The PSYCHEDELIC REVIEW

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EDITORIAL

The age-old issue of freedom *versus* control has entered a new stage in our era. Many critics have described and denounced the prevailing external control of our activities and resources, and particularly the ideological indoctrination and psychological manipulation to which we are subject through the mass media. Modern science has discovered and developed a vast repertoire of techniques which can be used to control and manipulate mind and behavior. The question: "Who controls the controller?" becomes especially crucial when man's freedom of consciousness is at stake.

We can no longer accept the notion of a value-free science or espouse a naive optimism with regard to scientific and technological progress. We need to complement our technical skill in controlling the external world with a corresponding development of our inner resources. The adulation of sheer technique, scientific and economic-technological accomplishments, organizational skill and bureaucratization lead to the sacrifice of the unique individual and to the rejection of the validity of subjective experience. The intuitive, comprehensive, direct awareness of the essential unity of phenomena, and a sense of the interrelatedness of self and world, have been neglected and allowed to suffer. Cessation of function leads to atrophy of organ.

There are, however, many groups within our culture who are trying to call man back to himself. In psychology, for instance, there is a trend which pleads for a "humanistic revolution," away from behaviorism and biological-drive models toward a consideration of values and self-directed goals in human motivation. There is the powerful existential orientation both in philosophy and in psychiatry, which is beginning to make an impact in our society with its call for authentic existence, personal freedom, individual responsibility and self-determination. The unique individual is being rediscovered and the legitimacy of subjective experience affirmed.

Such a return to an inward orientation is not by any means new. Throughout history there have been attempts to reestablish the kind of direct relationship to the world which is celebrated in the myths of Paradise. From Plato's parable of the cave to Hesse's

Journey to the East, Western philosophers have written of experiences which go beyond our everyday shadowy perception and disclose with startling force a direct vision of reality. The quest for this experience and the awareness of its implications is far more highly developed in the East than in the West; hence the program has often been stated in terms of unifying the Eastern and Western approaches. Discerning men have stressed over and over that we have much to learn from the two great cultures of the East: India with its highly differentiated practical understanding of different states of consciousness; and China with its superbly developed sensitivity to the complexities and nuances of social interaction.

The synthesis of consciousness-expanding substances, which we regard as one of the most outstanding achievements of technological society, has now provided us with a means for transcending and overcoming many of the distortions which operate in the very society that has brought about such substances. It is now possible to affirm the general character of our social technocracy without succumbing to its totalitarian demands. The creation and furtherance of internal freedom for large numbers of people through the intelligent use of psychedelic substances are now a practical reality. Julian Huxley has predicted that the further evolution of man will not be biological but will take place in the noölogical or psychic dimension. He has drawn an analogy between the exploration of outer space and the exploration of inner space on the basis of the recent advances in the pharmacology and chemistry of consciousness.

These modern substances are but the synthetic equivalents of mind-changing plants and potions that have been known for thousands of years. Through them we now have powerful aids on the inward journey, a new key to the doors of perception, new access to the ancient problems of identity and reality. We therefore take as our motto the saying attributed to Heraclitus: "You would not find out the boundaries of the psyche, even by traveling along every path; so deep is its measure and meaning."

A systematic study needs to be made of the various ways, ancient and modern, which man has used to expand his consciousness. Many religions have used sacred foods in their central rites. In this issue, R. Gordon Wasson's article on the sacred mushroom of Mexico tells of his rediscovery of this central element in Mexican religious life. In subsequent issues we hope to publish reviews of our present knowledge of naturally occurring psychedelic substances and plants.

What can modern science tell us about consciousness-expanding techniques? A review of the literature on the pharmacology of the psychedelic substances appears in this issue. Since this literature is vast, only studies on the chemical and biochemical level are reviewed; subsequent papers will review physiological and psychological aspects. Others are planned on the effects of deprivation on consciousness — fasting, sensory isolation and sleep deprivation. Hypnosis, autogenic training, yoga breathing, zen meditation are other examples of Western and Eastern methods for altering consciousness and controlling the mind.

Historical studies are needed tracing the evolution of interest in altered states of consciousness and the role this has played in the evolution of culture. Gottfried Benn's essay in this issue is a first attempt to sketch a historical picture. Other essays are planned on the history of psychiatric research with psychedelic substances; on changing cultural attitudes toward mysticism and psychosis; and on related themes.

Philosophical studies exploring the epistemological and metaphysical implications of increased flexibility of consciousness are needed. Alan Watts' essay on the philosophical problems arising out of the possibility of increased control over mind delineates one of the major themes. Psychological studies are planned, attempting to explore problems in personality structure, motivation and perception, using insights derived from psychedelic experiences. Also, descriptions of psychedelic experiences in psychological terms and attempts to devise new models for communicating altered states of consciousness will be discussed. We present, in this issue, a summary of four recent studies of the subjective after-effects of psychedelic drug-experiences. Original research reports and theoretical articles on different aspects of psychedelic research will appear in future issues.

In the lives and work of artists and writers and in the aesthetic sphere in general, visionary experience has often played a significant role. In the 19th Century French Symbolist movement, for example, the consumption of hashish was pervasive and influential. Many individual artists from Thomas De Quincey to William Burroughs have used drugs in one way or another to shape their creative vision. Studies of the associations between drugs and creativity are anticipated.

The classical literature describing the interior journey will be discussed and reviewed. In this issue we present a brief extract from Plato on the use of consciousness-altering drugs, where he proposes a kind of psychological immunization. This idea has much relevance to the current controversy over the "psychotomimetic" property of psychedelic substances.

Each issue will also include publication of one or two subjective accounts of transcendent experiences, spontaneous or induced. These will come from a wide variety of sources, from artists, writers, scientists, laymen, students and teachers. The aim is to make available to the general reader first-hand accounts of the kinds of experiences which the articles in this journal discuss. George Andrews' "Annhilating Illumination" is an account in poetic form of an experience with mescaline.

Our lead article, by Gerald Heard, appears in *Horizon Mayazine* [Vol. V, No. 5, May, 1963] and is reprinted by permission. The accompanying declamatory statements, "pro" and "con," by Dr. Sidney Cohen and the Southern California Psychiatric Society, respectively, are omitted.

Mr. Wasson's article, "The Hallucinogenic Fungi of Mexico: An inquiry into the Origins of the Religious Idea among Primitive Peoples," is presented in its complete version, except for the Appendix listing the Mexican hallucinogenic mushrooms. It is taken from the Harvard *Botanical Museum Leaflets,* Vol. 19, No. 7, 1961.

The Editors invite suggestions and ideas for *The Psychedelic Review.*

STATEMENT OF PURPOSE

Recent years have witnessed a widespread increase of interest in the alteration and expansion of consciousness. The discovery of the psychedelic substances such as LSD, psilocybin and mescaline has been a major contributing factor in this development. Scientists and scholars from diverse areas as well as many laymen have recognized the importance of these substances as powerful tools for the exploration of consciousness and the production of visionary experiences. The effects of psychedelic substances pose fascinating problems for medical and psychological research and have far-reaching implications for many issues in the sciences and the humanities.

The Psychedelic Review is designed to serve as a forum for the exchange of information and ideas about these issues. It will publish original research reports, scholarly and historical essays, outstanding phenomenological accounts of spontaneous or induced transcendent experiences, and reviews of relevant pharmacological and other literature.

The journal is published and sponsored by the International Federation for Internal Freedom (IFIF), an organization whose purpose is "to encourage, support and protect research on psychedelic substances." The basic long-range goal of IFIF is to work to increase the individual's control over his own mind, thereby enlarging his internal freedom. The present journal is an attempt to contribute to the realization of this long-term objective.

However, the views expressed in articles published by *The Psychedelic Review* are solely the authors' and do not necessarily reflect the opinions of the editors or of IFIF. Conversely, the contributors do not necessarily subscribe to the principles and purposes of IFIF.

A word about the title. The substances discussed here have been referred to by many different names, including "psychotomimetic," "hallucinogenic," "consciousness-expanding" and others. The term "psychedelic," first proposed by Humphrey Osmond, is derived from the Greek and means "mind-manifesting." Strict compliance with linguistic protocol would have dictated the usual intervening vowel (*o*), but the present orthography is gaining wider acceptance.

"Can This Drug Enlarge Man's Mind?"

Narcotics numb it. Alcohol unsettles it.
Now a new chemical called LSD has emerged with phenomenal powers of intensifying and changing it — whether for good or ill is a subject of hot debate.

GERALD HEARD

Since earliest times man has felt impulses to rise above his everyday self and achieve either some higher insight or some release from mundane concerns — or both. Western saints and Eastern mystics have subjected themselves to strenuous spiritual exercises; others, less dedicated, have resorted to chemical aids, from the ceremonial wine of the ancients and the opiates of the Orient to the sacramental peyotl plant of Aztec tribes and the social stimulants of our own day.

In our time, moreover, psychologists and other students of human perceptions, from William James to Aldous Huxley, have tried out on themselves certain experimental drugs in an effort to induce states that would lend extraordinary lucidity and light to the mind's unconscious and creative processes — possibly even assistance to these. Today these newer drugs — mescaline, psilocybin, and the latest and most potent of them, Lysergic Acid Diethylamide, or LSD — are spreading so widely on a "research" basis that major questions are arising as to their effects and proper use.

Their enemies call them "mind-distorting" drugs, and warn that their therapeutic values are unproven, that they may upset even a normal person, and that they are already being abused for "kicks." Their proponents prefer to call them "consciousness-changing" agents, and argue that in selected cases, for individuals of strong mental and creative powers, LSD may widen their window on the world and on themselves as well. On the evidence so far, both sides seem agreed that LSD is not habit-forming; numerous takers of it report that the experience is a strenuous and exhausting one, to be repeated only after much thought.

Should man in any case put such a potentially dangerous substance into his system? It is claimed for LSD that it is far less toxic

than alcohol, tobacco, or caffeine. At the same time one of its leading students and advocates, Dr. Sidney Cohen remarks: "It is quite possible that LSD attracts certain unstable individuals in their search for some magical intervention." Can trance-like insight produced by chemicals be the source of higher wisdom and creativity, like a kind of Instant Zen? This remains unproven — especially since so many persons coming back from LSD can describe their experience only as indescribable.

One of those who can describe it best is the writer of the following article, the distinguished philosopher Gerald Heard, author of The Eternal Gospel, The Doppelgangers, Is God in History?, *and other books, and a leading student of psychic research.*

What will men of the future consider the greatest achievements of our time? Releasing hydrogen energy? Putting a man on the moon? Extending the average human life to a century or more?

Last year Dr. Glenn T. Seaborg, Chairman of the United States Atomic Energy Commission, gave his forecast of what he thought might be our most revolutionary discoveries or advances in the next generation. Addressing the graduating class of Northern Michigan College in his home state, he asked his listeners to project themselves forward to their thirtieth reunion in 1992, and selected fifteen items on which to speculate. Fourteen of these — ranging from the realizing of space communications to capturing solar energy and the remaking of daily life by electronic computers — dealt with physical advances, and thus with the same objective that Francis Bacon had put before the pristine scientists of ten generations ago: "the relief of man's estate." The fifteenth, however, would not have occurred to Elizabethan England's "wide-browed Verulam," or indeed to any researcher until the last dozen years.

"Pharmaceuticals that change and maintain human personality at any desired level," was Dr. Seaborg's definition of this major new possibility of power — and, he was quick to add, of potential danger too. He was thinking of such recently introduced drugs as mescaline, psilocybin, and no doubt particularly of the phenomenal one known as LSD, about the uses of which much controversy is raging today. Of them he went on to say: "It may . . . become necessary to establish new legal and moral codes to govern those who prescribe use of these materials. Who should prescribe . . . and under what conditions, such a drug to a person in a position of high authority when he is faced with decisions of great consequence?"

Of course man has had mood-changing drugs at his disposal for millennia. First came alcohol, the great relaxant; then opium, the painkiller; then caffeine, the spur of the nervous system; then cocaine, hashish, and a score of other less common vegetable extracts. And in the last few years a wide variety of tranquilizers has been developed.

They all, however, fall into one or the other of two classes. They either weaken the mind's common-sense grasp of things, as does alcohol or opium, or they strengthen that grip, as does coffee or dexedrine. They do not leave the mind unclouded and yet at the same time permit it to view things in quite an uncommonsensical way. They do not raise the mind to high lucidity and yet at the same time make the world it views appear fraught with an intensity of significance that everyday common sense cannot perceive.

In LSD, or Lysergic Acid Diethylamide, however, a drug now exists that can accomplish all these aims. As Dr. Seaborg and several medical authorities cited in these pages emphasize, it is certainly not to be taken lightly, and research has only begun on its possibilities as a therapeutic aid in psychiatry. For many who have taken it under proper, controlled conditions, it has brought about an astonishing enlargement of sensitivity and perceptiveness, and it may thus cast new light on the wellsprings of creativity.

If you ask, Of what possible use is such a drug? or, What is the difference between the effects of taking LSD and, say, hashish in a Tangier dive or opium in Hong Kong? the answer might be given in terms of an early Franciscan, the ex-lawyer Jacoponi da Todi, when asked the same "what's the use" question after he spoke of the exhilarating effect that joining Saint Francis's company had on him. His response was, "a better order in all my living."

Not an opiate or a narcotic, LSD is a chemical able to produce profound changes of consciousness which, in healthily constituted persons, seem to leave no untoward aftereffects. And while it can give an ecstatic experience, at the same time it lends an extraordinary intensity of attention.

You see and hear this world, but as the artist and the musician sees and hears. And, much more important, it may also give far-reaching insights into one's own self and into one's relationship with others. Some takers of it have even felt that they had won an insight into the "nature of the Universe and the purpose of Life." These insights can be remembered and, if the person wishes, can be incorporated into his or her everyday living to bring it a "better order."

So here may be a major breakthrough that meets the problem of letting in a free flow of comprehension beyond the everyday threshold of experience while keeping the mind clear. And this seems to be accomplished by a confronting of one's self, a standing outside one's self, a dissolution of the ego-based apprehensions that cloud the sky of the mind.

The drug was discovered by accident in 1943. Dr. Albert Hofmann of Sandoz Ltd. in Switzerland, while doing research with derivatives of the ergot alkaloids, somehow absorbed synthesized LSD into his system and found it to have surprising effects on consciousness. It was soon recognized as the most potent and reliable of the consciousness-changing drugs. A remarkable fact about it is the extreme minuteness of the effective dose. The optimum dosage — that which produces for the subject the most informative results — lies between 100 and 150 "gamma"; and 100 "gamma" is approximately one ten-thousandth of a gram. (Mescaline, another of the "consciousness-changers," has to be taken in a dosage four thousand times that of LSD to produce similar mental results, and in this amount it does have physical effects on most subjects — sometimes unpleasant ones.)

A good psychiatrist, of course, must be the overseer of all LSD research. He must, as did the physicians who trained the volunteers for the ascent of Mount Everest, have "vetted" the subject. He must know whether this or that particular psyche is likely to function satisfactorily at these rare altitudes. Then, a person intimately acquainted with LSD should be at the side of the subject as he embarks on his journey. It should not be undertaken alone. A companion should be on call to act as an assistant — for instance, to play music, change the lighting, answer any questions, or write down any remarks the subject should wish recorded — and also as a monitor, or night watchman, so to speak, ready to report if possible trouble may be lurking ahead (in which case the voyage can be called off instantly by administering a counteracting chemical).

So, though the subject should not be intruded upon, he should not be left figuratively or literally in the dark. The optimal circumstances are simple, though contrary to present clinical and laboratory protocol. For the ideal setting is not a hospital or research lab, but rather an environment that is neither aggressive nor austere, and in which he may feel at home, perhaps a quiet house surrounded by a garden.

The first stage under LSD is surprising in a paradoxical way.

From what he has learned about this research, the subject is of course expecting a surprise. But during the first hour after swallowing the tiny pills, he usually experiences nothing at all. He may feel some relief at finding himself remaining completely normal, and perhaps a secret sense of superiority at the thought that possibly he is too strong to give in to a drug that will take him away from reality. An uncommonly able businessman, the head of a major corporation, who had much wished to take LSD, in fact waited fully three and one-half hours for something to "happen." Although it is uncommon for LSD to be so long in taking effect, the occasions on which this has occurred have led some researchers to speculate that the onset of the experience can be held at bay for an extra hour or two by the subject's unconscious nervousness or his suspicion that he might have been given nothing more than an innocuous placebo.

