLIN. PHARMACOL. & THERAP. 3: 314-320, 1962.
280. Murphree, H. B., Jenney, E. H., and Pfeiffer, C. C.: Comparison of the effects of congeners of LSD-25 and tryptophane in normal human volunteers, Pharmacologist 2:64, 1960.
281. Nandy, K., and Bourne, G. H.: The effects of D-lysergic acid diethylamide tartrate (LSD-25) on the cholinesterases and monoamine oxidase in the spinal cord: A possible factor in the mechanism of hallucination, J. Neurol. Neurosurg. & Psychiat. 27:259-267, 1964.
282. Nunes, E. P.: Studies on LSD. Investigacoes com a dietilamida do acido lisergico, J. brasil. psiquiat. 4:407-418, 1955.
283. O'Reilly, P. O., and Funk, A.: LSD in chronic alcoholism, Canad. Psychiat. A. J. 9:258-261, 1964.
284. O'Reilly, P. O., and Reich, G.: Lysergic acid and the alcoholic, Dis. Nerv. System 23:331-334, 1962.
285. Osmond, H.: On being mad, Saskatchewan Psychiatric Services, Journal 1:168-172, 1953.
286. Osmond, H.: Ololiuqui: The ancient Aztec narcotic, J. Ment. Sc. 101:526-537, 1955.
287. Osmond, H.: Research in schizophrenia, *in* Abramson, H., editor: Neuropharmacology, Trans. of the Second Conference, New York, 1956, Josiah Macy, Jr., Foundation, pp. 183-233.
288. Osmond, H.: Function as the basis of psychiatric ward design, Ment. Hosp. 8:23-30, 1957.
289. Osmond, H.: A review of the clinical effects of psychotomimetic agents, Ann. New York Acad. Sc. 66:418-434, 1957.
290. Ostfeld, A. M.: Effects of LSD-25 and JB-318 on tests of visual and perceptual functions in man, Fed. Proc. 20:876-883, 1961.
291. Ostfeld, A. M., Visotsky, H. M., and Lebovits, B. Z.: A comparison of the psychotomimetic effects of scopolamine, LSD and JB-318, Clin. Res. 6:416, 1958.
292. Page, I. H.: Serotonin (5-hydroxytryptamine): The last four years, Physiol. Rev. 38:277-335, 1958.
293. Peerman, D.: Instant mysticism: A book review of "The joyous cosmology: Adventures in the chemistry of consciousness," by Alan W. Watts, The Christian Century, Aug. 1, 1962, Pantheon Books, pp. 938-939.
294. Pennes, H. H.: Clinical reactions of schizophrenics to Sodium Amytal, pervitin hydrochloride, mescaline sulfate and LSD-25, J. Nerv. & Ment. Dis. 119:95-112, 1954.
295. Pfeiffer, C. C., Jenney, E. H., Murphree, H. B., and Goldstein, L.: EEG effects of lysergic acid diethylamide (LSD) in normal volunteers and schizophrenic patients, Pharmacologist 4:166B, 1962.
296. Poloni, A.: Serotonia e schizofrenia. 1. Osservazioni sulle interferenze fra L'azioni della serotonina (S) e della dietilamide dell'acido lisegico (LSD-25) alla mescalina (M) e alla bulbocapnine (3) sul tracciato EEG di schizophrenica, epilettici e altu ammalate de mente, Cervello 31:271-294, 355-382, 1955.
297. Poloni, A., and Maffezzoni, G.: Variations in cholinergic activity of cerebral tissue due to bulbocapnine, mescaline and LSD, Sistema. nerv., Milano 4:578-581, 1952.
298. Purpura, D. P.: Electrophysiological analysis of psychotogenic drug action. I. Effect of LSD

on specific afferent systems in the cat, Arch. Neurol. & Psychiat. 75:122-131, 1956.

299. Purpura, D. P.: Electrophysiological analysis of psychotogenic drug action. II. General nature of LSD action on central synapses, Arch. Neurol. & Psychiat. 75:132-143, 1956.
300. Purpura, D. P.: Experimental analysis of the inhibitory action of LSD on cortical dendritic activity, Ann. New York Acad. Sc. 66:515-536, 1957.
