animal models of schizophrenia: the case for lsd-25*

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Some Difficulties With the Animal Model

A recent convergence of ideas which I believe is evident in schizophrenia research suggests that it is worth taking a new look at attempts that have been and are being made to establish the biological basis of the disorder through the study of an appropriate animal model. Part of the purpose of this paper is to suggest a new strategy. Before the arguments for adopting the strategy to be proposed are presented, however, it is necessary to consider some of the difficulties inherent in trying to erect an animal model of schizophrenia. These are fourfold.

First, it is conceivable that schizophrenia is an entirely human condition—a view held by those who consider disorders of language, thinking, and social communication to be essential pathognomonic signs of the disease. If this were so, then the search for an equivalent in lower animals, while not completely fruitless, would be extremely difficult. It is true, as Matthysse and Haber (1975) have recently pointed out, that it might be possible to extract certain nonlinguistic characteristics of schizophrenic thinking which could be studied in animals. Indeed, it might ultimately be possible to extend into the area of psychopathology recent work on, for example, social interaction and language acquisition in non-human primates. Unfortunately, while such an approach offers an exciting challenge for the future, its feasibility is at present severely limited by our knowledge, both of schizophrenia and of animal behavior. For the moment our belief that an animal model is viable must rest on the assumption that there are certain essential symptoms of schizophrenia which are mediated through more primitive neurophysiological mechanisms.

In my view there is evidence that this is so. Careful analyses of experiential data obtained from schizophrenics, such as those reported by Chapman (1966) and by Freedman (1974), suggest that thought disorder may be either a secondary elaboration of a more primary physiological disturbance or represent the later stages of an ongoing pathophysiological process which, in the human, inevitably involves the highest cortical functions. Thus, many schizophrenics report that the earliest indication of a change in their mental state, and one which may antedate their hospital admission by weeks, months, or years, is often an initially fleeting alteration in, for example, brightness or size perception or a difficulty in focused attention. As these experiences worsen, the patient may become progressively more anxious and, in an attempt to hold onto reality, develop increasingly bizarre behavioral and thought strategies, such as autism, social withdrawal, and ideas of reference. It seems possible, therefore, that certain core features of schizophrenia reflect a disturbance of brain function that could be accessible to laboratory study in an appropriate animal species. Comparative research might then help to unravel at least part of the total disorder—a part which, in any case, would need to be thoroughly understood before one could go on to study, even in animals, the more complex symbolic and social aspects of schizophrenia.

Nevertheless, narrowing down on the crucial symptomatology of schizophrenia, and doing so in a way which can be plausibly translated across species, is not without difficulty. Here a comparison with depression is instructive. Although the etiology of depression, like that of schizophrenia, is the subject of much controversy, its clinical characteristics can at least be agreed upon. They are easily recognizable, are relatively circumscribed, and are of a form which

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can be reproduced as a reasonably convincing animal paradigm, as the recent work of Seligman (1975) on “learned helplessness” has demonstrated. In the case of schizophrenia there are, as far as I am aware, no obvious parallel behaviors which occur in animals, either naturally or under experimental conditions. Those that have been studied as possible clinical “markers” seem to be either trivial or very nonspecific. In the first category are the various stereotyped behaviors produced by amphetamine psychosis, which some workers have discussed as a chemical model for schizophrenia (Ellinwood, Sudilovsky, and Nelson 1973, Randrup and Munkvad 1975, and Snyder 1973). Equally unconvincing is the emphasis placed on some general emotional characteristic, as was done in a recent ethological study reported by Chamove, Eysenck, and Harlow (1972). The aim of their experiment was to isolate clusters of monkey behavior corresponding to the Eysenckian dimensions of extraversion, neuroticism, and psychoticism (Eysenck and Eysenck 1975 and 1976). On the basis of factor analysis of their observational data, the authors claimed to have identified a psychoticism component, defined in terms of behavioral units associated with aggressiveness. It is interesting that their alignment of psychotic tendencies with aggressive behavior coincides with Gray’s (1973) recent speculation that the activity of the amygdaloid fight/flight mechanism might provide a biological basis for Eysenck’s psychoticism dimension. In my view, however, it seems unlikely that aggressiveness, per se, could be regarded as a behavior with sufficient specificity to define schizophrenia, or even one form of it. For one thing, such behavior is not particularly evident in many schizophrenics; on the contrary, passivity is a more commonly observed feature. Furthermore, the trait is found over too wide a range of psychopathological disorders to hold much promise as a criterion behavior for identifying schizophrenia—and nothing else—in an animal species.

The third problem facing animal research into schizophrenia arises from the great heterogeneity observed in the behavior of human psychotic patients. Indeed, many writers would consider it more proper to speak of “the schizophrenias.” Variations in the clinical manifestations of schizophrenia have been handled, though not very successfully, in a number of ways. These have included the traditional subdivisions into hebephenic, catatonic, paranoid, and simple types, as well as the broader dichotomies of paranoid/nonparanoid, process/reactive, and acute/chronic schizophrenia. The existence of such individual variation raises the question whether the different forms of schizophrenia represent quite distinct disorders. If this were the case, comparative research would need to seek, not one, but several animal models of psychosis. An alternative view of the observed heterogeneity is that with the exception of those phenocopies due to definable organic causes such as temporal lobe damage, all forms of schizophrenia arise from a common underlying dysfunction manifesting itself in different ways according to such factors as age, intelligence, preexisting personality, strength of genetic loading for the disorder, and so on. Here a parallel with the effects of lysergic acid on human behavior is worth drawing. Quite apart from the question of whether LSD “psychosis” is an appropriate model for schizophrenia (I will argue later that it is), the response to the drug is certainly known to vary considerably both between individuals and within the same individual on different occasions. Where recognizably “psychotic” symptoms appear, they may take many forms: elated mood, blunted affect, delusional ideation, slowing or poverty of thought, catatonic withdrawal, and so on. These different effects appear to reflect partly situational factors and partly personality variations observable in the normal state, the interaction between them representing the idiosyncratic ways in which individuals handle what presumably is, initially at least, a uniform effect of the drug on the central nervous system. It is quite conceivable that the variations observed between and within individuals in the naturally occurring psychotic states can be explained in a similar way; if this were true, the task for comparative research in the field would, in one respect at least, be somewhat easier since it would involve isolating a single neurophysio-
logical dysfunction which might, in any case, show less heterogeneity because of the fewer sources of individual variation available in animal species.