Yet as the first hour wears away, quite a number of subjects become convinced that they are feeling odd. Some, like the witches of *Macbeth,* feel a pricking in their thumbs. Others — and this, too, is a common reaction to the weird, the uncanny, the "numinous" — feel chill, with that tightening, or horripilation, of the skin as, in the vernacular, "a goose goes over one's grave." They report, "I am trembling" — but, putting out their hands, find them steady.

In the second hour, however, most subjects enter upon a stage which can leave no doubt that a profound change of consciousness is occurring. For one thing, the attending psychiatrist, or "sitter," can see that the pupils of the subject's eyes are now nearly always dilated. This symptom is the first and often the only undeniable and visible physical effect of LSD, and it gives the physiologist almost his only clue as to which area of the brain is now being acted upon. For the center that controls the pupils' reaction to light is known, and it lies deep.

During this second hour we can say that the subject is "gaining altitude." How does he record this heightening of consciousness? By far the most common remark refers to the growing intensification of color. Flowers, leaves, grass, trees, are seen with tremendous vividness — "with the intensity that Van Gogh must have seen them," is an often-used description. They seem to pulse and breathe; in fact, even everyday, fixed objects around the room may take on "flowing," "waving" shapes, as if invested with some life force of their own. Intensification of sounds, too (such as the singing of birds, though far away), is often commented on with fascinated surprise. Music frequently becomes an absorbing delight even to the nonmusical —

while to the musical it has on occasion become almost unbearably intense. "Under LSD I asked that my favorite recording of my favorite Beethoven quartet (Opus 135) be played," one musical taker reported; "but after a few minutes I had it turned off. Its emotions had become too searing — and besides, I had suddenly made the discovery that one of the instruments was playing ever so slightly off pitch."

Another effect is stranger and deeper. The subject feels that time itself — time urgent, pressing, hurried, or contrariwise, time slack, lagging, heavy on his hands — is now in "right time." When he discovers what an ample store of unhastened attention he can give to all the rich content brought him by eye and ear, he finds it hard not to believe that somehow time has been stretched. But a glance at his watch tells him it is a new-given power of superattention that is allowing him to make such full use of every moment.

It is, however, in the next couple of hours that for most people the full power of the experience comes over them. Till then, however absorbed, the subject has still been an observer. Now, although sights and sounds, the artistic splendor of the world, and the magic of music may still amaze him, they are, as it were, the décor, the scenery of a drama. Now the whole outside world becomes a composition that embraces and interfuses everything. And yet this composition, though constantly changing, is also (strange paradox) all the while complete and instant in a fathomless peace. At this point one could say that he crosses a watershed. In this all-pervading Energy he feels around him, the subject realizes that he cannot be isolated. It is flowing through him, as it flows through all that surrounds him.

Here his experience with time goes still further. Time appears to have stopped, disappeared. What has now befallen the "voyager" is not merely that he is on the high seas with his ship in a vast calm, but that the ship itself no longer seems distinct from the infinite ocean. He stands outside of and apart from his familiar ego, all its protective barriers having been shed; and this can lead in some to transcendent experience, while in others to a deep panic. To those for whom their ego is their only possible self, the only possible mode of consciousness, its disappearance is a kind of death.

It is here that the subject, however independent-minded, may literally welcome a helping hand. Of all the senses, touch is naturally most firmly anchored in the material world. So it is the least liable to illusions. It has been found that if at the moment of this "trans-

valuation of all values," this double change of the view of one's self and one's view of nature, a hand is actually held out to the subject, he will be able to keep his bearings. If the subject uses this simple "sea anchor," he may discover that he is not merely "riding the swell" but has entered a condition of what until then may have been inconceivable. With his consciousness enlarged out of all bounds, he may — if all goes well — find that he no longer feels anxiety about past or future.

It is not that he has gone into amnesia. He can clearly recall past concerns and future appointments; but he recalls them as a wise guardian carries in his mind the affairs of his ward. His personal appetites, meanwhile, generally become suspended. Most people never eat or drink during the experience, though it may last a full day; even constant smokers, while they may start with a cigarette, put it down as soon as they begin to "climb." There is not the slightest repugnance to food and drink. It is simply that the subject feels the appetites are irrelevant. Any sexual sensation, any erotic fantasy or preoccupation, is nearly always reported as absent. So, for all its liberating powers, LSD remains noneuphoric: as the Greeks would say, it is "eudaemonic" — "a possession by the spirit of wholeness."

After these climactic hours, during which he may either have sat still and wordless while contemplating the myriad images borne in on him, or conveyed volubly to his companion or monitor what he has seen and felt, the voyager returns gradually to shore, sometimes dipping back into the tides of the far sea until the lingering powers of the chemical disperse.

In the *Odyssey* Penelope, the first hostess in recorded history, gives what one might call the first psychoanalytic interpretation of a dream. The returning Ulysses, appearing in disguise and keeping his identity concealed from her after his ten years' absence, questions her about a dream she has had concerning the fate of her exigent suitors. She answers:

> *Many and many a dream is mere confusion,*
> *a cobweb of no consequence at all.*
> *Two Gates for ghostly dreams there are: one gateway*
> *of honest horn, and one of ivory.*
> *Issuing by the ivory gate are dreams*
> *of glimmering illusion, fantasies,*
> *but those that come through solid polished horn*
> *may be borne out, if mortals only know them.*

I doubt it came by horn, my fearful dream —
too good to be true, that, for my son and me.

What Penelope is saying is that there are two categories, or channels, of subconscious insight: one, coming in through the "Gate of Horn," of things that "may be borne out" (that is, having to do with events, both present and future, in our actual lives) and the other, through the "Gate of Ivory," of apparently the sheerest fantasy. And it is certainly recognized by all students of psychical research that there is a deep current of the mind which brings to the surface (sometimes by way of dreams, but not necessarily always) raw data — an incoherent babbling, irresponsible glossolalia, sufficiently confusing to justify the epithet "glimmering illusion, fantasies." Clues as to this second traffic, when they do appear, are ambiguous; symbols are so fractured that for a long while they are quite unrecognizable.

Here lies one reason why many decades of modern psychical research into this anomalous traffic have produced such baffling and frustrating results. Another is that whereas the flow running through Penelope's "Gate of Horn" is as constant and copious as the daily tides, the springs that feed the "Gate of Ivory" seem sporadic and indeed capricious. No wonder then that psychoanalysis, which confines itself to the masses of sea wrack brought up through the "Gate of Horn" and stranded on the beaches of our waking mind, attracts such an army of deep-sea psychobiologists, while those who wait by the other water gate have but a few minnows to show after nearly three generations of research.

Psychoanalysis is concerned mainly with man's conflicts between his sexual urges and the taboos imposed upon him by society, and with the effects of these conflicts on his everyday living. But the traffic we associate with the "Gate of Ivory" deals with data apparently belonging to those higher registers of the mind which very few researchers outside the psychical field have even noticed. It is true that mystics and saints have reported, time and again, "out-of-this-world," indescribable experiences that did change their lives and bring a "better order" in their living. But these experiences came as the result of many years of severe mental and physical discipline carried out within a doctrinal frame of reference, which often brought them to the brink of insanity. For many the experience was only a brief flash. For some it came two or three times during a lifetime of discipline. For instance Plotinus, so his biographer and disciple Porphyry tells us, only three times in his long life of striving for it attained to "the state." But until now there has been no other way

of opening up this other passage of perception, of keeping it open for any length of time, or of doing it at will. How is this free flow of findings to be obtained?

We now recognize that our minds have, as oculists say of our eyes, not one but a number of focal lengths. The aperture of our understanding alters, in the way that we alter the aperture of our telescopes and microscopes to bring objects into clear focus at specific ranges. But, though our minds do shift, though our range of perception will at times change gear, we cannot make that shift deliberately, consciously. Nor when it occurs can we hold on to it. And when the most common, as well as the most profound shift — that from waking to sleeping — takes place, we are not able to observe it as we experience it. This problem has teased psychologists for sixty years, and the greatest of them, William James, saw that if it was to be solved, the experimenter must use psychophysical means on himself. He tried nitrous oxide as a means of enlarging consciousness, only to find that at a certain point communication ceased, and he came back murmuring, "The Universe has no opposite." Then he tried peyotl, the button cactus that grows along the Rio Grande and is used in the religious rites of Indians in the Southwest as a sacrament lending lucidity — only to be daunted by the stumbling block of severe nausea.

Leave chemicals aside for the moment. There is an "other" state of mind, known to and described by poets as well as higher mathematicians and other scientific geniuses, in which a deeply "insightful" process can take place. The current president of India, the philosopher Dr. Sarvepalli Radhakrishnan, has termed this process "integral thought" as against "analytic thought" — the latter being the inductive procedure whereby through the patient gathering, analysis, and arranging of data there would at last emerge a general "law." "Integral thought" is the art of the sudden insight, the brilliant hypothesis, the truly "creative" leap. To have truly original thought the mind must throw off its critical guard, its filtering censor. It must put itself into a state of depersonalization; and from such histories as Jacques Hadamard's *The Psychology of Invention in the Mathematical Field* we know that the best researchers, when confronting problems and riddles that had defied all solution by ordinary methods, did employ their minds in an unusual way, did put themselves into a state of egoless "creativity" which permitted them to have insights so remarkable that by means of these they were able to make their greatest and most original discoveries.

Paracelsus found that there was a "ledge of the mind," free of all caution, to which wine could lift him; there, though unable to hold a pen, he could still dictate, until intoxication swept him into speechlessness. Descartes, sleeping on the floor with writing paper beside him, scrawled down the insights that flashed across his mind in a half-waking state, when the creative and critical levels of his brain were both working. Harvey, the discoverer of the circulation of the blood, told his biographer Aubrey that if he stayed in a disused coal shaft in total dark and silence, his uninterrupted mind would reach a span it could not encompass above ground, when trying to "think regardless of consequence" amid the wary, hostile medical world of his day. Henri Poincaré, the great French mathematician, described his subliminal processes of discovery in these words: "It is certain that the combinations which present themselves to the mind in a kind of sudden illumination after a somewhat prolonged period of unconscious work are generally useful and fruitful. . . . This, too, is most mysterious. How can we explain the fact that, of the thousand products of our unconscious activity, some are invited to cross the threshold, while others remain outside?" (In his classic study of poetic creation, *The Road to Xanadu,* John Livingston Lowes cited this passage as bearing on the deep movements of Coleridge's own psyche.)

Can LSD provide any assistance to the creative process? Even when given under the best of conditions, it may do no more (as Aristotle said when appraising and approving the great Greek Mysteries) than "give an experience." Thereafter the subject must himself work with this enlarged frame of reference, this creative *schema.* If he will not, the experience remains a beautiful anomaly, a gradually fading wonder — fading because it has no relevance to "the life of quiet desperation" which Thoreau saw most of us living and which we cannot help but live.

What, then, should be done about it? LSD is certainly one of the least toxic chemicals man has ever put inside his system. Compared with alcohol, nicotine, coffee — our three great stand-bys — it could be called almost a docile mare as against these mettlesome stallions, so far as most people are concerned. Is it of any use with psychotics? Most researchers doubt it. With the extreme neurotic? Again there seems to be considerable question. Although among these categories LSD appears to do no physical harm, cases of severe adverse psychological effects have been reported. It is the unique quality of *attention* which LSD can bestow that will or will not be

of benefit. Intensity of attention is what all talented people must obtain or command if they are to exercise their talent. Absolute attention — as we know from, for example, Isaac Newton's and Johann Sebastian Bach's descriptions of the state of mind in which they worked — is the most evident mark of genius functioning. On the other hand, the masterful Sigmund Freud remarked that psychoanalysis, even when exercised by himself, would not work with the extreme neurotic because of the hypertrophied ego-attention which such a patient had sacrificed his life to build up. The psychotic is even more absorbed in his distortive, self-obsessed notion of reality. Give, then, either of these victims of their own egos still greater capacity to attend, and it is highly unlikely that they will do other than dig still more deeply the ditch of their delusion and build more stubbornly the wall of their self-inflicted prison.

But for the truly creative person (and I refer specifically to that person capable of exercising "integral thought") LSD may be of some use. It could help him to exercise integral thought with greater ease and facility, and at will. And for a number of sensitive people willing to present themselves for a serious experiment in depth, LSD has shown itself of some help in permeating the ego, in resolving emotional conflicts, and in reducing those basic fears, the ultimate of which is the fear of death. However, the practical answer to What should be done about it? seems to be that LSD remain for the time being what it is: a "research drug," to be used with greatest care to explore the minds of those who would volunteer to aid competent researchers by offering themselves as voyagers to the "Gate of Ivory."

The Subjective After-Effects of Psychedelic Experiences:

A Summary of Four Recent Questionnaire Studies

The results presented below were extracted from four recent studies in which LSD or psilocybin was given to volunteer subjects and the after-effects of one experience assessed by means of questionnaires. The studies selected are concerned only with *subjective claims,* not with objective ratings or indices. Studies of specific descriptions of the content of psychedelic experiences are not included; the questionnaires were used to obtain from the subjects *general evaluations* of their experience and its effects.

Subjects, methods and background of each of the four studies will be briefly described. Only a brief discussion is given of the tables (the original papers may be consulted for more extensive evaluation). The purpose of this summary is to present these strikingly similar and in part hitherto unpublished data together in convenient form.

(1) Ditman, K.S., Hayman, M. and Whittlesey, J.R.B. "Nature and Frequency of Claims Following LSD." *J. Nervous & Mental Disease,* 1962, 134, 346-352.

The data are based on 74 questionnaires returned by subjects who had been given 100 micrograms of LSD six months to three and one-half years previously. The LSD was given in "a permissive but non-treatment" setting in order to compare the LSD experience with that of delirium tremens. . . . "Our subjects received no intended psychotherapy during the LSD experience. In general, the atmosphere was relaxed and permissive, with the subjects well-protected from outside disturbances. They underwent the experience in a darkened room, and were allowed various sensory stimuli such as

music, paintings, and exposure to sunlight in a garden setting. Usually, the LSD was given to groups of three to five subjects. At least one 'sitter' was constantly present who himself had experienced LSD." Half the subjects were patients, i.e., undergoing some form of psychotherapy. The others were colleagues, psychotherapists, lawyers, writers, etc. This study will be referred to subsequently as the *"Ditman Study."*

(2) Sherwood, J.N., Stolaroff, M.J., and Harman, W.W., "The Psychedelic Experience — A New Concept in Psychotherapy." *J. Neuropsychiat.,* 1962, 3, 370-375. And Savage, C., Harman, W., Fadiman, J. and Savage, E., "A Follow-up Note on the Psychedelic Experience," in Sanford M. Unger (Ed.), *Psychedelic Drug Therapy: A New Approach to Personality Change.* To be published early in 1964.

A questionnaire overlapping much of the questionnaire in the Ditman Study was used, and the results are presented together in Tables (1) and (2). All subjects had undergone the LSD experience 3 to 14 months previously. All 96 subjects were paying patients. Subjects were typically given 100-200 μg of LSD plus 200-400 mg of mescaline, individually, after intensive preparation. This preparation included discussion of aims, of willingness to surrender old concepts and preconceived ideas, and of the necessity for trust. "All of the pre-treatment contacts aid in the development of these key factors within the subject, willingness and trust, which are essential to the movement into and most effective use of the psychedelic experiences." The inhalation of a 30% CO_2 and 70% oxygen mixture B is also used in the preparation, which "gives the subject an opportunity to 'practice' the sort of surrender which will be called for on the day of the LSD session."

"The psychedelic session is held in the congenial surroundings of a tastefully furnished room containing a tape-and-record player console and various carefully chosen works of art. The subject spends a good fraction of the day lying comfortably on a couch listening to music. . . . The therapist will usually initiate rather little conversation during the session. The subject is ordinarily encouraged alternately to explore within, and to respond to stimuli in the outer environment (such as flowers, room furnishings, works of art, photographs of close relations, etc.). . . . The subject is urged to postpone analyzing his experience until after the session and to accept the experience as it occurs without labeling or evaluating." This study will be referred to subsequently as the *"Savage Study."*

(3) A survey of 194 questionnaire returns from the file of Dr. Oscar Janiger was presented by W. M. McGlothlin in *"Long-Lasting Effects of LSD on Certain Attitudes in Normals: An Experimental Proposal,"* a RAND corporation reprint (1962).