301. Purpura, D. P., Pool, J. L., Ransohoff, J., Frumin, M. J., and Housepian, E. M.: Observations on evoked dendritic potentials of human cortex, Electroencephalog. & Clin. Neurophysiol. 9:453-459, 1957.
302. Rinaldi, F., and Himwich, H. E.: The cerebral electrographic changes induced by mescaline and corrected by Frenquel, J. Nerv. & Ment. Dis. 122:424-432, 1955.
303. Rinaldi, F., and Himwich, H. S.: Frenquel corrects certain cerebral electrographic changes, Science 122:198-199, 1955.
304. Rinaldi, F., and Himwich, H. E.: Drugs affecting psychotic behavior and the function of the mesodiencephalic activating system, Dis. Nerv. System 16:133-141, 1955.
305. Rinaldi, F., and Himwich, H. E.: Frenquel corrects certain cerebral electrographic changes, Science 122:198-199, 1955.
306. Rinkel, M.: Discussion at the One Hundred Sixth Annual Meeting of Psychiatric Assoc., Detroit, J. Clin. & Exper. Psychopath. 12:42, 1951.
307. Rinkel, M.: Experimentally induced psychoses in man. Neuropharmacology, Trans. of the Second Conference (edited by H. A. Abramson), New York, 1956, Josiah Macy, Jr., Foundation, p. 235.
308. Rinkel, M.: Biochemical reflections on the psychosis problem. LSD and mescaline in experimental psychiatry, New York, 1956, Grune & Stratton, Inc., p. 13.
309. Rinkel, M.: Pharmacodynamics of LSD and mescaline, J. Nerv. & Ment. Dis. 125:424-427, 1957.
310. Rinkel, M., DeShon, H. J., Hyde, R. W., and Solomon, H. C.: Experimental schizophrenia-like symptoms, Am. J. Psychiat. 108:572-578, 1952.
311. Rinkel, M., Hyde, R., and Solomon, H. C.: Experimental psychiatry. IV. Hallucinogens: Tools in experimental psychiatry, Dis. Nerv. System 16:229-232, 1955.
312. Rinkel, M., Hyde, R. W., Solomon, H. C., and Hoagland, H.: Experimental psychiatry. II. Clinical and physiochemical observations in experimental psychosis, Am. J. Psychiat. 111:881-895, 1955.
313. Rostafinski, M.: Experimental hallucination in epileptic patients, Rocznik Psychi. (Pol. 38:109, 1950.
314. Rothlin, E.: Pharmacology of lysergic acid diethylamide and some of its related compounds, J. Pharm. & Pharmacol. 9:569-587, 1957.
315. Rothlin, E.: Pharmacology of lysergic acid diethylamide and some of its related compounds, *in* Garattini, S., and Ghetti, V., editors: Psychotropic drugs, New York, 1957, Elsevier Press, Inc., pp. 36-47.
316. Rothlin, E.: Lysergic acid diethylamide and related substances, Ann. New York Acad. Sc. 66:668-676, 1957.
317. Rothlin, E., and Cerletti, A.: Pharmacology of LSD-25, *in* Cholden, L., editor: Lysergic acid diethylamide and mescaline in experimental psychiatry, New York, 1956, Grune & Stratton, Inc., pp. 1-7.
318. Rudolph, G. G., and Olsen, N. S.: Glucose oxidation in prostatic tissue from normal and hypoglycemic dogs and the effect of LSD, Fed. Proc. 16:110, 1957.
319. Ruiz-Ogara, C., Marti-Tusquets, J. L., and Gonzales-Monclus, E.: Psychosis caused by LSD, Rev. psiquiatr. y psicol. méd. 2:566-590, 1956.
320. Sackler, A. M., Weltman, A. S., and Owens, H.: Effects of lysergic acid diethylamide on urinary 17-ketosteroid and 17-0 corticosteroid levels of female rats, Nature 198:1119-1120, 1963.
321. Salmoiraghi, G. C., and Page, I. H.: Effects of LSD-25, BOL-148, bufotenine, mescaline and ibogaine on the potentiation of hexobarbital hypnosis produced by serotonin and reserpine, J. Pharmacol. & Exper. Therap. 120:20-25, 1957.
