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LSD: A Missed Opportunity?

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Despite its early promise as 'the chemical key to schizophrenia', and its manifest properties as a psychotomimetic, LSD failed to catch on as a drug model for human psychosis. The reasons for this and the longstanding preference, instead, for the amphetamine model are examined. It is argued that the rejection of LSD was not just a scientific decision, but was influenced by increasing disaffection in psychiatry and society at large with psychological (existentialist) interpretations of schizophrenia with which LSD, as a recreational drug, was associated. The proscription of LSD and the shift towards a strongly organic view of schizophrenia created a climate where it was easier to accept the simpler amphetamine (dopamine) model. Flaws in the latter, its further recent undermining as an exclusive theory, and challenges to an overly organic psychiatry by a more psychobiological approach, are all discussed in the light of the perceived need for a more elaborated neurochemical account of schizophrenia; this includes a rôle for central serotonergic influences in the disorder, removing much of the previous objection to LSD as a drug model. Several ways are suggested in which data about LSD could still usefully be drawn upon in schizophrenia research; including, in animal experimentation, its direct use to test the viability of the various biological models of schizophrenia on offer. Some examples of the latter are given, including a study of LSD from the author's own past work.

KEY WORDS—LSD, animal model, schizophrenia, psychosis, history, amphetamine, dopamine, serotonin.

INTRODUCTION

The textbook history of LSD will be familiar to most readers of this journal: its synthesis, as d-Lysergic acid diethylamide, in 1938 in the Sandoz Laboratories; Hofmann's stumbling, five years later, on the weird mental effects of the substance; the excitement in psychiatry at the fortuitous discovery of what promised to be a powerful chemical key to human psychosis; the expressed disillusionment with that; the relatively short life of LSD as a legal drug; and finally its banishment to the dubious margins of society, where it has remained ever since—joined, indeed overtaken, by other newer 'psychedelics' (as they were once called). Beneath that account, however, there is another story—one which the Editor asked me to try to piece together, following some remarks I made about LSD during an interview that he published in a previous issue (Claridge and Healy, 1994). My comments concerned the failure of LSD to catch on as a drug model for psychosis, despite its manifest superiority to the more favoured amphetamine (dopamine) paradigm. I should add that in discussing the question here the emphasis will not be so much on arguing the case for LSD: this was done in an early paper of my own (Claridge, 1978) and later by Fischman (1983) in a more comprehensive review of phenomenological and pharmacological evidence. Although occasionally drawing on those discussions and some later evidence, the present paper will concentrate rather more on the reasons for the neglect of LSD.

The gist of the story can be summed up in a single question: How could it possibly have come about that a drug which even commonsense tells us can turn us temporarily crazy—and which pharmacologists actually labelled 'psychotomimetic' and 'hallucinogenic'—failed at a certain point to continue to have at least *some* scientific interest for those seeking to understand naturally occurring forms of madness? (Here for 'drug' we could of course substitute 'drugs' and include other psychotomimetics such as mescaline, but it is LSD that spearheaded the downfall of the line of enquiry to which I am referring). The ostensible scientific reasons, to be discussed later, are well-rehearsed and, taken individually and without much further thought, might appear to be convincing; they have certainly been happily accepted and reiterated by several generations of clinicians and basic researchers. Then there have been the practical constraints imposed on research by criminalization of LSD: this was bound to stifle the opportunity and motivation to work on the drug.

Nevertheless, the ignoring of LSD might still

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seem remarkable to an external, but informed, observer. The legal restrictions were always less problematical for animal research; while, on the human side, even before the official proscription of LSD a not inconsiderable amount of information on its effects had accumulated. Here I am referring not to experiential and clinical data—which of course have been profusely documented—but to laboratory studies covering a wide range of physiological and behavioural phenomena, including sensation, perception, psychomotor performance, and EEG and autonomic functioning. As early as 1960 such evidence—alongside reference to the pharmacodynamics of LSD—figured prominently in, for example, Uhr and Miller's edited book, *Drugs and Behaviour*, and the same themes were elaborated by Leavitt (1974) in his later volume of the same name. So, even with the possibility of further human research ruled out, there was already a body of knowledge about LSD available for interested scientists to draw upon, had they wished to try to sketch out an albeit rudimentary model for psychosis. But the majority chose not to do so and that particular line of thought, together with the studies that might have supported it, sank out of sight and are rarely, if ever, referred to in the contemporary literature.