"Of the 194 subjects 73 were undergoing psychotherapy and took LSD an average of 3.6 times as a therapeutic aid. The remaining 121 subjects were volunteers and averaged 1.9 sessions. The average interval between the administration of LSD and the completion of the questionnaire was 10 months and the average maximum dosage 171 μg." The non-therapy groups contained twenty physicians, seven psychologists, one dentist; artists, writers, musicians, ministers; teachers, engineers, housewives, secretaries, students and others. "The conditions under which LSD was administered varied somewhat. The therapy group was made up of patients under several psychotherapists and the conduct of the session depended on their orientation. It should be mentioned that for some of this group LSD was somewhat incidental to their overall treatment and the results are perhaps not comparable to those of patients for whom drug treatment played a major role. The artists participated in a creativity study in which they were asked to paint specific objects while under the effects of LSD. The other non-therapy subjects were generally left undisturbed, and wrote a subjective report the following day." This study will be referred to subsequently as the *"Janiger Study."*

(4) Timothy Leary, George H. Litwin and Ralph Metzner. "Reactions to Psilocybin Administered in a Supportive Environment." (To be published in *J. Nervous & Mental Disease.*)

The data presented are based on questionnaires returned by 98 subjects, one day to three weeks after they had been given psilocybin. Occupationally, the subjects included graduate students, professional writers and artists, psychologists, musicians, housewives and inmates in a correctional institution. They were given doses of psilocybin ranging from 4 mg to 100 mg, with a medium dose of 16 mg. "The drug was given in comfortable home-like surroundings, with no medical or experimental procedures introduced during the session. Subjects were given all available information on the drug and were allowed to regulate their own dosage, within a maximum set by the experimenter. Subjects were free to explore whatever aspects of an experience they wished." Preliminary discussions and reading were designed to prepare the subjects for a pleasant experience involving insight and expanded awareness. Therapy was not attempted during the session, although the inmate subsample were involved in an experimental behavior-change program and therefore expected change. Music, art, pictures, etc., were available during sessions, which were held in small groups ranging from 3 to 10 participants. A "guide" who had experienced psilocybin previously was always present. This study will be referred to subsequently as the *"Leary Study."* [1]

[1] Grateful acknowledgement is made to the authors of these studies and, in the case of the Ditman Study, to The Williams & Wilkins Company, Baltimore, for permission to reproduce these data.

TABLE (1)

"Looking back on your LSD experience, how does it look to you now?"

Item	*Percentage**	
	Ditman Study (N = 74)	*Savage Study* (N = 96)
A very pleasant experience	72	85
Something I want to try again	66	89
An experience of great beauty	66	81
Greater awareness of reality	64	92
Feel it was of lasting benefit to me	50	85
The greatest thing that ever happened to me	49	78
A religious experience	32	83
A very unpleasant experience	19	33
A disappointing experience	7	1
An experience of insanity	7	18
Did me harm mentally	1	1
Like travelling to a far-off land	39	
Very much like being drunk	32	
Return to feelings of childhood	28	
Physical discomfort and illness	17	

* Percentages are the responses in the first two of the following four categories: "Quite a bit," "Very much," "A little," "Not at all."

TABLE (2)

"How were you, or what were you left with, after your LSD experience?"

Item	*Percentage**	
	Ditman Study (N = 74)	*Savage Study* (N = 96)
A new way of looking at the world	48	85
A greater understanding of the importance and meaning of human relationships	47	86
A new understanding of beauty and art	43	64
A greater awareness of God, or a Higher Power, or an Ultimate Reality	40	90
A sense of greater regard for the welfare and comfort of other human beings	38	78
A realization that I need psychotherapy	17	26
More ability to relax and be myself	40	74
Improvement noted by person closest to me	42	64

Greater tolerance of others	40	75
A sense of futility and emptiness	7	8
A frightening feeling that I might go crazy or lose control of myself	3	8
Sense of relaxation and freedom from anxiety and tension	56	
A better understanding of the cause and source of my troubles	41	
A set of new decisions and new directions for my life	39	
A new sense of fun and enjoyment	39	
A sense of now knowing what life is all about	27	

* Percentages are the totals of the two categories: "Quite a bit" and "Very much."

TABLE (3)

Principal areas of claimed improvement attributed to LSD (Ditman Study)

Item	*Percentage* (N = 74)
More ability to relax	40
More comfort with people	37
More initiative since LSD	36
Less anxiety	34
Increased interest in:	
Nature	38
Art	34
Music	33
Changes in "perspective":	
Deeper significance to things	46
Things seem more real	40
Problems less important	39
Colors brighter	39
Changes in "attitude":	
More tolerant	40
More accepting of ideas	38
More broadminded	37
Less irritable	33
Changes in sense of values	47
Problems such as emotional, financial, drinking, legal, etc., improved	33

Improvement in income, living quarters and body-weight	15
Increased sex satisfaction	14

TABLE (4)

Changes attributed to LSD (Janiger Study)

Item	*Percentage* (N = 194)
Major objective changes (in job, marital status, etc.)	16
Positive change in interpersonal relations:	
with co-workers and employees	43
with acquaintances	41
Increased interest in:	
social reform	18
political and international affairs	22
anthropology	24
morals and ethics	35
Other universal concepts (meaning of life)	48
Positive change noticed by person closest	45
Changes in sense of values (money, status, human relationships, religion, etc.)	48
Looking back on the LSD experience, it was:	
a very pleasant experience	66
a very unpleasant experience	32
something I would want to try again	74
a religious experience	24
an experience giving greater understanding of myself and others	61
an experience of lasting benefit	58
LSD should be used for:	
becoming aware of oneself	75
gaining new meaning to life	58
getting people to understand each other	42

TABLE (5)

Subjective reactions to psilocybin (Leary Study)

Item	*Percentage* (N = 98)
1) How supportive (relaxing, warm, accepting) was the total situation?	
Very supportive	56

	Mildly supportive	22
	Neutral	10
	Mildly or very rejecting	11
2)	Was the experience pleasant?	
	Wonderful or ecstatic	32
	Very pleasant	38
	O.K.	23
	Unpleasant or very unpleasant	7
3)	Did you learn a lot about yourself and the world?	
	Tremendous insights	23
	Learned a lot	22
	Learned something of value	43
	Learned nothing	9
	More confused	2
4)	Has the mushroom experience changed you and your life?	
	Dramatically better	12
	Changed for better	50
	No change	37
	Worse	1
5)	How about taking the mushroom again under trustful, secure circumstances?	
	Very eager	56
	Like to	34
	Don't care	6
	Rather not	4

Discussion

Table (1) shows that in both the Ditman and Savage studies, a majority of the subjects claim that the experience was pleasant and gave them increased awareness. 50% in the Ditman study and 85% in the Savage study report lasting benefit. The higher figures in the Savage study are probably attributable to the more intensive preparations and to the conduct of sessions centered around the individual subject. The percentage of experiences reported to be harmful or unpleasant is very small in both studies.

Table (2) reviews some of the descriptions which subjects consider appropriate to their LSD experience. "Greater understanding of interpersonal relationships" and "a new way of looking at the world" are frequent in both samples. In the Savage study, "awareness of God or a Higher Power or an Ultimate Reality" is the most frequent item, and this is significantly correlated ($r = .68$)

with reports of lasting benefit. In the Ditman study, "those who had a religious orientation, particularly those with a mystical orientation, claimed the most benefit from the experience and found it the most pleasant." These results suggest that perhaps something akin to a religious conversion experience is taking place in some of the subjects.

Table (3) lists the principal area of improvement attributed to LSD in the Ditman study.

Table (4) gives comparable figures from the Janiger study; most frequently reported changes occurred in interpersonal relations and in values. 75% of all the subjects in this study indicated LSD should be used for increasing self-awareness.

Table (5) gives the results of the Leary study: 70% find the experience pleasant, 88% learn something from it, 62% report that it changed their life, and 90% want to try it again.

On some of the questions it is possible to collate the results from all four studies. Thus the percentages reporting a pleasant experience in the four studies are 72, 85, 66 and 70, or an average of 73%. Percentages reporting lasting benefit or change are 50, 85, 58, and 62, or an average of 64%. Percentages wishing to repeat the experience are 66, 89, 74, and 90, or an average of 80%.

In three of the studies, an attempt was made to evaluate the longevity of these claims, i.e., to what extent they are maintained after longer periods of time. In the Savage study, answers were compared at four time periods: less than three months after the LSD session, three to six months, six to twelve months and over twelve months. The results indicated that "felt benefit tends to become apparent some time after the LSD experience and to be sustained fairly well over at least the first year following." In the Janiger study, results were compared after: 0-100 days, 100-389 days, and more than 389 days. Results indicated that "there is a definite decrease in claimed effect as a function of time, and that the decrement is sharpest during the first six months or so. Of individual questions, "becoming aware of self," changes in values, and claims of "lasting benefit" seem to be fairly resistant to erosion by time. In the Ditman study 16 alcoholic patients returned a second questionnaire, approximately three and one-half years after their original LSD experience. They "made fewer claims than they had on the first questionnaire. About two-thirds still claimed periods of abstinence ranging from one to one and one-half years, as they had on the first questionnaire, and three-fourths of these alcoholics still claimed some lasting benefit (fewer arrests, increased self-understanding and esthetic interest).

None of the *S*s, however, had maintained their sobriety to the time of the second questionnaire.

It should be remembered that these four studies are all reports of *subjective* claims and need to be supplemented by studies of changes in objective behavioral indices. Furthermore, in general, these positive results do not agree with the majority of studies of psychedelic drugs in the psychiatric literature. There are two kinds of studies of drug-effects: those in which observations and evaluations are made by the researcher-psychiatrist, and those in which the subject records his own impressions and observations. The first kind of study tends on the whole to lead to negative evaluation — the substances are seen as "psychotomimetic," producing "depersonalization," space-time "distortions," etc. When subjects describe their own experiences, they use phrases such as "awareness of higher reality," "transcendence of time and space," of what may be essentially similar subjective effects. It is important to keep this relativity of observations and labels in mind, in evaluating these results.

The Editors

The Hallucinogenic Fungi Of Mexico:

An Inquiry Into The Origins of The Religious Idea Among Primitive Peoples

R. GORDON WASSON

This paper was first given as the *Annual Lecture* of the Mycological Society of America, Stillwater, Oklahoma, 1960. It is reprinted here, with the author's permission, from the *Botanical Museum Leaflets*, Harvard University, 1961, 19(7).

WHEN I RECEIVED in Mexico your President's invitation to speak here today, I knew that your Committee had made an unorthodox choice, for I am not a professional mycologist. As the appointed hour approached my trepidation kept mounting, for I saw myself an amateur about to be thrown to a pack of professionals. But your President's gracious introductory remarks, however unmerited, have put me at my ease and lead me to hope that we shall all enjoy together a mushroom foray of a rather unusual nature.

Those of you who do not know the story will be interested in learning how it came about that my wife, who was a pediatrician, and I, who am a banker, took up the study of mushrooms. She was a Great Russian and, like all of her fellow-countrymen, learned at her mother's knee a solid body of empirical knowledge about the common species and a love of them that are astonishing to us Americans. Like us, the Russians are fond of nature — the forests and birds and wild flowers. But their love of mushrooms is of a different order, a visceral urge, a passion that passeth understanding. The worthless kinds, the poisonous mushrooms — the Russians are fond, in a way, even of them. They call these "worthless ones" *paganki*, the "little pagans," and my wife would make of them colorful centerpieces for the dining-room table, against a background of moss and stones and wood picked up in the woods. On the other hand, I, of Anglo-Saxon origin, had known nothing of mushrooms. By inheritance, I ignored them all; I rejected those repugnant fungal growths, expressions of parasitism and decay. Before my marriage, I had not once fixed my gaze on a mushroom; not once looked at a

mushroom with a discriminating eye. Indeed, each of us, she and I, regarded the other as abnormal, or rather subnormal, in our contrasting responses to mushrooms.

A little thing, some of you will say, this difference in emotional attitude toward wild mushrooms. Yet my wife and I did not think so, and we devoted a part of our leisure hours for more than thirty years to dissecting it, defining it, and tracing it to its origin. Such discoveries as we have made, including the rediscovery of the religious role of the hallucinogenic mushrooms of Mexico, can be laid to our preoccupation with that cultural rift between my wife and me, between our respective peoples, between the mycophilia and mycophobia (words that we devised for the two attitudes) that divide the Indo-European peoples into two camps. If this hypothesis of ours be wrong, then it must have been a singular false hypothesis to have produced the results that it has. But I think it is not wrong. Thanks to the immense strides made in the study of the human psyche in this century, we are now all aware that deep-seated emotional attitudes acquired in early life are of profound importance. I suggest that when such traits betoken the attitudes of whole tribes or peoples, and when those traits have remained unaltered throughout recorded history, and especially when they differ from one people to another neighboring people, then you are face to face with a phenomenon of profound cultural importance, whose primal cause is to be discovered only in the well-springs of cultural history.

Many have observed the difference in attitude toward mushrooms of the European peoples. Some mycologists in the English-speaking world have inveighed against this universal prejudice of our race, hoping thereby to weaken its grip. What a vain hope! One does not treat a constitutional disorder by applying a band-aid. We ourselves have had no desire to change the Anglo-Saxon's attitude toward mushrooms. We view this anthropological trait with amused detachment, confident that it will long remain unchanged for future students to examine at their leisure.

Our method of approach was to look everywhere for references to mushrooms. We gathered the words for "mushroom" and the various species in every accessible language. We studied their etymologies. Sometimes we rejected the accepted derivations and worked out new ones, as in the case of "mushroom" itself and also of 'chanterelle." We were quick to discern the latent metaphors in such words, metaphors that had lain dead in some cases for thousands of years. We searched for the meaning of those figures of speech. We

sought for mushrooms in the proverbs of Europe, in myths and mythology, in legends and fairy tales, in epics and ballads, in historical episodes, in the obscene and scabrous vocabularies that usually escape the lexicographer; in the writings of poets and novelists. We were alert to the positive or negative value that the mushroom vocabularies carried, their mycophilic and mycophobic content. Mushrooms are widely linked with the fly, the toad, the cock, and the thunderbolt; and so we studied these to see what associations they conveyed to our remote forebears. Wherever we traveled we tried to enter into contact with untutored peasants and arrive at their knowledge of the fungi — the kinds of mushrooms that they distinguished, their names, the uses to which they put them, and their emotional attitude toward them. We made trips to the Basque country, to Lapland, to Friesland, to the Provence, to Japan. We scoured the picture galleries and museums of the world for mushrooms and we pored over books on archeology and anthropology.

I would not have you think that we ventured into all these learned paths without guidance. We drew heavily on our betters in the special fields that we were exploring. When we were delving into questions of vocabulary, when we worked out an original etymology for a mushroomic word, we were always within reach of a philologist who had made of that tongue his province. And so in all branches of knowledge. Sometimes it seems to me that our entire work has been composed by others, with us merely serving as rapporteur. Since we began to publish in 1956, persons in all walks of life have come to us in increasing numbers to contribute information, and ofttimes the contributions of even the lowliest informants are of highest value, filling a lacuna in our argument. We were amateurs unencumbered by academic inhibitions, and therefore we felt free to range far and wide, disregarding the frontiers that ordinarily segregate the learned disciplines. What we produced was a pioneering work. We know, we have always known better than the critics, the flaws in ours, but our main theme, which we adumbrated rather diffidently in *Mushrooms Russia and History* in 1957, seems to have stood up under criticism. If I live and retain my vitality, you may see published over the coming years a series of volumes, to be called perhaps *Ethnomycological Papers,* and, at the end of the road, there may be a new edition of our original work, reshaped, simplified, with new evidence added and the argument strengthened.