322. Salmoiraghi, G. C., McCubbin, J. W., and Page, I. H.: Effects of LSD and its brom derivative on cardiovascular responses to serotonin and on arterial pressure, J. Pharmacol. & Exper. Therap. 119:240-247, 1957.
323. Salmoiraghi, G. C., Sollero, L., and Page, I. H.: Blockage by brom-LSD (BOL) of the potentiating action of serotonin and reserpine on hexobarbital hypnosis, J. Pharmacol. & Exper. Therap. 117:166-168, 1956.
324. Sandison, R. A.: The clinical uses of LSD, *in* Cholden, L., editor: LSD and mescaline in experimental psychiatry, London, New York, 1956, Grune & Stratton, Inc., p. 27.
325. Sandison, R. A.: Psychological aspects of the LSD treatment of the neuroses, J. Ment. Sc. 100:508-515, 1954.
326. Sandison, R. A.: LSD treatment of psychoneurosis, LSD for release of repression, Nurs. Mirror, London 100:1529, 1955.
327. Sandison, R. A.: Certainty and uncertainty in the LSD treatment of psychoneurosis, *in*

Crocket, R., Sandison, R. A., and Walk, A., editors: Hallucinogenic drugs and their psychotherapeutic use, Proc. Royal Med. Psychol. A., London, 1963, H. K. Lewis & Co., Ltd.

328. Sandison, R. A., Spencer, A., and Whitelaw, J. D. A.: The therapeutic value of LSD in mental illnesses, J. Ment. Sc. 100:491-507, 1954.
329. Sandison, R. A., and Whitelaw, J. D. A.: Further studies in the therapeutic value of LSD in mental illnesses, J. Ment. Sc. 103: 332-343, 1957.
330. Sankar, D. V. S., and Bender, L.: Biochemistry of lysergic acid diethylamide psychoses, *in* Wortis, J., editor: Recent advances in biological psychiatry, vol. 2, New York, 1960, Grune & Stratton, Inc., pp. 363-370.
331. Sankar, D. V. S., Broer, H. H., Cates, N., and Sankar, D. B.: Studies on biogenic amines and psychoactive drug actions with special reference to lysergic acid diethylamide, Tr. New York Acad. Sc. 26:369-376, 1964.
332. Sankar, D. V. S., Gold, E., and Sankar, D. B.: Metabolic effects of psychoactive drugs, *in* Wortis, J., editor: Recent advances in biological psychiatry, vol. 4, New York, 1962, pp. 247-256.
333. Sankar, D. V. S., Phipps, E., Gold, E., and Sankar, D. B.: Effect of LSD, BOL and chlorpromazine on neurohormone metabolism, Ann. New York Acad. Sc. 96:93-97, 1962.
334. Sankar, D. V. S., Sankar, D. B., Phipps, E., and Gold, E.: Effect of administration of lysergic acid diethylamide on serotonin levels in the body, Nature 191:499-500, 1961.
335. Sargant, W.: Battle for the mind: A physiology of conversion and brain washing, Garden City, N. Y., 1957, Doubleday & Company, Inc.
336. Sauri, J. J., and deOnorato, A. C.: Schizophrenia and LSD. 1. Variations in mood, Acta neuropsiquiátr. argent. 1:469, 1955.
337. Savage, C.: LSD, alcoholism and transcendence, J. Nerve. & Ment. Dis. 135:429-435, 1962.
338. Savage, C.: Lysergic acid diethylamide. A clinical psychological study, Am. J. Psychiat. 108:896-900, 1952.
339. Savage, C.: The resolution and subsequent remobilization of resistance by LSD in psychotherapy, J. Nerv. & Ment. Dis. 125:434-437, 1957.
340. Savage, C.: LSD, transcendance and the new beginning, J. Nerv. & Ment. Dis. 135:425-439, 1962.
341. Savage, C., and Cholden, L.: Schizophrenia and the model psychoses, J. Clin. Exper. Psychopath. and Quart. Rev. Psychiat. & Neurol. 17:405-413, 1956.
342. Savage, C., Harman, W. W., Fadiman, J., and Savage, E.: An evaluation of the psychedelic experience, Annual Meeting of American Psychiatric A., St. Louis, Mo., May 9, 1963.
