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Biological Theories, Drug Treatments, and Schizophrenia: A Critical Assessment

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This article questions the adequacy of several genetic and biochemical hypotheses as comprehensive explanations of conduct labeled schizophrenia and suggests that unacknowledged effects of psychotropic drug treatments and biases in drug effectiveness research interfere with the interpretation of clinical and experimental studies. Furthermore, their mechanistic-causal underpinnings and their disregard for the valuation dimension ensure that biological approaches will not be able to provide a completely satisfactory solution to the puzzle of schizophrenia. Emerging epistemologies, recent findings about brain-behavior interactions and the long-term course of psychotic phenomena suggest that a contextualist approach to understanding unwanted conduct is a preferred alternative to the more reductionist and mechanistic one employed by biological researchers. The contextualist alternative recognizes that behavior called schizophrenic results from the complex interaction of a large number of factors in a context.

Psychiatry in the 1980s is firmly planted in biomedical soil. The psychiatric profession's adoption of biological models and chemical treatments to explain and control the widest range of mental disorders exemplifies this. Akiskal (1985), for example, states that a "neuroscientific revolution now permeates all aspects of psychiatry" (p. 645). Accordingly, it is felt today that those behaviors variously called "schizophrenia," "the schizophrenias," or "schizophrenic disorders" are best studied and understood as manifestations of one or several biological disease processes (perhaps an error of metabolism or atrophy) which directly affect the brain. Although investigators from various disciplines have argued that this approach is inadequate (Bannister, 1982; Braginsky, Braginsky, and Wing, 1969; Sarbin and Mancuso, 1980; Scheff, 1976, 1984; Szasz, 1976, 1978), the brain-disease model exhibits renewed vigor, enough for some leading proponents to claim that recent biological

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findings have established its validity beyond contention (Andreasen, 1984; Flor-Henry, 1983; Greist, Jefferson, and Spitzer, 1982; Torrey, 1980, 1984).

This brain-disease model has become an entrenched yet versatile construct, manifesting some characteristics Kuhn (1970) imputed to "paradigms." Indeed, Akiskal (1985) calls the model "the *Zeitgeist* of the new psychiatry" (p. 645). For its adherents, it may be that "the transfer of allegiance from paradigm to paradigm is a conversion experience that cannot be forced" (Kuhn, 1970, p. 151). The allegiance is partly maintained by the assurance that the older paradigm will solve the problems it has generated or made evident.

In psychiatry and abnormal psychology, one of these problems has been the failure of the mechanistically-derived disease model to meet an essential requirement: the construction of causal statements rigorously specifying certain antecedent events as the independent variables which "cause" the resulting symptoms, the dependent variables. Until quite recently in the biological sciences, the success of the disease model was measured on the basis of such conceptual constructions which manifested great predictive validity. In the biologically-oriented research enterprise devoted to schizophrenia, however, it appears that the disease model persists not because it has shown as high a degree of internal consistency or predictive validity as the biological model it emulates, but because its proponents *believe* that the cause of schizophrenia, the independent variable, will be discovered as a result of continuing research efforts.

The work of Richter (1976), representative of the prolific biochemical research tradition, suggests that to obtain information on possible biochemical factors involved in the appearance of schizophrenic symptoms, we need to discover what underlying neurological systems and transmitter mechanisms are involved. Naturally, chemical and neurological processes and systems are involved in *all* activities of the brain. Nerve cells are stimulated by nerve impulses, and chemicals are transmitted across synaptic gaps between cells. Thought, mood, and behavior are modulated as billions of these neurochemical transactions occur simultaneously. In general, biochemical theories assume that imbalances in these processes are responsible for the appearance of schizophrenia. The brain is estimated to contain about 10 billion neurons, each with about 1500 synapses, each again with about one million receptor molecules. Approximately 200 known substances are presumed to act as neurotransmitters. To determine which of these processes are significant, and how they are so, is a formidable challenge indeed. The recent explosion of knowledge in genetics and the neurosciences, however, has strengthened the belief that just around the corner lies the vital new finding which will uncover the precise determinants of those unwanted and incomprehensible behaviors that lead some individuals, under some conditions, to be diagnosed as suffering from schizophrenia.

Research reports suggest or state that a familial or genetic basis, and

biochemical as well as neurological, radiological, and immunological abnormalities have been described and established in schizophrenic patients (Torrey, 1984). Yet, after decades of intensive biological research, no one has yet marked a single biological abnormality of any sort identified with schizophrenics and only schizophrenics, no matter how broadly or narrowly diagnosed, grouped, or categorized. Since there is no diagnostic test which can confirm a diagnostician's impression that an individual so designated is, in fact, schizophrenic—or that a "normal" person is not, in fact, schizophrenic—we still have not established that schizophrenia is a disease, what sort of disease it is, or what causes it.

The major renewal of interest in diagnosis, sparked by the development of DSM-III and quantitative approaches to classification, has led to improvements in diagnostic reliability, but it has not produced the desired results in terms of treatment: a diagnostic system which consistently passes the test of practice (Colby and Spar, 1983). As Dumont (1984) notes, although one might expect trained users of DSM-III to improve their agreement about when a label should apply to a particular set of behaviors, diagnosticians assessing the characteristic ambiguities of real-life situations, rather than characteristic case vignettes, often fare poorly. Two recent studies highlight existing problems. Lipkowitz and Idupuganti (1985) demonstrate that two years after the adoption of strict DSM-III guidelines for the diagnosis of schizophrenia, "American psychiatrists continued to view this disorder in highly individualistic terms, each convinced of the validity of the diagnosis but with no consensus on pathognomic signs and no reliability in the selection of findings that would identify the syndrome" (p. 636).