It would give me pleasure to enumerate the names of those to whom we are indebted, but how tedious the roll call would be for

you who are obliged to listen! There is one name, however, that in this audience I must cite. For more than ten years, we have been collaborating closely with Professor Roger Heim, Membre de l'Institut, and on all matters mycological he has been our guide and teacher. For these many years, he has been the director in Paris of the Laboratoire de Cryptogamie and, even longer, editor of the *Revue de Mycologie*. More recently, he has also borne the burden of directing the Muséum National d'Histoire Naturelle, that renowned center for advanced teaching and research in the biological studies, one of the glories of French culture. But these titles to academic distinction, though themselves of the highest order, do not tell you the story. Vast as is his learning and his experience in field and laboratory, sound as is his judgment in the vexed problems that you mycologists face every day, formidable as he is in polemic, it is as a rare human being that I commend him to you. Patient with the beginner, inspiring as a teacher, model of generosity toward others, prodigious worker in field and laboratory, and classical stylist in the French language, who could be more delightful whether in his published writings, or as correspondent, or as companion in the field? In the presence of Roger Heim, the time-worn conflict between science and the humanities fades away. One senses that the field of science for him is merely the New World that civilized man, the exponent of the humanities, is exploring and assimilating. What guardian angel had me in his keeping when, after the Second World War, I ascended the steps of his laboratory in Paris to meet him for the first time, a stranger, an American, an ignoramus in the complex, the vast, the exacting discipline that you and he share together? At once he made me feel at home and it was not long before he was developing enthusiasm for our ethnomycological inquiries. Later he became our indispensable and beloved partner in our Middle American forays.

I do not recall which of us, my wife or I, first dared to put into words, back in the '40's, the surmise that our own remote ancestors, perhaps 4,000 years ago, worshipped a divine mushroom. It seemed to us that this might explain the phenomenon of mycophilia vs. mycophobia, for which we found an abundance of supporting evidence in philology and folklore. Nor am I sure whether our conjecture was before or after we had learned of the role of *Amanita muscaria* in the religion of several remote tribes of Siberia. Our bold surmise seems less bold now than it did then. I remember distinctly how it came about that we embarked on our Middle American explorations. In the fall of 1952 we learned that the 16th century writers,

describing the Indian cultures of Mexico, had recorded that certain mushrooms played a divinatory role in the religion of the natives. Simultaneously we learned that certain pre-Columbian stone artifacts resembling mushrooms, most of them roughly a foot high, had been turning up, usually in the highlands of Guatemala, in increasing numbers. For want of a better name, the archeologists called them "mushroom stones," but not one archeologist had linked them with mushrooms or with the rites described by the 16th century writers in neighboring Mexico. They were an enigma, and "mushroom stone" was merely a term of convenience. Some of these stone carvings carried an effigy on the stipe, either a human face or an animal, and all of them were very like mushrooms. Like the child in the Emperor's New Clothes, we spoke up, declaring that the so-called "mushroom stones" really represented mushrooms, and that they were the symbol of a religion, like the Cross in the Christian religion, or the Star of Judea, or the Crescent of the Moslems. If we are right — and little by little the accumulating evidence seems to be in our favor — then this Middle American cult of a divine mushroom, this cult of "God's flesh" as the Indians in pre-Columbian times called it, can be traced back to about B.C. 1500, in what we call the Early Pre-classic period, the earliest period in which man was in sufficient command of his technique to be able to carve stone. Thus we find a mushroom in the center of the cult with perhaps the oldest continuous history in the world. These oldest mushroom stones are technically and stylistically among the finest that we have, evidence of a flourishing rite at the time they were made. Earlier still, it is tempting to imagine countless generations of wooden effigies, mushroomic symbols of the cult, that have long since turned to dust. Is not mycology, which someone has called the step-child of the sciences, acquiring a wholly new and unexpected dimension? Religion has always been at the core of man's highest faculties and cultural achievements, and therefore I ask you now to contemplate our lowly mushroom — what patents of ancient lineage and nobility are coming its way!

It remained for us to find out what kinds of mushrooms had been worshipped in Middle America, and why. Fortunately, we could build on the experience of a few predecessors in the field: Blas Pablo Reko, Robert J. Weitlaner, Jean Bassett Johnson, Richard Evans Schultes, and Eunice V. Pike. They all reported that the cult still existed in the Sierra Mazateca in Oaxaca. And so we went there, in 1953. In books and articles we have described time and time again

our later adventures, and some of you, surely, are familiar with them. So far as we know, we were the first outsiders to eat the mushrooms, the first to be invited to partake in the agapé of the sacred mushroom.* I propose here this evening a new approach, and will give you the distinctive traits of this cult of a divine mushroom, which we have found a revelation, in the true meaning of that abused word, but which for the Indians is an every-day feature, albeit a Holy Mystery, of their lives.

Here let me say a word parenthetically about the nature of the psychic disturbance that the eating of the mushroom causes. This disturbance is wholly different from the effects of alcohol, as different as night from day. We are entering upon a discussion where the vocabulary of the English language, of any European language, is seriously deficient. There are no apt words in them to characterize your state when you are, shall we say, "bemushroomed." For hundreds, even thousands, of years we have thought about these things in terms of alcohol, and we now have to break the bonds imposed on us by the alcoholic association. We are all, willy nilly, confined within the prison walls of our every-day vocabulary. With skill in our choice of words we may stretch accepted meanings to cover slightly new feelings and thoughts, but when a state of mind is utterly distinct, wholly novel, then all our old words fail. How do you tell a man born blind what seeing is like? In the present case, this is especially true because superficially the bemushroomed man shows a few of the objective symptoms of one intoxicated, drunk. Now virtually all the words describing the state of drunkenness, from "intoxicated" (which, as you know, means "poisoned") through the scores of current vulgarisms, are contemptuous, belittling, pejorative. How curious it is that modern civilized man finds surcease from care in a drug for which he seems to have no respect! If we use by analogy the terms suitable for alcohol, we prejudice the mushroom, and since there are few among us who have been bemushroomed, there is danger that the experience will not be fairly judged. What we need is a vocabulary to describe all the modalities of a Divine Inebriant.

These difficulties in communicating have played their part in certain amusing situations. Two psychiatrists who have taken the mushroom and known the experience in its full dimensions have been criticised in professional circles as being no longer "objective." Thus it comes about that we are all divided into two classes: those who

* This was on the night of June 29-30, 1955.

have taken the mushroom and are disqualified by our subjective experience, and those who have not taken the mushroom and are disqualified by their total ignorance of the subject! As for me, a simple layman, I am profoundly grateful to my Indian friends for having initiated me into the tremendous Mystery of the mushroom. In describing what happens, I shall be using familiar phrases that may seem to give you some idea of the bemushroomed state. Let me hasten to warn you that I am painfully aware of the inadequacy of my words, any words, to conjure up for you an image of that state.

I shall take you now to the monolingual villages in the uplands of southern Mexico. Only a handful of the inhabitants have learned Spanish. The men are appallingly given to the abuse of alcohol, but in their minds the mushrooms are utterly different, not in degree, but in kind. Of alcohol they speak with the same jocular vulgarity that we do. But about mushrooms they prefer not to speak at all, at least when they are in company and especially when strangers, white strangers, are present. If you are wise, you will talk about something, anything, else. Then, when evening and darkness come and you are alone with a wise old man or woman whose confidence you have won, by the light of a candle held in the hand and talking in a whisper, you may bring up the subject. Now you will learn how the mushrooms are gathered, perhaps before sunrise, when the mountain side is caressed by the pre-dawn breeze, at the time of the New Moon, in certain regions only by a virgin. The mushrooms are wrapped in a leaf, perhaps a banana leaf, sheltered thus from irreverent eyes, and in some villages they are taken first to the church, where they remain for some time on the altar, in a *jícara* or gourd bowl. They are never exposed in the market-place but pass from hand to hand by prearrangement. I could talk to you a long time about the words used to designate these sacred mushrooms in the languages of the various peoples that know them. The Aztecs before the Spaniards arrived called them *teo-nanácatl,* God's flesh. I need hardly remind you of a disquieting parallel, the designation of the Elements in our Eucharist: "Take, eat, this is my Body. . . ."; and again, "Grant us therefore, gracious Lord, so to eat the flesh of thy dear son. . . ." But there is one difference. The orthodox Christian must accept by faith the miracle of the conversion of the bread into God's flesh: that is what is meant by the Doctrine of Transubstantiation. By contrast, the mushroom of the Aztecs carries its own conviction; every communicant will testify to the miracle that he has experienced. In the language of the Mazatecs, the sacred mushrooms are called *'nti*[1]

šï³tho³. The first word, *'nti*¹, is a particle expressing reverence and endearment.* The second element means "that which springs forth." In 1953 our muleteer had travelled the mountain trails all his life and knew Spanish, though he could neither read nor write, nor even tell time by a clock's face. We asked him why the mushrooms were called "that which springs forth." His answer, breathtaking in its sincerity and feeling, was filled with the poetry of religion, and I quote it word for word as he gave it:

El honguillo viene por sí mismo, no se sabe de dónde,
como el viento que viene sin saber de dónde ni porqué.
The little mushroom comes of itself, no one knows whence,
like the wind that comes we know not whence nor why.

When we first went down to Mexico, we felt certain, my wife and I, that we were on the trail of an ancient and holy mystery, and we went as pilgrims seeking the Grail. To this attitude of ours I attribute such success as we have had. It has not been easy. For four and a half centuries the rulers of Mexico, men of Spanish blood or at least of Spanish culture, have never entered sympathetically into the ways of the Indians, and the Church regarded the sacred mushroom as an idolatry. The Protestant missionaries of today are naturally intent on teaching the Gospel, not on absorbing the religion of the Indians. Nor are most anthropologists good at this sort of thing. . . . For more than four centuries the Indians have kept the divine mushroom close to their hearts, sheltered from desecration by white men, a precious secret. We know that today there are many *curanderos* who carry on the cult, each according to his lights, some of them consummate artists, performing the ancient liturgy in remote huts before minuscule congregations. With the passing years they will die off, and, as the country opens up, the cult is destined to disappear. They are hard to reach, these *curanderos*. Almost invariably they speak no Spanish. To them, performing before strangers seems a profanation. They will refuse even to meet with you, much less discuss the beliefs that go with the mushrooms and perform for you. Do not think that it is a question of money: *no hicimos esto por dinero*, "We did not this for money," said Guadalupe, after we had spent the night with her family and the *curandera* María Sabina. Perhaps you will learn the names of a number of renowned *curanderos*, and your emissaries will even promise to deliver them to you, but then you wait and wait and they never come. You will brush

* The superscript digits indicate the pitch of the syllable, ¹ being the highest of four. The initial apostrophe indicates a glottal stop.

past them in the market-place, and they will know you, but you will not know them. The judge in the town-hall may be the very man you are seeking; and you may pass the time of day with him, yet never learn that he is your *curandero*.

After all, would you have it any different? What priest of the Catholic Church will perform Mass to satisfy an unbeliever's curiosity? The *curandero* who today, for a big fee, will perform the mushroom rite for any stranger is a prostitute and a faker, and his insincere performance has the validity of a rite put on by an unfrocked priest. In the modern world religion is often an etiolated thing, a social activity with mild ethical rules. Religion in primitive society was an awesome reality, "terrible" in the original meaning of that abused word, pervading all life and culminating in ceremonies that were forbidden to the profane. This is what the mushroom ceremony is in the remote parts of Mexico.

We often think of the mysteries of antiquity as a manifestation of primitive religion. Let me now draw your attention to certain parallels between our Mexican rite and the Mystery performed at Eleusis. The timing seems significant. In the Mazatec country the preferred season for "consulting the mushroom" is during the rains, when the mushrooms grow, from June through August. The Eleusinian Mystery was celebrated in September or early October, the season of the mushrooms in the Mediterranean basin. At the heart of the Mystery of Eleusis lay a secret. In the surviving texts there are numerous references to the secret, but in none is it revealed. Yet Mysteries such as this one at Eleusis played a major role in Greek civilization, and thousands must have possessed the key. From the writings of the Greeks, from a fresco in Pompeii, we know that the initiate drank a potion. Then, in the depths of the night, he beheld a great vision, and the next day he was still so awestruck that he felt he would never be the same man as before. What the initiate experienced was "new, astonishing, inaccessible to rational cognition." * One writer in the 2nd century A.D., by name Aristides, pulled the curtain aside for an instant, with this fragmentary description of the Eleusinian Mystery:

Eleusis is a shrine common to the whole earth, and of all the divine things that exist among men, it is both the most awesome and the most

* For this and the following quotations see Walter F. Otto: The Meaning of the Eleusinian Mysteries, published in *The Mysteries*, 1955, ed. by Joseph Campbell, Pantheon Books, Bollingen Series XXX, 2; pp. 20 et seq. Italics are mine.

luminous. At what place in the world have more miraculous tidings been sung, where have the dromena called forth greater emotion, *where has there been greater rivalry between seeing and hearing?*

And then he went on to speak of the "ineffable visions" that it had been the privilege of many generations of fortunate men and women to behold.

Just dwell for a moment on that description. How striking that the Mystery of antiquity and our mushroom rite in Mexico are accompanied in the two societies by veils of reticence that, so far as we can tell, match each other point for point! Our ancient writers' words are as applicable to contemporary Mexico as they were to classic Greece! May it not be significant that the Greeks were wont to refer to mushrooms as "the food of the gods," *brōma theon,* and that Porphyrius is quoted as having called them "nurslings of the gods," *theotróphos**? The Greeks of the classic period were mycophobes. Was this because their ancestors had felt that the whole fungal tribe was infected "by attraction" with the holiness of some mushrooms and that they were not for mortal men to eat, at least not every day? Are we dealing with what was in origin a religious tabu?

In earliest times the Greeks confined the common European word for mushroom, which in their language was *sp(h)óngos* or *sp(h)óngê,* to the meaning "sponge," and replaced it by a special word, *múkês,* for the designation of mushrooms.‡ Now it happens that the root of this word *múkês* in Greek is a homonym of the root of the Greek word for "Mystery," *mu.* A bold speculation flashes through the mind. The word for "Mystery" comes from a root that means the closing of the apertures of the body, the closing of the eyes and ears. If the mushroom played a vital and secret role in primitive Greek religion, what could be more natural than that the standard word for "mushroom" would fall into disuse through a religious tabu (as in Hebrew "Yahweh" gave way to "Adonai") and that the Greeks substituted an alternative fungal term that was a homonym of "mystery"? You can hear the pun, see the gesture, "Mum's the word," with the index finger over the mouth. . . . We must remember, in considering this problem, that in antiquity the

* Giambattista della Porta: *Villa,* 1592, Frankfort, p. 764.

‡ Holger Pedersen in an early paper contended that the basic fungal words of Europe were identical: Old High German *swamb,* Slavic *gomba,* Lithuanian *gumbas,* Latin *fungus,* Greek *sp(h)óngos, sp(h)óngé,* and Armenian *sung, sunk.* (Published in Polish: 'Przyczynki do gramatyki porównawczej

ecology of Greece and the Greek isles was different from now. Deforestation and the goats had not wrought the havoc of the intervening centuries. They had not left the mountains naked to the sun. On the wooded isles and in the forests of the mainland, there must have been a wealth of mushrooms.

Let us consider possibilities other than the mushroom. In the Mazatec country the Indians, when there are no mushrooms, have recourse to alternatives. Thanks to the brilliant work of Dr. Albert Hofmann of Sandoz, the Swiss pharmaceutical firm, we are now sorting out and identifying a whole series of indoles that have remarkable psychotropic properties. As you all know, he has isolated the active agents in some of our Mexican mushrooms, psilocybin and psilocin, two tryptamine derivatives and members of the indole family of substances. He has defined their molecular structure. The magic indoles are present in other plants used widely among the Indians of Mexico. He has isolated and identified three of the active agents in *ololiuqui,* the famous seeds, subject of many studies, that have long been used in Mexico for their psychotropic properties.* In the Mazatec country the seeds of *ololiuqui* are one of the alternatives used when the sacred mushrooms are not available. Imagine our surprise, when we began looking for these seeds in quantity last year, to discover that the Zapotec Indians employ two seeds: in some villages one, in others the other, and in some both. There is no question which seed was the *ololiuqui* of the Aztecs. It is a climbing morning-glory known to science as *Rivea corymbosa* (L.) Hallier filius.** The seeds

jezyków slowianskich,' in *Materyaly i Prace Komisyi Jezykowej Akademii Umiejetnosci w Krakowie,* Cracow, 1(1): 167-176.) Since then some philologists have declined to accept this thesis as more than a possibility, especially as to the Slavic term, but Professor Roman Jakobson in a recent personal communication to me says: 'The etymology of Holger Pedersen, the great Danish specialist in the comparative study of Indo-European languages, seems to me and to many other linguists, e.g., the distinguished Czech etymologist V. Machek, as the only convincing attempt to interpret the fungal name of the European languages. Not one single serious argument has been brought against Pedersen's "attractive" explanation, as Berneker defines it, and not one single defensible hypothesis has been brought to replace this one.'