The final problem about animal research on schizophrenia flows very largely from the previous two just discussed—namely, that because of the great difficulty of defining schizophrenia clinically, experimental studies of human patients have so far failed to identify a unique set of parameters which reproducibly describe the condition in all its forms. This is a serious lack because even if it is accepted that the gross clinical features of schizophrenia are difficult to translate across species, the demonstration of a narrower set of laboratory phenomena which consistently accompany the disorder in humans would at least offer some safe criteria by which to define an animal model of the condition before looking at its neurophysiological determinants. The failure to find such phenomena is not for want of trying. The staggering literature on schizophrenia attests to the fact that virtually every single biological or psychological characteristic has been explored. Studies have ranged from analyses of the blood, urine, sweat, cerebrospinal fluid, postmortem brains, and fingerprints of schizophrenics to investigations of their vigilance, reaction time, perceptual response, conditionability, drug tolerance, autonomic reactivity, and EEG patterns. The frustrating outcome is not that no abnormalities have been demonstrated (they have many times), but that the range of defects observed has been too great and too variable from study to study to permit much coherent theoretical interpretation. This, of course, has not deterred individual investigators from trying to set up animal paradigms based on their personal evaluation of part of the evidence about human schizophrenia. Apart from work using psychotomimetic drugs, which I will return to later, there are two examples which spring immediately to mind and which will, if nothing else, help to illustrate the problem.

The first has been based on a theory of schizophrenia proposed by Stein and Wise (1971) who argued that the disorder is due to a defect of the "reward system" of Olds and Milner, resulting in an accumulation of 6-hydroxydopamine. Their claim that this substance, injected into the ventricles of experimental animals, reduced self-stimulatory behavior was seen as a parallel to the schizophrenic's postulated inability to appreciate or appropriately perceive reward. Unfortunately, aside from the difficulty of extrapolating these particular data across species, it is by no means obvious that a failure of reward-directed behavior is central to schizophrenia. Certainly, the model proposed by Stein and Wise does not seem to derive from any appreciation of what most workers in human schizophrenia research would regard as the mainstream of evidence or theory about the disorder.

This criticism, at least, cannot be leveled against the second animal model to be quoted, that attempted by Kornetsky (Kornetsky and Markowitz 1975). He has argued that a fundamental deficit in schizophrenia is an impairment of selective attention—a view which, as discussed in the next section, seems to be well supported by the experimental evidence, to which Kornetsky himself has contributed. In his own research on humans, Kornetsky has concentrated on two particular experimental tasks, one of continuous motor performance and the other a more complex digit-symbol substitution test. He considers that behavior on these two tasks reflects the activity of different neural mechanisms—roughly subcortical and cortical in origin—which may be differentially impaired in schizophrenia. Two kinds of evidence are quoted in support of this hypothesis: first, the pattern of scores found in schizophrenics, relative to other individuals, on the two tasks and, second, the differences observed in the way phenothiazines and barbiturates affect test performance. In an attempt to explore the physiological implications of his model, Kornetsky devised a version of his continuous performance task suitable for use with the rat, in which he has investigated the effects of various experimental manipulations, including direct stimulation of the ARAS and administration of chlorpromazine and noradrenaline. Although it is possible to discern some similarity
between the results obtained across species, it is not at all clear from the findings reported so far that Kornetsky has succeeded in establishing an animal representation of the true deficit in schizophrenia. On the human side, his choice of parameters for describing schizophrenia seems somewhat idiosyncratic and the theory to which it gives rise is too vaguely stated to convince one that he is not—as he himself admits may be the case—"modeling some unessential correlate of the disease."

It is clear that given our present knowledge of schizophrenia, any decision to pursue the search for an animal model of the disorder must involve a leap into the dark, based on (one hopes) inspired and very much personal guesses about the significance of existing theory and experimental literature. Of course, some constraints can be imposed, and I would suggest three criteria which ought reasonably to be met before any model could be considered potentially viable. First, the general area of behavior studied should be one which experimental psychopathologists agree seems central to schizophrenic disorder. Second, the particular phenomena chosen for investigation should look unusual enough to appear unique to schizophrenia rather than being some nonspecific correlate of disordered behavior in general, or, which is most likely, of the emotional arousal that universally accompanies such behavior. Third, the experimental procedures used for studying the phenomena should be unambiguously reproducible in an appropriate animal species.

The case to be argued here represents an attempt to arrive at a strategy which meets these three criteria. It does so by drawing together certain ideas and experimental data from several different fields bearing on schizophrenia research as they stand at the present time. In constructing the arguments that follow, it was considered useful to let several threads run through the discussion. One is historical and covers the background against which current psychological research on schizophrenia has evolved. Another is theoretical and focuses on the sorts of explanatory model of schizophrenia that psychologists have tried to develop. The third is strategic and concerns methods and data from research in areas allied to, but not specifically directed at, the study of the schizophrenic patient.

Experimental Psychopathology of Schizophrenia

Perception, Attention and Thinking

Until very recently, research by psychologists on schizophrenia has followed an obvious course. It has tried to find laboratory or semi-laboratory parallels of the more prominent clinical symptomatology, usually through comparisons of diagnosed schizophrenic and nonschizophrenic people on tasks derived from general experimental psychology. Among the favorite areas of behavior chosen for investigation have been those of perception, attention, and thinking. No attempt will be made here to give a detailed survey of these studies since they have been thoroughly reviewed by Venables (1964), summarized by McGhie (1969), and are probably familiar by now to most readers. All that will be done here is to draw some general conclusions from this area of schizophrenia research. Before doing so it is perhaps worth inserting a reminder that refers back to the point made earlier, namely that very few studies have demonstrated a difference between schizophrenics and other psychiatric patients (as distinct from normal subjects) that holds up over more than one or two replications of the experiment. This is partly due to the absence of any universally accepted criteria for diagnosing schizophrenia and partly to the heterogeneity of the condition even where the overall diagnosis can be agreed upon. Different investigators have in effect, therefore, been studying dissimilar patient populations. Many workers have further confounded the problem by failing to take account of acute/chronic differences, by using inappropriate control groups, and by ignoring the fact that their patients were on physical treatments which affect the very phenomena they are studying.
For summary purposes it is probably unnecessary to distinguish between the very closely related areas of perception and attention. At the purely perceptual end, an early preoccupation of psychologists was with abnormalities such as those of size constancy that were demonstrable in schizophrenics. Although these experimental results have proved too fragile to withstand repeated replication, they did start off a strand of theorizing which is still relevant. Thus, it was suggested by Silverman (1964) that the size constancy differences observed in schizophrenics were due to abnormalities in physical scanning of the environment, although early attempts to confirm this by recording eye movements were not particularly successful. A recent study by Holzman et al. (1974) has suggested that schizophrenics (and their healthy relatives) may indeed show abnormal pursuit eye movements though, more recently still, doubts have been thrown on the specificity of their findings (Brézinova and Kendell 1977).