Lipton and Simon (1985) reevaluated the charts of 131 randomly selected patients at the Manhattan Psychiatric Center and interviewed 43 of them. They confirmed only 16 out of 89 diagnoses of schizophrenia, assigned presumptive diagnoses of affective disorders to 50 patients (35 more than had received that diagnosis in their chart) and diagnosed organic disorders in 26 patients (19 more than had been so diagnosed in their hospital records). Interestingly, despite the medicalization of hospital psychiatric practice and a particular emphasis in the literature on the need for thorough physical examinations of psychiatric and especially schizophrenic patients, it appears from this latest study that organic disorders often go unnoticed in actual practice (see Taylor, 1982, for a thorough discussion of this problem). Lipton and Simon estimate that in the New York State hospital system alone, 7,138 patients were misdiagnosed as schizophrenic. The authors remind us of the consequences of such potential misdiagnoses by noting that "almost all of these patients were receiving medications inappropriate to their presumably more valid diagnoses" (1985, p. 372). Such findings point to the discrepancy between psychiatric diagnosis and diagnosis in other branches of medicine, but also

fit well with the fact that some biological anomalies found in some schizophrenic patients are also found in persons with other diagnoses. This leads Dumont (1984) to argue for the non-specificity of mental illness.

A diagnosis depends on a number of factors, including the school of thought to which a psychiatrist adheres, his or her individual preferences, the nature of the interaction between the psychiatrist and the patient, the amount and type of data available for evaluation, and the purpose of the evaluation. For these reasons, it is not entirely surprising that, as Lipkowitz and Idupuganti (1985) document, there remains considerable disagreement concerning the interpretation of such a diagnostic term as schizophrenia. Yet, the construct schizophrenia is useful, otherwise it would be discarded. According to Cromwell (1984), it works for us in helping us classify (and sometimes segregate) that one percent of the population who comes to behave in ways that meet our operational definition. This partial reinforcement serves to keep a scientific construct in place, until it becomes "real."

The field of biological psychiatry is enormously varied and productive. We concentrate in this paper on two areas we feel are fairly representative of current research efforts to elucidate the causes of schizophrenia: the development of genetic and biochemical hypotheses. Our assessment of the results in these areas leads us to think that biological formulations, and especially their mechanistic-causal foundations, cannot serve as a basis for comprehensive explanations of unwanted conduct.

The Contribution of Genetic Hypotheses

The hypothesis that schizophrenia results partly from a genetically transmitted morphological defect has been explored in a number of well known studies (Gottesman and Shields, 1972, 1982; review by Kety, 1983). The central conclusion drawn from these studies supports the view previously expressed by Heston (1970), that "the contribution of genetic factors to the etiology of schizophrenia has been confirmed decisively" (p. 249); and reiterated by Roberts (1985), that "genetic transmission has been unequivocally demonstrated" (p. 93). This conclusion justifies biochemical investigations. A central tenet of molecular biology is that genes express themselves exclusively through biochemical processes. Thus, if there are genetic factors operating in mental illness, biochemical factors should also be important (Kety, 1978).

The landmark Danish adoption study by Kety, Rosenthal, Wender, and Schulsinger (1968) found a higher incidence of schizophrenia in the biological relatives of adopted schizophrenics than in the adoptive relatives. Kety et al. obtained this difference by creating a "schizophrenia spectrum" of disorders. This included categories such as "borderline state," "inadequate personality,"

and "uncertain borderline state." A single "chronic schizophrenic" was found in each set of relatives.

Several authors have criticized the Danish adoption studies and the many reevaluations of data by Kety and his associates. Sarbin and Mancuso (1980) and Stewart (1980) question the broad interpretation the Kety group made of its findings. Dumont (1984) concludes that the findings "have the quality of microscopic measurements of lines drawn on the sand as measurements of the tides" (p. 330). Abrams and Taylor (1983), and Lidz and Blatt (1983) find errors in the sampling and statistical procedures. The most recent and detailed criticism is that of Lewontin, Kamin, and Rose (1984). They examined the entire series of adoption studies—including previously unpublished data furnished by the original investigators—and conclude that "the weaknesses of the Danish adoption studies are so obvious upon critical review that it may be difficult to understand how distinguished scientists could have regarded them as eliminating all the artifacts that beset family and twin studies of nature and nurture" (p. 227).

The twin study by Gottesman and Shields (1972) represents a careful investigation of the genetic transmission hypothesis. The assumption guiding twin studies is that monozygotic twins, sharing the same genetic material, would show a greater concordance rate of schizophrenia than would either dizygotic twins or other siblings. Data from this long-term study does support that assumption: in about 45 percent of the cases, if a monozygotic twin is diagnosed as schizophrenic, the other twin will receive the diagnosis. In about ten percent of the cases, if a dizygotic twin is diagnosed as schizophrenic the co-twin will also receive the same diagnosis. However, because the suspected genetic anomaly does not produce effects (culminating in the acquisition of the diagnosis by a co-twin) in over half of the cases where a monozygotic twin is diagnosed as schizophrenic, Stromgen (1975) as well as others claim that the only unquestionable result of twin genetic studies is that they demonstrate the extensive contribution of "environmental" factors to the etiology of the disorder.

This point is no longer seriously in dispute today—for example, DSM-III (1980, p. 186), notes this lack of certainty concerning genetic origins—but it does seriously complicate the search for the "causes" (genetic or other) of schizophrenia. The major genetic models so far advanced (monogenic, polygenic, and genetic heterogeneity) have not answered how a mental disorder is inherited (Cromwell, 1984; Tsuang and Vandermey, 1980). Gottesman and Shields (1982) note that the premorbid schizophrenic is currently not identifiable—no *corpus delicti* can be equated with a genotype for schizophrenia. This supports Zubin's (1983) point that there is still no direct evidence that the inherited genetic make-up of the person who develops one or more episodes of schizophrenia is in any way different from that of those

who do not. In a recent review, Zubin, Steinhauer, Day, and van Kammen (1985) confirm that the primary questions Zubin raised in 1951 about schizophrenia—including the need to understand etiology—are still with us and "unlike old soldiers they do not even fade" (p. 219).