* The Chemistry of Natural Products, paper read by Dr. Hofmann, Aug. 18, 1960, in the I.U.P.A.C. Symposium, Melbourne.

** The best summary of the *ololiuqui* literature and problem is Richard Evans Schultes' A Contribution to Our Knowledge of *Rivea corymbosa,* the Narcotic Ololiuqui of the Aztecs, Botanical Museum, Harvard University, 1941. Also see Humphrey Osmond's Ololiuqui: The Ancient Aztec Narcotic, *Journal of Mental Science,* July 1955, 101(424): 526-537. Dr. Osmond reports on the effects of the seeds on himself.

are brown and almost round. The second plant was identified at the National Herbarium in Washington as *Ipomoea violacea* L.,‡ also a climbing morning-glory but easily distinguished in the field from *Rivea corymbosa*. The seeds are long, black, and angular, and so far as we now know, they are used only in some parts of the Zapotec country. Both are called in Zapotec *badoh*, but the black seeds are *badoh negro*, black *badoh*, to distinguish them from the true *ololiuqui* seeds.•

Dr. Hofmann found that the alkaloidal components of the two seeds were identical, and they yielded d-lysergic acid amide and d-isolysergic acid amide, in the LSD 25 family of substances and known heretofore only as derivatives of ergot. Is it not surprising to find in higher plants such as the Convolvulaceae the same lysergic acid derivatives as in the lower fungi? The third substance found

‡ **Ipomoea violacea** Linnaeus Pl. Sp. (1953) 161.
Convolvulus indicus Miller Gard. Dict. (1768) No. 5.
Ipomoea tricolor Cavanilles Icon. Pl. Rar. 3 (1794) 5.
Convolvulus violaceus Sprengel Syst. 1 (1825) 399.
Convolvulus venustus Sprengel Syst. 1 (1825) 399.
Ipomoea rubrocoerulea Hooker Bot. Mag. (1834) t. 3297.
Pharbitis violacea (L.) Bojer Hort. Maurit. (1837) 227.
Tereietra violacea (L.) Rafinesque Fl. Tellur. 4 (1839) 124.
Ipomoea Hookeri G. Don Gen. Syst. 4 (1838) 274.
Pharbitis rubrocoeruleus (Hook.) Planchon Fl. des Serres 9 (1854) 281.
Convolvulus rubrocoeruleus (Hook.) D. Dietrich Syn. Pl. 1 (1839) 670.
Ipomoea puncticulata Bentham Bot. Voy. Sulph. (1945) 136.

• Credit for the discovery of the ceremonial use of *Ipomoea violacea* seeds goes to Thomas MacDougall and Francisco Ortega ("Chico"), famous Zapotec guide and itinerant trader. They have not yet delimited the area of diffusion, but they have found *badoh negro* seeds in use in the following Zapotec towns and villages in the uplands of southern Oaxaca: San Bartolo Yautepec, San Carlos Yautepec and Santa Catarina Quieri, all in the district of Yautepec; Santa Cruz Ozolotepec and San Andrés Lovene, District of Miahuatlan; and finally a settlement called Roalo, between Zaachila and Zimatlan, just south of the city of Oaxaca. In San Bartolo *I. violacea* is used to the exclusion of *Rivea corymbosa*, but in the other towns both are used. These data are based on personal correspondence and also Thomas MacDougall: *Ipomoea tricolor*: A Hallucinogenic Plant of the Zapotecs, in *Boletín* of the Centro de Investigaciones Antropológicas de México, No. 6, March 1, 1960. Reports from Juquila, to the west of the Zapotec towns mentioned above, indicate that *I. violacea* seeds may also be used among the Chatino Indians.

in these seeds was *chanoclavine*, also isolated by Dr. Hofmann et al. some years ago from a culture of *Claviceps* species.*

Thus it comes about that, thanks to the achievements of our biological chemists, we may be on the brink of rediscovering what was common knowledge among the ancient Greeks. I predict that the secret of the Mysteries will be found in the indoles, whether derived from mushrooms or from higher plants or, as in Mexico, from both.

I would not be understood as contending that only these substances (wherever found in nature) bring about visions and ecstasy. Clearly some poets and prophets and many mystics and ascetics seem to have enjoyed ecstatic visions that answer the requirements of the ancient Mysteries and that duplicate the mushroom agapé of Mexico. I do not suggest that St. John of Patmos ate mushrooms in order to write the Book of the Revelation. Yet the succession of images in his Vision, so clearly seen and yet such a phantasmagoria, means for me that he was in the same state as one bemushroomed. Nor do I suggest for a moment that William Blake knew the mushroom when he wrote this telling account of the clarity of "vision":

> The Prophets describe what they saw in Vision as real and existing men, whom they saw with their imaginative and immortal organs; the Apostles the same; the clearer the organ the more distinct the object. A Spirit and a Vision are not, as the modern philosophy supposes, a cloudy vapour, or a nothing: they are organized and minutely articulated beyond all that the mortal and perishing nature can produce. *He who does not imagine in stronger and better lineaments, and in stronger and better light than his perishing eye can see, does not imagine at all.* [Italics mine. From *The Writings of William Blake*, ed. by Geoffrey Keynes, vol. III, p. 108]

This must sound cryptic to one who does not share Blake's vision or who has not taken the mushroom. The advantage of the mushroom is that it puts many (if not everyone) within reach of this state without having to suffer the mortifications of Blake and St. John. It permits you to see, more clearly than our perishing mortal eye can see, vistas beyond the horizons of this life, to travel backwards and forwards in time, to enter other planes of existence, even (as the Indians say) to know God. It is hardly surprising that your emotions are profoundly affected, and you feel that an indissoluble bond unites you with the others who have shared with you in the sacred agapé. All that you see during this night has a pristine quality: the land-

* A. Hofmann with R. Brunner, H. Kokel, and A. Brack, *Helv. Chem. Acta*, 1957, 40:1358.

scape, the edifices, the carvings, the animals — they look as though they had come straight from the Maker's workshop. This newness of everything — it is as though the world had just dawned — overwhelms you and melts you with its beauty. Not unnaturally, what is happening to you seems to you freighted with significance, beside which the humdrum events of everyday are trivial. All these things you see with an immediacy of vision that leads you to say to yourself, "Now I am seeing for the first time, seeing direct, without the intervention of mortal eyes." (Plato tells us that beyond this ephemeral and imperfect existence here below, there is another Ideal world of Archetypes, where the original, the true, the beautiful Pattern of things exists for evermore. Poets and philosophers for millennia have pondered and discussed his conception. It is clear to me where Plato found his Ideas; it was clear to his contemporaries too. Plato had drunk of the potion in the Temple of Eleusis and had spent the night seeing the great Vision.)

And all the time that you are seeing these things, the priestess sings, not loud, but with authority. The Indians are notoriously not given to displays of inner feelings — except on these occasions. The singing is good, but under the influence of the mushroom you think it is infinitely tender and sweet. It is as though you were hearing it with your mind's ear, purged of all dross. You are lying on a *petate* or mat; perhaps, if you have been wise, on an air mattress and in a sleeping bag. It is dark, for all lights have been extinguished save a few embers among the stones on the floor and the incense in a sherd. It is still, for the thatched hut is apt to be some distance away from the village. In the darkness and stillness, that voice hovers through the hut, coming now from beyond your feet, now at your very ear, now distant, now actually underneath you, with strange ventriloquistic effect. The mushrooms produce this illusion also. Everyone experiences it, just as do the tribesmen of Siberia who have eaten of *Amanita muscaria* and lie under the spell of their shamans, displaying as these do their astonishing dexterity with ventriloquistic drum-beats. Likewise, in Mexico, I have heard a shaman engage in a most complicated percussive beat: with her hands she hits her chest, her thighs, her forehead, her arms, each giving a different resonance, keeping a complicated rhythm and modulating, even syncopating, the strokes. Your body lies in the darkness, heavy as lead, but your spirit seems to soar and leave the hut, and with the speed of thought to travel where it listeth, in time and space, accompanied by the shaman's singing and by the ejaculations of her percussive

chant. What you are seeing and what you are hearing appear as one: the music assumes harmonious shapes, giving visual form to its harmonies, and what you are seeing takes on the modalities of music — the music of the spheres. "Where has there been greater rivalry between seeing and hearing?" How apposite to the Mexican experience was the ancient Greek's rhetorical question! All your senses are similarly affected: the cigarette with which you occasionally break the tension of the night smells as no cigarette before had ever smelled; the glass of simple water is infinitely better than champagne. Elsewhere I once wrote that the bemushroomed person is poised in space, a disembodied eye, invisible, incorporeal, seeing but not seen. In truth, he is the five senses disembodied, all of them keyed to the height of sensitivity and awareness, all of them blending into one another most strangely, until the person, utterly passive, becomes a pure receptor, infinitely delicate, of sensations. (You, being a stranger, are perforce only a receptor. But the Mazatec communicants are also participants with the *curandera* in an extempore religious colloquy. Her utterances elicit spontaneous responses from them, responses that maintain a perfect harmony with her and with each other, building up to a quiet, swaying, antiphonal chant. In a successful ceremony this is an essential element, and one cannot experience the full effect of the role of the mushroom in the Indian community unless one attends such a gathering, either alone or with one or at most two other strangers.) As your body lies there in its sleeping bag, your soul is free, loses all sense of time, alert as it never was before, living an eternity in a night, seeing infinity in a grain of sand. What you have seen and heard is cut as with a burin in your memory, never to be effaced. At last you know what the ineffable is, and what ecstasy means. Ecstasy! The mind harks back to the origin of that word. For the Greeks *ekstasis* meant the flight of the soul from the body. Can you find a better word than that to describe the bemushroomed state? In common parlance, among the many who have not experienced ecstasy, ecstasy is fun, and I am frequently asked why I do not reach for mushrooms every night. But ecstasy is not fun. Your very soul is seized and shaken until it tingles. After all, who will choose to feel undiluted awe, or to float through that door yonder into the Divine Presence? The unknowing vulgar abuse the word, and we must recapture its full and terrifying sense. . . . A few hours later, the next morning, you are fit to go to work. But how unimportant work seems to you, by comparison with the portentous happenings of that night! If you can, you prefer to

stay close to the house, and, with those who lived through that night, compare notes, and utter ejaculations of amazement.

As man emerged from his brutish past, thousands of years ago, there was a stage in the evolution of his awareness when the discovery of a mushroom (or was it a higher plant?) with miraculous properties was a revelation to him, a veritable detonator to his soul, arousing in him sentiments of awe and reverence, and gentleness and love, to the highest pitch of which mankind is capable, all those sentiments and virtues that mankind has ever since regarded as the highest attribute of his kind. It made him see what this perishing mortal eye cannot see. How right the Greeks were to hedge about this Mystery, this imbibing of the potion, with secrecy and surveillance! What today is resolved into a mere drug, a tryptamine or lysergic acid derivative, was for him a prodigious miracle, inspiring in him poetry and philosophy and religion. Perhaps with all our modern knowledge we do not need the divine mushrooms any more. Or do we need them more than ever? Some are shocked that the key even to religion might be reduced to a mere drug. On the other hand, the drug is as mysterious as it ever was: "like the wind it cometh we know not whence, nor why." Out of a mere drug comes the ineffable, comes ecstasy. It is not the only instance in the history of humankind where the lowly has given birth to the divine. Altering a sacred text, we would say that this paradox is a hard saying, yet one worthy of all men to be believed.

If our classical schloars were given the opportunity to attend the rite at Eleusis, to talk with the priestess, what would they not exchange for that chance? They would approach the precincts, enter the hallowed chamber, with the reverence born of the texts venerated by scholars for millennia. How propitious would their frame of mind be, if they were invited to partake of the potion! Well, those rites take place now, unbeknownst to the classical scholars, in scattered dwellings, humble, thatched, without windows, far from the beaten track, high in the mountains of Mexico, in the stillness of the night, broken only by the distant barking of a dog or the braying of an ass. Or, since we are in the rainy season, perhaps the Mystery is accompanied by torrential rains and punctuated by terrifying thunderbolts. Then, indeed, as you lie there bemushroomed, listening to the music and seeing the visions, you know a soul shattering experience, recalling as you do the belief of some primitive peoples that mushrooms, the sacred mushrooms, are divinely engendered by Jupiter Fulminans, the God of the Lightning-bolt, in the Soft Mother Earth.

PLATO:

A Touchstone For Courage

From time to time the editors will reprint significant passages from literature relevant to consciousness-expansion. It is fitting that our first passage comes from the fount of Western thought — the philosophy of Plato. *The Laws,* the product of his mature wisdom, were written a few years before his death. A conversation takes place between an Athenian Stranger, a Cretan, and a Spartan on the subject of good and bad laws in the constitution of the ideal state. The passage below is taken from Book I. (Translation by A. E. Taylor)

In the discussion of the role of interior states, the comments on the effects of alcohol and the idea of drug-induced psychological immunization, this passage anticipates by 2000 years important modern concepts. It is possible that Plato's discussion of the fear-inducing drug was based on first-hand psychedelic experience. The Eleusinian Mysteries are believed by some scholars to have involved the consumption of a psychedelic potion as the central rite.[1] If, as has been suggested, Plato was initiated into the mysteries,[2] he would be under a vow of secrecy, which he circumvents in this passage by his use of the subjunctive.

ATHENIAN: One person has within himself a pair of unwise and conflicting counselors, whose names are pleasure and pain?

CLINIAS: The fact is as you say.

ATHENIAN: He has, besides, anticipations of the future, and these of two sorts. The common name for both sorts is *expectation,* the special name for anticipation of pain being *fear,* and for anticipation of its opposite, *confidence.* And on the top of all, there is *judgment,* to discern which of these states is better or worse, and when judgment takes the form of a public decision of a city, it has the name of *law.*

CLINIAS: I fear I hardly follow you, yet pray proceed with your statement as though I did.

MEGILLUS: I, too, find myself in the same condition.

ATHENIAN: Let us look at the whole matter in some such light as this. We may imagine that each of us living creatures is a puppet made by gods, possibly as a plaything, or possibly with some more serious purpose. That, indeed, is more than we can tell, but

one thing is certain. These interior states are, so to say, the cords, or strings, by which we are worked; they are opposed to one another, and pull us with opposite tensions in the direction of opposite actions, and therein lies the division of virtue from vice. In fact, so says our argument, a man must always yield to one of these tensions without resistance, but pull against all the other strings — must yield, that is, to that golden and hallowed drawing of judgment which goes by the name of the public law of the city. The others are hard and ironlike, it soft, as befits gold, whereas they resemble very various substances. So a man must always co-operate with the noble drawing of law, for judgment, though a noble thing, is as gentle and free from violence as noble, whence its drawing needs supporters, if the gold within us is to prevail over the other stuff. In this wise our moral fable of the human puppets will find its fulfillment. It will also become somewhat clearer, first, what is meant by self-conquest and self-defeat, and next that the individual's duty is to understand the true doctrine of these tensions and live in obedience to it. . . . And when we intend to make a man immune from various fears, we achieve our purpose by bringing him into contact with fear, under the direction of law.

CLINIAS: So it would appear.

ATHENIAN: But now, suppose our aim is to make him rightly *fearful*. What then? Must we not ensure his victory in the conflict with his own lust for pleasures by pitting him against shamelessness and training him to face it? If a man can only attain mature courage by fighting the cowardice within himself and vanquishing it, whereas without experience and discipline in that contest, no man will ever be half the champion he might be, is it credible he should come to fullness of self-command unless he first fights a winning battle against the numerous pleasures and lusts which allure him to shamelessness and wrong, by the aid of precept, practice, and artifice, alike in his play and in his serious hours? Can he be spared the experience of all this?

CLINIAS: The view, certainly, does not seem plausible.

