explode into extreme intensities
constantly generating golden brilliance
face to face with the annihilating illumination
how much revelation can an organism sustain and stay alive
mortals beware the rays of the absolute
Nerval: "They consider me insane but I know
that I am a hero living under the eyes of the gods."
glistening tender stars in the organs of all forms of life
trembling jewels flicker as they crawl like snakes
hidden energy roots of the soul body contact
subtle link between the sun and our life metabolism
invisible fiery wheel inside me
one spark that transforms everything
I've been to paradise and out the other side
zoomed through it like the midnight express through a whistle stop
I have been torn apart by the fingers of the flash
flayed alive on my electric skeleton
pulverized by the power of the spasm
I am the bridge between the living and the dead
I am the spirit in the shaman's drum
I quiver to the rhythm of the Sphinx
I visit my own body as a stranger
incredible paroxysms of the luminous protoplasm
kindle multiple modulations of rare royal reality
to know that at each moment the crown jewels of the absolute
are dancing in the slime of my tissue
the play of the light in the growing cell
pours through the pulse of my perception
phoenix singing in my flesh
bird that breathes lightning as we breathe air and fishes water
intricate egg of fire fluctuating
in the magnetic field of my affinities and repulsions
where myriads of globules circulate crosswires hum
most amplified fantasy of the diamond body harvest
I free my nucleus gathering ecstasy for the ages
my psyche digests the apocalyptic wisdom
interplanetary nausea
perfection signals tremor on the skin
O frail fine blue star
your faint fragile tonalities swoon triumphant rainbows
as the berserk fury of the thunder's roar fades into words on paper.

The Pharmacology of Psychedelic Drugs

I: Chemical and Biochemical Aspects.

RALPH METZNER

The term "psychedelic," taken from Osmond (1957), is used here to refer to a group of substances whose primary effect on human subjects is the radical alteration of consciousness, perception and mood. They have been variously called "psychotomimetic," "hallucinogenic," "psychotogenic," "consciousness-expanding," "consciousness-altering," or "mysticomimetic." No attempt is made here to describe or analyze the subjective psychological effects of these drugs and plants, and the reader may be referred to the excellent reviews by Osmond (1957) and Unger (1963) for this purpose.

Many drugs and still more plants with unknown chemical constitutents are known to alter consciousness, perception and mood. The amphetamines induce arousal or mood elevation; the barbiturates produce somnolence or narcosis. The more recent tranquilizers and anti-depressants seem to vary on a parallel but more subtle dimension. The present group of substances excludes these as well as the opiates, cocaine and other anaesthetics, and atropine and its derivatives. The "psychedelic" drugs reviewed here were selected according to the following criteria:

(1) their somatic effects are relatively unimportant, compared to the marked psychic effects;

(2) no cases of addiction or dependence have been reported;

(3) though tolerance develops, there is no abstinence syndrome on withdrawal;

(4) they have been described in the psychiatric literature as "psychotomimetic";

(5) they have also been described in the psychiatric literature as useful in therapy.

With these criteria in mind a group of about fifteen drugs was selected, which may be classified chemically into the following five categories: (1) phenylethylamine derivatives, of which mescaline is an example; (2) lysergic acid derivatives, of which LSD is an example; (3) tryptamine derivatives, of which psilocybin is an example; (4) piperidyl benzilate esters, of which JB 329 or Ditran is an example; and (5) phencyclidine (Sernyl).

A word about similarities and differences between these drugs. There seems to be general consensus that the drugs in the first three groups are essentially alike in their effects, differing only in duration of action (Unger, 1963; Szara, 1957; Wolbach *et al.*, 1962a). The relationship of these drugs to Ditran and Sernyl is less well understood, but they are alike in producing

"psychotic-like" hallucinatory episodes in which contact is maintained and which may result in reintegration and insight (English, 1962). For the purposes of this paper, they will be assumed to be sufficiently alike to warrant searching for common or parallel pharmacological mechanisms.

Support for the assumption of common mechanisms comes also from data on cross-tolerance: subjects who have developed tolerance to one of the drugs respond less to others (Wolbach *et al.*, 1962b; Isbell *et al.*, 1961; Balestrieri, 1960).

A preliminary discussion of some of the substances which have been excluded from the present review seems in order. First, according to Osmond, Hoffer and others, *adrenochrome* and *adrenolutin* have "psychotomimetic" properties but this has not been generally accepted; they are discussed in the section on epinephrine and its derivatives below. The harmala alkaloids, *harmine* and *harmaline*, are found in two plants used for mystical purposes: *Peganum harmala*, which grows in Asia, and the South American vine *Banisteriopsis caapi* (known also as yajé, caapi or ayahuasca). According to Gunn (1935), harmine produces tremors and has pharmacological effects similar to quinine. Pennes and Hoch (1957) claim harmine is "psychotomimetic," although Turner *et al.* (1955) deny this. It seems likely that the caapi vine contains other alkaloids besides harmine. However, the few studies on the pharmacology of harmine will be mentioned in the present review. The African root *Tabernanthe iboga* is said to cause madness, hallucinations and prophetic visions in those who take it. The active principle *ibogaine* has been described as an indole alkaloid with central-stimulant properties (Schneider and Sigg, 1957). No studies of its psychological effects in man have been found. The hallucinogenic plant, *ololiuqui* (*Rivea corymbosa*), will not be discussed separately since its active components have been isolated and identified as *d*-lysergic acid amide and *d*-isolysergic acid amide, which are included in the group of lysergic acid derivatives (Hofman, 1961). The subjective effects of the seeds of this Morning Glory have been described by Osmond (1955) and seem to be essentially similar to LSD with some sedative activity. The following chemicals have been reported to be "psychotomimetic" but these reports await further confirmation: nalline, a morphine antagonist, and WIN-2299, a synthetic anticholinergic (Pennes and Hoch, 1957); an unidentified indole compound labelled "BGE" (Sherwood, 1957); and dimethylacetamide (Weiss *et all.*, 1962).

The oldest known consciousness-altering drug, hashish or marihuana, (derived from Indian hemp, *Cannabis indica*) which has been used for thousands of years, is not included in the present review because (a) its properties seem to be somewhat different from the other "psychedelics" and (b) almost nothing is actually known about its biochemical effects. The active principle in marihuana is tetrahydrocannabinol; and its effect is shared by numerous isomers, homologs and analogues (Loewe, 1944). The psychological effects of marihuana seem to include impairment of complex psychomotor reactions, impairment on speed-accuracy tests of intellectual functioning, and lessening of emotional inhibitions. There is no addiction, tolerance is limited, and therapeutic applications have been suggested (Wallace, 1944). However, there is little evidence for the occurrence of any of the extensive alterations in consciousness and perception which occur with the other psychedelics.

Finally, the alterations in consciousness brought about by *carbon dioxide* in various concentrations will not be discussed here, since they have recently been extensively described in a monograph edited by Meduna (1958).

A general caution may be necessary at this point. As is now becoming more and more clear, in the field of psychopharmacology the action of any drug (as of any stimulus) is a product of both specific and non-specific factors. Non-specific factors include personality of the subjects, setting of the experiment and attitudes of the researcher. These are ignored here in an effort to isolate the specific effects of the drug on the body's systems. A complete explanation would of course have to take into account both specific and extra-drug factors. In this paper only studies on the biochemical level are reviewed; physiological and psychological aspects will be discussed in separate papers. The review is divided into four parts: I. Chemical Structure and Its Relation to Pharmacological Activity; II. Distribution and General Metabolism; III. Specific Biochemical Changes; and IV. Summary and Conclusions.

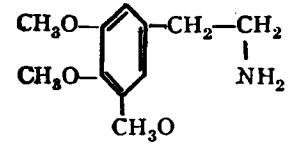
I. Chemical Structure and Its Relation to Pharmacological Activity

(1) *Phenylethylamine derivatives* (see Fig. 1)

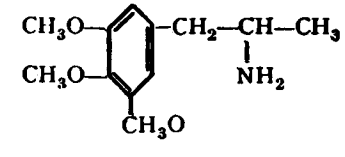
This group includes mescaline (3,4,5-trimethoxy-phenylethylamine) and TMA (3,4,5-trimethoxyphenyl-β-aminopropane). They are structurally closely related to epinephrine and amphetamine, and, like these, have a marked sympathomimetic or adrenergic effect on the autonomic nervous system (ANS). Mescaline is the principal psychoactive alkaloid of the peyote cactus (*Lopho-*

Figure 1

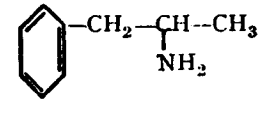
Chemical Structure of Mescaline and Related Compounds



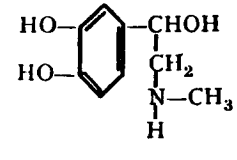
Mescaline



TMA



Amphetamine



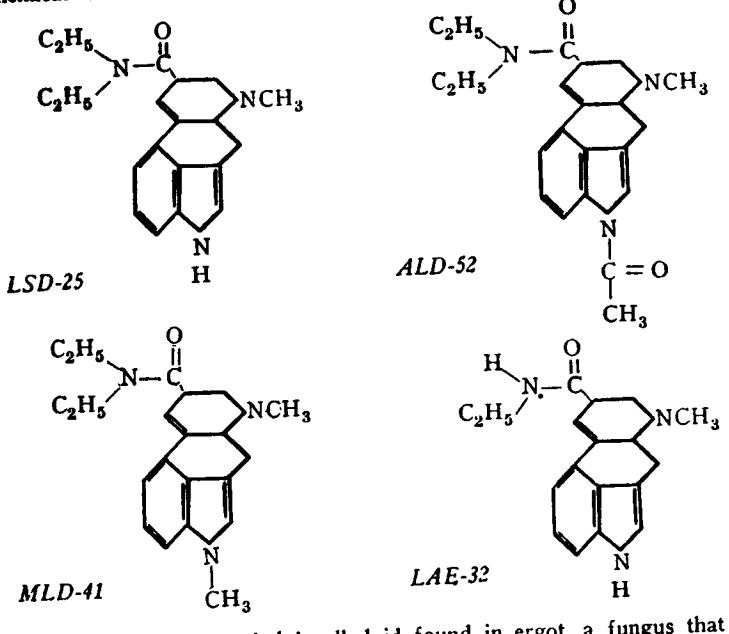
Epinephrine

phora Williamsii). TMA (Peretz *et al.*, 1955), in structure and apparently effects, is halfway between mescaline and amphetamine. Smythies and Levy (1960) have reported on the comparative action of various mescaline analogues on the rope-climbing of rats. Using this test they concluded that (1) loss of the methoxy group in the 5 position of mescaline reduces activity 50%; (2) replacement of the 4-methoxy group by a hydroxyl group eliminates activity; and (3) replacement of the 4-methoxy group by a benzyloxy group increases activity. Other phenylethylamines are discussed by Alles (1957). Clark *et al.* (1958) found that 3,4,5-trimethyl-β-phenylethylamine and certain di- and monomethyl-substituted β-phenylethylamines induced profound behavior changes in cats similar to those produced by large doses of LSD.