Organism-Environment Interactions

To account for their data, twin and adoption studies have had to postulate complex interweavings between genetic and environmental factors, interweavings as yet undefined (Stewart, 1980), and possibly undefinable. At least in most cases of complex psychobiological traits, these factors are so enmeshed as to make it impossible to separate them. In fact, it is now clear that the difficulty in disentangling genetic from environmental influences is present even from the earliest phase of the history of the neuron itself (Purves and Lichtman, 1985). Developing neurons respond to their environment—other neurons—by changing their chemical structure, a process which then alters the structure of the surrounding neurons (Hofer, 1981). Varela (1984) describes a similar circularity which results in the appearance of autonomous cells: "A cell stands out of a molecular soup by defining and specifying boundaries that set it apart from what it is not. However, this specification of boundaries is done through molecular productions made possible through the boundaries themselves" (pp. 311–312).

Recent expositions of etiological models of schizophrenia (Ciompi, 1984; Zubin et al., 1985) make skillful attempts to incorporate genetic hypotheses with clinical observations of the long-term course of psychotic phenomena, suggesting a genetic vulnerability/information-processing hypothesis. This hypothesis, which allows for a multitude of possible triggering and intervening variables (endogenous and exogenous stressors, life events, etc.), highlights that the state of our knowledge concerning the etiology of schizophrenia results more from what we have failed to confirm with biological studies rather than from an abundance of positive research results.

In their review of quantitative models of the genetic transmission of schizophrenia, Faraone and Tsuang (1985) state that a multi-factorial polygenic model has received the most support from the literature. They do recognize that this model relates genetic factors to an amorphous pool of small, indistinguishable components, none of which are necessary or sufficient for pathogenesis. The general lack of explanatory or predictive success of genetic models, according to Crowe (1981), "may be because our mathematical sophistication exceeds our diagnostic sophistication" (p. 92). Although Faraone and Tsuang are writing about developments in a field where the amount of knowledge doubles every 24 months (J. Rifkin, 1984), their conclusion is identical to Crowe's above comment. They write that "the sophistication of cur-

rently available [statistical] techniques far exceeds the reliability and validity of phenotype specification" (p. 63).

This supports the notion that a decisive confirmation of a genetic effect in schizophrenia will have to await nothing less than the discovery of a precise genetic mechanism, perhaps related to a relevant genetic marker. Much of the biochemical research of the last fifteen years has been directed toward this goal. One portion of this research, to which we turn below, has been concerned with the significance of monoamine oxydase (MAO), an enzyme that metabolizes amines in the brain.

MAO and the Search for a Genetic Marker

Research exploring the role of MAO, like much of schizophrenia biochemical research in general, illustrates three points: (1) scores of studies result in scores of inconclusive findings, (2) the influence of hidden variables hinders the interpretation of results, and (3) most interpretations lack a comprehensive theoretical basis.

The activity of MAO is considered relevant for several reasons: it is partly under genetic control (Nies, Robinson, Lamporn, and Lampert, 1973); it is consistent with other major conceptions of biochemical abnormalities in schizophrenia (Teller, 1979); and it has been associated with stable behavioral profiles in animals such as rhesus monkeys, and with depressive and antisocial behaviors in humans (Buchsbaum, Coursey, and Murphy, 1978).

The first report linking blood platelet MAO (pMAO) activity to schizophrenia was Murphy and Wyatt's (1972) study which reported finding significantly lowered pMAO activity in a group of chronic, hospitalized schizophrenics as compared with normal controls. Since then, several dozen studies have investigated the significance of this putative genetic marker of schizophrenia. (Other markers currently under investigation include smooth pursuit eye movement index, continuous performance task, dichotic listening with distraction, and span of apprehension.)

Findings of decreased pMAO activity in schizophrenics, however, are not universal (Jackman and Meltzer, 1983; Wyatt, Potkin, and Bridge, 1980), and whatever the diagnosis, a considerable degree of overlap between patient and control values is a standard finding (Sandler, Reveley, and Glover, 1981). As reviewed by Wyatt, Potkin, and Murphy (1979), it does appear that findings of low pMAO activity are fairly consistent in chronic schizophrenics, but not at all in "acute" schizophrenics. Yet, as Del Vechio and associates (1983) remark, the biological significance of pMAO activity in chronic schizophrenia is still open to debate: an influence of drug treatment, institutionalization, diet, or hormonal status cannot be ruled out. These authors also note that there now exists a considerable amount of data supporting a lowering effect

of major tranquilizers on MAO activity. Although previous evidence had suggested that such a link did not exist, a well-designed study by Jackman and Meltzer (1980) showed a highly significant tendency for these drugs to decrease pMAO activity in a group of hospitalized schizophrenics, leading Kendler and Davis (1981) to caution that this result makes "interpretation of previous studies in which patients were on neuroleptics quite problematic" (p. 704). We elaborate on this crucial point in the following section.

Attempts to use measures of pMAO activity to predict "outcome" in schizophrenia reveal some of the other difficulties of this particular approach. For example, whereas Bierer, Docherty, Young, Giller, and Cohen (1984) conclude their study with the observation that low MAO activity may distinguish schizophrenics "with poorer ego functioning and for whom a worse outcome may be expected" (pp. 259–260), Malas and van Kammen (1983) find that in their group of 36 schizophrenics, low pMAO was associated with "increased sociability", "significantly better symptomatic adjustment", and, at three to seven year follow-up, "better outcome in some facets of their illness" (p. 795). One interpretation of these seemingly contradictory findings is that we are observing at least two disease entities on which pMAO may have differential influence. That the MAO variable appears to have little if anything to do with outcome in schizophrenia is another plausible inference. In another context, Hutt and Hutt (1983) express a methodological criticism which may apply to the outcome studies under discussion. They suggest that "to correlate behavioral measurements of the crudity of better-worse, more-less with physiological variables measured to two decimal places in micrograms is, to say the least, faintly ridiculous" (p. 24).

Another explanation for conflicting reports on the association between pMAO activity and schizophrenia may be that different laboratories use different methodologies. Ask et al. (1979) compared determinations of identical pMAO samples at one Swedish and one American lab, and found that the American lab discovered significantly lower MAO activity in schizophrenics when benzylamine or β-phenylethylamine was used as a substrate (but not with tryptamine), while the Swedish lab obtained a similar result with tryptamine (but not with benzylamine or β-phenylethylamine).