As a background to understanding why this happened, we first need to examine briefly the clinical concept of psychosis and how differences and changes in viewpoint about it have influenced basic research in the area. The debate has been mostly conducted, as it will be here, with reference to schizophrenia. However, one issue, itself contentious but relevant to the LSD story, should be mentioned (it will occasionally be returned to): according to some opinion there is only an arbitrary distinction to be made between schizophrenia and other, affective, forms of psychotic disorder and a common theory might account for both.

THE PSYCHIATRIC BACKGROUND

The history of schizophrenia research is a history of controversy. The most enduring point at issue—and the one at the nub of many of the other disputes—concerns the relative emphasis to be placed on the psychology, as compared with the biology, of the disorder. This question has been formulated in a number of different ways and discussed with varying degrees of polarized opinion; but it still continues (for a contemporary version of the debate see *Journal of Mental Health* 1993). The argument reached its most furious in the 1960s and early 1970s, with the presence of the school of so-called 'radical psychiatry', represented in Britain in the writings of R. D. Laing (1960) and his followers. Laing's (and others') exclusively sociopsychological account of schizophrenia, as a disorder originating in family dynamics, was revolutionary in two respects. First, it was political in a general sense, challenging the existing social order on behalf of individuals whom others had previously labelled as ill but who, by now having their odd experiences legitimized, felt themselves to be liberated in their deviance. Secondly, it threatened an Establishment psychiatry which at that point was, paradoxically, broadminded in its approach to mental illness, but thereby weak in alternatives: although neuroleptics and other physical treatments were in routine use and biological (including genetic) investigations of schizophrenia already had a long history, there was no sense that a systematic nervous system theory of psychosis existed.

LSD (and other hallucinogens) formed, of course, a seamlessly joined part of that era. Thanks to Laing, the existentialist preoccupations of the schizophrenic and of the LSD-tripper were alike since, after all, their mental states were sometimes indistinguishable; at least they were similar enough often enough for some psychiatrists and clinical psychologists to take LSD (as I did) in order to try to get some feel for the inner world of their psychotic patients. It is true that psychiatry, in the interests of a neat nosology, tried and still tries to make a formal distinction between LSD psychosis and acute schizophrenia; but this has never seemed very convincing and has little factual basis (Vardy and Kay, 1983). In the same vein, but for another purpose—arguing against LSD as a suitable drug model in research—it has been persistently stated that there are crucial differences in phenomenology; *viz.* that LSD produces largely visual, and acute schizophrenia largely auditory, effects. As both Fischman (1983) and I myself (Claridge, 1978) pointed out, this too is flatly contradicted by the evidence. Taken in isolation the mistake is relatively trivial, but it nevertheless assumed considerable force as a piece of received wisdom in subsequent attempts by psychiatry to distance itself from LSD and other hallucinogens.

When it came, the backlash against the radical movement was brutal, as psychiatry entered its present thoroughly organic phase and strong biological theories of the psychotic states were reasserted. Considering the implications for the

progress of LSD (which by the late 1960s had been banned in Britain), it is scarcely possible after several decades to determine the precise motivations and directions of causation in the events that occurred. But it is also difficult to believe that the sidelining of LSD did not cause some sighs of relief in certain quarters of conventional psychiatry. With emphasis constantly being placed on the drug's mind-altering qualities LSD had always raised awkward questions about what should be regarded as the valid data for study in schizophrenia and the other psychoses. In this respect it is instructive to note that Fischman's defence of LSD ranged widely, attempting an integration of material as far apart as neuropharmacology and ego-psychology. Yet when it appeared in 1983 his remarkable article would already have seemed time-warped to the unsympathetic: such conceptualizations did not sit easily in a discipline which by then was well on the way to defining its subject matter in objective medical terms and, in the case of the psychoses, as diseases of a neurological type. (This retreat from the psychological should not be underrated and has recently led to some realization that psychiatry's neglect of the schizophrenic's subjective experience has gone too far (*Schizophrenia Bulletin*, 1989)).