(2) *Lysergic acid derivatives* (see Fig. 2)

Figure 2

Chemical Structure of Lysergic Acid Diethylamide and Related Compounds



Lysergic acid is an indole alkaloid found in ergot, a fungus that grows on rye. The diethylamide (LSD) was synthesized in 1938, and accidentally found to have hallucinogenic properties by Hofmann in 1943. LSD is a very potent pharmacological antagonist of 5-Hydroxytryptamine (5-HT), which is thought by many to play an important role in the central nervous system. Cerletti (1959) and Isbell *et al.* (1959) have reported studies of 18 lysergic acid derivatives, in which the antagonism to 5-HT and the "psychotomimetic" effects were systematically compared. From these studies the following conclusions may be drawn: (1) LSD is the most potent of all the congeners so far studied, in its mental effects. The one most closely resembling it is ALD-52 (*d*-1-acetyl lysergic acid diethylamide). This was confirmed in another study of 10 lysergic acid derivatives by Abramson (1959). MLD-41, in which a methyl group is substituted at position 1, is about one-third as powerful as LSD in its mental effects and can produce tolerance to LSD (Abramson *et al.*, 1958). (2) The stereoisomers, i.e., *l*-lysergic acid diethylamide, and *d*- and *l*-isolysergic acid diethylamide, have no mental effects and do not antagonize 5-HT. (3) Variations in the amide group tend on the whole to reduce the mental effects considerably. Solms (1958), comparing LSD (lysergic acid diethylamide), LAE (lysergic acid ethylamide) and LA (lysergic acid amide), concluded that the hallucinogenic effect increased with the number of ethyl groups at the amide-N, and that drowsiness and lethargy increased as the number of ethyl groups decreased, LA producing most drowsiness. (4) The greatest reduction in mental effects was caused by changes in position 2 of the indole ring. BOL-148 (*d*-2-brom lysergic acid diethylamide) produced no mental effects in doses up to 500 μg in man, although it has marked anti-5-HT effects. (5) 1-methylation of both LSD and BOL increases the 5-HT antagonism (Cerletti and Doepfner, 1958). (6) In general, there is no correlation between the potency of a compound as a 5-HT antagonist and its psychic effects. This makes untenable the hypothesis that the mental effects of LSD are due entirely to its inhibition of 5-HT.

(3) *Tryptamine derivatives* (see Fig. 3)

Tryptamine is an indole amine derived by decarboxylation from the essential amino acid, tryptophane. Two sets of derivatives of tryptamine are psychologically active: the alkyl derivatives and the hydroxy derivatives.

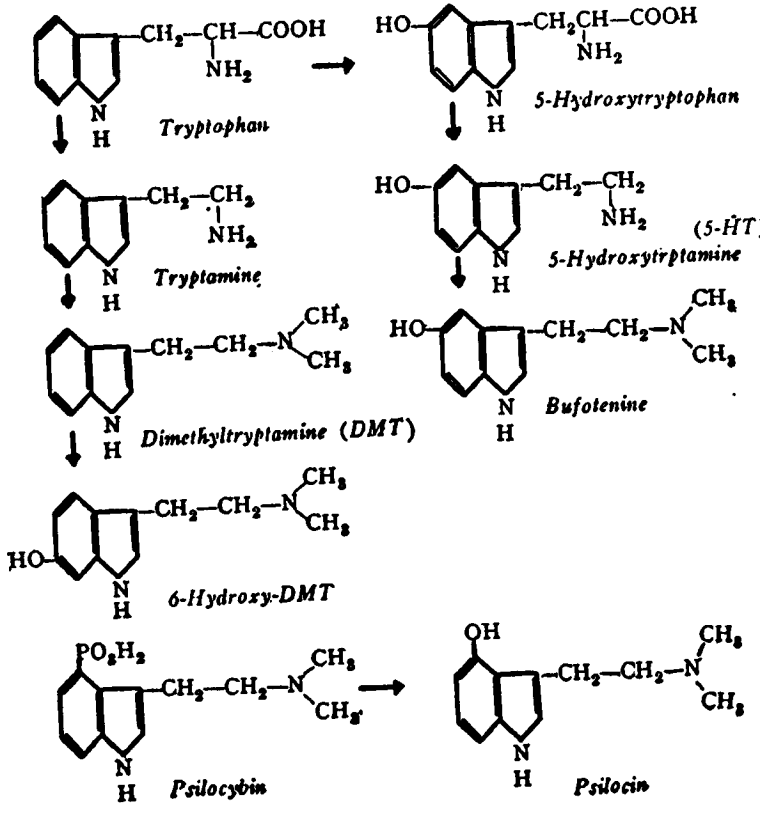
(a) N,N-dimethyltryptamine (DMT), N,N-diethyltryptamine (DET) and N,N-dipropyltryptamine, in doses of 1 mg/kg, similar to LSD or mescaline, but with a shorter duration of effect. The dibutyl derivative gives slight effects, while the dihexyl compound is completely inactive. The psychotropic activity is proportional to the rate of metabolism in the liver, and the ability to be 6-hydroxylated (the higher homologues are 6-hydroxylated slowly or not at all). Szara and Axelrod (1959) reported that DMT is metabolized to 6-hydroxy-DMT, which is a stronger "psychotomimetic" than its parent substance. These findings were later extended when it was found that a dose of 10 mg. of 6-hydroxy-DET produced mental effects equivalent to those of 60 mg of DET (Szara and Hearst, 1962). It is therefore likely that both DMT and DET exert their psychic effects after being converted to their respective 6-hydroxy analogues. DMT is one of the active substances in the cohoba snuff (*Piptadenia peregrina*) used by some South American Indian tribes (Hofmann, 1961).

(b) Tryptophane may be hydroxylated to 5-hydroxytryptophane (5-HTP) and then decarboxylated to 5-hydroxytryptamine (5-HT, or serotonin). Enzymes for both of these reactions have been found in mammalian tissues. The dimethyl derivative of 5-HT is bufotenine, a hallucinogenic compound (Fabing and Hawkins, 1956). Bufotenine is found in the South American mystical

snuff cohoba (*Piptadenia peregrina*), in the secretion of the parotid gland of the toad *Bufo marinus*, and in trace amounts in *Amanita muscaria*, the poisonous mushrooms alleged to induce "going berserk" (Buck, 1961; Fabing, 1956). Axelrod (1961) has reported the presence of an N-methylating enzyme in rabbit lung that can convert 5-HT and tryptamine to bufotenine and DMT, respectively. If the hydroxy group is in position 4, rather than 5, we have psilocin (4-hydroxy-N-dimethyltryptamine), which is one of the active compounds in the Mexican sacred mushroom *teonanacatl* (*Psilocybe mexicana* Heim and other species). Actually the primary active component of the mushroom is psilocybin, which is psilocin with an additional phosphoryl group in position 4. Brack *et al.* (1961) have shown that the psilocybe fungus can incorporate tryptophan, and suggested that psilocybin therefore could be

Figure 3

Chemical Structure of Tryptamine and Its Derivatives[1]



[1] Arrows indicate possible metabolic pathways.

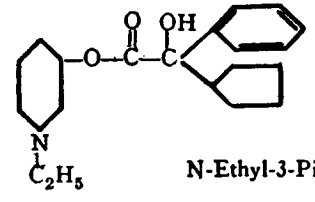
produced by 4-hydroxylation of tryptophane, analogously to the biosynthesis of 5-HT.

According to Weidmann and Cerletti (1960), the 4-hydroxy derivatives psilocin and psilocybin differ from the 5-hydroxy derivatives bufotenine and serotonin in that the former stimulate the patellar reflex of spinal cats, whereas the latter block it; in a study of 30 tryptamine derivatives only the 4-substituted derivatives of dimethyltryptamine were found to have this stimulating action.

(4) *Piperidyl benzilate esters* (see Fig. 4)

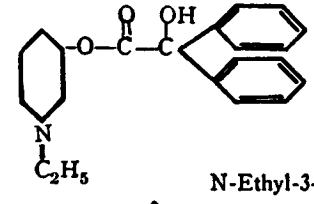
Figure 4

Chemical Structure of Benzilate Esters and Phencyclidine



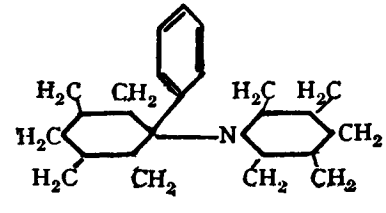
JB-329 (part of Ditran)

N-Ethyl-3-Piperidyl Cyclopentylphenylglycolate



JB-318

N-Ethyl-3-Piperidyl Benzilate



Phencyclidine (Sernyl)

1—(1-Phenylcyclohexyl) Piperidine

Abood and Meduna et al. (1958) reported that N-methyl-3-piperidyl benzilate produced "psychotomimetic" effects in normals, at doses of 51 mg. A series of twelve benzilate esters and congeners were studied by Abood *et al.* (1959), who found that if one of the phenyl groups in benzilic acid was substituted by a cyclopentyl, the duration and intensity of hallucinogenic action was increased. Other findings on structure-activity relationships are summarized as follows by Abood (1957): referring to the N-ethyl compound, "an

important factor for hallucinogenic effect is the length of the chain between the diphenyl and the piperidine molecule. As that begins to increase, then the hallucinogenic properties diminish, although the atropine-like or anticholinergic properties persist, and do not seem to be altered perceptibly. Hydroxyl substitution on a carbon adjacent to the diphenyl is essential. On the nitrogen in the piperidine ring, methyl substitution still retains activity, and as propyl and higher aliphatic chains are reached, the activity begins to diminish." Although all of the compounds are anticholinergic and are pharmacologically related to atropine and scopolamine, there was no correlation between anticholinergic and "psychotogenic" potency. Anticholinesterases are effective only against the autonomic, not the central, effects of these compounds. A synthetic compound, JB-329 (Ditran), which is a mixture of the two isomers, N-ethyl-3-piperidyl phenylcyclopentylglycolate and N-ethyl-3-pyrrolidylmethyl phenylcyclopentylglycolate, has been widely used as an anti-depressant (Meduna and Abood, 1959). In a comparative study (Gershon and Olariu, 1960), 0.2 mg/kg of Ditran produced effects stronger than 0.5 mg/kg of mescaline or 5 μg/kg of LSD. Whether the effects are qualitatively alike is difficult to tell from present evidence. JB-329 is not an indole compound, unlike all the other substances mentioned so far; it is not sympathomimetic and does not antagonize 5-HT. If the psychic effects are similar the indicates that different autonomic and peripheral mechanisms may accompany or "trigger off" similar central effects.

(5) *Phencyclidine*

Sernyl, which is 1-(1-phenylcyclohexyl) piperidine, originally used as an anesthetic, was reported to be "psychotomimetic" by Luby *et al.* (1959) and has also been used in psychotherapy (Davies 1960, 1961). Chemically, it is related to the previous group of piperidyl benzilate esters, but differs in not antagonizing acetylcholine and in other respects. The main difference in the type of action induced by Sernyl as compared to other hallucinogens is its strong sedative effect (Gershon *et al.*, 1960).