The controversy over the significance of pMAO activity might fade, as it did for the CPK hypothesis, the "Mauve Spot", and other biochemical hypotheses before it. In a recent review of the status of research on MAO in schizophrenia, Jackman and Meltzer (1983) conclude that schizophrenic patients as a group do not have any significant abnormality in pMAO activity that would justify its use as a biological marker of their disorder. Still, with the current trend to finely divide psychotic phenomena into as many diagnostic categories as conceptually possible, this conclusion merely changes the focus of research, and investigators now ask how the life of a schizophrenic

with low pMAO activity differs from that of one with normal activity (Bierer et al., 1984), or how we might discover if MAO is actually an episodic, residual, or vulnerability marker (Zubin et al., 1985).

Thus, it appears that research questions are growing exponentially, encouraging the search for a genetic marker of schizophrenia along the most varied lines. Turner (1981), for example, proposes that "What a psychiatrist with sufficient curiosity needs to do is ask a patient 'Is there any illness or trivial condition which occurs in your relatives?' Regardless of the reply, one continues with a question such as 'Does anyone have such things as teeth out of line or too widely spaced; or skin condition . . . ; or peculiar fingernails; or red urine after eating beets; or eye troubles? Can you roll your tongue?' " (p. 83).

The search for biochemical deficits or inheritance of specific genetic defects may yet lead to useful outcomes, although a serious problem would still remain. We do not have a starting point to speculate on the connections between a person's genetic substrate or enzyme levels and the fact that that person exhibits those behaviors—holds bizarre beliefs, speaks incoherently or in literal metaphors, adopts strange postures, reports hallucinations, claims false identities, etc.—that usually earn one a diagnosis of schizophrenia. Sarbin and Mancuso (1980) and Turner and Edgley (1983) point out the inadequacy of the idiographic postulate that *bad* chemical functioning leads to *bad* thoughts and *bad* conduct. "No one has yet advanced a theory that links a physiological malfunction to a person's acceptance of unverified imaginings" (Sarbin and Mancuso, 1980, p. 149).

Biological research has generated challenging conceptual models of neuronal function, provided detailed information about brain chemistry, physiology, plasticity, and created specific tools for monitoring brain activity. However, although we have many new facts about the workings of the brain, we do not have many new facts about schizophrenia. In the field of biological psychiatry, it also has not often been the case that a treatment originated as a result of a carefully tested clinical hypothesis. On the contrary, biological hypotheses themselves have emerged from observing treatment effects. An example of this is the development of the dopamine (DA) hypothesis, which we now turn to consider.

Antipsychotic Drugs and the Dopamine Hypothesis

For over fifteen years, the DA hypothesis—which postulates relatively excessive activity of specific brain DA neuronal systems—has dominated biochemical research on schizophrenia. Yet, although explored in countless studies, it still has not received any convincing direct support (Teller, 1979; Zubin et al., 1985). What does it rest on? We believe that its support derives

almost entirely from the widespread assumption that the major tranquilizers are "antagonistic" to "psychotic" behavior.

When first introduced into hospital psychiatric practice in the 1950s, phenothiazine-related substances were called, for obvious reasons, "major tranquilizers". Currently, however, they are known as "antipsychotics" or "neuroleptics." Because these drugs appear to inhibit the action of the neurotransmitter DA at certain receptor sites, and because they are used, and judged, to suppress undesirable behaviors in schizophrenics, then, by implication, it is assumed that excess DA levels in the central nervous system play a significant role in producing psychotic behaviors (Carlsson, 1978; Spokes, 1980). We stress that this is not too simple a picture of the logical value of the DA hypothesis. To quote from Carlsson (1975), one of its leading investigators, "the crucial question [of the DA hypothesis] is whether the so-called anti-psychotic agents possess true antipsychotic activity" (p. 114).

If it is assumed that phenothiazines (and similar compounds) are truly "antipsychotic" and not merely "tranquilizing"—that is, they only suppress psychotic behavior—then the argument for a specific role of dopamine in schizophrenia appears strengthened. If instead, as Sarbin and Mancuso (1980) suggest, these drugs produce "a sophisticated chemical extirpation of a large group of neural connections—a kind of removal of the human spark plugs" (p. 145)—then they would appear to suppress *all kinds* of behaviors.

Breggin (1983) provides considerable support for this view. He suggests not only that the major tranquilizers (as well as other commonly used psychiatric drugs) *directly* impede and damage various parts and functions of the brain, but that the psychological effects associated with this brain dysfunction—a general subduing, apathy, emotional flatness, etc.—are the very therapeutic effects treatment clinicians seek, whose appearance they note, and whose presence they regard as signs of improvement. Breggin's provocative "brain-disabling hypothesis" finds support from an unusual source. No less an authority on schizophrenia than Manfred Bleuler writes, commenting on the passivity and inactivity of the schizophrenic, "years ago he was shackled, strapped to his bed, or isolated. Today the entire pressure of social therapy and pharmacotherapy with psychotropic drugs and neuroleptics works out toward the same end. For this reason it may be said that the adynamia of the schizophrenic can be interpreted as a partially successful therapeutic effort" (1978, pp. 217–218).

Bias in Drug Effectiveness Research

Yet, scores of studies indicate that drugs improve patients enough to require briefer hospital stays, and help prevent relapses and rehospitalizations (see review by Task Force, 1980). Without reviewing in detail the arguments

for and against these conclusions, we wish to put the idea of pharmacologic effectiveness in a different perspective.

Breggin (1983) questions the notion of unbiased research in the area of drug effectiveness. He notes that in the history of psychiatry, but more so in the twentieth century, "the vast majority of articles tout all [biological] psychiatric treatments to be astonishingly effective" (p. 59). Treatments like etherization, insulin coma, lobotomy, and electroshock were described as very effective, and new treatments were justified as less damaging than other commonly used treatments. The original enthusiasm of those who try the treatment contributes to these positive findings.