A slightly different, though related, formulation has been used to try to explain the other major defect observed in schizophrenics, namely the abnormality of selective attention. The latter has been a major focus of research by psychologists, who have usually derived their explanatory models from those constructed in general psychology, particularly that developed by Broadbent (1958). Thus, a number of workers have proceeded on the basis that one of the most prominent features of schizophrenia is abnormal filtering of information flowing into the nervous system. Data from the field of attention that have been quoted in support of that theory are varied. Some of it comes from the work of McGhie (1969) using techniques like dichotic listening and reaction time testing with and without distraction. A somewhat different source of evidence, though one worth special mention, is research carried out by Callaway and his colleagues on the auditory evoked response (Callaway and Jones 1975 and Callaway, Jones, and Layne 1965). Their method of correlating successive sets of averaged evoked responses to physically identical auditory stimuli has demonstrated that schizophrenics, possibly due to poor focused attention, show greater variability than normals. Other work on the evoked response has also carried a similar notion through into the very recent literature on schizophrenia. Thus, Rappaport et al. (1975), in a recent study, have shown much greater than normal variability in the visual evoked response of schizophrenics—a result which might be taken to indicate poor filtering of sensory input by such patients. This last study is noteworthy for its careful selection of the patient sample, while the results are particularly interesting because of the extent to which they parallel some effects of LSD to be considered later.

Convergence on a filtering model has also been evident in work on the thinking of schizophrenics. A favorite bridging concept has, of course, been "overinclusion," the most extensive investigations of that notion being carried out by Payne (Payne 1971 and Payne and Hewlett 1960), who postulated that the disorder may be due to a defective cognitive filter which prevents the schizophrenic from screening out irrelevant ideas and maintaining adequately circumscribed conceptual boundaries. Payne's original studies made use of tasks, such as sorting tests, developed within clinical psychology for diagnosing thought disorder. Subsequently, however, in testing out his filter theory, he moved on to examine the performance correlates of overinclusion on dichotic listening, reaction time, and other tasks of attention (e.g., Payne, Hochberg, and Hawks 1970). Thus, although starting from a different point of view, the form and theoretical underpinning of his work eventually merged with that of people like McGhie.

Needless to say, many of the ideas and techniques developed over the past 20 years within this general area of research on schizophrenia have begun to show the frailty of their age. Experimental results have failed to be replicated, clinical tests derived from them have proved diagnostically useless, and abnormal psychologists have been chided for clinging to models of attention that cognitive theorists in general psychology abandoned long ago (Marshall 1973).

Nevertheless, one cannot fail to be impressed
by the frequency with which the same theme recurs throughout a now considerable literature: that schizophrenics show, as a fundamental characteristic, some disorder of their ability to respond selectively to stimuli; or, as Venables (1964) in a brave attempt to find a unifying concept named it, some form of “input dysfunction.” Although reliable measurement of the disorder has so far eluded experimental psychologists, its importance as a central feature of schizophrenia has, in my view, been established sufficiently for its explanation to be a necessary requirement of any future theories of psychotic behavior. By the same token, any alternative strategy for getting at the biological basis of schizophrenia, such as the use of animal models, would need to demonstrate some form of “input dysfunction” as a defining criterion of the psychotic state.

Arousal as a Mediating Variable

Ever since the 1930s when the notion of “arousal” first became popular in psychology, attempts have been made to use it as an explanatory concept for various psychiatric syndromes. Schizophrenia is no exception. The hope that the condition might reduce to a simple disorder of central nervous system arousal has, over the years, stimulated a great many studies trying to demonstrate abnormalities on physiological indices of EEG and peripheral autonomic activity. Although individual studies have shown differences between schizophrenics and nonpsychotics, the total picture is, to say the least, utterly conflicting. This is partly due to a lack of comparability between different types of measure and to the difficulty of interpreting them as indices of a single global process of “arousal.” Another problem has been the usual one of dissimilarity between samples of patients, the finding of great heterogeneity within schizophrenic groups, and the tendency (even now!) to ignore the influence of treatment.

Even if these difficulties are set aside, however, the idea that schizophrenia would reduce to a simple upward or downward shift in central nervous system arousal has never, in my view, been a compelling one. Such an explanation could not account for the easily demonstrable fact (Claridge 1967) that similar variations in arousal can be observed in other psychiatric patients, such as neurotics, and that where the latter are used as appropriate controls the differences claimed for schizophrenics disappear. Clearly, if arousal is disturbed in schizophrenia, it can only form one part of a more complex disorder of the central nervous system. Attempts to recognize this fact are contained in those models which have construed arousal as a variable mediating other prominent symptoms of the condition, particularly those discussed in the previous section. Some examples will help to illustrate the point.

The first is the theory of schizophrenia proposed some years ago by Mednick (1958). He argued and provided some evidence that an important feature of schizophrenia is a tendency toward greatly increased stimulus generalization during conditioning, a characteristic thought to be responsible for the schizophrenic’s heightened responsivity to remotely associated stimuli in the real-life situation. Thus, Mednick proposed what was, in effect, a learning theory equivalent of overinclusive perception, though he suggested in addition that the high stimulus generalizability of the schizophrenic was coupled to a low threshold for anxiety arousal, the two together combining to make the patient increasingly responsive to remote emotional cues, both internal and external. More recently he has tested out and found some support for this model in his, now classic, high risk study of conditioning and psychophysiological response in the children of schizophrenic mothers (Mednick and Schulsinger 1973).

Other, simpler, examples of the use of arousal as a mediating variable concern the application to schizophrenic behavior of two principles taken over from general psychophysiology, namely the “narrowed attention” and “inverted-U” (or Yerkes-Dodson) principles. The first of these contains the idea that the span of attention broad-
ens and narrows with, respectively, decreases and increases in the arousal level of the organism. Several investigators have used this principle to explain various perceptual and attentional deficits in schizophrenia. Included among these is the altered size constancy referred to earlier which, so the argument goes, is due to an abnormal state of arousal influencing the appreciation of the peripheral cues upon which size judgment depends. Even wider use has been made of the inverted-U principle—that is, the notion that there is an optimum level of arousal for effective performance beyond which behavior “goes into reverse.” The principle has appeared in various forms, most notably as the idea of “threshold for transmarginal inhibition” found in Pavlovian physiology (Gray 1964). Applied to schizophrenia a classic example of its use was in the explanation of catatonia, in which extreme behavioral immobility and unresponsiveness may be accompanied by excessively high levels of physiological arousal and where paradoxical alerting effects of barbiturates have been observed (Stevens and Derbyshire 1958).

In general, however, neither of these last two ways of handling arousal as a mediating construct for schizophrenic behavior has achieved much more than very limited explanatory status. The problem is that like the use of arousal alone as an explanatory concept, both principles have found too wide an application to other forms of behavior; that is, their operation is not unique to schizophrenia. This is particularly true of the inverted-U or transmarginal inhibition principle which is commonly found to apply in a wide variety of situations; more to the point, it has been fairly successfully used in the general personality field—for example, to explain differences in the “strength of the nervous system” of normal introverts and extraverts (Gray 1967).

Although a disorder of central nervous arousal, on the one hand, and a disorder of perception and attention, on the other, seem to be the two most prominent features of schizophrenia, it is clear that conventional ways of handling their interrelationship have proved of limited value. It was out of an attempt to construe the problem from a different point of view altogether that my own approach to schizophrenia developed (Claridge 1967). The basis of this approach was a series of experiments which, for convenience, can be called the “covariation studies” and which will be discussed in the next section.