II. Distribution and general metabolism

(1) *Phenylethylamines*

The data on the absorption and excretion of mescaline indicates that from 20-70% of ingested mescaline is excreted within 24 hours, with peak excretion occurring in the first six hours (Fischer, 1958). Studies with mice (Block, 1958) and dogs (Cochin *et al.*, 1957) using mescaline labelled with radioactive carbon-14, have shown that the highest concentrations of mescaline are found in the kidney and liver and lowest in the brain. Block (1958) has presented evidence that the maximum psychological effects (e.g., hallucinations) do not coincide in time with the maximum concentration of mescaline in the brain, but come later. This suggests that some metabolite of mescaline is responsible for the hallucinogenic action. From studies with mice, Block (1958) concluded that mescaline is not broken down for a long time but is incorporated in bound form in liver proteins and that this is the psychotropic form. Friedhoff and Goldstein (1962) and Spector (1961), studying rats,

have presented evidence that mescaline is first metabolized to aldehyde (3,4,5-trimethoxyphenyl acetaldehyde) and then either oxidized to acid or reduced to alcohol, with the acid as the major end-product. Iproniazid, which inhibits monoamine oxidase (MAO), prevents the first step and greatly increases the amount of unchanged mescaline excreted. When iproniazid was given together with mescaline, the behavioral effects (in rats) could not be distinguished from the equivalent doses of mescaline alone. Thus an increase in concentration of unmetabolized mescaline did not enhance the mescaline effect, but neither was the effect diminished. Presumably, therefore, both the amine itself and its products are responsible for the total effect. Both the aldehyde and the alcohol (3,4,5-trimethoxyphenylethanol) produced mescaline-like effects at much lower dosages than mescaline itself. Similar studies will have to be done with humans, but these do suggest that the effects of mescaline ingestion are due primarily to its breakdown products.

Peretz *et al.* (1955) report that when TMA is given iv to dogs, 20-35% is recovered unchanged in the urine, with peak excretion occurring between two and five hours after injection.

(2) *LSD-25*

Boyd (1958) and Stoll *et al.* (1955) have traced C^{14}-labelled LSD in rats and mice, finding highest concentration in liver, kidney and lung, and lowest in brain. Boyd (1959) found four different radioactive metabolites in the bile after injection of labelled LSD. Lanz *et al.* (1955), using a bioassay procedure based on the antagonism of LSD to 5-HT, and Haley and Rutschmann (1957), using radioactive LSD, showed that LSD disappears from the brain very rapidly, even after intracerebral injection. Only 8-10% of the dose of LSD was found in the brain of cats ten minutes after intracerebral injection, indicating that extremely low concentrations of the drug are required to produce profound central changes (Haley and Rutschmann, 1957). Using a specially developed estimation procedure specific for LSD, Axelrod *et al.* (1957) traced LSD (in cats) in the following descending order of concentrations: bile, plasma, lung, liver, kidney, brain, intestine, spleen, cerebrospinal fluid, muscle and fat. They found also that the drug is extensively bound to plasma proteins, passes the blood-brain barrier easily and is almost completely metabolized, less than 1% being excreted in urine or stools.

On the basis of *in vitro* studies, they concluded that 2-oxy-LSD, which has no central effects, is the major metabolite, but this does not agree with the findings of Boyd (1959).

Two studies have been reported on the distribution of LSD *within* the brain. Hoagland (1956) gave C^{14}-labelled LSD to rats, and dissected the brain 30 minutes after injection. The following, theoretically equal, radioactivity counts were found: cortex 31, thalamus 28, cerebellum 26, brainstem 17, hypothalamus 16. It is interesting to compare this with the 135 found in the liver. Arnold *et al.* (1958), 20 minutes after injection in mice, found concentrations in the following order: brainstem, cerebrum, medulla oblongata, cerebellum.

Keup (1958), comparing distributions of labelled LSD in young and mature rats, found that in immature rats higher concentrations were found in the liver than in the cortex, whereas the reverse was true of mature animals. In the latter, two-thirds of the radioactivity was detected in cortex cell protein and two-fifths in liver cell protein. Keup (1959) also reports data on rats given labelled LSD which are analogous to the studies of Block with mescaline in mice. When concentrations were determined at various intervals after injection, the maximum of free LSD for most organs came at one to two hours. The maximum of LSD bound in proteins was reached at 6 hours.

(3) *Tryptamine derivatives*

In a study of the fate of psilocin in the rat, Kalberer *et al.* (1962) report that 65% of a dose of 10 mg/kg is excreted in the urine in 24 hours. Some work has been done on metabolic transformations of these substances. As already mentioned, dimethyl- and diethyl-tryptamine are probably converted to their 6-hydroxy analogues, which have been found to be hallucinogenic at lower dosages (Szara and Hearst, 1962). 6-hydroxylation may proceed by one of three pathways: N-methylation, N-acetylation or the production of indoleacetaldehyde (Szara, 1961). Horita and Weber (1961) have reported that when psilocybin is incubated with rat kidney homogenates, the dephosphorylated product, psilocin, is liberated by the action of alkaline phosphatase. Psilocin can pass the blood-brain barrier more easily than psilocybin. They suggested that in the intact animal, psilocybin is rapidly dephosphorylated to psilocin and is active in that form; and further that its duration of effect may be controlled by the oxidation of the latter compound to an O-quinone type of structure. Axelrod (1961) has identified S-adenosylmethionine-methyl as an N-methylating enzyme found in rabbit lung which can convert 5-HT to bufotenine, and tryptamine to DMT. Thus, there is a known pathway for the formation of psychedelic substances from normally occurring compounds. The enzyme was also found to N-methylate other amines such as tyramine, dopamine (an epinephrine precursor) and mescaline. Bufotenine, the dimethyl derivative of serotonin (5-HT), is the only known hallucinogenic compound which has been identified in human urine (Fischer *et al.*, 1961; Bumpus and Page, 1955), albeit in minute concentrations.

According to Gessner *et al.* (1960), the vasopressor effects of 5-HT, bufotenine and psilocybin are proportional to, and probably related to, the rate at which these compounds are inactivated by monoamine oxidase. 5-HT, which is rapidly oxidized, has a very short vasopressor action. *In vivo* experiments confirmed that bufotenine and psilocybin are not readily destroyed by MAO, and that alternate pathways are probably more important. Delay *et al.* (1959) found increased excretion of 5-hydroxyindoleacetic acid, the 5-HT metabolite, after psilocybin.

By comparing the effects of 5-HT and bufotenine with their respective methoxy analogues, Gessner *et al.* (1961) concluded that O-methylation of indole amines is not an inactivation mechanism as is O-methylation of catechol amines; it decreased the vasopressor activity of 5-HT but increased vasopressor activity of bufotenine and increased behavioral mistakes (in rats).

According to Blashko and Levine (1960), psilocin, DMT and other hydroxyindoles may be broken down by other copper-containing oxidases, found in the gill-plates of *Mytilus edulis* and as caeruloplasmin in mammalian tissue. This suggestion is supported by the finding of Hollister and Hartman (1962) that psilocybin increased copper oxidase activity. According to Kalberer *et al.* (1962), 25% of psilocin is excreted unaltered.

(4) *Benzilate esters*

Studies in rats with tritium-labelled Ditran have shown that over 90% of the ingested drug is excreted unchanged in the urine within two hours of administration. Though some of the drug remained in the brain after 24 hours, it was less than .01% of the total dose; caudate nucleus and hypothalamus having the largest concentrations. When cytoplasmic fractions of rat brain were isolated by centrifugation, most of the Ditran was localized in the mitochondria (Gershon and Olariu, 1960). Distribution data for Sernyl have not been found.

III Specific biochemical changes

In this section, studies of biochemical effects of psychedelic drugs will be reviewed in five sections: effects on carbohydrate and phosphorus metabolism, effects on choline and cholinesterases, effects on catechol amines, relation to serotonin and indole metabolism, and miscellaneous effects. A brief summary of the normal metabolic functions in each of these areas will precede each section, in order to facilitate the interpretation of studies of drug effects.

(1) *Carbohydrate and phosphorus metabolism*

(a) *Normal functioning.* The brain derives its supply of energy by the oxidation of glucose, consuming in the process one-fifth of the total bodily consumption of oxygen. The utilization of oxygen and the production of carbon dioxide by the tissues in the process of cellular respiration is only the final phase of biological oxidation. A series of intermediate steps involving hydrogen and electron transfer precede the final step. Oxidation is initiated by the action of a dehydrogenase, specific to the metabolite, which catalyzes the removal of hydrogen and thus oxidizes the metabolite. The aerobic (oxygen-using) dehydrogenases transfer hydrogen directly to molecular oxygen. Others, the anaerobic dehydrogenases, require intermediary systems, which include DPN (diphosphopyridine nucleotide), TPN (triphosphopyridine nucleotide), the flavoproteins and the cytochromes. High-energy phosphate compounds, such as ATP (adenosine triphosphate) or PC (phosphocreatine), store and transmit the energy involved in these oxidation and reduction processes. The hydrolysis of the terminal phosphate bond of ATP to produce ADP (adenosine diphosphate) liberates the energy which is apparently universally used by the cells of the body to support their metabolic activities. The resynthesis of the phosphate esters, i.e., the incorporation of inorganic phosphate into a high-energy linkage with an organic compound, requires the simultaneous incorporation of an amount of energy equal to that liberated on hydrolysis of the high-energy bond. This energy is obtained from the oxidative breakdown of various metabolites such as sugars and lipids. In this manner, the energy

yielded by the breakdown of these metabolites can be stored by the formation of high-energy phosphate bonds. These high-energy bonds, by storing energy and delivering it later by hydrolysis of the bond, may be regarded as "biological storage batteries." In the gradual oxidation of metabolites, the storing of liberated energy in high-energy phosphate bonds can proceed step by step, coupling the phosphorylation with the oxidation. This system prevents wasteful production of energy and maintains a high level of efficiency where as much as 40% of the output may be recovered as useful work. If phosphyralation is "uncoupled" from oxidation, the excess energy which cannot be stored is liberated as heat.

In muscles, the breakdown of ATP to ADP supplies the energy for contraction. Phosphocreatine acts as a reserve for the resynthesis of ATP. In the resting state, muscle contains four to six times as much PC as ATP. In nerve tissue, the precise role of phosphate compounds is not yet known, although several mechanisms have been suggested. Most likely they provide the energy for the resynthesis of acetylcholine, a chemical mediator substance.

The oxidation of glucose, which is the main energy source for the brain, proceeds in two phases: the glycolytic (Emden-Meyerhof) pathway, whose end-products are lactic and pyruvic acid, and the later conversion of pyruvic acid to carbon dioxide and water via the citric acid (Krebs) cycle. It has been estimated that 38 high-energy phosphate bonds may be derived from the complete oxidation of one molecule of glucose via these pathways. An alternative to the Emden-Meyerhof breakdown of glucose is the so-called direct oxidative pathway, or hexosemonophosphate (HMP) shunt. In this pathway oxidation occurs early, CO_2 being derived from glucose-6-phosphate, and the end-products are fructose and glyceraldehyde.

It is evident that glycolysis, oxidation and phosphorylation, while they may be separated analytically and in laboratory conditions, actually form an interdependent, self-regulatory system, and in the long run, neural function requires the integrity of all of them.