Breggin also notes the difficulty of adhering to the classic double-blind design in effectiveness studies because the major tranquilizers produce such dramatic neurotoxic effects that both patients and observers know who is receiving the treatment. Investigator bias, however, shows clearly in the selection of symptoms for analysis. The obvious effects of tranquilizers—apathy, indifference, or even stupor in the higher dose ranges—are simply unmentioned in the vast majority of effectiveness studies. This bias can easily lead to overestimating the drugs' positive effects.

The powerfully levelling, non-specific effects of tranquilizers are described in detail in the early studies reporting on the administration of chlorpromazine (in relatively low doses by today's standards) to institutionalized psychiatric patients (Delay and Deniker, 1952; Lehmann, 1955; Lehmann and Hanrahan, 1954). Breggin (1983, p. 17) quotes the following passage—a description of *maximum benefit*—from Noyes and Kolb's 1958 edition of *Modern Clinical Psychiatry*:

> If the patient responds well to the drug, he develops an attitude of *indifference* both to his surroundings and to his symptoms. He shows *decreased interest* in a response to his hallucinatory experience and a *less assertive* expression of his delusional ideas. Even though not somnolent, the patient may lie quietly in bed, *unoccupied and staring ahead.* He may answer questions readily . . . but offer *little or no spontaneous conversation*; however, questioning shows that he is fully aware of his circumstances. [Breggin's emphasis]

From the very first experiments with chlorpromazine, Delay and Deniker (1952) recognized that the drug effects mimicked a bizarre disease, epidemic or lethargic encephalitis, characterized by fever, lethargy, and the development of sometime irreversible dyskinesias and Parkinsonism. Deniker (1970) offers this most unusual retrospective comment:

> It was found that neuroleptics could experimentally reproduce almost all the symptoms of lethargic encephalitis. In fact, it would be possible to cause true encephalitis epidemics with the new drugs. Symptoms progressed from reversible somnolence to all types of dyskinesia and hyperkinesia, and finally to parkinsonism. The symptoms *seemed* reversible on interruption of medication. . . . Furthermore, it might have been feared that these drugs . . . might eventually induce irreversible secondary neurologic syndromes.

> Such effects cannot be denied: it has been known for years that permanent dyskinesias may occur. . . . (cited in Breggin, 1983, pp. 79–80)

Explicit parallels between the action of chlorpromazine and the specific symptoms of lethargic encephalitis were also made by several other researchers during the decade following the introduction of phenothiazine tranquilizers. Unfortunately, the creation of an epidemic of neurologic disease did not remain a possibility. Indeed, the prevalence of drug-induced dyskinesias may now be considered a major iatrogenic disaster of modern history (Applebaum, Schaffner, and Meisel, 1985). Conservative estimates of the prevalence of the most serious and often irreversible drug complication—tardive dyskinesia—in populations undergoing long-term drug treatment, are at least 10%–25% (Task Force, 1980). Individual studies have demonstrated a prevalence in certain populations of more than 50% (Gualtieri, Quade, Hicks, Mayo, and Schroeder, 1984; Jeste and Wyatt, 1982; Tepper and Haas, 1979). The issue of responsibility and compensation for tardive dyskinesia has already raised a host of complicated legal and legislative issues (Applebaum et al., 1985; Baker, 1984; Gualtieri and Sprague, 1984).

Our comments are meant to suggest that in the climate of feverish research to develop and use effective treatments for what appears to be a baffling disorder, assessments of drug effects may not always approximate the ideal of objective, detached evaluation. An avid search is ongoing among a number of pharmaceutical laboratories to find phenothiazine-like compounds without the toxicity of the phenothiazines (Bassuk, Schoonover, and Gelenberg, 1983). We hope that researchers and practitioners remain attentive to lessons from the past, but the signs are not very encouraging. In a recent opinion, Havens (1985) admonishes his mental health colleagues for "exaggerat[ing] the victories pharmacological psychiatry has so far achieved. . . . [D]einstitutionalization resulted in part from the belief that psychotropic medication would do for schizophrenia . . . what penicillin had done for syphilis. . . . Moreover, this expectation persists. . . . Such opinions [on the effectiveness of drug treatments] are more than academically misleading. . . . The great investments of energy, time, and imagination necessary for the care of chronic patients are being dismissed" (p. 811).

Holding drugs responsible for reducing length of hospitalization appears to ignore the influence of the interaction of several other important factors: family situation, patients' desires and legal status, treatment alternatives, social and community services after discharge, public or private nature of the hospital, administrative and fiscal pressures on institutions, diagnosis-related-groups regulations, ethical dilemmas, and community tolerance. In addition, many patients dislike drugs very much and go to great lengths to avoid them—including leaving the hospital as quickly as possible. Again, this point is overlooked in the majority of drug effectiveness studies. Similarly, few if any

studies have examined to what extent a discharged patient alienates family, psychiatry, and any available social support network if he or she ceases drugs. One might argue that it is this network—this social, economic, and emotional support—that does most to keep patients out of hospital (Coleman, 1984; Crotty and Kulys, 1985).

Our preceding comments cannot ignore the obvious: many patients appear to benefit from their drugs and take them willingly. They feel that the calming effects are worth a degree of discomfort or diminished alertness. Nevertheless, as Coleman (1984) points out, it makes a difference whether a patient takes drugs because he or she finds them helpful or because the patient believes that modern science has discovered a brain abnormality that can be treated with drugs.

On the contrary, the DA hypothesis has generated a mass of observations which seem to contradict each other. For example, a post-mortem examination of the brain material of nine schizophrenics and ten controls by Crow and Baker (1979) concludes that "no support was found for the hypothesis that [DA] neurons are overactive in schizophrenia" (p. 249); a one-year study by Clow, Jenner, Theodorou, and Marsden (1980) on changes in cerebral DA metabolism of schizophrenics during and after phenothiazine regimen suggests "that the changes reported in the brains of schizophrenics might be due to neuroleptic drug administration" (p. 53); and Smythies (1982), who notes that studies of DA and its metabolites in the brains of schizophrenics have failed to produce any convincing evidence of abnormalities, states, "what evidence there is would suggest a *decrease* in DA levels and turnover in schizophrenia that is positively correlated with the clinical severity of the illness" (p. 732) [emphasis added].