Another consequence of the more forceful organic style that developed in psychiatry, and which is relevant here, concerns the narrowing of the boundaries used to delineate different psychotic disorders. This was particularly true in the United States where—reflecting the strong influence of psychological formulations of the disorder—a very broad definition of schizophrenia had held sway; it was considerably pared down when revising the *Diagnostic and Statistical Manual (DSM)* into its third edition (American Psychiatric Association, 1980). In Britain the definition had always been more circumscribed, but this was now emphasized more, in keeping with the strict formulation of schizophrenia as a discrete disease entity which, it was hoped, might prove to have a single identifiable cause. As it has turned out, this has not so far been the case; furthermore even the differentiation of schizophrenia from affective psychosis has again recently been challenged on several fronts (Kendell, 1991; Taylor, 1992). But, at the time, the idea that was emerging—of a more restrictive, organically based view of schizophrenia—was an appropriate antidote to the open, wishy-washy psychiatric thinking with which LSD was inevitably associated. The suggestion in basic research that there might be an appropriately matching, straightforward drug model for schizophrenia, without the embarrassing complications of LSD, was a godsend to this new psychiatry.

CHOOSING A DRUG MODEL: AMPHETAMINE VERSUS LSD

The events related above form only one theme in the story of the abandonment of LSD. On the scientific front the search for a cause of schizophrenia in some form of brain dysfunction has gone on for most of this century and the use of LSD as a vehicle for conducting such enquiry forms the serious side of the history of the drug. Such research was carried out much in the spirit already outlined, *viz.* with hope of discovering a single neurophysiological or neurochemical aberration that could account for the symptoms of schizophrenia. Indeed, very early on the answer seemed to be signalled, in Woolley and Shaw's (1954) proposal—leading to the 'serotonin hypothesis'—that LSD blocked 5HT receptors in the brain. But it was the alternative 'dopamine hypothesis' that won the day, to become the standard biochemical explanation of the aetiology of schizophrenia. The timing of the appearance of this model, compared with the 5HT theory, is probably significant. Developed more than a decade later, it did not get into its full stride for some time, making the *Schizophrenia Bulletin*—the serialised guidebook for workers in the area—by 1976 (Meltzer and Stahl, 1976); in other words, at the optimum point to feed into psychiatry's new organic phase. Since the latter coincided with increased efforts to discover improved antipsychotic medications, it was also natural that the dopamine theory should be extensively examined—and substantially developed—within a pharmacological context, utilizing a drug-based animal model of schizophrenia. The choice of amphetamine for this purpose henceforth defined a major research strategy for workers in the field.

On the face of it, the arguments for the amphetamine/dopamine model are logically watertight, being based on several apparently mutually supportive assumptions about the reciprocal dopaminergic and behavioural effects of amphetamine and of the neuroleptic drugs. The neurochemical link here is beyond dispute; but close inspection shows the rationale elsewhere to be quite flawed. The most obvious point is a simple one about 'ecological validity'—a concept from psychology which, roughly

translated, denotes the extent to which a laboratory phenomenon has a convincing reference point in the real world. Judged by this criterion, amphetamine has poor ecological validity: the drug is not a natural psychotomimetic and, although capable of producing some limited features of schizophrenia in human subjects, it generally does so only in large doses and/or chronic usage and perhaps even then only in the predisposed. (As David Healy pointed out in our interview, women took it for years as a slimming aid, without it apparently causing any great problems). Finding behavioural equivalents of schizophrenia in amphetamine-treated animals is therefore bound to be strained. By comparison, the excellent ecological validity of LSD can even be discovered in the spontaneous comments made by animal researchers on the behaviour of their subjects administered the drug. Here are two examples. The first is taken from Jacobs and Trulson (1979) who, discussing the possible consequences of LSD on serotonergic neurons, note: '... [that it] consistently produces an animal that is hypersensitive to virtually all environmental stimuli and hyperactive in virtually all situations. Through a general inhibitory function, serotonin neurons may serve to modulate an organisms's behavior and *maintain it within narrowly specified limits*' [my italics].

The second example is a remark made by Key (1961) in one of a number of early papers emanating from the Birmingham University neuropharmacology group, which in the late 1950s and early 1960s conducted a series of unique LSD experiments with cats. In the study in question Key examined the effect on discrimination and sensory generalization; he concluded that unlike amphetamine (examined elsewhere (Key, 1964)): '... LSD 25 is able to alter the level of significance or meaningfulness of stimuli, thereby producing an increased amount of generalization. ... the level of significance of sensory information is altered [and] ... distortions of perception may occur, for the animal now responds, pays attention or arouses to stimuli which normally would not produce such an effect.'