**Covariation Studies of Arousal and Perception**

Since the early 1960s there has been a narrow thread running through schizophrenia research starting from an unusual and fortuitous observation made independently and almost simultaneously by Venables and myself in the course of a series of experiments on the psychophysiology of psychotic patients. The observation was that although schizophrenics did not seem to differ from other individuals on measures of arousal or perception, per se, they did differ markedly if one looked at the correlation or covariation between such measures. In my own work this phenomenon was most apparent in the case of two measures which, though rather unusual, were of some theoretical interest at that time, namely the sedation threshold and the Archimedes spiral aftereffect (Herrington and Claridge 1965). The former test, being a measure of the individual’s tolerance for injected barbiturates, was considered to provide an index of central nervous arousability while the perceived movement illusion of the spiral aftereffect was thought to reflect, albeit crudely and indirectly, some aspect of sensory input processing. Theory at that time predicted an obvious relationship between them, namely that individuals with high arousal (sedation threshold) would perceive longer movement aftereffects and vice versa. This prediction was fully borne out in neurotic patients (who were the main focus of the study), but a quite different relationship was observed in psychotics. In the latter group the normally expected relationship between the two measures was reversed, schizophrenics with high sedation threshold reporting weak aftereffects and vice versa. Furthermore, psychotics and neurotics did not differ significantly in the range covered on either measure taken individually but only in the correlation between them.

Around the same time Venables (1963) re-
ported a similar finding using two different psychophysiological techniques, namely skin potential (as an index of autonomic arousal) and a measure of the subjectively perceived fusion of brief light flashes (two-flash threshold). Comparing chronic schizophrenics and normal subjects, he showed that apart from a very small group of coherently paranoid patients, schizophrenics differed from normals entirely with respect to the covariation between the two experimental measures.

These two experiments suggested, therefore, that an important characteristic of schizophrenics may be that for any given level of central nervous arousal their degree of perceptual responsivity differs markedly from normal, being either abnormally high or low. Both Venables and myself speculated at the time that this may be due, not so much to a simple shift in either arousal or perceptual function alone, but rather to a failure of homeostatic regulation between the two.

Later attempts to examine this hypothesis further have, with two exceptions, narrowed down on the relationship between two-flash threshold and electrodermal activity, either skin potential or skin conductance. Of the two exceptions one was a study by Krishnamoorti and Shagass (1964) replicating our own findings on sedation threshold and spiral after-effect. The other is a much more recent investigation by Shagass, Straumanis, and Overton (1975) who compared, in different groups, the correlation between background EEG and certain parameters of the evoked response. Having successfully demonstrated the discriminating power of this technique, the authors concluded that the covariation between different psychophysiological measures may be more significant for understanding psychopathology than the absolute levels of the measures themselves.

Subsequent work on Venables' original measures in psychiatric samples has run a somewhat erratic course, with the phenomenon of altered covariation sometimes appearing, though weakly (Gruzelier, Lykken, and Venables 1972 and Gruzelier and Venables 1975), and in one case (Lykken and Maley 1968) appearing in the opposite direction to that shown by Venables! One complicating factor that has emerged is the discovery that the relationship between two-flash threshold and electrodermal level is nonlinear. Another difficulty is the neglect of drug effects by investigators of the phenomenon, since the patients studied either currently or very recently had been on large doses of phenothiazines, which almost certainly distort the psychophysiological relationships being sought.

Partly for theoretical reasons and partly in order to escape the impasse of working with patients who are either drugged and testable or untreated and possibly uncooperative, we have complemented our patient research with studies of two-flash threshold/electrodermal relationships in normal subjects. The rationale for this strategy was the emerging "dimensional" view of schizophrenia—namely the idea that severe forms of the disorder may only form the endpoint of a continuum defining a general personality dimension of "psychoticism" running through the normal population. The arguments for this model have been detailed elsewhere (Claridge 1972 and 1976), but very briefly are as follows.

First, it is being increasingly recognized that the classic schizophrenic syndromes probably represent only severe forms of a broad range of milder conditions, for which the term "spectrum disorders" has been coined (Reich 1975). Second, and in line with this view, the genetic evidence about schizophrenia now makes it at least plausible that the biological characteristics underlying the condition are inherited as a polygenically determined trait or set of traits defining a continuously variable predisposition to psychotic breakdown (Gottesman and Shields 1973 and 1976). Third, there is acceptable evidence (Reichenstein 1976 and Young 1974) that schizophrenic "symptoms" are widely dispersed and frequently observed in otherwise normal people. Fourth, factor-analytic studies of personality traits in normal individuals have demonstrated the existence of a personality dimension recognizable as "psychoticism" and measurable by self-report inventory, the P-scale of the Eysenck Personality Questionnaire (EPQ) (Eysenck and Eysenck 1975 and 1976). Admittedly the validity of the new Eysenck scale leaves something to be de-
sired when judged against its ability to discriminate schizophrenics from other clinical groups, especially psychopaths. Fortunately, however, other evidence for its validity suggests that the scale may be tapping, if imperfectly, some set of characteristics relevant to schizophrenia. Thus, in her study of the prevalence of schizophrenic symptoms among normal subjects, Reichenstein (1976) found a significant positive correlation between her own inventory and the Eysenck scale. Furthermore, investigations of the cognitive style of individuals with high P scores have demonstrated that they show “loosened” thought processes as measured by divergent thinking tests (Woody and Claridge 1977) and by clinical tests of overinclusion (Walker 1974). Finally, although not throwing direct light on the validity of the Eysenck questionnaire itself, a recent study by Nielsen and Petersen (1976), who constructed a similar scale of what they called “schizophrenism,” should be mentioned. The particular interest of Nielsen and Petersen’s work is their finding that normal individuals high in the trait showed rapid recovery of the galvanic skin response (GSR), a characteristic which, in longitudinal research, has received considerable attention as a possible psychophysiological indicator for detecting individuals at high risk for schizophrenia (Mednick 1974a and Venables 1977).

These arguments for the dimensionality of psychotic behavior suggest that the study of appropriately selected normal subjects can provide valid data on the biological basis of schizophrenia. With this in mind we have over the past few years been examining two-flash threshold/electrodermal relationships in normal subjects scoring high on the Eysenck psychoticism scale, comparisons being made with individuals equally high in neuroticism, but with low P scale scores. Before those results are considered, some general remarks should be made about the experimental procedure and method of analysis adopted in this and other studies we have done of two-flash threshold and electrodermal activity. Full details can be found in the original publications.