343. Sawyer, C. H.: Rhinencephalic involvement in pituitary activation by intraventricular histamine in rabbit under nembutal anesthesia, Am. J. Physiol. 180:37-46, 1955.
344. Schmiege, G. R.: The current status of LSD as a therapeutic tool, J. M. Soc. New Jersey 60:203-207, 1963.
345. Schultes, R. E.: A contribution to our knowledge of Rivea corymbosa: The narcotic ololiuqui of the Aztecs, Botanical Museum of Harvard University, Cambridge, Mass., 1941.
346. Schwarz, B. E., Bickford, R. G., and Rome, H. P.: Reversibility of induced psychosis with chlorpromazine, Proc. Staff Meet. Mayo Clin. 30:407-417, 1955.
347. Sheldon, W.: Atlas of men, New York, 1954, Harper & Brothers.
348. Shelton, J.: LSD notes on the psychotherapeutic use, Mind 1:339-342, 1963.
349. Sherwood, J. N., Stolaroff, M. J., and Harman, W. W.: The psychedelic experience: A new concept in psychotherapy, J. Neuropsychiat. 3:370-375, 1962.
350. Sherwood, S. L.: Effect of drugs on the behavior of animals and on psychoses of man, *in* Abramson, H. A., editor: Neuropharmacology, New York, 1956, Josiah Macy, Jr., Foundation.
351. Silverstein, A. B., and Klee, G. D.: Effects of LSD-25 on intellectual functions, Arch. Neurol. 80:477-480, 1958.
352. Silverstein, A. B., and Klee, G. D.: Effects of LSD-25 on Dual Pursuit performance, J. Clin. & Exper. Psychopath. 21:300-303, 1960.
353. Simpson, C. R., and West, E.: Ergot poisoning on cattle, Florida Ag. Exper. Circular 543:1, 1952.
354. Slater, P. E., Morimoto, K., and Hyde, R. W.: The effect of group administration upon symptom formation under LSD, J. Nerv. & Ment. Dis. 125:312-315, 1957.
355. Sloane, B., and Doust, J. W. L.: Psychophysiological investigations in experimental psychosis: Results of the exhibition of d-lysergic acid diethylamide to psychiatric patients, J. Ment. Sc. 100:129-144, 1954.
356. Slotkin, J. S.: The peyote religion, Glenco, Ill., 1956, The Free Press.
357. Smith, C. M.: A new adjunct to the treatment of alcoholism: The hallucinogenic drugs, Quart. J. Stud. Alcohol 19:406-417, 1958.
358. Smith, C. M.: Some reflections on the possible therapeutic effects of the hallucinogens, Quart. J. Stud. Alcohol 20:292-301, 1959.
359. Sokoloff, L., Perlin, S., Kornetsky, C., and Kety, S. S.: The effects of d-lysergic acid

diethylamide on cerebral circulation and overall metabolism, Ann. New York Acad. Sc. 66: 468-477, 1957.

360. Solms, H.: Relationships between chemical structure and psychoses with the use of psychotoxic substances, J. Clin. & Exper. Psychopath. 17:429-433, 1956.
361. Spencer, A. M.: Permissive group therapy with lysergic acid diethylamide, Brit. J. Psychiat. 109:37-45, 1963.
362. Sprince, H.: Indole metabolism in mental illness, Clin. Chem. 7:203-229, 1961.
363. Sprince, H.: Biochemical aspects of indole metabolism in normal and schizophrenic subjects, Ann. New York Acad. Sc. 96:399-418, 1962.
364. Sprince, H., Parker, C. M., Jameson, D., and Alexander, F.: Urinary indoles in schizophrenic and psychoneurotic patients after administration of tranylcypromine (Parnate) and methionine or tryptophan, J. Nerv. & Ment. Dis. 137:246-251, 1963.
365. Stefaniuk, B., and Osmond, H.: Unpublished study, Dept. of Public Health, Saskatchewan, 1952.
366. Stevenson, I.: Comments on the psychological effects of mescaline and allied drugs, J. Nerv. & Ment. Dis. 125:438-442, 1957.