What is remarkable about these observations is the extent to which they chime with the theoretical and clinical focus of schizophrenia research at the time (Venables, 1964; McGhie, 1969). Yet they appear to have been made in ignorance of that work; at least the authors include no reference to the relevant human literature—or even, in the case of Key, to schizophrenia!

Another, rarely voiced, criticism of the amphetamine/dopamine model concerns the assumed unequivocal therapeutic action of the neuroleptic drugs in schizophrenia. This crucially underpins the model; yet it can be challenged on two grounds. First is the well-documented failure of a proportion (up to 25 per cent) of schizophrenics to respond to conventional neuroleptics, coupled to carefully researched data that in some cases non-neuroleptic treatment might actually signify better long-term outcome (Matthews *et al.*, 1979). Secondly there is the evidence, discussed for example by Healy (1990) and confirmed in the introspective reports of patients themselves, that the so-called antipsychotics do not actually have much of their primary influence on the central 'positive' symptoms of schizophrenia (e.g. those reliably induced by LSD); where these are mitigated it appears to be through secondary effects on more general mood and motoric symptoms.

There is the impression, then, that the amphetamine/dopamine model has always had an illusory precision and that the preference for amphetamine over truer psychotomimetics was always an uneasy compromise between social acceptability and intellectual rigour. On the scientific side, the choice seems to have been partly dictated by the simultaneous existence of the dopamine hypothesis, leading to some circularity of reasoning when combining the various assumptions into an integrated theory. It should be added that such criticisms are now being preempted by the emergence of a more broadly based approach to the neurochemistry of psychotic disorder; this has brought with it the virtual demise of the simplistic version of the dopamine hypothesis, which is now coming under fire as an exclusive biochemical account of schizophrenia (Lieberman and Koreen, 1993). Part of the impetus for the change has come from work on the atypical antipsychotic drugs, covering a range of new compounds (Gerlach, 1991). The therapeutic effectiveness of some of these substances (e.g. clozapine) cannot be solely attributed to their blockade of dopamine (D2) receptors in the mesolimbic system—the traditionally proposed mechanism for antipsychotic drug action and one which, as Meltzer (1991) points out, has been 'a basic tenet of neuropsychopharmacology for more than three decades.' The search for alternative routes to clinical efficacy therefore now includes the study of other neurotransmitter systems, among them 5HT; indeed, ironically for the ageing advocates of LSD, serotonin is assuming a revived importance in

schizophrenia and other mental health research (Bleich *et al.*, 1988; Leonard, 1994).

Given the limitations of the original amphetamine/dopamine model, it might be asked why it survived for as long as it did. Perhaps the main scientific reason is that an inexact theory is better than none, and work inspired by the paradigm did help to establish beyond doubt that a disturbance of brain dopamine is implicated in psychotic disorder. This in itself was a major achievement, even though the success might not be attributable to any unique specificity of the model, as a theory either of psychosis or of drug treatment: such a 'hit' might have been inevitable anyway, given the rôle of dopamine in those (limbic) brain areas which mediate general emotional and attentional processes known to be disturbed in most mental illnesses, including schizophrenia. It is also possible that, once the model was formulated, it was necessary to pursue a single-minded track in schizophrenia research, as a necessary precursor to developing more elaborate theories. Scientists were no doubt helped in this endeavour by the narrow disease mentality that, as noted earlier, increasingly pervaded psychiatry and didactically influenced the style and aims of basic research on serious mental disorder. Thus, the notion of schizophrenia as a single cause organic disease did not encourage looking beyond the predefined boundaries of possible aetiology. Nor did it indicate a need to bring to bear on laboratory data any insight into the clinical features of the disorder being studied: few experimental neuroscientists will ever have talked to a schizophrenic. Had they done so, they might have been struck sooner by the limitations of the models they were using, including, in drug research, their pharmacological strategies.

As it was, it took others outside the main axis of influence in schizophrenia research to challenge some preconceptions in the field and establish an alternative line of thinking about the nature of psychosis. Originating in a convergence of clinical, personality, and experimental psychology it has within it only a very narrow thread concerned with drugs, and an even narrower one relating to the present topic. Nevertheless it needs to be considered, as part of the LSD story.

