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Schizophrenia: a critical examination

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CHAPTER 15

Schizophrenia: A Critical Examination

Charles A. Sanislow and Robert C. Carson

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Introduction

The editors commissioned us to write a chapter that challenges the notion of schizophrenia, thus providing the “other” viewpoint. It seems that the admittedly provocative view taken in the preceding edition of this chapter (Carson & Sanislow, 1993) has earned that request. At once, however, we find ourselves bewildered about what that “other” might be. Are we to represent the antithesis to the prevailing biological zeitgeist of psychopathology? Is this goal to keep alive the epistemological perspectives that have been issued by those of a Szaszian stripe? Or, are we plainly missing the boat? We are, to say the least, uncomfortable with any of these possibilities. However, the mere suggestion that “schizophrenia” may not be a viable construct inspires expectations consistent with at least one of these propositions. We warn against such expectations.

All provocation aside, there is reason for alarm in the light of the lack of progress during the past century. Hegarty and colleagues (1994) conducted an ambitious and rigorous quantitative analysis of worldwide long-term outcomes in schizophrenia

over what roughly constitutes the entire span of the construct’s existence. The results they found were not good. Overall, the social recovery rate was 40.2% for the period 1895 through 1991. When comparing the contemporary time frame (years 1986–1991) to the period with the most stable plateau (1926–1955), there was no significant difference. Following the introduction of neuroleptics in 1955, the social recovery rates rose to about 50%, but curiously, these rates fell back again around 1975. The authors attributed this drop to the more stringent diagnostic criteria of recent years, a hypothesis related to one of the major impediments of meaningful progress in this area.

On the other hand, the primary focus in this era appeals to the bewildering array of biological correlates in defense of the modern “disease” concept of schizophrenia (because of the lack of progress made during the last century?). In the context of a seemingly endless array of positive results, Crow (1997a) commented as follows on the resultant incoherence of the evidence:

The problem is that many changes in many different anatomical structures are reported. Which of these is reliably associated with the disease process? If, as seems likely, there is more than one such change, which is primary and which is secondary?... We need to find changes characteristic at least of a subtype of psychopathology.... But there is an embarrassment of riches. (p. 521)

Despite our concerns that the present approaches to biological aspects of the disorder provide resolution that is far less than satisfactory, our position

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should not be mistaken as antibiological. Modern biotechnological methods offer potentially enormous contributions, but there are some serious problems that will be given due consideration later on. Foremost among them, the usual and customary bifurcation of biological and environmental variables lends itself to a dichotomous style of thinking that is at odds with a developmental understanding of psychopathology. We hope that our presentation here will suggest a more productive approach.

Beyond this issue, however, there remains a more fundamental problem: It is still not known exactly what schizophrenia is (this assertion should not be mistaken for deconstruction; we hold the premise that an adequate taxonomy of psychopathology is fundamental to the advancement of knowledge). Noted schizophrenia researcher Nancy Andreasen (1998) pointed out that schizophrenia is a supposed disorder with no visible neuropathology and has warned that, in the light of this fact, the withering dearth of clinical research in this area is a gaping liability. In the absence of a clearly demarcated disorder, advancing research is likely to be accompanied by substantial confusion, thereby undermining the potential knowledge acquired. This, in fact, is the predominant pattern. As will be shown in our review of the multiple changes in the diagnostic approaches, a shifting core without a firm footing is a perennial problem for schizophrenia research.

Having set an appropriately skeptical tone, we remind the reader that the behaviors conventionally associated with the term schizophrenia have been seen for many years and quite properly so, as the most stubbornly opaque, perplexing, frustrating, and in certain eras professionally demoralizing in the entire domain of mental health disciplines and in all probability, of the priestly forebears of the latter. We hope that we have prepared the reader for the idea that much of what can be said for this class of disorder does not cohere in a neat and tidy way, and some of it may be quite disconcerting in its refractoriness to satisfactory conceptualization. Major revisions in the way that the disorder is thought about and studied will be necessary for real progress.

In this chapter, we will address the following areas: The identification of the core, if any, of the disorder(s) (Taxonomic Issues), how genetic and environmental variables are thought about in a developmental context (Etiologic Considerations),

and consideration of the treatment process (Treatment Perspectives). In short, we think that much of what follows will demonstrate that this is not a domain in which simple answers—for example, that schizophrenia is a definite, unitary, but as yet imprecisely localized brain disease—have even a minimal likelihood of achieving convincing confirmation in the foreseeable future.