367. Stoll, W. A.: Lysergsaure—Diathylamid, un Phantastikum aus der Mutterkorngruppe, Schweiz. Arch. f. Neurol. u. Psychiat. 60:279-323, 1947.
368. Stoll, W. A.: Mental effects of an ergot derivative in unusually low dosage. Lecture to Assoc. of Physicians of Zurich, Schweiz. med. Wchnschr., May 20, 1948.
369. Stoll, W. A.: A new hallucinatory agent, active in very small amounts, Proc. of the One Hundred Eighth Meeting of the Swiss Society of Psychiatry, Zurich, Schweiz. Arch. f. Neurol. u. Psychiat. 64:483, 1947.
370. Stoll, A.: Chemical investigations on ergot alkaloids, Progr. Allergy 3:388-433, 1952.
371. Stoll, A., and Hofmann, A.: Partialsynthese von Alkaloiden vom Typus des Ergobasins, Helvet. chim. acta 26:944-965, 1943.
372. Szatmari, A., Hoffer, A., and Schneider, R.: The effect of adrenochrome and niacin on the electroencephalogram of epileptics, Am. J. Psychiat. 111:603-616, 1955.
373. Tabachnick, I. I., and Grelis, M. E.: Inhibition of cholinesterase hydrolysis of dihydromurexine by LSD and its two bromo derivatives: A selective relationship, Nature 182: 935, 1958.
374. Taber, W. A., and Heacock, R. A.: Location of ergot alkaloid and fungi in the seed of Rivea corymbosa (L) Hall "f" "ololiuqui," Canad. J. Microbiol. 81:137-143, 1962.
375. Taber, W. A., Heacock, R. A., and Mahon, M. E.: Ergot type alkaloids in vegetative tissue of Rivea corymbosa (L) Hall "f," Phytochemistry 2:99-101, 1963.
376. Taber, W. A., Vining, L. C., and Heacock, R. A.: Clavine and lysergic acid alkaloids in varieties of morning glory, Phytochemistry 2:65-70, 1963.
377. Terrill, J.: The nature of the LSD experience. J. Nerv. & Ment. Dis. 135:425-429, 1962.
378. Thompson, R. H. S., Tickner, A., and Webster, G. R.: Cholinesterase inhibition by LSD. Biochem. J. 58:19, 1954.
379. Thompson, R. H. S., Tickner, A., and Webster, G. R.: The action of LSD on mammalian cholinesterases, Brit. J. Pharmacol. 10:61-65, 1955.
380. Tonini, G.: Special aspects of the central actions of LSD amides and 5-hydroxytryptamine, Boll. Soc. ital. biol. sper. 31:768-771, 1955.
381. Tonini, G., and Montanari, G.: Effects of experimentally induced psychosis on artistic expression, Confinia neurol. 15:225-239, 1955.
382. Tremere, A. W.: Ergot Seminar, University of Saskatchewan, College of Agriculture, Jan. 16, 1963.
383. Trendelenburg, V.: The action of histamine on the sympathetic nervous system, *in* Wolstenholme, G. E. W., and O'Connor, C. M., editors: Histamine, London, 1956, J. & A. Churchill, Ltd., pp. 278-279.
384. Unger, S. M.: Mescaline, LSD, psilocybin and personality change, Psychiatry 26:111-125, 1963.
385. Unger, S. M.: Mescaline, psilocybin and the issue of rapid personality change: A review, Psychiatry 26:111-125, 1963.
386. Unger, S. M.: The current scientific status of psychedelic drug research. Conference on Methods in Philosophy and the Sciences, New York, May 3, 1964.
387. Vining, L. C., and Taber, W. A.: Estimation of ergot alkaloids in cultures of Claviceps purpurea, Canad. J. Neurobiol. 5:441-451, 1959.
388. Wapner, S., and Krus, D. M.: Effects of lysergic acid diethylamide and differences between normals and schizophrenics on the Stroop Color Word test, J. Neuropsychiat. 2:76-81, 1960.
389. Wapner, S., and Krus, D. M.: Behavioral effects of lysergic acid diethylamide (LSD-25): Space localization in normal adults as measured by the apparent horizon, Arch. Gen. Psychiat. 1:417-419, 1959.