AN ALTERNATIVE CONSTRUCTION OF PSYCHOSIS

Simultaneously with the Laingian revisionism of the 1960s, another, less advertised, challenge to orthodox psychiatric thinking began to emerge. Also opposed to the medical model and to constructions of psychological disorders as simple neurological diseases, in other respects it differed entirely from the radical psychiatry movement. Contrary to the latter's emphasis on sociopsychological causes, explanations of disorder were thoroughly biological. However, unlike organic psychiatry, accounts of mental illness were formulated, not as discrete pathophysiology, but as extreme aberrations of central nervous system processes considered responsible for normal temperament or personality: the dimensionality between normal and abnormal, at both behavioural and biological levels, was therefore a central feature. Eysenck (1967), as a pioneer in this approach, applied it initially to the less serious psychological disorders and only later, and on a broader theoretical front, was it used to encompass the psychoses, including schizophrenia. Now, as a perspective on the latter it comprises a significant body of knowledge coming under the heading of 'schizotypy (or, more generally, psychosis-proneness) research.' Here schizotypy refers to a set of biological, cognitive, and personality traits, capable of being present in healthy individuals, but otherwise predisposing to psychosis; it has been and is currently being extensively investigated from many points of view, including the genetic, the psychometric, and the experimental (for reviews see Claridge, 1987, 1994a; Meehl, 1990; Raine *et al.*, 1994).

Several other features of this theoretical approach need to be stated, in order to underscore the differences between the medical and experimental psychological positions. First, it is important to emphasize the latter's essentially *psychobiological* view of psychiatric illness (Claridge, 1994b). This means that, in psychotic disorder for example, the subjective state assumes as much importance as the biology for constructing theoretical models or choosing research strategies; hence the significance placed earlier on ecological validity in comparing LSD and amphetamine as drug models. Secondly, unlike discrete disease theories, there is no commitment to the idea of single causes leading to discontinuous illness states. On the contrary, a necessary precondition for understanding the biology of psychosis would be an understanding of the biology of 'psychosis-proneness' as a confluence of individually normal personality traits. These, it is accepted, are likely to be multiply determined; so that, with respect to the neurochemistry, the idea of anything other than a complexly inter-

acting system would be quite foreign. In the same vein, drug manipulations are mostly seen as serving to test out macroscopic theories, the detailed biochemistry of which is, for the moment, necessarily somewhat sketchy; more important is the perceived 'match' between the drug used and the individual differences (normal and abnormal) under investigation. Here drugs offer a complementary way of exploring otherwise naturalistically occurring biological variations.

For obvious reasons, testing out such ideas with respect to psychosis, by administering LSD to human subjects, is rare. But in my 1978 article, arguing the case for LSD as an animal model, I quoted an example that formed part of my own early work on the psychophysiology of schizophrenia. Details are contained in the original paper and the references cited there, but the basic observations were as follows. From a series of laboratory experiments utilizing measures of perceptual sensitivity and of general arousal we had concluded that an unusual, and perhaps unique, feature of the psychotic nervous system is a degree of 'dissociation' of function, possibly stemming from relatively weak homeostatic regulation. The empirical evidence for this proposal was a peculiar profile observed on the psychophysiological measures we were using; such that, different from control comparisons, the degree of sensory responsiveness was out of keeping with the subject's prevailing level of physiological activation; e.g. a very high sensitivity to visual stimuli could occur in conjunction with very low tonic arousal. The effect was demonstrated in acute untreated schizophrenic patients, normal subjects high in psychotic traits, and, subsequently, schizophrenics' relatives (Claridge *et al.*, 1985). It was also exactly reproducible in human volunteers under LSD (but not dexamphetamine).

At the end of the 1978 article I concluded that the 'arguments for reviving the use of LSD as a method of inducing a "psychotic state" in an animal therefore seems strong.' However, it was some years before the opportunity arose to pursue that idea—in the monkey, using as a 'marker' behaviour a measure of the 'dissociation' between arousal and sensory sensitivity previously observed in our human subjects. The eventual paper reporting the substantive part of that work remained in the drawer (Claridge *et al.*, unpublished), after several failed attempts at publication—not, I hasten to add, in this journal! The present Editor has agreed to indulge my vanity by agreeing to the inclusion here of a 'paper-within-a-paper' summary of that report, as a logical sequel to and illustrative example of the earlier case I made for LSD as an animal model.