This interdependence is illustrated in the effects of stimuli or drugs on this system. Barbiturates, tranquilizers and hypoglycemia decrease the overall cerebral oxidative rate: glucose and oxygen consumption are reduced, lactic acid formation is reduced. But the effects on phosphates differ: barbiturates increase levels of phosphocreatine and decrease levels of inorganic phosphate, hypoglycemia has the reverse effect, chlorpromazine seems to prevent synthesis of ATP (Quastel, 1962). In seizures and after electrical stimulation, there is a fall in the levels of phosphocreatine, an increase in inorganic phosphorus, and increased oxidation of glucose. The phosphate changes, in general, precede the changes in oxidation. Thus decreased oxygen consumption is more likely a consequence of the deactivation of neuronal units, rather than a cause of reduced activity; and increased oxygen consumption is probably an after-effect, rather than a cause, of excessive neural activity. [The foregoing account is based on Harper (1961), Wikler (1957), and Heald (1960).]

(b) *Effects of psychedelic drugs.* Quastel and Wheatley (1933) showed that mescaline inhibited the oxidation of glucose by minces of guinea-pig

brain. These findings were confirmed by Schueler (1948), using rat brain. However, the concentrations used in these experiments far exceed those one would expect to find *in vivo* after the administration of mescaline. Lewis and McIlwain (1954) found no effect of mescaline on oxygen uptake, but when the brain slices were stimulated electrically, the normal increase in oxygen consumption was prevented by mescaline. Clark *et al.* (1954) report that mescaline inhibits the oxidation of pyruvate in brain homogenates. *In vivo,* Deniker (1957) and Denber (1961) report an increase in blood glucose levels after the administration of mescaline, and a decrease in circulating eosinophils. The latter is a sign of increased secretion of corticotrophic hormone (ACTH) which regulates the phosphate uptake of gray matter. Feld *et al.* (1958) report a 40% reduction of the eosinophil count after LSD. Bergen and Beisaw (1956) report a 50% decrease in inorganic phosphates after LSD. Hollister and Hartman (1962) report a fall in urinary excretion of inorganic phosphates after 5 mg/kg of mescaline, 1 μg/kg of LSD, and 150 mg/kg of psilocybin. These *in vivo* findings are consistent with the idea that mescaline reduces phosphate formation and cerebral oxidation.

Mayer-Gross *et al.* (1953) reported that LSD stimulated glucose oxidation of guinea pig brain homogenates, and inhibited the breakdown of hexose-monophosphate (HMP). This is one of the few *in vitro* studies employing concentrations approximating those which are active in *in vivo* studies. They also reported (Mayer-Gross *et al.*, 1951) a fall in blood glucose levels and a rise in HMP levels of subjects given LSD. As Bain (1957) has pointed out, the accumulation of hexose-monophosphates is difficult to interpret, because of the method used. "Assuming that it is glucose-1-phosphate or glucose-6-phosphate . . . the accumulation of either of these two phosphates implies a block of both the Emden-Meyerhof shunt and the pentose shunt which are the main pathways for the breakdown of glucose, and yet there was stated to be an increase in the oxidation of glucose." It should be noted that according to Mayer-Gross *et al.* (1951), mescaline does not prevent HMP breakdown in contrast to LSD.

Unfortunately, the results of Mayer-Gross *et al.* have not been confirmed by later experiments. Lewis and McIlwain (1954) observed inhibition of oxygen uptake only in stimulated brain slices, analogous to their results with mescaline. Bain and Hurwitz (1954) were unable to repeat the experiments of Mayer-Gross *et al.* Clark *et al.* (1954) reported inhibition of succinic dehydrogenase and stimulation of cytochrome oxidase from brain tissue. Geronimus *et al.* (1956) report that LSD does decrease oxygen consumption of guinea pig brain homogenates. Starbuck and Heim (1959) report no effect. Cahn *et al.* (1957) report that glucose consumption of rabbit brain is reduced by LSD. Sankar (1961) reports that LSD increases oxidation of glucose in the cerebrum, whereas in the cerebellum LSD inhibits it markedly. Abood and Romanchek (1957) report that LSD, along with many other drugs, inhibits oxidative phosphorylation in rat brain mitochondria. Bain (1957), however, reports that neither LSD nor mescaline has this effect.

Rudolph and Olsen (1957) report a study having some bearing on the

question of whether there is selective interference with one of the two major pathways of glucose metabolism. In dog prostate slices, they found that more CO_2 was derived from glucose-1-C^{14} than from glucose-6-C^{14}. This would imply that the direct oxidative shunt is the main pathway for this type of tissue, since on the Emden-Meyerhof route, the two carbons of glucose are metabolized in the same manner (Harper, 1961). Rudolph and Olsen (1957) found that LSD decreases the CO_2 in glucose-6-C^{14} but not in glucose-1-C^{14}. The implication is that LSD may interfere with one of these two pathways more than the other.

Arnold *et al.* (1957) have reported that both succinic acid and glutamic acid, which participate in the Krebs cycle, temporarily inhibit the psychic effects of LSD and have some therapeutic effects in schizophrenia. It is suggested that this action is due to the correction of disturbed glucose oxidation. Schueler (1948) reported that succinic acid temporarily interrupted mescaline intoxication. Succinic acid also antidotes Sernyl (Gershon and Olariu, 1960).

Hoagland (1957) has put forward a theory linking the effects of LSD on phosphate metabolism to schizophrenia. Hoagland *et al.* (1955) found, like others, that LSD decreases urinary inorganic phosphate excretion, and that ACTH reverses this effect. Schizophrenics have lower phosphate excretion rates than normals and ACTH has a similar effect on these, as in LSD-treated normals. Hoagland (1957) suggests that "LSD and some endogenous metabolite that acts in a similar manner in schizophrenics either facilitates the conjugation of phosphates with organic substances or decreases the phosphate turnover rates. The role of adrenal steroids, as seen in the enhanced output of urinary phosphates following the administration of ACTH, appears to be either to release the conjugated phosphate, speed the turnover rate, or both. That adrenal steroids modify phosphorylating mechanisms by affecting several phosphorylating enzyme systems, has been demonstrated." Supporting the idea of decreased phosphate turnover are the findings of Callieri and Mariani (1957), that LSD and LAE reduce serum phosphate activity; and the findings of Lingjaerde and Skaug (1956), that large doses of LSD in rats significantly increase the uptake of labelled phosphorus in the adrenal medulla. Sankar and Sankar (1962) report that while LSD decreases urinary excretion of inorganic phosphates (and chlorpromazine increases it) the effect on blood phosphate content is opposite: LSD elevates blood levels of inorganic phosphates in animals and children; furthermore, schizophrenic children have higher levels of plasma inorganic phosphates than normal children, phosphate content decreases with age, and is higher in children with I.Q.'s less than 50.

In view of the contradictory results of cerebral oxidation studies *in vitro*, the only study so far reported studying cerebral metabolism in human subjects, is worthy of note. Sokoloff *et al.* (1957) measured cerebral blood flow and associated functions before and at the height of action of 120 μg of LSD given i.v. to 13 normals and 9 schizophrenics. Although the characteristic psychic changes were observed, there were no changes in cerebral blood flow, vascular resistance, oxygen and glucose utilization or respiratory quotient. Slight elevations in arterial blood pressure and in arterial hemoglobin con-

centrations were observed. Thus, at the normally effective doses, the mental effects of LSD cannot be attributed to disturbances of carbohydrate metabolism; although, at the very high concentrations usually employed in *in vitro* studies, disturbed glucose oxidation may well result from the administration of LSD.

Further light on this problem is shed by a series of studies by Cahn and his associates (Cahn and Herold, 1957) on the effects of chronic LSD administration. When rabbits were given 50 μg of LSD daily for two weeks the following effects were observed: decreased cerebral consumption of glucose and of inorganic phosphates, diminished production of CO_2, increased lactate consumption and increased glutathione reduction. Cerebral circulation was also decreased. It was suggested that glutathione reduction is the source of energy, as over-all oxidative processes are reduced. Egana and Candiani (1957) report reduced oxygen consumption in rats given 25 μg of LSD daily for one to two months. Cahn *et al.* (1958) report that if ATP is given after chronic LSD treatment, the reduced glucose consumption is restored to normal levels; and ATP and ascorbic acid together reverse all the metabolic changes caused by LSD and restore the desynchronized EEG to normal. It is difficult to assess the significance of these results of chronic LSD administration because not much is known about the psychological effects of prolonged administration of LSD in high doses, except that tolerance develops.

A few studies of other drugs have been reported. Adrenochrome inhibits glycolysis and uncouples oxidated phosphorylation (Bain, 1957). Sernyl stimulates oxygen uptake of rat liver homogenates and uncouples oxidative phosphorylation slightly (Lees, 1962). JB-336, JB-840, and JB-329 inhibit respiration and glycolysis in electrically stimulated brain tissues (O'Neill *et al.*, 1962). Harmaline, which is an MAO inhibitor, has been shown to increase bloodlevels of lactic and pyruvic acid, indicating increased glycolysis (Gey and Pletscher, 1961).

To summarize, considering the contradictory results, and the discrepancy between *in vitro* and *in vivo* concentrations, there is still much uncertainty in this area. It seems likely that at the normal effective dosages, LSD interferes in some way with phosphate turnover; whether this action is selectively restricted to certain metabolic functions or to particular areas, is unclear. An effect on oxidative processes has not been demonstrated except with chronic administration *in vivo* and very high concentrations *in vitro*. The most frequent finding from *in vitro* studies is that psychedelic drugs inhibit glucose oxidation or uncouple it from phosphorylation.

(2) *Effects on cholinesterases*

(a) *Normal functioning.* Acetylcholine was the first chemical mediator or neurohormone substance to be discovered. Injected, it simulates the action of the parasympathetic division of the autonomic nervous system. It has been shown that it is released, and transmits the nerve impulse at, (a) myoneural junctions, connecting motor nerves to muscles, (b) autonomic ganglia, and (c) all parasympathetic (and some sympathetic) postganglionic synapses. The corresponding role in the sympathetic system is played by norepinephrine.

Some also believe that acetylcholine (ACh) is involved in axonal transmission of nerve impulses, but this is not generally accepted. ACh is found in the brain mostly in "bound" form, which protects it from breakdown, and is released during nerve transmission. During anesthesia and sleep, the concentrations of bound ACh in the brain are increased (nervous activity is reduced); in convulsions and excitement, the concentrations are decreased. ACh is hydrolyzed by cholinesterase, and its resynthesis is accomplished by the enzyme choline acetylase, with energy from the breakdown of ATP. Two types of cholinesterases are known: one, found in nervous tissue, is specific to the breakdown of ACh, and is called true or acetylcholinesterase (AChase). The other, found in serum, hydrolyzes a wide variety of subtrates, and is known as pseudocholinesterase. Cholinesterase inhibitors, by preventing the breakdown of ACh, prolong parasympathetic nervous activity. Examples of these are physostigmine, which causes reversible inhibition of AChase, and DFP, which causes irreversible cholinesterase inhibition. Anti-cholinesterases are the principal ingredients in insecticides and so-called "nerve gas." Atropine, which is a substance blocking transmission at autonomic (and central) ganglia and a specific ACh antagonist, can be used to counteract the effects of drugs like DFP.