390. Wasson, V. P., and Wasson, R. G.: Mushrooms, Russia and history, New York, 1957, Pantheon Books.
391. Weckowicz, R. E.: Notes on the perceptual

world of the schizophrenic patient, Ment. Hosp. 81:25, 1957.
392. Weckowicz, R. E.: The effect of lysergic acid diethylamide (LSD) on size constancy, Canad. Psychiat. A. J. 4:255-259, 1959.
393. Weintraub, W., Silverstein, A. B., and Klee, G. D.: The effect of LSD on the associative processes, J. Nerv. & Ment. Dis. 128:409-414, 1959.
394. Weintraub, W., Silverstein, A., and Klee, G. D.: The "correction" of deviant responses on a word association test: A measure of the defensive functions of the ego, Arch. Gen. Psychiat. 3:17-20, 1960.
395. West, L. J., Pierce, C. M., and Thomas, W. D.: Lysergic acid diethylamide: Its effects on a male Asiatic elephant, Science 138:1100-1102, 1962.
396. Weyl, B.: An attempt at a psychopathological analysis of the effects of LSD, Diss. Freiburg i. Br. Munchen., 1951, University of Freiburg.
397. Whitaker, L. H.: Lysergic acid diethylamide in psychotherapy, M. J. Australia 1:5-8 and 36-41, 1964.
398. Wilder, J.: The law of initial values in psychiatry, Proc. of Third World Congress of Psychiatry, Montreal, 1961, McGill Am. Press, pp. 341-345.
399. Woolley, D. W.: Production of abnormal (psychotic) behaviour in mice with LSD and its partial prevention with cholinergic drugs and serotonin, Proc. Nat. Acad. Sc. U. S. A. 41:338-344, 1955.
400. Woolley, D. W.: Manipulation of cerebral serotonin and its relationship to mental disorders, Science 125:752, 1957.
401. Woolley, D. W.: Participation of serotonin in mental processes: *in* Rinkel, M., and Denber, H. C. B., editors: Chemical concepts of psychosis, New York, 1958, McDowell, Obolensky, pp. 176-189.
402. Woolley, D. W.: Serotonin in mental disorders, Res. Publ., A. Res. Nerv. & Ment. Dis. 33:381, 1958.
403. Woolley, D. W., and Shaw, E.: Some neurophysiological aspects of serotonin, Brit. M. J. 2:122-126, 1954.
404. Woolley, D. W., and Shaw, E.: A biochemical and pharmacological suggestion about certain mental disorders, Proc. Nat. Acad. Sc. U. S. A. 40:228-231, 1954.
405. Woolley, D. W., and Shaw, E. N.: Evidence for the participation of serotonin in mental processes, Ann. New York Acad. Sc. 66:649-665, 1957.
406. Yamada, T., and Takumi, A.: Histamine effect upon the symptoms of LSD intoxication, Fol. psychiat. jap. 10:163, 1956.
407. Zehnder, K., and Cerletti, A.: Hemmung der Menschenserum—pseudocholinesterase Durch Lysergsaure Diathylamid und 2 Brom Lysergsaure Diathylamid, Helvet. physiol. et pharmacol. acta 14:264-268, 1956.
408. Zsigmond, E. K., Foldes, F. F., and Foldes, V. M.: The in vitro inhibitory effect of LSD, its congeners and 5-hydroxytryptamine on human cholinesterases, J. Neurochem. 8:72-80, 1961.
409. Zsigmond, E. K., Foldes, F. F., and Foldes, V. M.: The inhibitory effect of psilocybin and related compounds to human cholinesterases, Fed. Proc. 20:393, 1961.
410. Zsigmond, E. K., Foldes, V. M., and Foldes, F. F.: The inhibitory effect of l-epinephrine on purified concentrated human plasma cholinesterase, Pharmacologist 3:70, 1961.
411. Zsigmond, E. K., Foldes, F. F., and Foldes, V. M.: The lack of correlation between the psychopharmacologic and anti-cholinesterase effect of LSD and its congeners, Fed. Proc. 19:266, 1960.

Because of the unusual length of the review on LSD, certain of the regular departments have been omitted from this issue; they will appear in the next.

The Editor