Taxonomic Issues

Background of the Schizophrenia Diagnosis

In 1860, Belgian psychiatrist Benedict Morel described the case of a 13-year-old boy whose functioning severely deteriorated from that of a brilliant pupil to an increasingly withdrawn, lethargic, seclusive, and delusional boy with substantial intellectual decline. Morel hypothesized that the deterioration was the result of irrecoverable brain degeneration of hereditary origin. He used the term *démence précoce* to describe the condition and to distinguish it from the dementing disorders associated with old age. Based on this early belief of intellectual deterioration—a belief that, as will be shown in more detail later, is not well-supported—Kraepelin subsequently adopted the Latin form of this term to refer to a group of conditions that all seemed to have the feature of mental deterioration beginning early in life.

Bleuler (1911/1950) objected to the term in part because he believed that both of its elements were erroneous and misleading. He reportedly observed numerous patients who otherwise met the descriptive criteria for dementia praecox but whose disorders did not progress inexorably into profound cognitive deterioration and did not first appear at a young age. Bleuler felt that he had identified by careful observation a theretofore unrecognized set of “fundamental symptoms” that were invariant and basic properties of the disorder. He believed that these should be its defining features as well as the criterial specifications for rendering the diagnosis. For Bleuler, the central feature of the disorder was that of the “splitting” of different psychic functions, and therefore named the disorder schizophrenia. However, he issued the important caveat (and one that we would submit still holds true today): “For the sake of convenience, I use the word in the singular although it is ... apparent

that *the group includes several diseases*" (Bleuler, 1911/1950, p. 8, emphasis added). Indeed, persons who earn the designation "schizophrenic" are an extremely heterogeneous lot both behaviorally and biologically, far more so than "normals" in many dimensions of comparison. The recognition of such heterogeneity has spawned a variety of proposed subtypes of schizophrenia over the years and has led some investigators (e.g., Bellak, 1979) to conclude that "schizophrenia" is merely a final common pathway of varied ego dysfunctions produced by numerous distinct causal patterns. Such a view raises questions about the need for an overarching and potentially misleading construct such as schizophrenia. At the same time, evolving diagnostic systems make zeroing in on the core of a disorder like trying to hit a moving target.

Developmental History of the DSM-IV Criteria

To fully understand the modern diagnosis of schizophrenia, according to the most prominent system (i.e., DSM), requires a careful look at the history of the ways by which the disorder has been defined. Bleuler was the first to coin the term schizophrenia, but Kraepelin—at least as it appears by the current climate in psychiatric diagnosis—has been credited the status of father of the disorder.

Early Formulations by Kraepelin. In outlining the following symptomatology for dementia praecox, Kraepelin noted that the "... disease picture appears so varied that upon superficial observation the fundamental symptoms are not recognized" (Defendorf, 1902, p. 154). He went on to note the moderate effects of what we would now term anxiety (i.e., "clouding of consciousness") and the presence of hallucinations early in the course of the disease, suggesting a source for the distress. It seems that, for Kraepelin, a perplexing aspect of the disorder concerned the fact that those in the throes of it were apparently unaffected in their abilities to perceive the majority of their surroundings and orientation in accurate terms, although delusional states could impose major distortions of specific aspects of the patient's surrounding reality. The other major symptom areas concerned attentional difficulties, primarily the inability to control attentional processes, and disturbance of "emotional field" which referred to a loss of interest or pleasure in routine daily activ-

ities. Finally, in some cases, there was a disturbance of conduct, or a "disappearance of voluntary activity" that also appeared on occasion at the other extreme in the form of impulsive acts (e.g., outbursts of smashing things such as breaking dishes).

Kraepelin noted several areas of progressive deterioration associated with dementia praecox. These, he noted, were primarily in the areas of memory and judgment. For the former, Kraepelin noted that it was the memories formed after the onset of the disorder that were in fact impaired; memories before the onset of the disorder remained intact. The worsening of judgment was largely attributed to behavior that was performed in response to persecutory delusional states. Finally, Kraepelin noted the absence of a definite external cause and the limitation of the methods of the time to establish an anatomical pathological basis for the disease. Indeed, his way of thinking about the disorder has been increasingly embraced in more recent times (i.e., the assumption of a discrete anatomical cause and also, his emphasis on the deterioration feature of the disorder). Kraepelin outlined a clinical description of dementia praecox, but it was somewhat lacking in diagnostic specification, and there was at least some implication of a manic component. For instance, "The whole disturbance can be very gradual ... and the symptoms so ill-defined that relatives see them only as a weakness in character... He may still show the same or even greater industriousness, apply himself tirelessly to his books, engage in massive, inappropriate and indigestible reading ..." (Kraepelin, 1896/1987, p. 13). It was left to Bleuler to attempt to better isolate the clinical entity in more discrete clinical terms.