In determining two-flash thresholds we have always used a method of limits procedure to obtain ascending and descending thresholds, the two-flash threshold being taken as the mean of these two estimations. The concomitant measures of electrodermal level used have been those coincident in time with the estimations of the two-flash threshold. A single index of each experimental variable for a given individual has then been arrived at by averaging several measurements taken during a recording session, and it is these data on which any group comparisons of two-flash threshold/electrodermal relationships have been based. The method of analysis has simply involved examining correlations between two-flash threshold and electrodermal level, but here it is necessary to draw attention to one important point which, while slightly anticipating the results, is relevant to their interpretation. Like others working in this area we have consistently found that the regressions of two-flash threshold on measures of electrodermal level are markedly nonlinear. Furthermore the most clear-cut relationships between the two variables have usually been observed in the low range of electrodermal level, that is, up to the midpoint of the distribution of skin conductance or skin potential. Beyond that point the relationships with two-flash threshold have been less reliable. For clarity of presentation here the results described initially, therefore, will be for the low range data from the various experiments. I will then come back to consider in more detail, and illustrate, the form the data take when the whole range of electrodermal activity is taken into account.

The result from the first study we carried out in our work on psychoticism in normal subjects (Claridge and Chappa 1973) is shown in fig. 1. The groups compared there were selected on the basis of scores on the PEN inventory, an early version of Eysenck’s EPQ questionnaire. High P subjects were defined as those with scores of 3 or more, and low P subjects as those with scores of 2 or less, on the psychoticism scale. Matching for neuroticism—necessary because of a correlation between P and N on the PEN inventory—was achieved by selecting from the low P group those subjects with N scores of 12 or above.

It can be seen from fig. 1 that as predicted
Figure 1. High P and high N subjects compared at skin conductance less than 10.25 \( \mu \)hos

Note.—Correlation and regression lines show the opposite relationships between two-flash threshold and skin conductance in normal subjects with, respectively, high and low scores on Eysenck’s P (psychoticism) scale. These results refer to the low range of autonomic arousal (see text). Note that in this and subsequent figures, two-flash threshold is plotted so that changes in an upward direction indicate improved perceptual discrimination.

from the patient research, the difference between the two groups lay, not in either experimental measure by itself, but in the covariation between them, the correlations being highly significant and opposite in sign in high P and low P subjects. A small replication study by Claridge and Birchall (1973) confirmed this result, which continued to hold up with the addition of further subjects to the sample, the correlations between two-flash threshold and skin conductance now obtained by Birchall being \(-.65\) \((p<.005)\) and \(+.43\) \((p<.05)\) in 18 high P and 18 high N subjects, respectively.

Another strategy we have used, and one which actually antedated that just described, was an early investigation of the “covariation phenomenon” in normal subjects given LSD-25 (Claridge 1972). Comparisons were made of two-flash threshold and simultaneously recorded skin potential in subjects receiving, on separate occasions, either a placebo or 100 micrograms of LSD. As shown in fig. 2, the main effect of the drug was to cause a marked reversal of perceptual sensitivity as it related to ongoing autonomic arousal, the results exactly paralleling those found using the individual differences strategy of selecting subjects according to their self-rated degree of psychoticism.

Finally, in the previously mentioned recent study (Claridge and Clark, in preparation) of untreated schizophrenics tested immediately on admission to the hospital, exactly the same result has emerged; that is, as shown in fig. 3, a significantly negative correlation was found between two-flash threshold and, in this case, skin conductance level, the only difference here being that in order to demonstrate the phenomenon it was necessary to apply range correction to the electrodermal measures.

In comparing figs. 1, 2, and 3, it is clear that there is a striking similarity in the results obtained in a variety of situations in which states of psychoticism or psychosis can be inferred: in diagnosed schizophrenic patients, in normal subjects selected by questionnaire, and in individuals under the influence of a psychotomimetic drug.
What is especially convincing about this convergence of evidence is the particular direction of the empirical relationships observed in the data. Close examination of figs. 1, 2, and 3 shows that for the "psychotic" condition the covariation of two-flash threshold and electrodermal level is always negative over the low range. That is, at low levels of autonomic arousal, perceptual sensitivity is paradoxically excessively high, worsening toward the mid-range. This finding is entirely contrary to the general psychophysiological principle that perceptual sensitivity should improve with increasing arousal, as indeed it does under the "nonpsychotic" conditions of the experiments. Our guess is that the counterintuitive nature of the results found in the psychotic state is not without significance in pointing toward an appropriately unique feature of the central nervous organization as it relates to schizophrenia.
A complication to all of the data described above, however, is the fact, mentioned earlier, that in all three kinds of investigation we have carried out, systematic covariation between autonomic arousal and perceptual sensitivity is most reliably observed in the low range of electrodermal activity. Beyond the mid-range the data always appear to "break away" from linearity of regression. This is most clearly illustrated in the results from the LSD experiment, as shown in figs. 4 and 5. It can be seen that under the placebo condition of that study (fig. 4) something approaching a conventional inverted-U relationship was observed. Under LSD (fig. 5), on the other hand, the data took on a curious U-shaped appearance, suggesting that beyond the mid-point of electrodermal activity perceptual acuity paradoxically began to improve again. A similar picture was discernible, though less clearly, in the data for acute schizophrenics (fig. 6) and in Claridge and Chappa's (1973) data on high P normals (fig. 7). It was also found in Claridge and Birchall's (1973) replication of the latter experiment.

It is obvious that compared with the low range of autonomic arousal (cf. previous figures and see text), the relationship between two-flash threshold and skin potential over the full range of autonomic arousal is shown.

**Figure 3. Two-flash threshold and skin conductance level (low range) in acute untreated schizophrenics—First testing day**

**Figure 4. Relationship between two-flash threshold and skin potential—Placebo condition**

Note.—In the placebo condition of the LSD experiment, the relationship between two-flash threshold and skin potential over the full range of autonomic arousal is shown.
data, those for the upper range are much less convincing and only weakly confirm a similarity between the results of the three types of experiment. Such as it is, however, the trend seems to be a reversal of the relationship found in the low to moderate range of electrodermal activity, the overall regression being suggestive of a very peculiar U-shaped function—seen most clearly in the LSD study. If one bears in mind the unusual nature of the results found in these experiments, it does at least seem possible to conclude that LSD-25 has psychophysiological effects which can be aligned theoretically with findings obtained using other strategies for investigating the biological basis of schizophrenia. Since it is to be argued here that LSD might therefore provide a useful vehicle for establishing an animal model of schizophrenia, it is appropriate at this point to consider other evidence in support of that thesis.

Figure 5. Relationship between two-flash threshold and skin potential—LSD-25 condition

Note.—In the LSD-25 condition, the relationship between two-flash threshold and skin potential over the full range of autonomic arousal is shown.
LSD as a Psychotomimetic

During its relatively brief history LSD-25 (lysergide) has been the subject of controversy even greater than that which usually greets new scientific discovery. Synthesis of the drug and observations of its remarkable psychological effects led to an early hope that here at last was the pharmacological agent which would finally unravel the biochemical basis of schizophrenia. The failure to do so, while not surprising—given the limited disease views of the disorder current at that time—led to a period of pessimism about the drug's scientific usefulness. This phase coincided with the "discovery" by drug-cultists of the psychedelic properties of LSD and led eventually, of course, to its proscription by society and to severe limitations of its use in serious research. Actually it was perhaps with some relief that research workers concerned with schizophrenia felt able to dismiss the scientific interest of LSD and to abandon the study...
of it, though they did so precisely at the time when progress on other fronts of schizophrenia research began to make some, albeit very slow, progress.