ATHENIAN: Now, tell me, has any god bestowed on mankind a specific to induce fear — a drug (pharmakon) whose effect is that the more a man permits himself to imbibe of it, the darker he fancies his fortunes at every draught, present and future alike grow increasingly alarming, and the climax is abject terror in the bravest, though

when the subject has recovered from his stupor and shaken off the effects of the potion, he regularly becomes his own man again?

CLINIAS: Nay, sir, where in all the world can we find a liquor like this?

ATHENIAN: Why, nowhere. But suppose one could have been found. Would the lawgiver have availed himself of it to develop courage? I mean, it would have been very much to the purpose to discuss it with him to some such effect as this. Pray, sir legislator —whether it is for Cretans or for any other society your legislation is intended — in the first place, would you be thankful for a touchstone of the courage or cowardice of your citizens?

CLINIAS: And he would, no doubt, be sure to say yes.

ATHENIAN: Well then, would you like the touchstone to be safe and applicable without serious risks, or the reverse?

CLINIAS: There, again, he would be certain to prefer safety.

ATHENIAN: You would employ it to bring your citizens into such a state of fear and test them under its influence, thus constraining a man to become fearless, by encouragement, precept, and marks of recognition, as well as of disgrace for those who declined to be such as you could have them in all situations? He who shaped himself to this discipline well and manfully would be discharged from the test unscathed, but on him who shaped badly you would lay some penalty? Or would you simply refuse to employ the liquor, supposing you had no fault to find with it on other grounds?

CLINIAS: Why, of course he would employ it, my dear sir.

ATHENIAN: It would, at least, give us an infinitely readier and safer training than our present arrangements, whether for the individual, for small groups, or for groups of any desired numbers. A man would do pretty right to save endless trouble by providing himself with this single specific and training himself in privacy to face his fears, isolating himself, of course, from public view behind his regard for decorum until he had obtained a satisfactory result. And, again, he would do right, when confident that he was already adequately prepared by native endowment and preliminary practice, to prosecute his training in the company of fellow drinkers, and make public exhibition of the virtue which enables him to transcend and master the effects of the inevitable disturbances due to the potion,

without once suffering a serious fall or deterioration, though he would leave off before he reached the final draught from fear of our universal human weakness before the liquor.

CLINIAS: Why yes, sir, even such a man as you speak of would be wise to do that.

ATHENIAN: Then let us resume our conversation with the legislator. Very good, we shall say to him, as for such a fear-inducing specific, providence has given us none, and we have invented none ourselves, for we need not take quacksalvers into account, but what about fearlessness, excessive confidence, improper confidence at the wrong moment? Is there a liquor which has these effects, or is there not?

CLINIAS: He will, of course, say yes, and he will mean wine.

ATHENIAN: And are not its effects the very opposite of all we have just mentioned? When a man drinks it, its first immediate effect is to make him merrier than he was, and the more he takes, the more it fills him with optimistic fancies and imaginary capacity. In the very final phase the drinker is swollen with the conceit of his own wisdom to the pitch of complete license of speech and action, and utter fearlessness; there is nothing he will scruple to say, nothing he will scruple to do. I think this will be universally conceded.

[1] See the article by Wasson in this issue.
[2] Friedlander, P. *Plato: An Introduction.* New York, Pantheon Books, 1959, pp. 70ff.

Provoked Life:

An Essay On The Anthropology Of The Ego

GOTTFRIED BENN

Gottfried Benn (1886-1956) was one of the leading German lyric poets of this century and the major spokesman of the writers of the expressionist period in Germany. A physician by profession (he practiced medicine throughout his life) he did a considerable amount of original research in his field. In poetry he stood for the exploration of novel and often extreme experiences for the expression of which he created a new language combining divergent elements from the medical, vernacular and refined poetic vocabularies, coining new expressions, using daring images, and revolutionary ideas.

A trenchant social critic, Benn exposed the dangers of our technological era and the trend toward overemphasis of the rational and intellectual. He was anything but conservative in his writings and supported unlimited creative expansion and expression. He strove for a reconciliation between the natural, instinctual basis of man and his intellect; he worked for the resolution of dichotomies characterizing our lives, inner and outer, real and unreal, natural and artificial. Benn advocated the realization of our "antinaturalistic" nature, the creation of a "cerebral reality," a "provoked Life out of the materials of dream and stimulation."

The essay *"Provoziertes Leben"* (Provoked Life) was written in the early 1940's and appeared in the volume: "Ausdruckswelt, Essays und Aphorismen," 1949, Limes Verlag, Wiesbaden, Germany. We gratefully acknowledge the permission of the Limes Verlag, Wiesbaden, Germany, to translate and reprint this essay.

I

Several years ago a film was shown in Berlin, a film about Negroes called "Hosiannah," in which one saw Negroes getting intoxicated through communal singing. The disposition to do this lies in their nature, the process itself was sensual and conscious. Similar phenomena are reported about the North American Indians: The "Great Nightsong" is one of their principal ceremonies, where the men hold one another, move rhythmically and go into a trance. Closeness to intoxication is evidently a primitive quality as is the transition to a collectively heightened sense of being. The assembly provokes the transition through rites, movements, and certain ancient chants. It is a call of the race. Its nature is religious and mythical, an exciting communion with the totality which expands individual existence.

Over against the trances induced by ritual movements and rhythm, are those induced by plant extracts, whose distribution is far more universal. Several million of the earth's inhabitants smoke or drink Indian hemp, as countless generations have done so through two thousand years. Three hundred million people chew betel; the great rice-eating population would sooner give up rice than the areca-nut; not to chew means to die. The three largest continents stimulate themselves through caffein; in Tibet, time is measured using a cup of tea and its effects; tea was found among the remains of prehistoric people. Chemicals which affect the brain, means of altering consciousness — these were primitive man's first approaches to his nervous system. How the effects were discovered is a mystery. A primal urge and a secret. Among a thousand roots, shrubs, trees, mushrooms, flowers — this one! Countless individuals probably died of poisoning before the race had reached its goal: enhancement, expansion — provoked life. Caravans with opium travel through the desert. Sykone is renamed Mekone, i.e. poppy-ville. On the tomb of Ariadne, a bearded god bends over her sleeping form, the god of sleep, carrying poppy-heads and the poppy-horn. The queen of the Incas was named after the miraculous plant Erythroxolon Coca; Mama Cuca; the stone idols have one cheek filled with coca leaves as a sign of divinity; everywhere there are bottle-shaped pumpkins, in which the leaf is kept, mixed with chalk and plant ashes, ready to be taken; the long needle with which you take it out is moistened by mouth. The effects of a mouthful of coca last forty minutes, equivalent to three kilometers on flat terrain, two kilometers in the hills — this is the dosage measure.

The ingestion takes place in the rancho of dreamers in Ecuador, in tents, while the medicine man beats the drums, or in empty cellars lined with stone projections used as seats by the guests, sometimes with the women, sometimes without: the "black drink," the "white water," the "happiness pills," or the "weed of graves," which brings unity with the spirits. Stages of excitement, stages of dream — you are beside yourself, but you feel, you learn from twitches and breathing disturbances, you get apathy or mobility as desired. From hidden centres, from the depths it emerges: to rest, to move no more: withdrawal, regression, aphasia. Hours are filled with the satisfaction of the desire to drift along as formless life. To call this animalistic is to be mistaken: this process is far below the animals, below the reflexes, it is near roots, chalk and stone. This is not the apathy of a dying race, not degeneration, these are youthful

people; it is something more primary: defense against the beginnings of consciousness, its senseless imperative projects — thus, change space, obliterate time, blow away the grim passage of hours.

As long as memory traces, and civilizations, have existed in the brain, this organ of classification: forget them! In front of the Bistro drawn figures, home-owner idealists, worn out child-bearers, curves without deflections, normalized garbage — ah — garcon — another cocain-pulque, or in the restroom a pinch of snuff applied to the mucous membrane of the anus; or plug a soaked filling into a specially cultivated decayed tooth — ah — already the perspectives are beginning, ceaselessly spilling out of crosslines, winding and flickering; — Helena gave the heroes Nepenthes with their food, certainly an opiate preparation, when the mood was low or just before the battle, — ah, my battle too begins — first fields, colored like jewels, then red birds, — a *purely cortical reality* — lattice patterns are particularly frequent — "jewelers and artists should see this, they could take patterns from it," the colors become finer, strings are hanging from the surfaces, marvels are looking out of things.

The ego disintegrates, the places of disintegration are the planes of attachment. There is a kind of cosmic coldness, sublime and icy, in the structure, but fire in the medial axis; feelings of limbs lengthening and shortening, feelings of swelling and joining; simultaneously more sensitive thresholds: a storm of impressions, suggestibility to external influences, directed toward something universal, a feeling of totality: "Noon feeling." The senses exchange functions: "at the stroke of the clock purple color emerges"; alternating experiences of merging and distanciating; cutting through ego-feeling, smiling without affect, crying without object. Feelings of capacity: "the solution of dimly sensed problems seems immanent," — "everywhere the unheard of rejoicing of powerful harmony" — "Lord, let me bloom," — (Bucke's "cosmic emotion").

Another: "A great tension came over me. Great things had to be revealed to me. I would see the nature of all things, all the problems of the world would dissolve. I was out of my senses." Promenade of a god on the banks of the Po. "Golden late afternoon light." Then: "Only beauty in the eternal transformation of forms and colors. An increasing feeling of liberation came over me. Here everything would be resolved, *in the end everything was rhythm.*" (Klages came to the same conclusion, not so suddenly, but at the

end of a long life and with the aid of many books. Quantum theory says the same thing.)

Strange penetration of depth, cosmic osmosis (Magnaosmose): "I need time to finish my world view, which in skeleton form already is grounded on one sentence: *God is a substance.*" God is a substance, a drug! An intoxicating substance with affinity for the human brain. Certainly possible, at any rate more probable than that he is an electroshock machine or a Spemann Tritonlarva, formed by stuffing tadpole tissue in the mouth area. . . .

Complex structures become brittle, one can see through the rifts: "I had a peculiar muscle sensation. I *could have removed every single muscle separately from my body.*" (Long, long ago! The "muscle soul" arises, its contribution to the development of consciousness.) The cortex loses its recently acquired property of specific sensory quality (seeing, hearing, smelling, tasting) and answers in forms of general resonance. The "external" is not yet there; grounds yes, but hunting and fishing grounds: — the prehistory of "reality."

II

With the formation of the concept of "reality" the crisis began, the premorbid stage, its depth, its nihilistic existence. Indian-Javanese art (the socle of Borobudur) was in the other stage as late as 800 A.D. In its almost obscene luxuriance and exuberance of limbs and shapes, in the endless relief of animals, plants, human growths, bears, flowers, Bahadurs, hermits, tortoises, jackals, monkey-princes, all represented without pointedness, undifferentiated, inexhaustible, — the human beings all with the same roundish, smooth, full bodies with relatively small heads, all the same shape, all naked: in all this you can read the "Tat-tvam-asi," the "you are this also" of the Hindu doctrine, you can see ethical and physiological promiscuity, the original monosexuality of the primitive organism, which performed seed-formation, copulation and impregnation within itself, but you can also see the inner world still accessible to everyone, serene, mild and joined in dance, a world that knows a binding principle which in constant renewal surrounds the spiritual core of being. From this core emerges the great Night-or-Day chant, the great chant of the socle, of prelogical worlds still capable of giving fulfillment.

1300 years before this socle, in the southern part of our continent, the concept of reality began to be formed. The Hellenistic-European agonistic principle of victory through effort, cunning, malice, talent. force, and the later European Darwinism and "superman," was instrumental in its formation. The ego emerged, dominated, fought; for this it needed instruments, material, power. It had a different relationship to matter, more removed sensually, but closer formally. It analysed matter, tested, sorted: weapons, object of exchange, ransom money. It clarified matter through isolation, reduced it to formulas, took pieces out of it, divided it up. Compared to the soft Javanese wave-feeling, this attitude appears brutal and low. Its price was the separation of ego and world, the schizoid catastrophe, the inevitable western neurosis: reality. A tortuous concept and all were tortured by it, the intelligence of countless generations was divided over it. A concept which hung like a punishment over the West, with which the West fought, without grasping it, to which it sacrificed enormous quantities of blood and happiness; a concept whose inner tension and fragmentations it was impossible to dissolve through a natural viewing or methodical insight into the inherent unity and peace of prelogical forms of being. At a certain critical juncture Kant attempted to insert formal protections, but succeeded only in driving the development still further, so that it ("reality") now contained only causal-analytical results, including those of biological experiments, everything else was dream, animism, psychogenic arabesque. Goethe alone succeeded in overcoming the split, in a process lasting several decades, publicly recorded; his was a permanent solution but it was of a purely personal nature. Except for him no one else overcame the concept, no one else could; instead the cataclysmic character of this idea became clearer and clearer, as for example with Nietzsche. The latter took the idea of "reality" so much at its face value that (in extremely bold fashion) he attempted to "penetrate" it with ideas and thoughts of breeding, sending out Zarathustra "to create the creator." Nothing would have been further removed from the mind of this ancient Ormudh-Ahriman dualist; he would presumably, after taking one look at the impenetrable sun, have contemplated the poppies growing between the rose fields of Schiras and then lightly touched the ground with his forehead: you gave the Schire-Teriak and I take it! Finally, a state, a social organization, a public morality, for which life is economically usable life and which does not recognize the world of provoked life, cannot accept its destructive force. A society, whose hygiene and race cultivation as a modern ritual is founded solely on hollow biological statistics, can only represent the external viewpoint of the mass; for this point of view it can wage war, incessantly, for reality is simply raw material, but the metaphysical background remains forever obscured. The preceding, however, deals with this

background and relates it to the problem of sublimation, to the "émotions sublimes" of Janet, i.e. to enhancement phenomena and expressive values.

III

The issue concerns the mythical collectivity as a foundation for life, as an unreflective sense of being, and its remnants in our nature and ways of realizing it. Compared to the tribal life of primitives which arises naturally from their inner properties, compared to the image-soaked faith of the Asistic peoples, what life-content the denatured European brains can realize in terms of occupational activities, clubs, family gatherings, summer excursions and so-called feasts can only be regarded as flat, conventional and shopworn; the few primal crimes which may occur in one decade are not sufficient to maintain the belief in a moral tradition of the race. Above all what is lacking is any systematic educational effort in the direction of conscious enhancement of vitality, since the epoch as a whole has no fundamental principles at all. If it were not so, one could, by increasing visionary states, say with mescaline or hashish, supply the race with a stream of spiritual insights, which could lead to a new creative period. Or they might hit on the idea of using hypnosis — at present exclusively in the hands of causal-analytical, norm-oriented physicians — not to increase potential in terms of economic utility, but for the liberation of the unconscious, i.e. suppressed, organic functions and archaic mechanisms — surprising experiences would be the result. Pervitin, instead of giving it to bomber pilots and explorers, could be purposefully used in the high schools and colleges for the induction of cerebral oscillations. This may sound extreme to some, but is merely the natural continuation of an old human idea. Whether through rhythm, drugs or autogenic training — we have the ancient human urge to overcome intolerable tensions between outer and inner, between god and not-god, between ego and reality — and we have the old and recent experience of having access to the means of overcoming them. The Buddha's systematic "prayer breathing," the ritual prayer postures of the early Christian hesychasts, Loyola's breathing with every verse of the Lord's Prayer, the dervishes, yogis, Dionysian rites, Mysteries, — all one family, which one could call the physiology of religion. German mysticism, according to Jakob Böhme "the unification of the natural self with the nothing" (note: with *nothing,* not with God), this mysticism, which one scholar has called "an almost experimental psychology of

religion of the most ruthless sort," is the same thing — in other words, provoked religion.