(b) *Effects of psychedelic drugs.* Poloni and Maffezoni (1952) reported that LSD caused an increase in the level of acetylcholine in the brain of the guinea pig, whereas mescaline produced no change. Thompson *et al.* (1955) found that pseudocholinesterase from human plasma and the brain was inhibited 50% by LSD, but the true esterase was only inhibited 10% by a concentration ten times as strong. Goldenberg and Goldenberg (1957) have compared several amines for their inhibitory action on human serum cholinesterase and determined the following order of potency: eserine > LSD > brom-LSD > neostigmine > LAE > chlorpromazine > 5-HT = tryptamine > mescaline. There does not seem to be any relation between psychological activity and cholinesterase inhibition, since (a) LSD and BOL are almost equally effective, yet BOL has no mental effects, and (b) chlorpromazine, which antidotes hallucinogenic effects, is a more potent inhibitor than mescaline. Zehnder and Cerletti (1956) have confirmed the finding that BOL inhibits cholinesterase as effectively as LSD. Zsigmond *et al.* (1959) reported that LSD and BOL inhibit both true and pseudocholinesterase. Zsigmond *et al.* (1961a), in a study of eight lysergic acid derivatives, report (a) no correlation between anticholinesterase activity (*in vitro*) and hallucinogenic activity, and (b) no correlation between anticholinesterase and antiserotonin activity. Evans (1960) found that LSD and BOL inhibited serum cholinesterase equally; chlorpromazine was slightly less effective but more potent than psilocybin; mescaline and amphetamine had no effect. He points out that "since the physiologic substrate of serum cholinesterase is not known, one can only conjecture which, if either, more accurately reflects the inhibition that obtains *in vivo*." Bain (1957) quoted Augustinsson on the finding that bufotenine and ibogaine have cholinesterase inhibiting effects. Zsigmond *et al.* (1961b) found that psilocybin and bufotenine inhibit human plasma cholinesterase more than does 5-HT, but

that with brain cholinesterase bufotenine was less effective than psilocybin or 5-HT. Finally, Fried and Antopol (1957) have reported that 5-HT and LSD inhibit pseudocholinesterase at high concentrations, as in the usual *in vitro* studies, but potentiate it markedly at lower concentrations, which are more like those likely to be found *in vivo*. Tonini (1955) has also reported cholinesterase potentiation in rat brain by LSD and 5-HT.

Choline acetylase, which is the enzyme catalyzing the formation of acetylcholine from choline, is potentiated by psilocybin and LSD (Boskovic and Przic, 1961).

Thus, there seems to be some consensus as to the fact that LSD and other psychedelic drugs antagonize the metabolites which break down acteylcholine and potentiate the enzyme which helps produce it; but these results obtain only at concentrations much higher than those found *in vivo*, and there is no relationship of this effect to mental activity of the drugs. Hence, the exact significance of these effects or their role in the overall action of these drugs remains unclear. When studies of specific brain areas or systems are undertaken, the nature of these changes may be clarified.

The role of acetylcholine in drug-induced alteration of consciousness received fresh interest by the discovery of the hallucinogenic activity of the piperidyl benzilate esters, all of which are anticholinergic, i.e., antagonize acetylcholine. In man, Ditran has the usual autonomic effects associated with atropine, the prototypical anticholinergic substance: mydriasis (pupil dilatation), tachycardia, and dryness of the mouth (Abood and Meduna, 1958). The anticholinesterases, by increasing endogenous acetylcholine, would be expected to inhibit the effects of Ditran. The better known anticholinesterases, like physostigmine and neostigmine, have been reported effective only against the peripheral autonomic effects, not the central psychic effects (Gershon and Olariu, 1960). These authors have, however, reported that THA (1,2,3,4-tetrahydro-5-aminoacridine), an anticholinesterase with central effects, is capable of completely blocking both central and peripheral effects of Ditran, regardless of clinical content. THA does not antidote the effects of Sernyl, LSD or mescaline. Thus the psychological effects of Ditran may be due to a decrease in the levels of endogenous acetylcholine in certain parts of the brain. The inventors of Ditran and related compounds were inclined not to accept this interpretation, since small alterations in the chemical structure could lead to psychically inactive substances which still had anti-acetylcholine effects. Thus, in a study of 14 piperidyl benzilates, Abood *et al.* (1959) concluded that there was no correlation between anticholinergic and psychic effect. Biel *et al.* (1962), in another study of piperidyl and pyrrolidyl glycolate esters, concluded that only those compounds with potent anticholinergic properties are also effective CNS stimulants (measured by rats' movements in a cage), although not every potent anticholinergic agent is necessarily an effective CNS drug. These studies indicate that other factors may be involved in the central action of Ditran besides the inhibition of acetylcholine.

Sernyl, which is not a peripheral ACh antagonist, has been reported to increase brain levels of acetylcholine (Freedman and Giarman, 1962).

To summarize this section:

(1) LSD and other psychedelic drugs increase endogenous ACh by antagonizing metabolites which break it down and by potentiating an enzyme which produces it. These results have been obtained only *in vitro*.

(2) There is some contradictory evidence that, at concentrations more similar to those occurring *in vivo*, LSD potentiates the breakdown of ACh.

(3) Ditran and other benzilate esters antagonize ACh and may act by decreasing its levels in certain parts of the brain.

(3) *Effects on catechol amines*

(a) *Normal functioning.* The biosynthesis of the catecholamines is now believed to occur via the following pathway: phenylalanine ⟶ tyrosine ⟶ DOPA ⟶ dopamine ⟶ norepinephrine (NE) ⟶ epinephrine. The last three have been identified in urine. Phenylalanine, the precursor, occurs as one of the essential amino acids in the diet. Epinephrine is formed from NE by N-methylation of the primary amino group. Epinephrine and NE are stored in two different types of cell of the adrenal medulla. The latter is a semi-distinct part of the sympathetic nervous system. Hence these substances have been described as "sympathomimetic." Both lead to an elevation of blood pressure, but by different means: epinephrine by increasing heart rate and cardiac output, NE by producing peripheral vasoconstriction. NE, besides being found in the adrenal medulla, is also stored in granules isolated from adrenergic nerve fibres. It is liberated when these fibres are activated, and may thus be regarded as the transmitter-substance for postganglionic sympathetic (adrenergic) fibres, much as acetylcholine is the transmitter-substance for parasympathetic (cholinergic) fibers, and for preganglionic fibers.

It has been suggested, by Funkenstein and others, that the release of NE is related to subjective anger and outward-directed aggression, whereas the release of epinephrine is related to inward-directed aggression, anxiety and tenseness. Plasma epinephrine levels are reduced during sleep or anesthesia, and increased during electroshock or convulsions. There is some evidence also that excretion rates of catecholamines are elevated during manic phases and reduced during depressive phases. Himwich (1963) has reported that in psychotic patients, increased behavioral "anxiety" is associated with increased urinary excretion of epinephrne and NE.

The two chief enzymes involved in the breakdown of the catecholamines are (1) monoamine oxidase (MAO) and (2) catechol-O-methyl transferase. Drugs which inhibit MAO, of which iproniazid is the prototype, potentiate the effect of norepinephrine, much as the anticholinesterases potentiate ACh.

The two main classes of drugs which antagonize the catecholamines are (1) ergot alkaloids, e.g., ergotamine, which block the effects of epinephrine and NE on smooth muscle and glands, and (2) reserpine alkaloids, which cause depletion of norepinephrine stores. Reserpine is a well-known tranquilizer.

The relationship of iproniazid and reserpine to norepinephrine and other catecholamines is similar to their relationship to the indole amines, chiefly 5-HT or serotonin, which will be discussed in the next section. MAO inhibitors

increase levels of these amines, and reserpine decreases them. [The foregoing account is based primarily on Sourkes (1962) and Himwich (1963).]

(b) *Effects of psychedelic drugs.* Liddell and Weil-Malherbe (1953) reported that 40-60 μg of LSD in mental patients at first increased, then decreased and finally increased again, the levels of adrenaline (epinephrine) in the plasma. Elmadjian *et al.* (1957) found significant increases in urinary epinephrine and NE in depressed patients after LSD, but no effect in schizophrenics. Rinkel *et al.* (1954) noted that the blood-pressure response to epinephrine was significantly reduced by LSD and suggested that LSD acts by interfering with epinephrine metabolism and the pituitary-adrenal stress system. However, Bliss *et al.* (1956) reported that although levels of 17-hydroxycorticosteroids in the plasma (as index of adrenocortical function) rose after the administration of LSD, this change was within normal limits and slighter than changes caused by insulin, ECT or moderate exercise. Ganong *et al.* (1961), who gave dogs extremely high doses (50 μg/kg) of LSD, also reported no significant effect on 17-hydroxycorticoid level or on levels of catechol amines in the blood. Dengler *et al.* (1961) observed that LSD had no effect on the uptake of norepinephrine by incubated slices of cat cortex, although this uptake was inhibited by reserpine, chlorpromazine, cocaine and mescaline.

Thus the effects of LSD on levels of catechol amines are in doubt. Since LSD is an ergot derivative, however, it might be expected to exhibit some of the epinephrine antagonism of this class of drugs. The altered blood-pressure response to adrenaline after LSD has already been mentioned. Holzbauer and Vogt (1955) report that LSD antagonizes the inhibitory action of adrenaline on the rat's uterus. Meier *et al.* (1957) state that LSD enhances the vasoconstrictor effect of norepinephrine on the hindleg of the rabbit, and weakly antagonizes the epinephrine effect. Savini (1956) found that LSD does *not* affect the vasoconstrictor response to adrenaline and noradrenaline, although BOL, which has no mental effects, does so. Luduena *et al.* (1959) report that LSD reduces the toxicity of epinephrine in rats. Goldstein (1962) reported that LSD blocks certain types of adrenergic responses in rabbits. Costa and Zetler (1958, 1959) have observed that pretreatment with LSD, 5-HT and bufotenine enhanced the actions of epinephrine (a) in depleting ascorbic acid from the adrenal medulla and (b) contracting the nictitating membrane of the cat.

A few studies of other drugs have been conducted. Harmaline and amphetamine inhibit monoamine oxidase (Nickerson and Parmar, 1961). DET, at very high concentrations, inhibits MAO (Satory *et al.*, 1961) and enhances the blood-pressure responses to epinephrine and norepinephrine (Borsy *et al.*, 1961). Mescaline and epinephrine compete for some receptors: pre-treatment with epinephrine reduces the hypoglycemia caused by mescaline (Fischer, 1958).

Adrenochrome and adrenolutin

Adrenochrome is one possible oxidation product of epinephrine, although the occurrence of this process has not been demonstrated. Hoffer *et al.* (1954) reported that adrenochrome produces EEG desynchronization, inhibits brain

tissue respiration and, in man, causes prolonged "psychotomimetic" episodes involving paranoia, space-time distortions, and "lack of insight." Osmond and Hoffer (1959) reported that adrenolutin, an unstable, fluorescent derivative of adrenochrome, may also be hallucinogenic. They proposed that disturbed epinephrine metabolism in schizophrenia results in the accumulation of one of these endogenous hallucinogens. They noted further that LSD increases plasma adrenochrome levels and, *in vitro,* increases the conversion of adrenochrome to adrenolutin (Hoffer, 1957, 1958). This suggested that the action of LSD may be indirect, by affecting levels of these other hallucinogens. But later workers claimed that the finding of adrenochrome in plasma was due to an artifact and was not repeated (Szara *et al.,* 1958; Feldstein, 1959). Furthermore, Smythies, one of the originators of the adrenochrome theory, in reviewing the evidence of five studies in which adrenochrome in doses as high as 75 mg had had no effect on humans, concluded that the hallucinogenic activity of these compounds is doubtful (Smythies, 1960). Agnew and Hoffer (1955) claimed that 200 mg iv nicotinic acid reduced the effects of 100 μg of LSD. The rationale for this was that it would suppress the conversion of norepinephrine to epinephrine and thus prevent the formation of adrenochrome. In contrast, however, Miller *et al.* (1957) found that atropine, niacin (nicotinic acid), or niacinamide did not alter the response to LSD when given simultaneously with it.