Bleulerian Criteria. The "splitting" that Bleuler believed characterized the essence of schizophrenic mentation was said to be manifest in three "altered simple functions": association, affectivity, and ambivalence. The other "simple functions"—those of sensation, perception, orientation, and motility—were said to be unaffected in schizophrenia. Certain "compound functions" were also regularly involved in the schizophrenic process, but the only deficit of this type uniformly present was a splitting in the person's relation to reality, termed *autism*. Bleuler's "four A's," as they came to be known, were considered the bedrock characteristics of the disorder for many years, and therefore deserve close attention.

The splitting deficit in *association*—in modern parlance variously termed formal thought disorder, loosening or derailment of association, incoherence, and cognitive slippage—was considered by earlier generations of clinicians the sine qua non of the schizophrenia diagnosis. In severe cases, the phenomenon is very striking and can be utterly baffling to listeners, but its subtler forms are far from obvious and may be detected only post hoc, if then, when clinicians realize on reflection that they have understood hardly anything of prior conversations with patients. The main difficulty is a failure to organize the elements of ideas into linear sequences; the patient's train of thought gets interrupted by intrusions and blockages, and the result is that verbalizations are at best imprecise and at worst mere "word salad."

Bleuler considered that the deficits of affectivity fundamental to schizophrenia are manifold. Often a profound indifference is the most striking feature of the patient's emotional life. Where emotions, even seemingly intense ones, are displayed, they often lack convincing depth and tend to be highly labile. In general, according to Bleuler, there is a discontinuity (splitting) between emotions and the remainder of the patient's mental life, such that thoughts and feelings may seem orthogonal. Unprovoked mood swings are common, as is a certain "blunting" with respect to matters of taste and social propriety. Bleuler gave as an example of the latter a patient's response (conveyed with blissful expression) to being reprimanded for drinking his own urine: "*Herr Direktor*, if you should taste it but once, you would never want to drink anything else" (p. 52). Bleuler (1911/1950) termed as "ambivalence" the tendency of the schizophrenia psyche to endow the most diverse psychisms with both a positive and a negative indicator at one and the same time" (p. 53). Three forms of schizophrenic ambivalence are discernible: (1) affective ambivalence, in which a particular concept or object simultaneously elicits pleasant and unpleasant feelings; (2) ambivalence of will, where the patient experiences co-occurring motives of an opposite or incompatible nature; and (3) intellectual ambivalence, involving the simultaneous maintenance of logically contradictory ideas.

Finally, Bleuler (1911/1950) noted that schizophrenia was always accompanied by a greater or lesser loosening of ties to reality (another type of splitting): "This detachment from reality, together

with the relative and absolute predominance of the inner life, we term *autism*" (p. 63, emphasis added). It is interesting that Bleuler, who had been influenced by psychoanalysis, considered that autism was essentially in the service of protecting the patient's "complexes." In other words, the patient's sense of reality tends to fail mostly in matters that have substantial personal import. However, Bleuler doubted that emotional complexes were *etiologically* significant in schizophrenia.

Schneiderian First-Rank Symptoms. Notwithstanding Bleuler's extraordinarily detailed and perceptive effort to refine the dementia praecox entity, it had become apparent by the 1950s, at least in the United States, that the distinctions he had proposed were either insufficiently understood (the English translation of Bleuler's major work did not appear until 1950) or too subtle to be adeptly applied by frontline mental health personnel. Interdiagnostician agreement in recognizing the presumed entity, as was shown in repeated studies, was unacceptably, even embarrassingly, low as a general rule, and a tendency had developed to employ idiosyncratic local conventions. The awesomely hopeless prognosis for the unfortunates who acquired the label only complicated matters.

These problems were temporarily alleviated somewhat with the widespread introduction of chlorpromazine, the first of the phenothiazine neuroleptics, in 1955. Now a person could be said to have probably been schizophrenic if he or she responded with notable symptom reduction to a trial on chlorpromazine. But this diagnosis by outcome was still (for various practical and theoretical reasons) a very unsatisfactory gambit. The time was ripe for a new approach to the diagnosis of schizophrenia, one that would permit drawing conclusions upon completion of relatively brief clinical evaluation, but might also yield a reasonable level of interdiagnostician agreement. The work of the German psychiatrist, Kurt Schneider (1959), fit the bill and was seized upon by a number of influential investigators in the United States.

Schneider's approach was organized around eleven pathognomonic signs or "first-rank" symptoms, any one of which, if present, was considered a strong indicator of the presence of a schizophrenic process. In contrast to the subtleties of the Bleulerian criteria, the plainness of Schneider's behaviorally described signs were terms that clinicians have relatively little difficulty in assessing.