The value of the DA hypothesis apparently rests upon our ability to control chemically the undesirable behaviors of schizophrenics. According to Meltzer and his colleagues (1983), treatment of schizophrenics by neuroleptics is based upon the hypothesis that a reduction of CNS dopaminergic activity alleviates psychotic symptoms. For Berger (1981), "The ultimate aim of the search for biochemical defects in schizophrenia is the development of rational drug treatments" (p. 92). The DA hypothesis thus appears inextricably tied to the practice of medicating schizophrenic patients.

Again, although this widespread practice is justified on the grounds that major tranquilizers produce dramatic improvements or remissions in many patients, we cannot deny another equally dramatic lesson of drug treatments. This is simply the reality that no drug has a single site of action. Foreign chemicals introduced into the nervous system are not site-specific "magic bullets." Rather, their interactions with the body's own chemicals are more like explosions of shrapnel flying in all directions. Thus, despite their actual or potential benefits, major tranquilizers still remain unpredictably dangerous.

For example, Bollini et al. (1984) report on the short-term effects of one drug regimen: a "routine" use of high-dose intramuscular haloperidol on 74 successive psychiatric patients produced complete recovery in six, complete lack of change in 23, adverse reactions in 42—severe enough to stop treatment in eight—and three deaths.

These and other observations run counter to the traditional notions about the unusually high therapeutic index of neuroleptics, and suggest that so-called effective doses of these drugs for the treatment of many psychotics are much lower than those commonly used. For example, Teicher and Baldessarini (1985) suggest, on the basis of their review of studies of schizophrenics maintained on injected neuroleptics, that 50 percent of those patients who receive the low dose of 5 mg of fluphenazine decanoate every two weeks would benefit from one-fifth that amount, the equivalent of 10 to 15 mg per day of oral chlorpromazine. This suggestion is striking, since according to *The Physicians' Desk Reference* (1983), the recommended adult dose of chlorpromazine for psychiatric patients ranges from 30 to 2000 mg a day, depending on the severity of the problem.

Although the general neurotoxicity of major tranquilizers is now increasingly recognized in the research literature, some of its necessary implications are not yet fully grasped. It is now common to question the validity of any findings of cerebral abnormalities in schizophrenics if the latter have been on drugs for any significant period of time. For this reason, investigators have their subjects undergo drug-free, "washout" periods—of an average duration of two weeks—prior to carrying out experimental procedures. Experiments are undertaken on the assumption that levels or effects of the drugs have cleared by the time of the investigation. Campbell and Baldessarini (1985), however, review findings from "balance" studies of the input and output of neuroleptics which report that small, but possibly significant, amounts of drug are not accounted for, and that drug material can be detected in the urine for months after discontinuation of "chronic" drug treatment. It appears that the brain may preferentially retain some neuroleptic molecules such as haloperidol (Cohen, Herschel, Miller, Mayberg, and Baldessarini, 1980). Campbell and Baldessarini (1985) further note that *single, small* doses of haloperidol in the rat "produce strikingly prolonged antidopaminergic effects for at least several weeks" (p. 637). It is therefore reasonable to assume that experimental subjects, many of whom have been maintained on neuroleptics for years, might exhibit cumulatively high antidopaminergic, and other, abnormalities. Some major tranquilizers thus have unexpectedly prolonged effects which may seriously interfere with the interpretations of scores of experimental and clinical studies. Discontinuation of drug treatment for only a few days or weeks may not ensure a "drug-free" status in experimental subjects.

Almost every biochemical substance known to be present in the brain or to play a part in the transmission of nerve impulses has, within a couple of years of its discovery, been studied for its possible involvement in schizophrenia. Results typically appear promising at first, but cannot usually be confirmed, and are then forgotten as new substances are discovered or new research technologies invented. Lewontin et al. (1984) mention that conflicting reports have implicated disorders in the metabolisms of serotonin (1955), noradrenalin (1971), dopamine (1972), acetylcholine (1973), endorphin (1976), and prostraglandin (1976). Cutting (1985) notes that "since the 1950s a number of theories have been proposed and then discarded, and a number of striking claims later shown to be false or artefact. In fact, of all the proposed causes of schizophrenia, biochemical ones have the shortest life-span" (p. 138).

One might expect an increase in scientific knowledge to produce a decrease in the number of theories scientists entertain. Yet, as Cutting (1985) remarks, "the 1980s have witnessed a bewildering proliferation of other biochemical hypotheses" (p. 138). It is difficult to understand why this plethora of new theories about a biochemical basis of schizophrenia would suggest optimism about an important, imminent breakthrough.

We cannot minimize the difficulties, the challenges, or the potential payoffs of such research, or cease searching for any solution to the problem of schizophrenia. We also cannot reject biology because of the failure of previously proposed hypotheses. Nor can a priori arguments alone eliminate the data collected in myriad studies of behavior-biology relationships (Sarbin and Mancuso, 1980). But we suggest that researchers are responding to a cultural, economic, and institutional demand—which they help maintain—that they provide biological explanations to enable the development of effective drugs (Duster and Garrett, 1984). Thus, the problem appears to be confounding the effect of a drug with the offer of an explanation, or the relief of suffering with a cure for the problem (Lewontin, Kamin, and Rose, 1984).

The Intersection of Research and Valuation

A perusal of biochemical studies of schizophrenics shows that investigators carefully select and describe various assaying, storing, and recording techniques as well as sophisticated electronic equipment. We note, however, a lack of corresponding attention to justify the selection of research subjects. They are believed to be suffering from a brain disease, but one defined only in behavioral terms. What are these behaviors? According to DSM-III, the characteristic symptoms of schizophrenia involve disturbances in the content of thought, in the form of delusions "with no possible basis in fact"; disturbance in the form of thought, for example, loose associations or in-

coherence; disturbances in affect, such as blunting or flattening; apathy; autism; and stilted or, at the extreme, catatonic behavior. "All these disturbances," Simpson and May (1982) note, "are seldom present in a single individual" (p. 147).