Summarizing this section, although there have been several theories and many studies allegedly relating the effects of LSD to epinephrine metabolism, the evidence seems clear that this is not the primary activity. The evidence on peripheral antagonism or potentiation of effects of catecholamines is also inconsistent.

(4) *Relation to serotonin and indole metabolism*

(a) *Normal functioning.* Serotonin (5-HT) has a distribution in the brain similar to that of norepinephrine: highest concentrations are found in the older parts of the brain, e.g., hypothalamus and brain stem, and lowest concentrations are found in the newer parts, e.g., cortex and cerebellum. 5-HT is formed by decarboxylation from 5-hydroxytryptophane (5-HTP), which in turn derives from the essential amino acid, tryptophane. The enzyme decarboxylase, which converts 5-HTP to 5-HT, also converts DOPA to dopamine, in the epinephrine pathway. 5-HT may (a) combine with receptor sites in its "free" form, (b) enter intracellular granules where it is "bound" or stored, or (c) be broken down by monoamine oxidase. The chief urinary metabolic product is 5-hydroxyindoleacetic acid (5-HIAA). Alternatively, some of the 5-HT may be converted to N-substituted derivatives such as bufotenine and melatonin. Tryptophane, instead of being converted to 5HTP and 5-HT, may be decarboxylated to tryptamine, the chief oxidation product of which is indoleacetic acid.

5-HT is found in many mammalian tissues besides the brain, and it seems to be stored primarily in blood platelets. Recently, Sankar *et al.* (1962a) have presented evidence indicating that the spleen is a major storage site for 5-HT and that it is metabolized most rapidly in kidney and liver. Reserpine,

as already pointed out, releases 5-HT from its bound form and depletes the stores, leading to increased excretion of 5-HIAA. However, since reserpine also depletes norepinephrine stores, it is not entirely clear to which of these processes its mental effects should be attributed. Recently, Costa *et al.* (1962) have summarized several studies which indicate that the central effects of reserpine are due to release of 5-HT and not to release of NE.

5-HT produces a wide variety of peripheral and central effects. Peripheral effects are the following: 5-HT causes contraction of most smooth muscle of most species. It apparently combines with the same pharmacological "receptors" as does tryptamine, but different ones from histamine. 5-HT causes constriction of peripheral blood vessels, but the effects of 5-HT injection on the cardiovascular system are complex and vary with the species, because 5-HT influences the circulation through several partly antagonistic mechanisms. In the respiratory system, 5-HT causes brief apnea followed by hyperpnea, as well as contraction of bronchial smooth muscle. In rats and dogs, 5-HT is said to be antidiuretic. The heart of the clam *Venus mercenaria* has often been used for bioassay of 5-HT, because it responds to extremely low concentrations of the drug.

Specific central effects have not been demonstrated (a) partly because vascular effects tend to overshadow central ones, and (b) partly because the blood-brain barrier is apparently impermeable to 5-HT. Because of this, studies of its central effects have been made by injecting the precursor 5-HTP and simultaneously blocking MAO. The resulting increased levels of brain 5-HT in dogs produced muscle tremors, incoordination, increased heart rate, increased respiration and pupillary dilatation.

Direct intracerebral injection of 5-HT in cats produced lethargy, muscle weakness, tremors and other non-specific behavioral effects. 5-HT also inhibits serum and brain pseudocholinesterase. The above account is based on Dews (1958) and Sourkes (1962).

There have been several theories about the functions of 5-HT in the organism. In particular, three peripheral functions may be involved: (1) facilitation of blood clotting through vasoconstriction, (2) regulation of arteriolar tone, (3) antidiuretic regulation of renal activity. Centrally, its functions have been more disputed: because of the similar distribution to NE, the interactions with reserpine and iproniazid, and its stimulation of some nerve endings, it has been suggested that it may function as a transmitter-substance, perhaps mediating the activity of central fibers. There is as yet, however, no direct evidence that 5-HT is released after electrical stimulation of nerve fibers.

A second role was ascribed to 5-HT, as a result of the highly specific antagonism between LSD and 5-HT. It was thought that since LSD antagonizes the peripheral effects of 5-HT, its central action may also be due to this antagonism. On the basis of the alleged similarity of the LSD state to psychosis, it was proposed that schizophrenia is caused by disturbed 5-HT metabolism. The action of reserpine in depleting 5-HT stores and tranquilizing psychotics seemed to fit this picture. But many lines of evidence oppose this concept: (1) compounds like BOL were found to be potent 5-HT antagonists

but had no central effects (Cerletti and Rothlin, 1955); (2) several compounds, like mescaline, have potent psychic effects similar to those of LSD, but do not antagonize 5-HT (Gaddum, 1958); (3) chlorpromazine also antagonizes peripheral 5-HT effects, but is the most effective antidote to the central effects of LSD (Gaddum, 1958); (4) persistent attempts to detect differences in the urinary indole metabolites or tissue concentrations of 5-HT between psychotics and normals have failed (Sourkes, 1962; Smythies, 1960).

It is possible that some more refined version of the theory may yet be accepted. Wooley and Campbell (1962), for example, have suggested that an excess of brain 5-HT causes agitation, whereas a deficiency causes depression. In general, this problem of the biochemistry of psychosis is extremely complex. One need only consider the fact that most studies attempting to detect biochemical differences between psychotics and normals assume psychiatric diagnosis, which is notoriously unreliable, as an accepted criterion. A more detailed discussion lies outside the scope of this paper. One interesting variant of the theory may be mentioned here, viz. that changes in 5-HT level are not characteristic of "schizophrenic" persons, but of their psychotic "episodes." Himwich (1963) has reported that increased excretion of indole metabolites (5-HIAA, tryptamine and 3-indoleacetic acid) are seen just before and during periods of "psychotic activation" in individual patients, whereas lowered rates are observed in "tranquil" periods (measured by ratings of word behavior). These findings, if confirmed by more controlled observations, are of extremely great potential importance. In any case, the question of the mechanism of action of psychedelic drugs is really separate from the problem of possible metabolic defects in psychosis.

(b) *Effects of psychedelic drugs.* This section will be divided into four parts: (i) effects on indole metabolism, (ii) effects on brain levels of 5-HT, (iii) effects on pharmacological actions of 5-HT, and (iv) interaction with reserpine.

(i) *Effects on indole metabolism.* Rodnight and McIlwain (1956) reported 100 μg of LSD caused a fall in the urinary excretion of serotonin in the following 24 hours. Sankar (1962) reported that both LSD and BOL increased the levels and the turnover of 5-HT in the liver and kidney of rabbits. LSD increased the level of 5-HT in the heart, whereas BOL and chlorpromazine decreased it. Wiseman-Distler and Sourkes (1962) found that psilocybin has no effect on 5-HT metabolism, but that psilocin decreases the rate of breakdown of 5-HT *in vitro; in vivo,* this effect was masked partly by the antagonism of psilocin to the pressor effect of 5-HT, which temporarily increased the rate of breakdown. Both LSD (Sankar *et al.,* 1962) and psilocybin (Delay *et al.,* 1959) increase urinary excretion of 5-HIAA, indicating that the turnover of 5-HT has been accelerated. DMT also increases urinary excretion of 5-HIAA (Szara, 1957).

(ii) *Effects on brain levels of 5-HT.* According to Bogdanski *et al.* (1958), 5-HTP caused LSD-like effects in animals together with a rise in CNS levels of 5-HT; LSD intensified this action. Brodie *et al.* (1956) reported that pre-treatment with LSD did not affect the release of 5-HT by

reserpine, indicating that LSD interacts with 5-HT in its liberated form. This finding was confirmed by Carlsson *et al.* (1957). In a series of studies by Sankar and his colleagues (Sankar *et al.,* 1961a, b; Sankar *et al.,* 1962a), it was shown that in rabbits given LSD either alone or after labelled 5-HTP, there was an overall increase of metabolism of 5-HT (indicated by the amount of radioactivity) in all parts of the brain except the cerebrum, and the levels of 5-HT found were increased 40% except in the cerebrum. BOL (a non-hallucinogenic 5-HT antagonist) decreased brain levels of 5-HT, though on visceral tissues it had the same effect as LSD. Chlorpromazine also decreased the 5-HT content of the brain. Giarman and Shanberg (1961) and Freedman and Giarman (1962) have reported elevation of whole brain 5-HT in the rat after LSD, as early as ten minutes after injection and returning to normal after 24 hours. If LSD was given after reserpine, the depleted levels of 5-HT were doubled by a single dose of LSD. Thus, LSD does not prevent the depletion of 5-HT stores by reserpine, but apparently facilitates binding and stimulates repletion. Freedman and Giarman (1962) also report unpublished studies indicating that LSD given after reserpine in man prolongs the usual psychological effects. The effects of LSD in elevating brain levels of 5-HT are not due to general stimulation, since amphetamine or electroshock after reserpine had no effect on 5-HT. UML, the most potent peripheral antiserotonin lysergic acid derivative, did not affect brain level of 5-HT, indicating that the peripheral and the central interactions of LSD and 5-HT are independent. BOL induced a rise in 5-HT levels, but it was very slight. By centrifugation of brain homogenates it was shown that the increase after LSD occurred primarily in the particulate fractions.

The ability to elevate brain levels of 5-HT seems related to hallucinogenic potency in man, and the duration of this effect seems to be the same as the period of tolerance induced by a dose of LSD (72 hours). The monoamine oxidase inhibitor, iproniazid, also elevates brain-levels of 5-HT, but does so by a different mechanism, viz. by preventing breakdown to 5-HIAA.

(iii) *Effects on pharmacological actions of 5-HT.* The standard oxytocic (uterus-contracting) response to 5-HT is abolished by LSD (Gaddum *et al.,* 1955), although the response to oxytocin (the pituitary hormone) is not abolished. Harmine and harmaline also antagonize this response (McIsaac *et al.,* 1961). Slaytor *et al.* (1959) reported that two metabolites of LSD, collected from bile, also exhibit the 5-HT antagonism on the uterus. Costa (1956) and Delay and Thuillier (1956), however, record that only high doses of LSD antagonize the 5-HT effect on the rat uterus, whereas in low doses, corresponding to those exerting psychological effects in man, LSD potentiates the effect of 5-HT on the uterus. Mescaline and amphetamine also have a potentiating effect on this action of 5-HT.