1. The patient hears voices speaking his or her thoughts aloud.
2. The patient is the subject of a discussion or argument among hallucinated voices.
3. Hallucinated voices describe the patient's ongoing activity.
4. Delusional percept (a normal perception is interpreted as having special and highly personal significance).
5. Somatic passivity (the patient is a reluctant recipient of bodily sensations imposed by an external agent).
6. Thought insertion (an outside force puts thoughts in the patient's mind).
7. Thought withdrawal (an outside force removes the patient's thoughts).
8. Thought broadcast (the patient experiences his or her thoughts being magically and involuntarily transmitted to others).
9. "Made" feelings (the patient experiences feelings as imposed and controlled by an external agent).
10. "Made" impulses (the patient experiences impulses as similarly imposed from outside).
11. "Made voluntary acts (patients experience their motor activity as similarly imposed from outside).

Schneider's approach to identifying schizophrenia differs fundamentally from that of Bleuler. Whereas Bleuler's criteria focus almost entirely on the formal properties of mentation independent of mental content, Schneider makes distinctive mental content in the form of certain types of delusional and hallucinatory phenomena the central defining property. In fact, Bleuler would have regarded every one of Schneider's signs as having mere "accessory" and inconstant status in instances of true schizophrenia. In any event, Schneider's approach has had a somewhat greater influence in determining the present diagnostic criteria than Bleuler's, as will be seen in what follows.

Whether such prominence is deserved is open to question. Findings from a variety of pertinent studies (e.g., Carpenter, Strauss, & Muleh, 1973; McCabe & Stromgren, 1975; Newmark, Falk, Johns, Boren, & Forehand, 1976; Wing & Nixon, 1975; World Health Organization, 1973) indicate that Schneider's signs show up with distressing frequency in patients for whom a primary diagnosis of schizophrenia would seem on other grounds to be inappropriate. We would also sug-

gest that it seems unwise to employ as a cornerstone of diagnosis alleged mental phenomena that have the status of private experience (e.g., the patients' voices) and can never be directly observed by the diagnostician or, for that matter, by anyone else. The standard scientific requirement of interobserver reliability is impossible to satisfy (in fact, meaningless) in such a context, unless it is specified that the focus of inquiry is exclusively on what the patient reports *about* mental happenings of this sort—in which case the observation itself loses much of its intrinsic force.

Other Diagnostic Systems. In the early 1970s, several other efforts were made to develop more precise criteria. These efforts were primarily by research investigators. Movements began in some research centers to eschew entirely the often vague, abstract, and theory-driven official criteria in favor of definitions stated in very concrete observational language (i.e., so-called operational criteria). Two proposed sets of such criteria—those of Feighner, Robins, Guze, Woodruff, and Munoz (1972) and a modified version by Spitzer, Endicott, and Robins (1975) that included definitions of schizophrenia—rapidly gained ascendancy among investigators, and it soon became commonplace in the method sections of research reports to read that subjects had been selected according to one or the other of these sets of fairly similar criteria. It was inevitable that the third edition of the *Diagnostic and Statistical Manual of Mental Disorders* (DSM-III; American Psychiatric Association [APA], 1980) would strongly reflect both of these efforts, especially the more current one of Spitzer et al. That is what happened pretty much across the board and particularly in relation to the diagnostic criteria for schizophrenia, which turned out to be largely a reproduction of the Spitzer et al. (1975) Research Diagnostic Criteria rules for making the diagnosis.

Endicott and colleagues (1986) reported in a study in which a given group of patients, after careful clinical study, was diagnosed according to seven different (but considerably overlapping) proposed systems for rendering the schizophrenia diagnosis and obtained results that were not encouraging. They found an eightfold variation among the systems in their rates of applying the diagnosis. *None* of the systems did very well in predicting patient status a mere 6 to 25 months later, although the DSM-III was comparatively among the least inadequate in this respect.

DSM-IV. Since the introduction of DSM-III, the changes in subsequent versions have been relatively minor (compared to the changes from DSM-II [APA, 1968] to DSM-III). The primary change concerns the duration of symptoms. From DSM-III to DSM-III-R (APA, 1987), a specification of at least a 1-week duration for the psychotic-delusional (criterion "A") symptoms was added, allegedly to exclude transient psychotic disorders. When DSM-IV (APA, 1994) was introduced, this specification was increased to 1-month, again to "reduce false positive diagnoses" (p. 779). A primary goal of the revisions made in DSM-IV included the provision that "... revisions that would result in substantial reclassification of patients relative to DSM-III-R were to be avoided" (Flaum, Andreasen, & Widiger, 1994, p. 1008). This suggested a recognition of the way changing conceptions of the disorder have stilted progress.