AN LSD EFFECT IN THE MONKEY

The subject was a male cynomolgus monkey in whom two psychophysiological indices were recorded. Sensory responsiveness was assessed with an EEG visual evoked potential (VEP) procedure once widely used in schizophrenia research and successfully employed in one of our human experiments referred to above (Claridge *et al.*, 1985). It consists of examining stable individual differences and state variations in the relationship between VEP amplitude and the intensity of the evoking flash stimuli. In the present instance EEG was recorded between electrodes implanted on the dura and positioned at sites corresponding to the human C_Z (vertex reference) and O_Z placements. VEPs (P_1–N_1 amplitudes) were obtained by averaging over 32 stimulus presentations at each of five flash intensities, *viz.* 6·3, 8·7, 13·5, 18·4, and 37·0 foot-lamberts. In order to sustain attention during VEP measurement the animal was taught to pull a handle in response to each flash onset and concomitantly, as a measure of general tonic arousal, skin conductance (SCL) (initially registered as resistance) was recorded throughout from the animal's left foot.

The experiment proper consisted of a series of testing periods, conducted on separate days and interspersing 17 saline control sessions with 17 sessions of intramuscular administration of 1·0 μg/kg LSD-25. The latter was deliberately (and successfully) chosen as a low dose in order to avoid disrupting the monkey's lever-pressing performance and hence introducing unwanted non-specific effects into the results. Even so, statistical analysis was confined to VEP data associated with performance levels exceeding 75 per cent correct responses to the flashes.

Interest centred on the pattern of covariation between SCL and VEP amplitude/intensity slope, especially over the low range of skin conductance, where it was expected, for LSD, that there would be relatively greater response to the brighter flashes. To examine this, VEPs were arranged according to flash intensity and then further sorted according to whether the simultaneously recorded SCL fell into a low or high range, respectively defined as $< 6{\cdot}0$ μmhos and $> 8{\cdot}0$ μmhos. The data in this form are shown in Figure 1, where

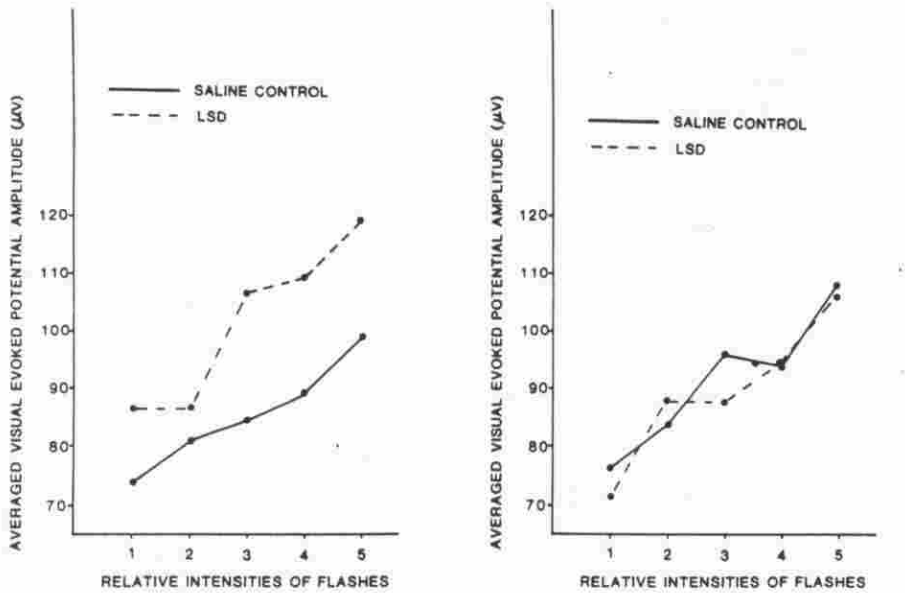

Figure 1. Mean VEP amplitudes at five flash intensities over two concurrently recorded ranges of SCL: low range (left) and high range (right)

it can be seen that LSD selectively and progressively—as a function of stimulus intensity—enhanced VEP amplitude in those cases where, paradoxically, general arousal was low. Statistical analysis by three-way ANOVA showed significant effects for the two important main factors (flash intensity and treatment) and for the SCL range × treatment interaction.