Together, these diverse signs and symptoms of psychosis represent thought, affect, and behavior that the society at large cannot understand. "One of [insanity's] important defining features is interpersonal: it takes two to make a psychotic—an observer and an actor" (Rosenberg, 1984, p. 300). This insight is easily overlooked if the vital characteristics of the psychotic are reduced to terse descriptions of his or her cerebrospinal fluids or cerebral ventricles. Barham (1984) reminds us that "it is social (and therefore moral) agents with whom we have to contend in talking about the 'course' of a schizophrenic illness, and not with a plurality of unfortunates who have absented themselves from history and therefore only merit discussion in the language of 'patienthood' " (p. 2). If we divorce the psychotic from the problems of ordinary living and the universals of individual development in a given culture or environment, we may ignore the vastly social construction of our disease categories and their manifestations. For example, whereas schizophrenic men are typically portrayed as passive and withdrawn, schizophrenic women are pictured as voluble, domineering, and highly-sexed (Al-Issa, 1980). Barham (1984) notes perceptively that the fate of women in the history of schizophrenia over the last 100 years deserves intensive study in its own right, adding that we could improve upon the suggestion that sexual differences in brain maturation explain differences in age of onset. Thus, as Sarbin and Mancuso (1980) suggest, "an adequate theory of human conduct [and therefore, of schizophrenia] must begin at the intersection of action and valuation" (p. 210).

Valuation is an integral part of biological psychiatric research. As Snyder (1983) remarks, "not only is each stance of the observer fundamentally related in an immediate manner to each expression of the observed phenomenon, but each such relation is fundamentally related to one another" (p. 399). Recent work in the sociology and philosophy of knowledge submits all scientific research to sociological analysis and suggests strongly that social and moral issues are involved not only in the dissemination of knowledge, but in shaping the language of research and discourse, and thus the very ground of scientific observation (Aronson, 1984; Gergen, 1985; Knorr, Krohn and Whitley, 1981; Law and Lodge, 1984; Mulkay and Gilbert, 1984; Scarr, 1985; Schneider and Kitsuse, 1984; Watzlawick, 1984).

On a more political level, we note Laing's (1982) observation that the research biochemist intervenes only because some people have decided that some experiences should be brought to an end. This meets Szasz's (1978) obstinate contention that the power dimension is the crucial variable which determines whether a person is diagnosed as schizophrenic. Whereas in

medicine a biological process is determined to be a pathological process on biological grounds, in psychiatry, research seeks to discover an appropriate biological process to explain "pathological" (that is, disturbed or disturbing) experiences. Precisely because we judge certain unusual experiences as pathological per se, and because we have the power to enforce our views, so do we seek their biochemical correlates or causes: because certain experiences are judged as pathological, any of their biochemical correlates might be assumed to be pathological, whether or not they are so for any "externally validated" biological reason.

Much recent biochemical research seeks to support the notion that there are several types of schizophrenias. The idea here is to subgroup schizophrenic patients on the basis of neuroanatomical and biochemical parameters. These subgroupings would make discussions about "schizophrenics" less ambiguous, and might lead to the development of drug interventions tailored to subtypes with presumably different clinical features and outcomes (Carpenter and Heinrichs, 1981; Smythies, 1982). The problem remains that there is yet no firm ground for focusing on any known biological parameter as a "symptom" deserving further classification (but see Seidman, 1983), *except* that the biological parameter is sometimes measured in individuals we have labeled schizophrenics.

Since the assignment of a psychiatric diagnostic label—the very act which justifies all subsequent interventions on the person so diagnosed—is in large measure a self-contained, repetitive social judgment process (Colby and Spar, 1983; Dumont, 1984; Endicott, 1983; Eysenck, Wakefield, and Friedman, 1983; Sarbin and Mancuso, 1980; Townshend, 1981), it may be difficult to refute Laing's (1982) assertion that "whatever its scientifically established validity, medical rhetoric seems to validate practices one would be hard-pressed to justify in any other terms" (p. 43).

The Emerging Models

Implicit in modern behavioral neurobiology is the metaphysical postulate which holds that the central nervous system is the organ of thought and action, in just the sense that the heart is the organ of circulation (Gallistel, 1981). Behind this postulate lies the idea called reductionism, which seeks to explain all phenomena by reducing them to their smallest observable components. The mind is explained by the physiology of the brain, in turn explained by conduction of stimuli through nerve cells, the nerve impulses, these again explained by the transport of molecules to their circuits, and these explained through the kinetics of chemical reactions finally reduced to the orbits of the electrons themselves. Reductionism, furthermore, excludes the possibility of any other causes.

Reductionism did allow us to see that elementary particles make up atoms, which make up molecules, cells, tissue, and organs—these again making up individuals, societies, cultures. In this connection, Riedl (1984) comments:

> If one asks for the explanation of a chicken's flight muscle . . . one will find that its structure and performance can be traced back to those of its cells, their biological molecules, atoms, and elementary particles, but an understanding of its form and function comes from its purpose in the wing, the form and position of the wing from the bird, the bird from its species, and the species from its environment. (p. 87)

The obviously reciprocal relationship between an interpretation of nature from the perspective of its forces or energies—the methods of the sciences—and one from the perspective of its purpose—the method of the humanities—here becomes quite visible. However, as Riedl (1984) notes further, whoever tries to negotiate across the boundaries of these sharply divided worldviews "must be prepared for the wrath of both sides" (p. 87).

Negotiation, however, not only appears inevitable but is already underway, if only because the once solid cornerstone of mechanistic models, the idea that a "cause" is followed in a one-way direction by an "effect," is crumbling under the impact of the latest thinking in biology, medicine, and physics (Capra, 1983). In medical research, for example, recent cybernetic models propose circular mechanisms of positive and negative feedback loops which have, as Vaisrub (1980) notes with frustration, "taken over in the operational depths of homeostasis. The chain of causation is fast dissolving before our eyes to be replaced by some form of invariable association that does not lend itself easily to a graphic, mathematical, or any other representation" (p. 830).