The vasoconstrictor action of 5-HT on pulmonary vessels, on hindleg vessels, and on rabbit ear is antagonized by LSD, although in the latter preparation, LSD itself has a vasoconstricting effect at higher dosages. LSD does not antagonize the vasoconstrictor action of epinephrine or norepinephrine (Ginzel and Kottegoda, 1953; Gaddum *et al.,* 1953; Savini, 1956). Meier *et al.*

(1957) showed that chlorpromazine and acetylcholine also inhibit the vasoconstrictor effect of 5-HT; and Salmoraghi *et al.* (1957) showed that there are considerable species differences for this effect of LSD.

LSD potentiates the relaxing, curare-like effect of 5-HT on the dorsal muscle of the leech (Poloni, 1955a) and the similar effect of 5-HT on the isolated rat duodenum (Levy and Michel-Ber, 1956).

The bronchoconstriction produced by 5-HT in isolated lungs is antagonized by LSD (Gaddum *et al.*, 1953; Bhattacharya, 1955). This effect is highly specific, since LSD does not inhibit the bronchial effect of ACh or histamine (Konzett, 1956a).

5-HT increases capillary permeability, and this effect is antagonized by LSD (Morsdorf and Bode, 1959; Halpern *et al.*, 1959).

Intra-arterial injection of 5-HT in vagotomized cats causes an initial increase and subsequent decrease in the flexion reflex; this effect was blocked by LSD (Slater *et al.*, 1955).

5-HT exerts an antidiuretic effect in rats, which is prevented, but not reversed, by LSD (Del Greco *et al.*, 1956).

Histological changes brought about by chronic 5-HT administration are prevented by LSD (Sacchi *et al.*, 1957). 5-HT given intracisternally to dogs produced catalepsy; this effect is prevented by pre-treatment with LSD, but not reversed by LSD given after 5-HT. These, and other results, suggest that LSD inhibits the effects 5-HT produces if given before, but is unable to displace 5-HT once it is fixed to receptor sites (Sacchi *et al.*, 1955; Fazio and Sacchi, 1959). Ulcers in the stomach and intestines of rats, produced by 5-HT, are prevented by LSD (Wilhelmi and Schindler, 1959).

Perris (1959) showed that LSD did not affect neuromuscular transmission and did not affect the anti-curare effect of 5-HT.

Mathies and Sziegoleit (1959) showed that 5-HT prolonged the effect of acetylcholine on the eyelid (reflex closure), although it did not evoke this response alone; this effect of 5-HT was abolished by LSD. The authors suggested that 5-HT does not act as a transmitter-substance but perhaps regulates the sensitivity of certain cholinergic synapses.

On the heart of the clam *Venus mercenaria*, 5-HT in extremely minute concentrations has an excitatory action. LSD produces a similar effect (Welsh, 1957).

A number of studies of the interaction between 5-HT and LSD on the gross behavioral level have been reported. Although not at present attributable to biochemical mechanisms of LSD, they are discussed here, since they do shed further light on the central effects of 5-HT and LSD.

5-HT prolongs the duration of sleep induced by hexobarbital and other barbiturates (Shore *et al.*, 1955a; Cahn *et al.*, 1956a,b), and LSD suppresses this effect. LSD alone exerts no effect on hexobarbital sleeping-time. Reserpine also prolongs the hypnotic effect, and this effect of reserpine is antagonized by LSD (Shore *et al.*, 1955b). Salmoiraghi and Page (1957), however, report that LSD, along with bufotenine, mescaline, ibogaine and BOL, enhances the effect of 5-HT on hexobarbital hypnosis, and antagonizes the effect

of reserpine. Taeschler (1956) found that, whereas both LSD and BOL inhibited the pentothal potentiation of 5-HT, only LSD inhibited the pentothal potentiation of reserpine. And further, BOL differed from LSD in the absence of sympathetic stimulation. He suggested, therefore, that the LSD antagonism to reserpine is based on sympathetic stimulation (norepinephrine cycle) rather than 5-HT. Brown (1957) studied the effects of a number of drugs on (1) hexobarbital sleeping-time, and (2) amount of spontaneous activity of mice in groups. 5-HT and reserpine both potentiated sleeping-time, and these effects were antagonized by LSD. 5-HT and reserpine both depressed spontaneous activity; LSD reversed the effect of 5-HT but did not change the effect of reserpine. This suggests that different central mechanisms are involved in the effects of reserpine. One possibility is that the effect of reserpine on hexobarbital hypnosis is due to release of 5-HT, and hence is antagonized by LSD. The suppression of spontaneous activity may, however, be mediated by the release of norepinephrine, which is unaffected by LSD. The dosages of LSD which are capable of reversing the effect of 5-HT, do not themselves have any effect on the amount of spontaneous activity. Iproniazid, which increases levels of endogenous 5-HT, also prolongs hexobarbital sleeping-time — more than 5-HT or reserpine, but this effect is not changed by LSD, indicating that perhaps this effect of iproniazid is not related to 5-HT. On the other hand, the depressant effect of iproniazid on spontaneous activity is reversed by LSD.

It can be seen from this study and others, that the central effects of 5-HT are quite complex, and that, at the present time, to attribute the effects of LSD to its 5-HT antagonism is not very informative, since the role of 5-HT is so unclear.

Two reports have claimed that 5-HT affects the LSD reaction in humans. Poloni (1955b) reported that 5 mg of 5-HT accelerated the onset of 50 μg of LSD, or of mescaline, potentiated the hallucinogenic effect and shortened the duration. Montanari and Tonini (1955) reported that 5-HT, given at the height of the LSD reaction, antagonized the LSD effect. These findings have not been repeated by other investigators.

Of the other psychedelic drugs, mescaline and the benzilate esters have no anti-5-HT effect. Borsey *et al.* (1961) reported that DET is a serotonin antagonist *in vivo* and *in vitro*. Delay *et al.* (1959) reported that psilocybin displaces 5-HT, analogously to reserpine. Barlow (1961) reported that BOL, DMT and two DMT derivatives antagonize the effect of 5-HT on guinea pig liver. According to findings by Stacey (1961), both tryptamine and 5-HT are taken up for storage by human platelets, but competitively. Wooley and Campbell (1962) report both serotonin-like and antiserotonin effects of psilocybin and psilocin.

(iv) *Interaction with reserpine.* As stated before, reserpine releases or "unbinds" both 5-HT and catechol amines from their stores, or "bound" forms. Reserpine exerts its prime action against the bound form of 5-HT, so that the proportion of free amine is increased. The changes in behavior observed by Himwich (1963) were correlated with concentrations of free 5-HT.

LSD does not prevent the release of 5-HT by reserpine (Brodie *et al.*, 1956); nor does it prevent the release of catecholamines from the adrenal medulla caused by reserpine (Mirkin, 1961). Neither LSD, chlorpromazine, or phenobarbital causes release of 5-HT from blood platelets; only reserpine and related rauwolfia alkaloids do so (Carlsson *et al*, 1957). Shore and Brodie (1957) reported that rabbits given iproniazid with reserpine showed effects similar to those of LSD, and DeMaar *et al.* (1960) reported similar results in a very small number of human subjects.

In the following studies, LSD and reserpine have been found to exert antagonistic actions: the studies already quoted on the LSD antagonism to barbiturate potentiation of reserpine; a study by Hammond (1956) in which LSD reduced gastric secretion stimulated by reserpine; Elkes (1956) reported that reserpine counteracted the decrease in the uptake of radioactive iodine by the thyroid gland produced by a large dose of LSD; Lessin and Parkes (1957) reported that LSD counteracted the hypothermia caused by reserpine, but this effect was not specific, since amphetamine has a similar effect. Conversely, however, reserpine given prior to LSD, potentiated the hyperthermia due to LSD (Elder and Shellenberger, 1961). Giberti and Gregoretti (1955) report that several days' pre-treatment with 7-12 mg reserpine antagonized the effects of 60-150 μg of LSD in patients.

A number of studies have been reported, however, showing enhancement of LSD effect after reserpine. Thus, Isbell (1956) reported that reserpine before LSD either had no effect or intensified the LSD reaction in humans. Glow (1959) also reported that the "behavioral disturbances" induced in rats by 60-250 μg/kg of LSD were intensified and prolonged by reserpine. Reserpine also enhanced the effect of LSD on the time taken by rats to climb ropes (Winter and Flataker, 1957). In cats, the characteristic rage reaction elicited by 400 μg/kg of LSD was enhanced by pre-treatment with reserpine (Elder *et al.*, 1957). The rise in body temperature produced by LSD is enhanced by reserpine (Horita and Gogerty, 1957; Eichenberger and Friolet, 1957; Elder and Shellenberger, 1961), and diminished by BOL (Horita and Gogerty, 1958).

Summarizing this section on the relation of psychedelic drugs to 5-HT (on which the evidence is by no means consistent or clear), one could tentatively propose the following conclusions:

(1) LSD, and perhaps the tryptamine derivatives, antagonize most of the peripheral effects of 5-HT; in some systems LSD exerts effects like those of 5-HT.

(2) LSD also antagonizes some of the central (behavioral) effects of 5-HT.

(3) LSD decreases the urinary excretion of 5-HT; but both LSD and the tryptamines increase the urinary excretion of 5-HT metabolites, like 5-HIAA.

(4) The peripheral and central interactions of LSD and 5-HT are independent of each other.

(5) LSD increases the rate of turnover of 5-HT in the body.

(6) LSD increases brain-levels of 5-HT, in all parts of the brain except the cerebrum; this increased brain 5-HT seems to last about as long as the period of tolerance to LSD.

(7) The effect of reserpine in releasing 5-HT from its bound form is not affected by LSD.

(8) LSD counteracts some of the central effects of reserpine, but it is possible that reserpine before LSD potentiates the effects of the latter.

(9 It is likely that one of the effects of LSD is to facilitate the binding or repletion of 5-HT in its stored form.

(5) *Miscellaneous biochemical changes induced by psychedelic drugs*

In this section a number of studies of specific biochemical effects of psychedelic drugs will be reviewed. They will not be discussed extensively, since their significance for the central effects of the drugs is unclear.

Hollister and Hartman (1962) noted an increase in plasma free fatty acids after LSD, mescaline and psilocybin. This is believed to reflect central sympathetic stimulation, since a similar rise occurs during stress or after injection of norepinephrine (Sourkes, 1962).

DeRopp and Snedeker (1961) reported that 240 mg/kg mescaline increased the level of free alanine in rat brain extracts, but Denber *et al.* (1962) observed that mescaline given to patients caused a decrease in total amino acids, and that severity of reaction to mescaline was correlated with extent of decrease in amino acid level.

Mescaline produces hypoglycemia, hence mescaline combined with insulin is more toxic than mescaline alone. Mescaline (500 mg) causes a transient disturbance in liver function, as shown by the hippuric acid test, whereas LSD (130 μg) does not. Another, more sensitive test, does show some disturbance of liver function after LSD (Fischer *et al.*, 1951).

Sankar *et al.* (1961c) reported that LSD and BOL inhibit glutamic acid dehydrogenase, thus preventing the breakdown of glutamic acid. Glutamic acid is believed to have a nonspecific stimulating effect on the sympathetic nervous system, causing an increase in blood sugar and plasma epinephrine levels; it has been used therapeutically in epilepsy and mental deficiency. Konzett (1956b) has reported that LSD causes hyperglycemia due to sympathetic stimulation, which can be blocked by hexamethonium.