The introduction of the DSM-III began a persistent trend to narrow the schizophrenia diagnosis. There are at least two studies in the literature, those of Winters, Weintraub, and Neale (1981) and Harrow, Carone, and Westermeyer (1985), in which a group of DSM-II-diagnosed schizophrenics was rediagnosed according to DSM-III criteria. The proportions of patients who survived the "cut" (i.e., retained the diagnosis) in the two studies were, respectively, 51 and 41%. Needless to say, such instability renders it uncertain to what extent volumes of pre-1980 research findings apply to the schizophrenias of today. The increase in the duration specification for criterion A, first to 1 week in DSM-III-R, and then to one month in DSM-IV, would be likely to further exclude subjects and perhaps select for a more chronic form of disorder.

To summarize the problems of the main criteria set for DSM-IV schizophrenia, it is neither Bleulerian nor Schneiderian, but a rather complex mixture of both, and considerably favors the latter. Moreover, if there is a clear and unifying concept underlying the various constituent criterial signs, it is not revealed in the accompanying DSM-IV commentary, nor have we been able to discern it on our own. Therefore, the list seems to be something of a hodgepodge of indicators traditionally associated with the concept of schizophrenia, where for the most part each makes an independent contribution to the diagnostic outcome. Certain of the quantitative rules (e.g., "two of the following"; why not one, or three?) are almost

entirely arbitrary. Moreover, for criterion A, only one (not two) of the characteristic symptoms is required if "... delusions are bizarre or hallucinations consist of a voice keeping up a running commentary on a person's behavior or thoughts, or two or more voices conversing with each other" (APA, 1994, p. 285). As can be seen, hallucinatory phenomena are strongly represented and entail the perplexing problems of intersubjective reliability discussed earlier. The naturally occurring overlap with mood disturbance is managed in an artificially exclusionary manner in a cosmetic attempt to enhance diagnostic reliability at the expense of clinical realities. Finally, despite "operational" pretensions, much room remains for subjective judgment in applying the criteria. For example, what is a delusion (see, e.g., Oltmanns & Maher, 1988), and at what intensity level does a phenomenon become "marked"?

No discussion of the schizophrenia diagnosis would be complete without considering the various schizophrenia subtypes that have been proposed, to which we now turn before wrapping up diagnostic issues.

Schizophrenia Subtypes

Given the pluralistic evidence of schizophrenias, it should be no surprise that the proposed subtypes have existed since the inception of the disorder. We will argue here that given the demonstrated elusiveness of the main category, it would be surprising if any of the subdivisions proved to have extraordinary robustness at the empirical level. Indeed, a major criticism of many of these studies is that too broad a spectrum of psychotic disorders is typically employed, so that it is not necessarily "schizophrenia" that is being subtyped (McGorry, Bell, Dudgeon, & Jackson, 1998). We describe the classical subtypes and also consider the more recent "positive" versus "negative" symptom differentiation.

The Classical Subtypes. Kraepelin described hebephrenic, catatonic, and two paranoid subtypes of the disorder (Defendorf, 1902). Later, Bleuler (1911/1950) described simple, hebephrenic, catatonic, and paranoid forms of the basic schizophrenic disorder, but it is clear that he considered that these qualitative distinctions related merely to varying profiles of "accessory" symptoms among different patients who shared the same fundamental deficits. He was not very impressed with them

in terms of their prognostic or predictive significance, and a wealth of evidence accumulated over subsequent decades indicates that he was largely right about this. It is, in fact, not uncommon for schizophrenic patients to display mixtures of these symptom clusters and move among them during the course of an episode.

Therefore, it is somewhat puzzling why the practice of applying formal classical subtype diagnoses has persisted, with only minor modification, to the present. From DSM-III on, the “simple” subtype, basically a symptomless personality description, has evidently (and wisely) been relegated to one or another of the Axis II personality disorders, but the other subtypes remain as originally described, and the “hebephrenic” is now called the “disorganized” subtype. The subtype “undifferentiated” was added to the DSMs long ago to apply to the many instances of mixed and/or highly unstable clinical pictures one sees in any psychiatric inpatient setting.