All these are historical facts, widespread experiences; even from a biological point of view they are psychological truths. In spite of this such a conception is totally alien to the modern state. On the contrary, the government recently instituted an anti-narcotics program, and its biologists think of themselves as progressive. It would be difficult to make it clear to them that their program has the same relation to the problem of humanity as the mailman does to world government. Moreover, the possibility of helping mountaineers at high altitudes through drugs is actively studied by official physiologists, but the possibility of enhancing formal-aesthetic functions is not studied at all. We now have the establishment of centers for the collection of human milk; for example, a recent report showed that in Frankfort 1200 mothers gave 10,000 litres in two years, one mother gave 753 litres alone, another provided 460 litres when her sixth child was born. *However, potent brains are not strengthened through milk but through alkaloids.* An organ of such small size and great vulnerability, which not only approached the pyramids and gamma-rays, lions and icebergs, but created and invented them, cannot be watered like a forget-me-not, it will find its own supplies. *Existence means nervous existence,* i.e. stimulability, discipline, enormous factual knowledge, art. To suffer is to suffer in one's consciousness, not over deaths. To work is to expand spiritual capacities. In one word: *life is provoked life.*

Of course, someone will immediately mention the notion of *damage,* individual and racial. Drugs, intoxications, ecstasies, spiritual exhibitionism — all this sounds infernal to most people. But the concept of damage belongs in the reference-frame of "causal analysis" and "biology" and has the limited applicability of these systems. But even within these systems, a state which wages wars in which three million men are killed within three years is hardly in a position to talk about damage; this is damage of individual and communal interests which far exceeds the damage of experiments on the expanding ability of drugs. The issue is not damage, but principles, and what kind you want to adopt. If you consider this idea of damage on a more general level, it becomes an interesting observation, that impairments suffered by an entire race have usually brought their compensation which far exceed the value of what was lost. So for example, the loss of skin pigment was initially for the white race an extremely dangerous disability exposing them to unheard of intensities of radi-

ation; but eventually it was compensated by another descendant of the same common primary seed, or ectoderm, namely the extremely powerful nervous system which was capable of dealing with danger. (The human brain was born as a result of or at least after, this impairment.) In other words, in talking of damage the context has to be considered. Whether the degenerating central European brain *can* be damaged is in any case an open question.

One will not reach any insights in this area who does not meditate at length on the nature of the brain. The brain is the perfect example for the pigmy-character of causal theories, it has travelled a most acausal path, all biological hypotheses fail to explain it. It seems clear, since the work of Vershuys, Poetzl and Lorenz, that the brain developed through doubling the number of neurones and simultaneously rearranging the outer (cortical) layers. "There are no intermediary forms." There is no trace of adaptation, summation of minute stimuli, gradual growth and decay until some purposive reorganization takes place — *there were always creative crises.* The brain is the mutative, revolutionary organ par excellence. Its nature was always form, not content, its means expansion, its needs—stimuli. This store-house of rudiments and catacombs brought everything with it from the beginning, it was not dependent on impressions, it produced itself when called for. It was by no means favorably predisposed towards "life," but was equally available for lethal activities, hunger, fasting, walking on nails, charming snakes, magic, bionegatives, death.

"Mens sana in corpore sano" was a proverb of the Roman warrior caste, which has had a modern resurrection in the gymnastics of Jahn and in the Bavarian health cults. Using inner criteria the extravagant body has accomplished more than the normal body; its bionegative characteristics created and carry the human world. By these criteria there is no reality, no history, just some brains which realize at certain time-intervals their dreams, images of the ancient original dreams, made in retrospective insight. This realization may take place in "stone, verse or flute-song" — then we have art; sometimes it takes place only in thoughts or ecstasies. A marvelous sentence from a novel by Thornton Wilder describes the situation: "We come from a world in which we have known unbelievable standards of perfection and we remember faintly the beauty, which we were unable to retain, and we return to this world." Clearly Plato is at hand; endogenous images are the last remaining vestigial forms of our happiness.

(Translated by Ralph Metzner)

The Individual As Man/World

ALAN W. WATTS

(*Prefatory Note*: The following was originally delivered as an impromptu lecture for the Social Relations Colloquium at Harvard University on April 12th, 1963. Although the subject was not discussed in the lecture itself, its theme is closely related to the expansion of consciousness achieved through psychedelic substances. With proper "set and setting," the psychedelics are very frequently successful in giving the individual a vivid sensation of the mutual interdependence of his own behavior and the behavior of his environment, so that the two seem to become one — the behavior of a unified field. Those who uphold the impoverished sense of reality sanctioned by official psychiatry describe this type of awareness as "depersonalization," "loss of ego-boundary," or "regression to the oceanic feeling," all of which, in their usual contexts, are derogatory terms suggesting that the state is hallucinatory. Yet it accords astonishingly well with the description of the individual which is given in the behavioral sciences, in biology and in ecology.

Theoretically, many scientists know that the individual is not a skin-encapsulated ego but an organism-environment field. The organism itself is a point at which the field is "focused," so that each individual is a unique expression of the behavior of the whole field, which is ultimately the universe itself. But to know this theoretically is not to *feel* it to be so. It was possible to calculate that the world was round before making the voyage that proved it to be so. The psychedelics are, perhaps, the ship, the experimental instrument by which the theory can be verified in common experience.)

There is a colossal disparity between the way in which most individuals experience their own existence, and the way in which the individual is described in such sciences as biology, ecology, and physiology. The nub of the difference is this: the way the individual is described in these sciences is not as a freely moving entity within an environment, but as a process of behavior which *is* the environment also. If you will accurately describe what any individual organism is doing, you will take but a few steps before you are also describing what the environment is doing. To put it more simply, we can do without such expressions as "what the individual is doing" or "what the environment is doing," as if the individual was one thing and the doing another, the environment one thing and its doing another. If we reduce the whole business simply to the process of doing, then the doing, which was called the behavior of the individual,

is found to be *at the same time* the doing which was called the behavior of the environment. In other words, it is quite impossible to describe the movement of my arm except in relation to the rest of my body and to the background against which you perceive it. The relations in which you perceive this movement are the absolutely necessary condition for your perceiving at all. More and more, a "field theory" of man's behavior becomes necessary for the sciences.

Yet this is at complete variance with the way in which we are trained *by our culture* to experience our own existence. We do not, generally speaking, experience ourselves as the behavior of the field, but rather as a center of energy and consciousness which sometimes manages to control its environment, but at other times feels completely dominated by the environment. Thus there is a somewhat hostile relationship between the human organism and its social and natural environment, which is expressed in such phrases as "man's conquest of nature," or "man's conquest of space," and other such antagonistic figures of speech.

It would obviously be to the advantage of mankind if the way in which we feel our existence could correspond to the way in which existence is scientifically described. For what we feel has far more influence upon our actions than what we think. Scientists of all kinds are warning us most urgently that we are using our technology disastrously, eating up all the natural resources of the earth, creating incredibly beautiful but wholly non-nutritious vegetables by altering the biochemical balances of the soil, spawning unbelievable amounts of detergent froth which will eventually engulf cities, overpopulating ourselves because of the success of medicine, and thus winning our war against nature in such a way as to defeat ourselves completely. All this advice falls on deaf ears, because it falls on the ears of organisms convinced that war against nature is their proper way of life. They have to be unconvinced, and can be, to some extent, by intellectual propaganda, scientific description, and clear thought. But this moves relatively few people to action. Most are moved only if their feelings are profoundly affected. We need to *feel* this view of our individual identity as including its environment, and this must obviously concern scientists who are trying to find ways of controlling human feelings.

This problem has an important historical background. It is curious how the ancient philosophical debates of the Western world keep coming up again and again in new forms. Any question of the definition of the individual always becomes involved with the old

argument between nominalism and realism. I do not wish to insult the intelligence of this learned audience, but, just to refresh your memories, the realistic philosophy of the Middle Ages and of the Greeks was not what today we call realism. It was the belief that behind all specific manifestations of life such as men, trees, dogs, there lies an archetypal, or ideal, form of Man, of Tree, of Dog, so that every particular man is an instance of that archetypal form, and that behind all men is something which can be called Man with a capital M, or the "substance" of man, of "human nature."

The nominalists argued that this was a mere abstraction, and that to regard Man (capital M) as possessing any effective existence was to be deluded by concepts. There are only specific, individual men. This idea is carried on in one of the most remarkable forms of modern nominalism, General Semantics, which argues that such abstractions as "The United States," "Britain," or "Russia," are so much journalistic gobbledygook.

Most people working in the sciences tend to be nominalists. But if you carry nominalism to its logical conclusion, you are involved in awkward problems. Not only would there be no such thing as Man, Mankind, or Human Nature, but it would also follow that there are no individual men, because the individual man is an abstraction, and what really exists is only an enormous amalgamation of particular molecules. If you pursue this further and inquire about the individual entities composing the molecules, there is an interminable array of nuclear and sub-nuclear realities, and if *these* in turn are to be regarded as the only realities, then the reality which we call a man is simply the association of discontinuous particles. This is the *reductio ad absurdum* of nominalism carried too far. The nominalist and realist viewpoints are actually *limits* — to borrow a term from mathematics. I have often thought that all philosophical debates are ultimately between the partisans of structure and the partisans of "goo." The academic world puts a heavy emphasis on structure: "Let's be definite, let's have rigor and precision, even though we are studying poetry." But the poets will reply: "We are for goo, and you people are all dry bones, rattling in the wind. What you need is essential juices, and therefore more goo is necessary to liven you up." But when we want to know what goo is, and examine it carefully, we eventually turn up with a structure, the molecular or atomic composition of goo! On the other hand, when we try to examine the structure itself to study the substance of its bones, we inevitably come up with something gooey. When the microscope

focus is clear, you have structure. But when you reach beyond the focus and what confronts you is vague and amorphous, you have goo because you cannot attain clarity. Structure and goo are essential limits of human thought; similarly, the nominalist-structural and the realist-gooey will always be essential limits in our thinking. We must be aware that today, the particular academic and scientific fashion leans heavily in the direction of structure and nominalism.

To take a specific example, we all know that in modern medicine nominalism and structuralism hold the field. When you go to a hospital, you are liable to go through a process of examination by specialists working upon you from different points of view. They will treat you as a non-person, from the very moment you enter. You are immediately put in a wheelchair — a symbol of the fact that you are now an object. You will be looked at piecemeal, X-rays will be taken of various organs, and special tests will be made of their functioning. If anything is wrong, you will be taken to a medical mechanic, i.e., a surgeon, who will use his equivalents of wrenches, screwdrivers and blowtorches to make certain mechanical alterations in your organism, and it is hoped you will get along fairly well with these repairs!

But the opposite, minority school of medicine will say: "This is all very well, and the services of the surgeon are sometimes greatly welcomed, but man must be considered as a whole. He has complicated metabolic and endocrine balances, and if you interfere with him seriously at one point, you will affect him unpredictably at many others, for man is an organic whole." Such are accused of being woolly-minded, old-fashioned doctors, mostly from Europe, with a kind of nature-cure background, who will use diet, complicated fasts, and massage. The poor layman doesn't know whether to deliver himself over to these old-fashioned naturalistic doctors or to Mr. Sawbones with his very up-to-date qualifications.

Fortunately, precise science is coming to the rescue of our man-as-a-whole. More recent studies are showing just how diseases formerly regarded as specific entities, or afflictions of a particular organ or area, are actually brought about by responses of the central nervous system, acting as an integrated whole. We are beginning to see how man, as a complex of organs, is not an *addition* of parts, like an automobile. His various organs are not to be treated as if they were assembled together, but by seeing the physical body as a unified or integrated pattern of behavior — which is just what we mean when

we talk about an entity or thing. What happens when we have the feeling that we understand something, when we say, "Oh, I see"? If a child asks, "Why are the leaves green?" and you answer, "Because of the chlorophyll," and the child says, "Oh!," that is *pseudo*-understanding. But when the child has a jigsaw puzzle and sees how it all fits together, then the "Oh!" has a different meaning from the "Oh!" following the chlorophyll explanation. To understand anything is to be able to fit various parts into a system which is an integrated whole, so that they "make sense."

As organic diseases are fitted into a whole, and problems of crime or phychosis in individual behavior are fitted in with a pattern of social behavior that makes sense, that is consistent with those kinds of behaviors, we say "Aha! — *now* I see!"

Fascinating work is being done in studying the ways in which the individual as a system of behavior is related to his biological and social environments, showing how his behavior may be explained in terms of those environments. One of the people who has done very important work in this sphere is our distinguished colleague, B. F. Skinner. I cite his work because it brings out these ideas in a marvellously clear, crucial, and provocative way, and because it is evidence for conclusions which he himself does not seem to have realized. One of his most important statements is in his book,
Science and Human Behavior:[1]

> The hypothesis that man is not free is essential to the application of scientific method to the study of human behavior. The free inner man who is held responsible for the behavior of the external biological organism is only a prescientific substitute for the kinds of causes which are discovered in the course of a scientific analysis.

He is talking, of course, about the chauffeur inside the body, or what Wittgenstein called the little man inside the head: this is for him a prescientific substitute for the kinds of causes for behavior which are discovered in the course of scientific analysis. He continues:

> All these alternative causes lie *outside* the individual. The biological substratum itself is determined by prior events in a genetic process. Other important events are found in the nonsocial environment and in the culture of the individual in the broadest possible sense. These are the things which *make** the individual behave as he does. For them he is not responsible and for them it is useless to praise or blame him. It does not matter that the individual may take it upon himself to control the variables of which his own behavior is a function or, in a broader sense, to engage in the design of his own culture. He

[1] New York: Macmillan, 1953, pp. 447-448.

> does this only because he is the product of a culture which *generates** self-control or cultural design as a mode of behavior. The environment determines the individual even when he alters the environment.[1]
> [*Emphasis mine—A.W.W.]

I am not going to quarrel with this finding. I am not a clinical or experimental psychologist and am therefore unqualified to criticize Skinner's evidence. Let's take it for Gospel, simply for the sake of argument.

But there is a rather heavy emphasis upon the individual being the puppet. "All these alternative causes," i.e., the kinds of causes discovered in the course of scientific behavior, "lie outside the individual," i.e., outside this wall of flesh and bag of skin. The individual is therefore passive. This is psychology in terms of Newtonian physics. The individual is a billiard ball upon which other balls impinge, and his seemingly active behavior is only a passive response. Skinner admits the individual does and can alter the environment, but when he does so, he is *being made* to do so. This is put forth in such a way as to make the individual appear passive and the things *really* controlling his behavior outside him.

But the reciprocal relationship between the knower and the known, common to all the sciences, is set aside here although he mentions it elsewhere.

> A laboratory for the study of behavior contains many devices for controlling the environment and for recording and analyzing the behavior of organisms. With the help of these devices and their associated techniques, we change the behavior of an organism in various ways, with considerable precision. But note that the organism changes our behavior in quite as precise a fashion. Our apparatus was designed by the organism we study, for it was the organism which led us to choose a particular manipulandum, particular categories of stimulation, particular modes of reinforcement, and so on, and to record particular aspects of its behavior. Measures which were successful were for that reason reinforcing and have been retained, while others have been, as we say, extinguished. The verbal behavior with which we analyze our data has been shaped in a similar way: order and consistency emerged to reinforce certain practices which were adopted, while other practices suffered extinction and were abandoned. (All scientific techniques, as well as scientific knowledge itself, are generated in this way. A cyclotron is "designed" by the particles it is to control, and a theory is written by the particles it is to explain, as the behavior of these particles shapes the nonverbal and verbal behavior of the scientist.)[2]

[2] "The Design of Cultures," *Daedalus*, Summer 1961, p. 543.

In one of his essays, he has a cartoon of one mouse saying to another, "Boy, have I got that guy up there fixed! Every time I press this bar, he gives me some food!"

Although Skinner seems in general to be stressing heavily the point of view that the individual is the puppet in the field in which he is involved, he is nevertheless stating here the opposite point, that the individual organism, mouse, or guinea pig, in the experiment is nevertheless determining the environment even when, as in a laboratory, the environment is designed to control the specific organism. The environment of a rat running in a barn is not designed to control the rat, but the more it is so designed, the more the rat is involved in and shaping its environment. He writes elsewhere that what he has been saying

> does not mean that anyone in possession of the methods and results of science can step outside the stream of history and take the evolution of government into his own hands. Science is not free, either. It cannot interfere with the course of events; it is simply part of that course. It would be quite inconsistent if we were to exempt the scientist from the account which science gives of human behavior in general.[3]

Now we might well object: "Look, Professor Skinner, you say we are completely conditioned behavior-systems. We cannot change anything. At the same time, you are calling upon us to embark upon the most radical program of controlling human behavior. How can you write *Walden II*, a utopia? Are you not a monstrosity of inconsistency by calling for responsible human action and at the same time saying that we have no freedom?" But is this actually a contradiction? He is saying two things, both of which can be valid, but he does not provide a framework in which the opposed points of view can make sense. Similarly, the physicist says light can be considered as a wave or as a particle system. These sound mutually exclusive to the non-physicist. In the same way, the advocacy of a planned development of human resources and potentials, coupled with the idea that the individual is not a self-controlling, skin-encapsulated ego, needs some further concept to help it along. The following passage clinches the problem.