An important factor which undoubtedly hastened the decline of interest in LSD was the view, already mentioned, that amphetamine constituted a better pharmacological model of schizophrenia. Work on that drug was linked to, and provided part of the evidence for, the increasingly popular hypothesis that schizophrenia may be due to an excess of dopamine in the central nervous system, especially in the limbic system. Among biochemists searching for the neurotransmitter crucially involved in schizophrenia there was, therefore, a shift of focus away from the “serotonin hypothesis” which the earlier work on LSD had prematurely spawned.

Although the alternative “dopamine hypothesis” has usefully extended our knowledge of the biochemistry of schizophrenia, its current status as an explanation of the disorder is still extremely uncertain (Meltzer and Stahl 1976 and Van Praag 1977). Thus, Meltzer and Stahl (1976), in concluding their recent review of the topic, comment as follows:

The evidence for a role for DA [dopamine] in the pathophysiology of schizophrenia is compelling but not irrefutable; the “smoking gun” has not yet been discovered. Evidence consistent with the hypothesis still cannot be transformed into basic principles that could conceivably become the theoretical framework into which the majority of clinical as well as biochemical data that concern schizophrenia might be comprehended. [p. 58]

Meltzer and Stahl go on to point out that even if dopaminergic hyperactivity is present in schizophrenia, it may simply be a secondary correlate of transiently increased central nervous system arousal due to some other basic defect. In any case, whether primary or secondary, the involvement of dopamine in schizophrenia does not preclude a pharmacological model based on LSD, since it is known that the latter drug is capable of activating dopamine receptors (Fuxe et al. 1976 and Kelly and Iversen 1975).

Given the still immature state of knowledge about the biochemistry of schizophrenia, there seem on biochemical grounds, therefore, to be no convincing reasons for continuing to reject LSD as a potentially useful drug model. As for its superiority or otherwise to amphetamine on grounds of clinical effect, some comments have been made on this point earlier in the paper. It was mentioned there that by comparison with LSD, amphetamine models only part of the schizophrenic spectrum in humans and even then only in chronic dosage, while in animals the “marker” behavior is somewhat trivial. In any case, since the preference for amphetamine has been inextricably linked to the dopamine hypothesis, most of the arguments in favor of the drug fall away given the still uncertain status of that hypothesis. Indeed, since there seems to be a real possibility that schizophrenia will not reduce to a disorder of any single neurotransmitter, there is something to be said at present for making one’s initial choice of a drug model simply on grounds of “face validity”—that is, which drug looks as though it reliably produces a state akin to, and includes the varieties of, natural psychosis. Were it not for the fierceness with which the amphetamine model has been defended and the LSD model rejected, it would be laboring the point unnecessarily to reiterate the latter’s obvious superiority.

Even so it may be, and has been, argued that LSD does not mimic the clinical features of schizophrenia well enough. A particular criticism has been that the disorders of perception observed are mainly auditory in schizophrenia and visual in the LSD-induced state. West (1975), for example, concludes that according to a “rough estimate” only about 5 percent of schizophrenics show visual hallucinations. However, more careful studies suggest a much higher incidence. The most thorough is that carried out some years ago by Chapman (1966) who, on the basis of extensive interviews, examined the subjectively reported symptoms of a group of early schizo-
phrenics. He found that visual perceptual disturbances were very common in such patients, while auditory disturbances, at least in the form of hallucinations, were actually rather rare. More recently a survey by Zarroug (1975) revealed that about 62 percent of schizophrenic patients reported visual hallucinations. That study was carried out in Saudi Arabia and the author emphasizes the possible importance of cultural factors in determining the form psychotic symptoms take, a comment which warns against hard and fast conclusions being reached about the "typical" phenomenology of schizophrenia.

A complicating feature of all of these studies, of course, may be the use of differing criteria for defining hallucinations, as distinct from other perceptual disturbances, such as illusory distortions of the external environment. A proper comparison of schizophrenia and the LSD state requires that similar criteria be applied to both. In such a study Young (1974) recently examined the psychotic symptoms reported by normal subjects, schizophrenics, and regular LSD-takers. Young concluded that LSD-induced and natural psychoses were in most major respects phenomenologically indistinguishable. The main differences related to the greater degree of unpleasant affect, especially anxiety, and the higher frequency of delusions in the schizophrenics. Neither of these, however, argues crucially against LSD psychosis being a good drug model for schizophrenia, if account is taken of the context in which each of these states occurs. Thus, the regular LSD-taker is entering the state voluntarily and with relative control over it; anxiety would therefore be much less than in spontaneously occurring natural psychosis. With regard to delusions, as Chapman (1966) and indeed many writers in the schizophrenia literature have pointed out, these can probably be best understood as attempts by the schizophrenic patient to explain the primary perceptual and attentional disturbances occurring early in the illness. Compared with the schizophrenic the LSD-taker would have less need for such thought strategies though, indeed, as we found in our own study of LSD they can occur, if rarely. Both of the differences between schizophrenia and LSD described by Young could therefore be said to be secondary elaborations on or reactions to a primary psychotic state which is similar in both cases.

In terms of the subjective report, then, the LSD state does not seem to differ from schizophrenia as much as some critics have argued, a view also taken by Davison (1976) who, after reviewing the same question, concludes that although not identical, "individual features of the drug reaction are remarkably similar to some of the experiences of the more acute schizophrenic psychoses" (p. 111). Of course, it could be said that to insist the two be identical is, in any case, to misunderstand the logic of drug research of this kind. Schizophrenia is a complex natural disorder of multiple causation and has many features which are almost certainly not part of the core defect of the disease. Earlier it was argued that the latter was probably some form of "input dysfunction" accounting for the anomalies of perception and attention observed in the early phases of schizophrenia. That defect does seem to be mimicked quite well by LSD, at least as assessed by subjective report.