Other unusual effects of LSD, reported more fully elsewhere (Wingate, 1982), were also noted in this and other experiments conducted then. For example, over time the drug caused a gradual increase in muscle tonus. On the other hand it had a marked *depressant* effect on SCL, both within and between sessions—observable as an immediate effect, even with a smaller dose of 0·5 μg/kg. These changes, together with those already described, closely parallel features we have observed in and in relation to human psychosis. They suggest that the LSD-induced and naturally occurring state are highly similar psychophysiologically; being characterized, not by a simple shift in, but by a complex 'dissociation' of, sensory, autonomic, and somatic arousal systems.

CONCLUSIONS

Seen in isolation and now considerably removed in time from the human research that inspired it, the experiment just described looks, even to me, like a bit of curiosity; for the physiological 'dissociation' that we found in both natural and drug-induced psychosis still defies a full explanation. The relevance here, however, is in illustrating how the study of LSD helped to validate an existing—and, I would argue, already empirically well-established—model for certain features of schizophrenia; at the same time, the experiment further strengthened the case for LSD as a drug model for the disorder. There might be a lesson here for current animal research in the area. Thus, it might be appropriate to use LSD (rather than amphetamine) to establish a bench-mark for the viability of theories of psychosis, whether these are neurochemical, neurophysiological, psychophysiological, or behavioural. The failure of LSD to have a 'psychotic' effect in the animal, as predicted by the model in question, could be seen as weakening that model and a possible reason for rejecting it. Two contrasting contemporary examples from near to my own field will help to illustrate the point.

The first concerns 'latent inhibition', an animal learning paradigm for schizophrenia that has enjoyed some popularity in certain quarters in recent years (e.g. Gray *et al.*, 1991). The neurobiological case for this model rests very heavily on simple amphetamine/dopamine theory, including observations that amphetamine abolishes latent

inhibition, in both animals and humans. However, I suggest that its specificity in modelling human psychosis is seriously undermined by the failure of LSD to have a comparable effect (reported in Cassaday *et al.*, 1993; and Cassaday, personal communication). A more optimistic conclusion can be reached with respect to the second example to be quoted. There the phenomenon of interest has been startle habituation, investigated within a general theory about failures in sensorimotor gating in schizophrenia (Geyer and Braff, 1987). In that case, LSD *has* been shown to have predictable effects in animals, consistent with observations in schizophrenic patient and other human subjects; thus indicating, I would argue, that the paradigm is along the right lines in trying to identify unique characteristics of the psychotic nervous system.

Complementing this use of LSD as a 'checking strategy' in animal modelling of schizophrenia, the study of the drug could have other applications, similar in aim but along different lines. Although further experimental research on humans is precluded, as noted in the Introduction, a considerable amount of information has already accumulated on the effects of LSD. This constitutes an invaluable data base which schizophrenia researchers could do worse than consult from time to time. Given the crab-wise fashion in which science proceeds, there are undoubtedly old findings in the LSD literature that at the time were relatively uninterpretable, but which might fall into place in the light of modern theory. As someone with a psychobiological view of psychotic disorder, I personally would wish to include here introspective data, in addition to laboratory findings. Finally, there is the possibility to re-examine the human effects of LSD among those who still take it, albeit illegally; a good example is Strassman's (1992) recent exploiting of that fact to provide further evidence of the serotonergic mediation of hallucinogenic drug action. Much might be learned about naturally occurring psychosis if such work were brought more into the centre stage of schizophrenia research.

The arguments in favour of LSD (or some equivalent hallucinogen) as a drug model for psychosis should hardly need labouring further; but its past neglect remains a fascinating piece of social history. Looked at now, from a distance and in the light of some retreat from simplistic accounts of the biology of schizophrenia, the rejection of LSD might just seem like a remarkably crass piece of scientific misjudgement. But as I have intimated earlier, it is unlikely that that was all it was. Science always has to operate within the sociopolitical constraints of its time and, to a degree, is only permitted or encouraged to pursue ideas with which the prevailing Establishment is comfortable. In the worst, and fortunately rare, instance—as in pre-war Germany—it can amount to deliberate collusion between science and political ideology (Müller-Hill, 1988). Mostly—to mix the analogies—it is a two-way osmosis, only subliminally perceivable. Such was the case, I believe, with LSD. Whether in the long run it mattered, as far as our understanding of serious mental illness is concerned, will perhaps only be known when the combination lock—as it is proving to be—on schizophrenia is finally opened.

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