If there is any justification for retaining this seemingly outmoded system of classic subtyping, it resides in a distinction between the paranoid and the remaining subtypes. As a group, paranoids seem different (Magaro, 1980). Schizophrenic patients who remain persistently paranoid often do not show the kind of striking cognitive and/or attentional deficits seen in other forms of the disorder (Rabin, Doneson, & Jentons, 1979). As a group they tend to have a more benign course and outcome (Ritzler, 1981), and they show less evidence of familial concordance (genetic loading?) for schizophrenia (Kendler & Davis, 1981). On the other hand, many patients originally subdiagnosed as paranoid later acquire alternate designations (Kendler & Tsuang, 1981), and it is a venerable item of clinical lore that some paranoid disorders prove extremely intractable and chronic. There is sufficient reason in all of this to maintain a distinction between paranoid and nonparanoid forms of schizophrenia in selecting subjects for research; the groups can always be collapsed if the data prove that the distinction is irrelevant.

Positive- and Negative-Symptom Schizophrenias. The changing terminology associated with this distinction has made the long history of these subtypes less obvious than the classical subtypes. This dichotomy can be traced back to the process-reactive distinction forms of schizophrenia. Discrimination between the two was a matter of estimating case characteristics in four bipolar

dimensions: (1) slow and insidious versus abrupt onset; (2) absence of identifiable precipitating stress versus severe stress experienced immediately prior to onset; (3) socially shut-in and withdrawn versus socially engaged premorbid functioning; and (4) flat, blunted affect versus volatile, intense affect expression. For each, the first refers more to a *process* pattern, whereas its opposite was said to be associated with the *reactive* one. As these terms suggest, extreme process schizophrenia was considered an endogenously determined pattern of inexorable deterioration, not in concept unlike Kraepelin’s dementia praecox, whereas the more reactive variety was seen as induced decompensation in the face of overwhelming life challenge (and therefore had a far more favorable prognosis). Unfortunately, however, the circumstances of many schizophrenic patients were such that they could not definitely be allocated to one or the other of these categories, and some “reactives” showed a distressing tendency over time to drift toward the process end of the continuum.

A later but conceptually similar effort along these lines focused more exclusively on the general competence and adequacy of the person’s social functioning before obvious breakdown; the distinction here was “poor premorbid” versus “good premorbid.” This strategy yielded a more reliable allocation of patients to the pertinent subtypes, but it too eventually succumbed to a variety of puzzling and contradictory research findings; some of them were undoubtedly attributable to the poorly understood effects of newly introduced phenothiazine drugs. Before its demise, however, this subtyping strategy had modest success in achieving, for the first time, a measure of order in attempts to conceptualize rampant schizophrenic heterogeneity (e.g., Garmezy & Rodnick, 1959).

The newest version of the presumed underlying dichotomy addressed in these efforts is the currently popular distinction between “negative” and “positive” schizophrenia. These terms refer, respectively, to behavioral characteristics that constitute a deficit relative to normal performance and to those that involve some added element not normally present. Thus, flat affect and social withdrawal are negative symptoms, whereas hallucinations and delusions are positive ones (see Andreasen, 1985, 1988; Andreasen et al., 1995, for a more extended discussion on these subtypes). Therefore, negative schizophrenia is roughly

equivalent conceptually to the old “process” or “poor premorbid” designations, whereas positive schizophrenia bears the same relationship to the “reactive” or “good premorbid” subtypes. A related differentiation that emphasizes biological variables and speed of onset more refers essentially to these same patterns as Type I (positive) and Type II (negative) schizophrenia (Crow, 1985). Although most patients exhibit both positive and negative signs during the course of their disorders (Breier et al., 1994; Guelfi, Faustman, & Csernansky, 1989), a preponderance of negative symptoms in the clinical picture, it has increasingly been shown, has relatively grave prognostic significance (e.g., Fenton & McGlashan, 1994; McGlashan & Fenton, 1993). Finally, there has been some suggestion that the negative symptoms bear some relationship to medication side effects (Kornhuber et al., 1989; see also Miller and Ereshefsky, 1997).

Disorganized schizophrenia is an independently discerned subtype of schizophrenia that has more recently gained recognition partially independent of the positive and negative subtypes (Ratakonda, Gorman, Yale, & Amador, 1998; Toomey et al., 1997). This subtype is characterized chiefly by chaotic and seemingly directionless speech and behavior, and it has been recognized as the classic hebephrenic subtype of schizophrenia. **Subtypes in the DSM-IV.** The DSM-IV retains subsequent versions of the classic subtypes, including paranoid, disorganized, catatonic, undifferentiated, and residual, despite the criticism that these subtypes evidence poor reliability, poor stability over time, and poor prognostic value (McGlashan and Fenton, 1994). It seems that these subtypes were left in mainly on the basis of “clinical tradition” and the belief that they do possess some prognostic value, despite evidence to the contrary (Flaum, Andreasen, & Widiger, 1994). Interestingly, Appendix B of DSM-IV (APA, 1994) contains a section on “Alternative Dimensional Descriptors for Schizophrenia.” These are shown in Table 1.