More objective evidence on this point, from experimental studies of the effects of LSD in humans, is not easy to fit into any coherent picture, partly because many such studies, particularly in the early days of LSD research, were of the empirical "look and see" variety. There was also usually no attempt to make comparisons with schizophrenics on similar tasks, although one study that did do so was an investigation by Wikler et al. (1965). They used a variable fore-period reaction time procedure to test the hypothesis that LSD-25 would have similar effects on "mental set" to those previously reported as one of the primary deficits in schizophrenia (Rodnick and Shakow 1940 and Shakow 1963). Although their hypothesis was confirmed, similar changes in mental set were also observed under morphine and pentobarbital, suggesting that the effects were nonspecific. Nevertheless, from this and other studies of LSD carried out around
the same time (Uhr and Miller 1960) it can at least be said that some of the impairments of performance observed in laboratory investigations of the drug were not inconsistent with those seen in schizophrenics—though admittedly this is a weak conclusion considering the chaotic nature of the evidence there. More recently, however, Silverman (1973) made an exceptional attempt to align LSD reactions and schizophrenia within a theoretical framework which emphasized alterations in sensory responsiveness, or stimulus modulation, as the disorder common to both. His account is interesting in proceeding from a discussion of subjective data of the kind referred to above, to a consideration of experimental studies of sensory sensitivity. In doing so, he pays particular attention to work on the "augmenting-reducing" phenomenon (Buchsbaum and Silverman 1968), the evoked response measurement of which continues to provide a valuable technique for examining sensory nervous system differences in relation to psychopathological states (Buchsbaum, Post, and Bunney 1977 and Landau et al. 1975). Although Silverman's arguments are occasionally somewhat inferential, his conclusion that LSD reactions and schizophrenia are similar psycho-physiologically is very convincing and would accord well with the results of our own studies, reported in the previous section, directly comparing the two states on two-flash threshold and electrodermal activity. While the results of the latter studies are rather narrow in thrust and their significance not entirely understood, they do suggest that given the right choice of parameters, a theoretically predictable match can be observed at the psychophysiological level between LSD-induced psychosis and naturally occurring variations.

A third source of support for the LSD state as an appropriate pharmacological model of schizophrenia is work on the drug's effect in animals. Here I shall confine myself to a limited group of studies which, although they are now rarely quoted (indeed never referred to in the schizophrenic literature) are, I believe, of great theoretical interest. The effects observed and the interpretations put on them show a remarkable parallel with some salient features of the work undertaken, albeit quite independently, on schizophrenia.

The studies in question date back, in some cases, almost twenty years and were carried out by Bradley and by Key and his colleagues in the Department of Experimental Neuropharmacology in Birmingham, England. The general theoretical background of the investigations was an early speculation by Bradley (1957) that LSD-25 has its main (alerting) effect on the brain, not through a direct influence on the arousal mechanisms as such, but indirectly by increasing the organism's responsiveness to environmental conditions. He considered that in this respect it differed from amphetamine which had a direct arousing effect on the brain. The evidence for this came from a study comparing the effects of the two drugs on the arousal thresholds (both EEG and behavioral) for direct reticular stimulation and externally applied auditory stimulation. It was demonstrated in cats that while amphetamine globally reduced thresholds for arousal, only that for auditorily-applied stimuli was—markedly—affected by LSD, the threshold for direct brain stimulation being uninfluenced. Interestingly, thiopentone and chlorpromazine showed parallel differences, though of course in opposite directions, to those found for amphetamine and LSD-25.

The hypothesis derived from this study—that LSD appears somehow to selectively alter the filtering properties of the brain—was examined in a further experiment by Key (1965), again in the cat. He looked at the effect of the drug on fluctuations in the auditory evoked response recorded from the dorsal cochlear nucleus. Recordings were made under two conditions, while the animal was in a soundproofed box and after transfer to the noisier open laboratory. Key found that compared with a control period, LSD had no effect, as measured by the variability of the evoked response, when the animal was kept under stimulus-attenuated conditions. Under noisier conditions, however, the drug produced marked evoked response variability, indicating
greatly increased sensitivity to environmental stimuli. This study is of particular interest in view of some recent reports, referred to in an earlier section, that schizophrenics show excessive variability of the evoked response, an observation interpreted along similar lines to the explanation offered by Key for his finding on LSD.

Finally, a third pair of studies by Key (1961 and 1964) is also relevant. Here he examined the effects of LSD-25 on sensory generalization in cats. In the first experiment the animals were taught a barrier-crossing avoidance response to an auditory stimulus (a pure tone). Generalization effects for tones of differing frequencies were then tested, comparisons being made between three conditions: LSD, chlorpromazine, and a saline control. The two drugs had opposite effects, LSD markedly increasing and chlorpromazine decreasing the amount of sensory generalization that occurred. Similar effects of LSD on generalization for visual stimuli were found in the later study which included a comparison with amphetamine. The latter drug also affected generalization, though only at the highest dose level, and even then the effect seemed to be dependent upon a general increase in responsiveness or arousal not evident under LSD. Key was led to conclude that LSD appears to act primarily by altering the level of significance or meaning that is attached to environmental events, thus causing the animal to respond to stimuli it would usually ignore. Although Key did not draw the parallel, there is clearly a close similarity between these data and their interpretation and those that have emerged out of schizophrenia research itself. That is particularly true of the work of Mednick (1958) who, as will be recalled, has based part of his own approach on a conditioned generalization view of the attention disorder in schizophrenia.

It seems therefore that there are a number of important ways in which LSD and schizophrenia research closely converge, so much so that in my view, LSD-25 still offers the most exact pharmacological equivalent to the natural disorder yet discovered. Its failure to be now recognized as such, apart from the reasons already given, appears to be due to the fact that the kinds of research data and theoretical interpretation—both about LSD and schizophrenia—emphasized here have rarely, if ever, been brought together within the same rubric of discussion. The pharmacological parallels sought in recent years have more often focused on alleged psychotomimetic effects of other drugs, notably amphetamine, and usually starting from a biochemical standpoint. To anyone familiar with the material presented here, that focus is actually somewhat surprising since amphetamine, by comparison with LSD, produces only a crude analogue of schizophrenia and even then only in very high doses in the human subject. It seems logical, on the other hand, if one is to pursue a pharmacological route into an animal model of schizophrenia, to choose a drug which produces the closest available parallel to the natural state. That drug, I believe, is still the remarkable, if sometimes cursed, psychedelic—LSD-25.

An Animal Research Strategy Using LSD-25

From the discussion so far two main conclusions can be reached. First, certain core features of schizophrenia appear to reflect disorder at a sufficiently "low level" in the central nervous system to be potentially reproducible in a non-human species. Secondly, LSD-25 has a number of effects which parallel those characteristics thought to be central to schizophrenia. The arguments for reviving the use of LSD as a method of inducing a "psychotic state" in an animal therefore seem very strong. The next problem to be considered is the selection of the optimum "marker behavior" for defining such a state objectively, before carrying out further analysis of its underlying physiological determinants. If one sets aside changes in gross behavior, which are difficult to define and measure reliably, the experimental literature already reviewed points to a number of possibilities. Thus, the changes in conditioned generalization and evoked response variability reported by Key might provide the basis for developing an appropriate index
of the effects of LSD. Or changes in performance on attentional tasks might be considered. Another possibility would be derived from the "covariation" strategy outlined earlier. This would involve trying to map out the effect of LSD by examining changes in the interrelationship between some measure of ongoing tonic arousal and an index of perceptual sensitivity, say an evoked response correlate of two-flash threshold. That approach would have several advantages.

First, as we have seen, it has already worked in human subjects given LSD and the extrapolation to animals would be minimal.

Second, results obtained using the strategy in humans under LSD are empirically consistent with those found elsewhere in schizophrenia research.

Third, the particular phenomenon of altered covariation of function seems to occur only in the context of studies focusing on psychotic behavior, whether drug-induced or observed naturally in normal humans or schizophrenic patients. It therefore seems unique enough to warrant further neurophysiological investigation.