> Just as biographers and critics look for external influences to account for the traits and achievements of the men they study, so science ultimately explains behavior in terms of "causes" or conditions which lie beyond the individual himself. As more and more causal relations are demonstrated, a practical corollary becomes difficult to resist: it

[3] *Science and Human Behavior*, p. 446.

> should be possible to *produce* behavior according to plan simply by arranging the proper conditions.[4]

There is the contradiction which necessarily arises in a psychology with a language system which incorporates into present scientific knowledge an outmoded conception of the individual — the individual as something bounded by skin, and which is pushed around by an environment which is not the individual. Skinner is naturally aware that his emphasis on our passive relationship to conditioning causes is rather unpalatable.

> The conception of the individual which emerges from a scientific analysis is distasteful to most of those who have been strongly affeeted by democratic philosophies . . . it has always been the unfortunate task of science to dispossess cherished beliefs regarding the place of man in the universe. It is easy to understand why men so frequently flatter themselves — why they characterize the world in ways which reinforce them by providing escape from the consequences of criticism or other forms of punishment. But although flattery temporarily strengthens behavior, it is questionable whether it has any ultimate survival value. If science does not confirm the assumptions of freedom, initiative, and responsibility in the behavior of the individual, these assumptons will not ultimately be effectve either as motivating devices or as goals in the design of culture. We may not give them up easily, and we may, in fact, find it difficult to control ourselves or others until alternative principles have been developed.[5]

There the book ends, and there is no suggestion as to what those principles might be, even though they are implied in his conclusions.

> When an individual conspicuously manipulates the variables of which the behavior of *another** individual is a function, we say that the first individual controls the second, but we do not ask who or what controls the first. When a government conspicuously controls its citizens, we consider this fact without identifying the events which control the government. When the individual is strengthened as a measure of counter-control, we may, as in democratic philosophies, think of him as a starting point. [* My emphasis—A.W.W.]

Isn't this political nominalism?

> Actually, however, we are not justified in assigning *to anyone or anything* the role of prime mover. Although it is necessary that science confine itself to selected segments in a continuous series of events, it is *to the whole series* that any interpretation must eventually apply.[6] [My emphases—A.W.W.]

[4] "Freedom and the Control of Men," *The American Scholar*, Vol. 25, No. 1, Winter, 1955-56, p. 47.

[5] *Science and Human Behavior*, p. 449.

[6] *Ibid.*, pp. 448-449.

We are now listening to a man who represents himself as a behavioristically oriented, non-mystical, on-the-whole materialistic, hard-headed scientist. Yet this passage is the purest mysticism, which might have come straight from Mahayana Buddhism: "We are not justified in assigning to anyone or anything the role of prime mover." No segment, no particular pattern of integrated behavior within whatever universe we are discussing can be called the prime mover. Now this is the *Dharmadhatu* doctrine of Mahayana Buddhism, that the universe is a harmonious system which has no governor, that it is an integrated organism but nobody is in charge of it. Its corollary is that everyone and everything is the prime mover.

In Skinner's language, the popular conception of the inner self, the little man inside the head who is controlling everything, must be replaced by the whole system of *external* causes operating upon the individual, the whole network of causal relationships. But this language obscures a very simple thing: when there is a certain cause in the external environment whose effect is always a particular individual behavior, you are using very cumbersome language for something you can describe more simply. For when you find these two things going together, you are actually talking about one thing. To say that Event A causes Event B is a laborious way of saying that it is one Event C. If I lift up this book by a corner, all the corners are lifted up at the same time. If I lift up an accordion, there is an interval between cause and effect. Similarly when we study the individual's behavior, we are studying a system of relationships, but we are looking at it too close up. All we see is the atomic events, and we don't see the integrated system which would make them make sense if we could see it. Our scientific methods of description suffer from a defective conception of the individual. The individual is not by any means what is contained inside a given envelope of skin. The individual organism is the particular and unique focal point of a network of relations which is ultimately a "whole series" — I suppose that means the whole cosmos. And the whole cosmos so focused is one's actual self. This is, whether you like it or not, pure mysticism. Skinner is saying that although science is a method of observation which, by reason of the blinkers of the head, is limited to our one-thing-at-a-time method of thought, science can only look at the world area by area. But science also becomes the method of understanding its own limitations. When you conduct any experiment, you must be careful to exclude variables you cannot measure. When you want to keep something at a constant tem-

perature, you must put it into some kind of heat-and-cold-proof or shock-proof, or cosmic-ray-proof system. So by excluding variables and by having to do it rigorously, you begin to understand how really impossible it is to do except in very special cases. In this way, the scientist, by attempting to isolate events and by looking as rigorously as he can at one segment of the world at a time, becomes aware of the fact that this looking at things simply in segments, although it is a form of very bright, clear, conscious knowledge, is also a form of ignorance. For it is a form of "ignore-ance," ignoring everything that is not in that segment. Therefore he becomes aware of the fact that just this is *ultimately* what you can't do. You *can* do it only to discover you *cannot* do it.

I commend these observations to you simply to show how a scientific thinker whose whole stance is in the direction of mechanism, of regarding the human being as a kind of biological puppet, must be forced by the logic of his own thinking to conclusions of a rather different kind. He states these questions in veiled language, so that neither he nor his colleagues will see their disastrously unrespectable implications!

Suppose, then, it becomes possible for us to have a new sense of the individual, that we all become conscious of ourselves as organism-environment fields, vividly aware of the fact that when we move, it is not simply my self moving inside my skin, exercising energy upon my limbs, but also that in some marvelous way the physical continuum in which I move is also moving me. The very fact that I am here in this room at all is because you are here. It was a common concurrence, a whole concatenation of circumstances which go together, each reciprocally related to all. Would such an awareness be significant? Would it add to our knowledge? Would it change anything, make any difference? Seriously, I think it would; because it makes an enormous difference whenever what had seemed to be partial and distintegrated fits into a larger integrated pattern. It will of course be impossible finally to answer the question, "Why does that satisfy us?,"because to answer this question exhaustively I would have to be able to chew my own teeth to pieces. In the pursuit of scientific knowledge, always watch out for that snag. You will never get to the irreducible explanation of anything because you will never be able to explain why you want to explain, and so on. The system will gobble itself up. The Gödel theory has roughly to do with the idea that you cannot have any system which will define its own axioms. An axiom in one system of logic must be

defined in terms of another system, etc., etc. You never get to something which is completely self-explanatory. That of course is the limit of control, and the reason why all systems of control have ultimately to be based on an act of faith.

The problem confronting all sciences of human behavior is that we have the evidence (we are *staring* at it) to give us an entirely different conception of the individual than that which we ordinarily feel and which influences our common sense: a conception of the individual not, on the one hand, as an ego locked in the skin, nor, on the other, as a mere passive part of the machine, but as a reciprocal interaction between everything inside the skin and everything outside it, neither one being prior to the other, but equals, like the front and back of a coin.

Annihilating Illumination

GEORGE ANDREWS

While being struck by lightning in slow motion
the fire sears away layer after layer
sizzles me down to my ultimate ash
I quiver shrieks of laughing crystals
the radiant frenzy of the storm's soul dwells in the guts of the dragon
the bomb in my belly blasts my body to bits
a million suns burst into being
naked free no rings around me but my own desire
I hold the lightning in embryo in my arms
the blood of the cactus is the blood of a snake and the blood of a star
magnetic dragon throbbing in each corpuscle
shining snake of the light wave our beings are based on
glyph of the nucleus of the cosmos
original flash of let there be light
the boat of the sun navigates through the underworld of my intestines
perpetual pilgrim doomed to wander through the chromatic repercussions
the intimate structure of the transparent signs
flower of light flowing through the blood of the universe
I wander through the mazes of the glory and the horror of the life slime
vital jelly swarming in all possible creatures
I see the dead and the living merge
the dead call to us the living may we recognise them at last
the dead are in our blood each corpuscle an ancestor
the day all the living die the dead shall live
herald of the apocalypse sound the doomsday horn
man stop the wheel of creation and look inside
the stars are all contained within our organs
galactic music spins inside the bones
coruscating symphonies coalesce iridescent vibrations
coupled poles of attraction combust the salt of a fantastic caprice
philosopher's stone cooking in the cauldron of my skull
drain the bitter cup to its last drop
potent is the sorcerer's broth
mighty as the giant bird who swoops down and carries me away

to the motionless point around which all motion spins
I see touch and count the seeds of destiny
I see how fate weaves its webs
dreaming worlds into being from the ooze of my own brain
God born of the goo of my membranes
and has suffered ever since the intricate combinations of the opposites
afloat forever abubble on the surface of reality
O to make one perfect thing at last of all the worlds of wandering
a ransom for the soul's pain
drink liquid lightning from the sacred river while it is before you
don't miss a drop no one sees it twice
fire swims and pulses through each cell of my being
the seed of strong delight stirs
myriad joys feel at home in an angel's nest
revolving wheels of splendor palpitate potent beauty
clear colors cascade undulating reflections
of the diamond in the brain the pituitary gland decalcified
the mirror in the mind
the heavenly heart awakens the first beat tells the worlds
germ in the guts of God or God in the guts of a germ
I am that I am the same dance is everywhere
the one law of cyclic change
that constantly accelerating fugue of incandescent experience
flaming sequences of rhythm patterns
I am alive within the living God
I throb unique among the infinite variations
and so what if all the evolution of consciousness only leads to the knowledge
that I am a germ in the guts of a greater being
I am older than creation older than all beings
the stars revolve within me
I voyage through the inner space between my atoms
I take space ships to the different parts of my body
each organ becomes a constellation as I spread across the sky
wheeling through the zodiac weaving the fate of future races
conceive a cosmos where life does not need to kill to live
create a system free from pain
in the spawn and seethe of the primeval ocean
out of chaos I pass the current
immortal diamonds shimmering on the foam of the instant now
scintillating images of the flux that never fixes

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.

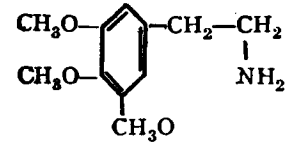
I. Chemical Structure and Its Relation to Pharmacological Activity

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

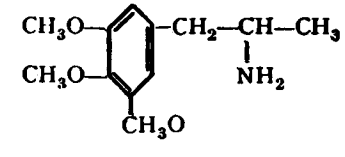
This group includes mescaline (3,4,5-trimethoxy-phenylethylamine) and TMA (3,4,5-trimethoxyphenyl-β-aminopropane). They are structurally closely related to epinephrine and amphetamine, and, like these, have a marked sympathomimetic or adrenergic effect on the autonomic nervous system (ANS). Mescaline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

Figure 1

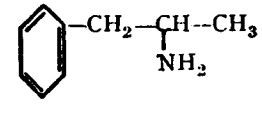
Chemical Structure of Mescaline and Related Compounds



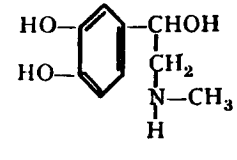
Mescaline



TMA



Amphetamine



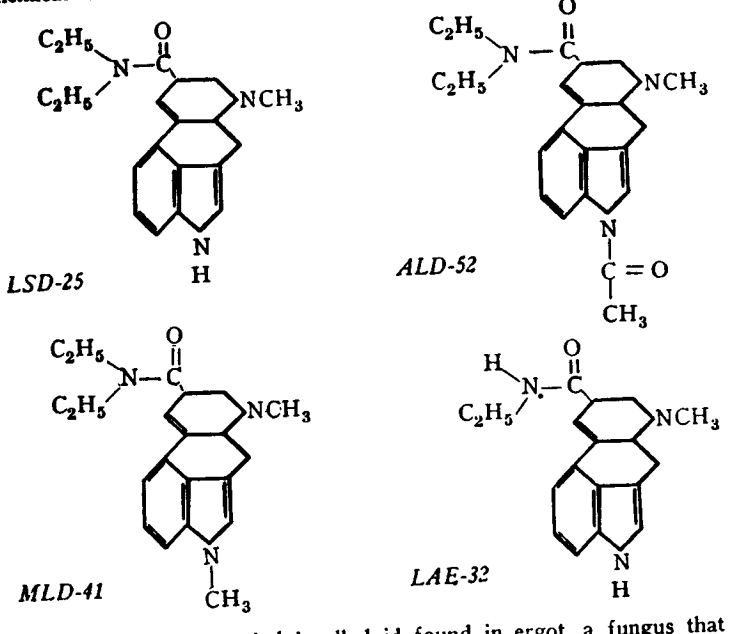
Epinephrine

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.

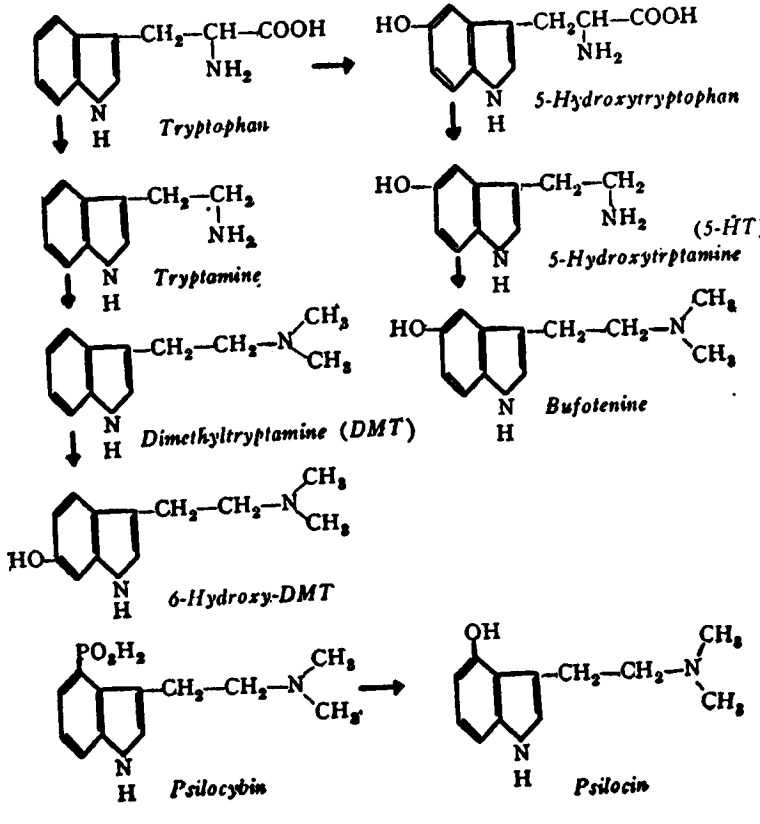
(a) N,N-dimethyltryptamine (DMT), N,N-diethyltryptamine (DET) and N,N-dipropyltryptamine, in doses of 1 mg/kg, similar to LSD or mescaline, but with a shorter duration of effect. The dibutyl derivative gives slight effects, while the dihexyl compound is completely inactive. The psychotropic activity 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.

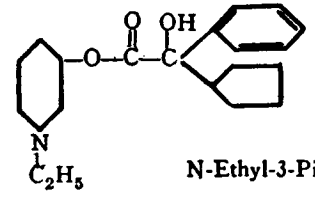
produced by 4-hydroxylation of tryptophane, analogously to the biosynthesis of 5-HT.

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)

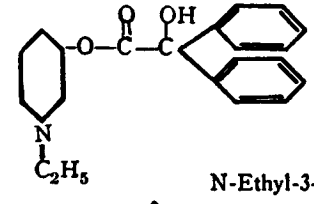
Figure 4

Chemical Structure of Benzilate Esters and Phencyclidine



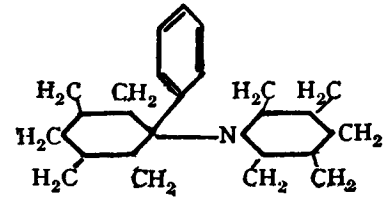
JB-329 (part of Ditran)

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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