**Commentary on the Current
Diagnostic State of Affairs**

In leveling these criticisms, we are in the awkward position of having nothing better to offer (and neither does the field). Debates about ways to

Table 1. Alternative Dimensional Descriptors for Schizophrenia from the DSM-IV (APA, 1994)^a

Dimension	Description
Psychotic	Hallucinations or delusions
Disorganized	Disorganized speech or behavior, or inappropriate affect
Negative	Affective flattening, avolition, alogia, avolition (exclude the effects of medication, depression, and positive symptoms such as hallucinations or delusions)

^aThe extent to which each dimension is present is rated as absent, mild, moderate, or severe, and ratings can be made for the present episode, and/or the past 6 months, or for the lifetime course of the disorder.

interpret findings from nosological studies of psychosis derived from DSM criteria sets continue along the lines of how many forms of psychosis actually exist. As many as six subclasses have been suggested (e.g., Kendler, Karkowski, & Walsh, 1998; McGorry, Bell, Dudgeon, & Jackson, 1998), and other investigators have provided evidence that suggests four factors (e.g., Dollhus et al., 1996). More parsimonious models have identified criteria sets corresponding to Bleulerian negative symptoms and Schneiderian first-rank systems, results that are not especially surprising in the light of our review of the development of the DSM diagnostic systems.

In any event, the field is presently plagued with debates about where to draw the line on the number of schizophrenic disorders, and the blurry boundary between psychotic and affective disorders has yet to be adequately resolved. We submit that these debates will largely turn out to be fruitless, mainly on the grounds that a multitude of diagnostic approaches drive the interpretation of the data in ways that are not necessarily empirically or theoretically grounded. We further suggest that the current diagnostic system needs a complete overhaul (see Carson, 1997, for careful consideration of this argument). We restrain ourselves from repeating those criticisms here, but it must be mentioned that progress in taxonomy would be better served by a move in the direction of parsimony, with the explicit goal of abandoning

the categorical format in favor of a dimensional one (e.g., Bell, Dudgeon, McGorry, & Jackson, 1998; Crow, 1997b). Thus, we view the “alternative” diagnostic scheme presented before as favorable and a step in the right direction.

Where is the field to go from here? An indispensable requirement is that we recognize an urgency to the taxonomic/diagnostic dilemma presented by those diverse aberrations of behavior that are traditionally and somewhat casually allocated to the schizophrenia rubric. In an article often cited in the field of psychiatry, Robins and Guze (1970) suggested minimal requirements for developing validity in psychiatric diagnoses. The basic requirements they put forth have not been adequately followed, and, in particular, a need remains for much neglected basic clinical research (Andreasen, 1998). The haphazard array of diagnostic criteria illustrate the slow progress in this area, and these limitations all but assuredly hamper research efforts aimed at etiology and treatment. In the most basic manner, the DSM system is plainly inadequate for these purposes. Andreasen (1998) made this point in a straightforward manner: “DSM was developed as a clinical manual to serve as a diagnostic ‘gatekeeper.’ Its descriptions of many disorders are intentionally sparse, simple, and incomplete. (*This is especially true for schizophrenia*)” (p. 1659, emphasis added).

Is the situation hopeless? Perhaps not. The compromise position is simply settling for a definition of the disorder that is more or less acceptable to practitioners and researchers but that is arbitrary in some sense. In fact, this is the strategy adopted by contemporary nosologists such as the authors of the DSMs (i.e., DSM-III and beyond). With such an approach, it is conceivable that systematic and meaningful patterns will be identified over time. And as understanding increases, the defining diagnostic criteria can be sharpened to reflect what might eventually become a valid construct. There is abundant evidence that a program of this sort, “bootstrapping” (Cronbach & Meehl, 1955) our way haltingly toward an understanding of the nature of these disorders, is already in place among mental health researchers. Alas, there is no better alternative, provided that we do not fool ourselves into thinking about “schizophrenia” in unduly reified terms and provided that we continue to seek a much-needed refinement of this *open construct*

in an informed and rigorous manner. This is the sense in which we shall be using the term in the remainder of the chapter.

Etiologic Considerations

There has been tremendous effort over the years to isolate or otherwise identify a genetic cause of schizophrenia. The process of this research is one that deserves at least parenthetical comment. An answer to “the question” (i.e., What is the cause of schizophrenia?) is never quite obtained, despite intermittent promises that loom on the horizon. The potentially promising results entice researchers, offering hope that the answer to the schizophrenia puzzle will soon be solved. Often, such findings are seized upon by the media, further encouraging simplistic answers to a very complex problem. This is a curious pattern, and one that we speculate is at least partly influenced by the desperation naturally associated with working with such a devastating and disabling disorder in the absence of any truly effective interventions (recall the lack of progress during the last century). Those entering the field should be warned against such potentially seductive claims.