Fourth, the method is relatively "passive" and, unlike a paradigm based on conditioned generalization, for example, it would involve little prior training of an animal. This would be particularly true if an evoked response measure were substituted for the two-flash threshold index used so far in the human studies. The possibility of doing so is strongly supported by evidence that there are detectable visual evoked response correlates of two-flash discrimination in the cat (Lindsley 1957) and in the human subject (Andreassi et al. 1971 and Vaughan 1966).

Whatever the "marker behavior" chosen to define an LSD-induced state, the purpose of doing so in an animal subject would, of course, be to investigate its underlying mechanisms through further physiological manipulations. The possible focus for such manipulations raises many difficult questions and is perhaps the weakest link in the chain of arguments presented here. However, it is worth considering briefly some of the ways in which psychologists have recently been led to speculate about the neurophysiological basis of "input dysfunction" in schizophrenia. These ideas will be discussed in the final section.

Some Physiological Speculations

As indicated in a previous section, the early theorizing about schizophrenia indulged in by psychophysicists was based on a very molar view of the nervous system—indeed it was scarcely physiological at all—and was descriptive rather than explanatory of the empirical data. The main conclusion that could be reached was that in schizophrenia there seems to be something wrong with both tonic and phasic aspects of arousal, perhaps due to a failure in the homeostatic regulatory mechanisms of the central nervous system and perhaps involving reticulo-cortical loops. Since that time speculation has become, if not less vague, at least more physiological; interest has converged on the hippocampus and, to a lesser extent, the amygdala as possible neural mediators of the attentional and arousal dysfunctions observed in schizophrenia. The definitive discussion of this hypothesis is a recent paper by Venables (1973) in which he attempts to bring up to date his earlier theorizing about schizophrenic "input dysfunction" (Venables 1964). In his later paper Venables draws a parallel between work on attention in schizophrenia and animal research on the hippocampus. In linking the two he quotes evidence that the hippocampus seems to be critically involved in attention, particularly through its role in "gating" or filtering sensory input (Douglas 1967, Douglas and Pribram 1966, and Kimble 1968). Venables further supports his argument with several other lines of evidence. The most convincing of these are the supposed selective action on the hippocampus of certain tranquilizing drugs (Killam, Killam, and Shaw 1957), the clinical similarity between schizophrenia and temporal lobe epilepsy (Flor-Henry 1969 and Slater and Beard 1963) and the appearance of schizophrenic-like...
symptoms in patients with hippocampal tumors (Malamud 1967).

Another psychophysiologist who has narrowed down on the hippocampus is Mednick (Mednick and Schulsinger 1973 and 1974a). He has done so on the basis of results emerging from his 20-year followup of the children of schizophrenic mothers, arguing for a similarity between the peculiarities of conditioning, extinction, and orientation found in his “sick group” and those observed in hippocampectomized animals. Admittedly his findings have not been replicated by more recent research (Mirdal et al. 1977), and in any case, as Kessler and Neale (1974) have recently pointed out, there are a number of flaws in Mednick’s argument relating these abnormalities to birth trauma. However, failure of Mednick’s anoxia hypothesis would not preclude the possibility that the hippocampus, through some subtle variation in its normal functioning, is critically involved in the attentional deficits observed in schizophrenia.

One particular feature of the hippocampus that may be of special interest in the present context concerns its supposed reciprocal relationship with the brainstem reticular formation (Redding 1967 and Vinogradova 1975). Variations in the feedback loop between these two structures have already been proposed as a possible physiological basis for certain normal personality characteristics (Gray 1970). In applying this model Gray has placed emphasis on variations arising from differences in the level of reticular arousal, the normal feedback properties of the loop being maintained. An entirely speculative, though not inconceivable, extension of the model is that alterations in the nature of reticulo-hippocampal feedback itself might give a physiological explanation of the failure of homeostasis postulated by Venables and myself to account for our findings of altered covariation between perceptual response and arousal in schizophrenia. Thus, it is perhaps not without interest that in theorizing some years ago about schizophrenia (Claridge 1967) I argued for the existence of two hypothetical systems whose functions were not dissimilar to those assigned to the hippocampus and ARAS. These were named at that time the “tonic arousal system” and the “arousal modulating system,” the latter having a role in selective attention and also exerting an inhibitory influence over tonic arousal. It was hypothesized that schizophrenia was accompanied by a relative dissociation of these two mechanisms resulting from a partial failure or reversal of feedback between them. There is clearly some alignment between this molar theory and the more physiological model, developed with different emphasis and from a quite different point of view, by Gray.

Postscript

The purpose of this paper has been to argue the case for reexamining LSD-25 as the basis for an animal model of schizophrenia. I think it is evident from the preceding discussion, however, that the conclusions reached emerged from an interdisciplinary view of research on schizophrenia and from a belief that continued progress in the area will only be possible if several different strategies, linked by a common conceptual thread, are used—simultaneously or by successively testing out on animals ideas generated in human research and vice versa. Of course, even if an animal model of schizophrenia is possible, it will be necessary to return, for our ultimate insight, to the schizophrenic patient; it is unlikely that animal research could provide a complete account of what, in some ways, is a peculiarly human disorder. If the arguments presented here are vindicated by the appropriate animal experimentation, it could well be that an important intermediate stage in understanding natural psychosis in man would be the revival of human research on LSD. As the example quoted earlier illustrates, particularly valuable might be further
work on its psychophysiological effects, since psychophysiology occupies a crucial position as a bridging discipline within which to examine, in the intact human subject, the implications of direct studies of the brain. Such research could be—indeed may be preferably—done using extremely small doses of LSD sufficient to produce detectable physiological change but without the disruption of psychological control sometimes associated with the drug. Even so, in the present climate of opinion such a suggestion is undoubtedly controversial and raises many ethical questions. Although the present paper has provided no answers to those questions it has perhaps drawn attention to some of the scientific evidence which bears on their debate.

Summary

Some of the difficulties of trying to establish an animal model of schizophrenia are first considered. Then, after a review of the evidence on the experimental psychopathology of schizophrenia, particularly that concerned with attention and arousal, it is concluded that the core feature which needs to be modeled in animals is some aspect of “input dysfunction.” It is argued that, of the pharmacological strategies, LSD-25 comes nearest to meeting that requirement, for two reasons. First, the phenomenology of an LSD “model psychosis” closely parallels that of the natural disease. Secondly, the experimental effects of the drug, both in animals and man, are very similar to or can be closely aligned theoretically with those of schizophrenia. An example is quoted from work in the author’s laboratory where LSD was found to produce psychophysiological effects virtually identical to those observed occurring naturally in acute psychotic patients and in normal subjects high in “psychotic” personality traits. It is suggested that the rejection of LSD as a drug model was premature, especially as the currently popular preference for amphetamine has not been vindicated, either by the latter’s ability to mimic an important central feature of the psychotic state or by work on dopamine as a specific common mediator of amphetamine psychosis and of schizophrenia.

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