In response to these challenges, new epistemologies are emerging, whose principles will undoubtedly have profound consequences on schizophrenia research. One of these is that behavior and consciousness are no longer seen just as "products" of the brain, but rather as crucial "ingredients" in its development. We now know that behavioral states—experiences—can influence brain physiology (Rosenzweig, 1984). Diamond (1985), emphasizing the plasticity of the human brain well into old age, proposes that "curiosity" might lead to the enrichment, specifically, the enlargement of nerve cells and dendrites, of the cerebral cortex. Eccles and Robinson (1984) have reported on their demonstration that a mental act of intention initiates the burst of discharges of a nerve cell. These and other findings suggest strongly that the mere discovery of a biochemical correlate to a behavior or set of behaviors cannot be said to "explain" behavior: rather, it confirms that the behaving organism functions as a psychobiological unit (Becker, 1964; Chorover, 1979; Eccles and Robinson, 1984; Penfield, 1976; Varela, 1984). As Sperry (1984) remarks, the relation between mental events and neural events is always one of a reciprocal relation with mutual interaction, where the human mind and consciousness

are seen as "inseparable attributes of an evolving, self-creating cerebral system" (p. 199). Sperry adds that ethical and moral values themselves becomes a very legitimate part of brain science, cannot be reduced to brain physiology, and exert "powerful causal influences in brain function and behavior" (p. 191).

If ethical and moral values are not reducible to brain physiology, and if ethical and moral values and mental attitudes somehow directly influence the neural configuration of our brains (as Diamond [1984] suggests on the basis of her experimental and clinical work), then we face some revolutionary—not to mention paradoxical—research implications, in which the brain may be treated as a dependent variable in one instance, and as an independent variable in the next (Turner and Edgley, 1983).

Perhaps the resolution of this paradox lies in what Ciompi (1985) calls the "principle of equifinality", derived from systems theory. This principle holds that identical states may be reached by way of very different combinations of influencing factors, while identical states can evolve, under varying circumstances, in very different directions. Ciompi (1985) claims, on the basis of his long-term studies of the lives of schizophrenics (Ciompi, 1984), that "both phenomena are currently observed in the long-term course of psychotic states diagnosed as schizophrenia" (p. 559).

In effect, the emerging perspectives we are sketching view the human being as constituting a dynamic interplay between cognitive and biological operations which mutually specify themselves, a process which Varela (1984) calls *autonomy* and which Von Foerster (1984) refers to as the "regulation of regulation" of living systems. This suggests that there may be no specific, final "cause" of psychotic or unwanted behavior that we can identify with CAT scans, alter chemically with psychotropics, or eventually prevent through genetic manipulation in order to produce a "normal" person. (And if there were, what exactly is the prototype of human perfection we would aim for?) Can we confidently claim that the nervous system or, ultimately, the genetic make-up of an individual *determines* that individual's behavior? Schizophrenia can no longer be conceived as anything but a huge structure of disparate behaviors with all kinds of cultural, historical, economic, and linguistic implications (Barham, 1984; Dumont, 1984). Can the structure of a gene "cause" the structure of schizophrenia? At the least, we must agree with Ciompi (1985) that a disease entity "schizophrenia" in the traditional sense does not exist; what we are faced with when we study schizophrenics are persons experiencing the most diverse problems with the most diverse and still unpredictable outcomes. If schizophrenia results from some sort of brain atrophy, as many reports suggest, it becomes difficult to explain the frequency of improvements many years after the onset of psychosis. Indeed, recent studies on the long-term course of chronic schizophrenia are discrediting the notion of the chronic schizophrenic as engaged in an irreversible course of deterioration (see Barham,

1984; Bleuler, 1978; Ciompi, 1984). For Zubin et al. (1985), "when we take the time to do the requisite research, we are going to find out that the greatest part of [schizophrenic] disability we face is actually a socially induced artifact . . ." (p. 236).

Perhaps psychiatric research might also benefit from asking how the psychological disintegration of some individuals' personal world image feeds and gets fed by the neural circuitry of the brain. To answer this difficult question, one would probably have to take into account the mutual biological, cognitive, and environmental factors which interact to fabricate the total experience which, in some contexts, then gets labeled as schizophrenia. At least, each of these factors must be included, however imperfectly, in current research designs, and a finding in one area must be interpreted in light of indications from the other areas. To the extent that what is called a mental disorder concerns what other people and the surrounding world do and mean to the target person, biochemical analysis may provide only the most partially illuminating clues. This takes on added urgency in view of psychiatry's near-total dependence on drug treatments for schizophrenics, and the near-total dependence of these treatments on biochemical theories which operate in a strange theoretical vacuum: we lack even the most rudimentary conceptions of how so-called normal behavior is linked to neurochemical processes.

The Challenge of Contextualism

Sarbin (1977) and Sarbin and Mancuso (1980) have provided a coherent conceptual framework as an alternative to the troubled mechanistic-causal paradigm predominantly used in the study of unwanted, disturbing behavior. In their attempt to revive "contextualism" (Pepper, 1942), they make a significant effort to meet challenges emerging from related fields.

A context does not explain—but integrates, clarifies, gives meaning and shape to an event. A contextualist formulation of unwanted conduct that is sometimes labeled schizophrenia would thus include: the specific acts of the target person, the judgment or verdict that his or her conduct is unwanted, the standards by which such a judgment is drawn, the relative power of the target person and of those who pass judgment on his or her acts, remote genetic action, the specific morphologies associated with this action, the particular interactions between the morphology and the environment—all imbedded in a multi-stranded context. However,

> None of the strands can be seen as *causing* any other strand. From a contextualist position one might, for heuristic purposes, speak of the cause of shifting *relationships* between strands in the context. But, as Pepper (1942) aptly observes, change is given in a contextualist position. Contexts continually flow. A contextualist tries to describe emerging contexts, not single features of the context. (1980, p. 130)

Such an approach greatly enlarges the scope of the problem under investigation and may be viewed with some frustration by researchers who note that a contextualist strategy does not immediately provide firm handles to hold (A. Rifkin, 1984). A much larger issue, however, encompasses the problem of schizophrenia: the issue of how to frame human action and human understanding. Like this issue, the problem of schizophrenia still remains irreducible to well-defined variables, whether "genetic," "biochemical," or "social."

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