Missere *et al.* (1961) found that LSD alters the electrophoretic protein pattern of liver extracts; presumably this change reflects the activities of the liver in detoxifying LSD. The change was reversible within 24 hours. Krawczynski (1961) reported that 250 μg/kg of LSD reduced the specific activity of cerebral proteins. BOL and 5-HT had similar effects.

Kar and Boscott (1956) and Soderberg (1958) have reported that LSD decreases the uptake of iodine in the thyroid gland. Iodine is used in the synthesis of the thyroid hormone, which regulates oxidation processes in the body.

The rise in body temperature caused by LSD and its relation to reserpine has already been mentioned (Eichenberger and Friolet, 1957).

Waser and Itzbicki (1959) found that LSD decreased the plasma concentration of histamine in rats, whereas chlorpromazine and reserpine increased it. Cates *et al.* (1962) similarly noted that LSD decreased levels of histamine in the heart and brain of rabbits. Histamine is widely distributed throughout the body and has effects on many systems, although its precise role or function is not known. It is released during anaphylactic shock, by snake venoms, toxins and stress-producing agents. Hence, a decrease in histamine concentrations presumably is part of a general physical stress reaction.

Härkönen and Konttinen (1958) reported, after 40 μg/kg LSD in the guinea pig, an increase in the white blood cell count of neutrophils and decrease in eosinophils. These changes resemble those produced by non-specific stress.

Klies *et al.* (1957) have reported that 100 μg LSD in humans exert a marked antidiuretic action (inhibiting urine formation) lasting approximately one hour. They suggest that this is due to hypothalamic stimulation resulting in the release of antidiuretic hormone.

Krivoy (1957) and Smith and Walaszek (1961) reported that LSD potentiated the stimulatory action of substance P on isolated guinea pig ileum, and inhibited destruction of substance P by brain extracts. The role of substance P, a polypeptide with stimulating effects on smooth muscle, is a matter of dispute; it is unevenly distributed in the nervous system with high concentrations in the hypothalamus. It has been suggested that it acts as (1) a transmitter-substance for somatic afferents, or (2) a central transmitter of inhibitory neurones.

Berde and Cerletti (1956) and Cano Puerta (1959) have reported that LSD causes darkening of the skin of the guppy fish, due to expansion of the melanophores. This effect is antagonized by 5-HT. A similar effect on the melanophores of the toad was noted by Burgers *et al.* (1958), who claimed, however, that the effects are indirect, via inhibition of the melanophore hormone. The effect of BOL on the melanophores was more powerful than that of LSD.

Geiger (1957), in a study of the effects of LSD on cortical brain cells in tissue culture, concluded that it produced the following effects: moving away of granules from the nuclear membrane and their dispersal throughout the cytoplasm; accelerated production and extrusion of nucleoproteins from the nucleolus into the cytoplasm; contraction of whole neuron; motility changes in synaptic areas. Miura *et al.* (1957) found that LSD caused growth of nerve cells, whereas chlorpromazine caused degeneration; movements of neuroglia cells were accelerated by LSD and 5-HT, inhibited by chlorpromazine, and unaffected by reserpine. Fischer *et al.* (1962) have reported that nervous tissue stimulated with LSD absorbs a purple dye more than non-excited tissue. Differences in the ability of drugs to induce such absorption, or in the affinity to certain proteins, is related by the authors to metabolic rate, and to mechanisms of physiological time and temperature regulation. These, however, are speculations.

V. Summary and Discussion

One conclusion that emerges from this review of the literature is that there is as yet no definite agreement as to the mode of action of psychedelic substances at the biochemical level. Many findings have been accumulated, but so far no theory has been put forward to integrate them into an adequate explanation. The major conclusions will be summarized and discussed here in the light of various theories that have been suggested.

(1) *Chemical structure and metabolism*

Studies of "structure-activity" relationships, in which the chemical compound is altered systematically and the changes in pharmacological activity are noted, have shown that for most of the psychedelic substances the one most frequently studied or used is not necessarily the most active compound of the series. For historical reasons, a particular compound may be frequently used, even though one of its derivatives may be more potent. Metabolic studies have confirmed that often the compound administered is converted to some other form. Thus, mescaline is converted to its aldehyde and alcohol forms, which are more potent. Psilocybin is probably reduced to psilocin. DMT and DET are converted to their 6-hydroxy analogues; in this form, they are six times as potent. The only exception is LSD, which is the most potent of its group. Several other lysergic acid derivatives have psychic effects but require higher dosages. Hallucinogenic potency has been shown to be directly related to the number of ethyl groups at the amide-N. Changes in the 2-position of the indole ring completely abolish the psychic effects. Thus, at least two features of the LSD structure are important in its effects: the diethylamide side-chain, and the indole ring.

It is possible that this may correspond to a dual action at pharmacological receptor sites. One part of the compound may trigger the cell's response, another part may serve to hold or "block" the substance in its position, preventing its diffusion or breakdown.

Although the exact metabolic fate of the psychedelic substances is not yet known, the available evidence indicates that they are metabolized mainly in the liver and kidney, and that relatively small amounts enter the brain. This suggests that the central changes form part of some kind of chain-reaction which is precipitated by the drug.

The compounds differ in the degree to which they are metabolically transformed or excreted unchanged. LSD is almost completely metabolized, mescaline and psilocybin are excreted about 25-30%, and 90% of Ditran is excreted unchanged. Such differences in metabolic fate may help to explain differences in time of onset and in duration of effect among the various drugs.

Finally, evidence has recently been found which suggests that certain substances occurring naturally in the body, i.e., tryptamine and serotonin, may be converted to psychedelic analogues by naturally occurring enzymes. One of these, bufotenine, has been found in trace amounts in normal human urine.

These findings may be the beginning of a biochemical analysis of normally occurring fluctuations in states of consciousness.

(2) *Carbohydrate and phosphate metabolism*

One early theory was that of Mayer-Gross and his associates, who proposed that LSD interferes with glucose metabolism, mainly on the basis of the *in vitro* oxidation of glucose by brain tissues stimulated with LSD. They suggested that LSD stimulates glucose oxidation, though studies by other investigators failed to support their findings. The only study with human subjects reported no effects on glucose utilization. Studies with chronic administration in animals have shown marked interference with carbohydrate metabolism. It is possible that LSD has different effects on glucose oxidation in different parts of the brain. Since the oxidation of glucose underlies all neural activity in the brain, it is likely that it is affected to some degree by any agent or stimulus which alters consciousness radically; it would seem unlikely, on present evidence, that direct interference with glucose metabolism is the primary mechanism of LSD.

Hoagland and his associates put forward a theory linking disturbances in phosphate metabolism to schizophrenia and LSD-states. The evidence indicates that, after LSD, urinary inorganic phosphates are decreased, but blood levels of inorganic phosphates are increased. Since ATP is centrally involved in all energy-exchange processes in the nervous system, it is difficult to determine whether the decrease in phosphate turnover would be considered a cause or a consequence of the action of LSD.

(3) *Acetylcholine*

Acetylcholine is a transmitter-substance which mediates the activity of the parasympathetic autonomic nervous system, and possibly some central activity as well. Although the evidence is not consistent, it indicates that the effects of Ditran are probably due to its inhibition of acetylcholine. THA, which is an anticholinesterase (i.e., increases the production of endogenous acetylcholine), is a specific antagonist: it antagonizes the effects of Ditran, but not of LSD or Sernyl. However, the precise function of acetylcholine in the central nervous system is not clear.

LSD, *in vitro,* has an inhibitory effect on some cholinesterases, thus increasing levels of ACh. The precise significance of this action cannot at present be evaluated.

(4) *Catecholamines*

Norepinephrine is the transmitter-substance mediating sympathetic activity of the autonomic nervous system. One early theory, put forward by Rinkel, was that LSD acts by interfering with epinephrine metabolism and the pituitary adrenal stress system. The evidence indicates, however, that there are no significant effects of LSD on plasma levels of catecholamines.

Some of the pharmacological actions of epinephrine and norepinephrine are antagonized or facilitated by LSD and other psychedelics.

Hoffer's theory that LSD acts by increasing the levels of the epinephrine metabolites adrenochrome and adrenolutin, has failed to gain acceptance on at least two grounds: first, these substances cannot be found in the body; second, they are not psychotomimetic.

(5) *Serotonin*

The role of serotonin in the mechanism of the LSD reaction, first emphasized by Wooley, has been somewhat obscured by the attempt to explain schizophrenia by the same mechanism. The findings relating LSD and 5-HT are summarized in Section IV above. In peripheral organ systems, LSD antagonizes most of the effects of 5-HT, although it mimics or enhances some of them. In the central nervous system, LSD increases levels of 5-HT in all parts of the brain except in the cerebrum. LSD may be regarded as an *antimetabolite* of serotonin.

> "An antimetabolite is a chemical substance which resembles in chemical structure an essential metabolite. The essential metabolites are compounds such as serotonin, norepinephrine, acetylcholine, which occur naturally in living creatures and which are necessary for specific normal life processes. . . . The antimetabolite is a molecule shaped sufficiently like the metabolite so that it can also combine with the active centre of the enzyme or receptor. . . . If an essential metabolite is used in an organism for more than one reaction, then it may turn out that a given antimetabolite of it may act as an antimetabolite in one or more of these reactions, but may act like the metabolite in another one of these reactions. . . . One understands this sort of behavior by saying that in some tissues the serotonin receptors are not as specific as in others" (Wooley, 1962).

In other words, since the effects of 5-HT in the body are varied, one cannot make direct inferences from the relation of LSD to 5-HT in one system, to its role in other parts of the body.

The most direct evidence for the idea that the interaction of 5-HT and LSD is involved in its central effects, comes from the studies in which brain levels of 5-HT are measured at different intervals after injection of LSD. LSD increases levels of 5-HT in all parts of the brain, except the newest part — the cerebrum. BOL, the non-active, closely related lysergic-acid derivative, decreases brain levels of 5-HT; so does chlorpromazine, which antidotes the psychic effects. The elevation of 5-HT levels lasts about as long as the period of tolerance after LSD. The mechanism by which LSD elevates 5-HT levels was suggested by Freedman to be the repletion or binding of free 5-HT into its bound form.

Although the functions of 5-HT in the brain are not established, if it acts as a transmitter-substance for subcortical brain systems, then this effect of LSD is equivalent to an enormous facilitation of neural activity in these areas. There are, however, other possible interpretations of these findings — e.g., the elevation in levels of 5-HT may be part of a general stress reaction.

Elevation of 5-HT levels in the brain is one effect of LSD. Whether it is the primary mechanism by which LSD exerts its psychic effects, is not certain. This interaction with serotonin is not found with all drugs exerting psychedelic effects: neither mescaline nor Ditran has this effect. Nor do all drugs which elevate brain levels of 5-HT have psychedelic effects (e.g., iproniazid).

In addition to its effects on the major neurohormones of the body (acetylcholine, norepinephrine, serotonin), there is evidence that LSD also affects histamine and substance P, two other candidates for the role of transmitter-substances. It is clear that LSD affects a very large variety of biochemical substrates.

The discussion has centered mainly on LSD, since this has been most exhaustively studied. From the preliminary evidence, the tryptamine psychedelics seem to act in essentially the same way. The benzilate esters, on the other hand, seem to act primarily through acetylcholine. The mode of action of mescaline is still rather obscure.

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