If, as we would anticipate, schizophrenia turns out to be a variety of separate and distinct disorders that happen to share some similar properties at the level of behavioral output (and the class “psychotic,” after all, has finite boundaries), it would seem unrealistic to search for some primary etiologic factor that controls a large proportion of morbid outcome variance. Another implication of the multiple-pathway notion is that the search will prove very difficult because such heterogeneity will impede the establishment of reliable commonalities of background across persons who acquire the diagnosis. As will be seen, both of these expectations are amply confirmed in the findings of etiologically relevant research.

It has become customary in discussions of this sort to treat separately purported biological and psychosocial causal influences in schizophrenia, as though it were reasonable to conceive that such influences somehow contribute to the outcome independently of one another; that is, in the merely additive, orthogonal fashion suggested by a simple version of the diathesis-stress model (Zubin & Spring, 1977). It is increasingly clear, however,

that some sort of combinatory function that operates between these two broad sources of causation is at least frequent and quite possibly routine in the development of schizophrenia. Accordingly, we will not employ the common but potentially misleading format of biological/psychosocial causation in what follows but will rather try to convey something of what we judge is the enormous complexity of relationships between the two as our discussion of distinct causal factors proceeds.

We have deliberately used the somewhat cumbersome expression *combinatory function* in the preceding paragraph, where in this context the term interaction is doubtless far more commonly employed. But the latter term may suggest a particular kind of joint determination of outcome, whereas we typically do not know the specific form in which the two classes of variables (biological and psychosocial) conjoin in contributing to the schizophrenic outcome. Hardly anyone doubts that some sort of "interaction," loosely defined, occurs among the variables so far identified and that they are probably implicated in producing schizophrenic outcomes. Indeed, the direct and indirect evidence pertaining to the operation of potent modifier variables with respect to essentially every factor suspected of having etiologic significance is so multifaceted and compelling that the task of finding one's way around in the thicket can be stupefying. It is precisely for this reason, we surmise, that investigators generally manifest strong propensities to focus on and treat genetic, other biological, and psychosocial factors as separable entities, even though it makes only limited sense to do so in light of the evidently convoluted etiologic pathways involved. An additional complicating factor is that these pathways will probably turn out to be highly idiosyncratic for individual instances of disorder (Meehl, 1978), thereby seriously compromising the research value of aggregating observations over subjects.

We have little choice but to follow the leads investigators have laid down, but in doing so, we should bear in mind that the strategies employed mask to a great extent the central fact of pervasive and developmentally continuous interplay among the contributory influences. The general problem here is well illustrated in connection with the suspected role of genetic variables in the intergenerational transmission of a propensity to develop schizophrenia. We turn now to a discussion of the evidence supporting this hypothesis.

Genetic Variables in Schizophrenia

The concept of interaction held by most psychologists derives from the ANOVA statistical model—where, for example, outcomes are allocated to cross-cutting genetic and environmental factors, to their interaction ($G \times E$), and to "error." This conception of interaction can be quite misleading because the constituent elements are erroneously considered independent and the natural events that unfold in the process of development are removed from the temporal sequences in which they occur. Variance components are extracted and treated as though they were distinct entities unaffected by one another over time. But discrete factors do not occur as such in nature, and the statistical model of necessity ignores the extent to which genes and environment covary over time; in fact, the variable of time, crucial for any developmental process, is discarded. What we are suggesting, then, is the necessity for a decidedly more fine-grained analysis of genetic–environment interaction if there is to be any hope of achieving a true understanding of the contribution of either component to schizophrenic outcomes. With these caveats in mind, we proceed to review the genetic evidence.

Inquiries into the genetics of schizophrenia can be roughly divided into two strategic approaches; each is a function of the progress of knowledge and methods available to scholars and scientists who work in this area. The first approach is based on the traditional Mendelian understanding of genetics, where the occurrence of traits (phenotypes) are identified and observed across generations for trends that will shed light on underlying genetic mechanisms. Working from the other direction, more modern techniques have been developed since the molecular elucidation of DNA and the subsequent development of biochemical techniques to study the encryption and expression of heritable information. The family (including twin and adoption methodologies) belongs to the traditional approaches, though what is in only some ways a less inferential examination of genetic processes is possible in the realm of molecular biology. Either approach faces an extreme limitation: A significant gap remains between what is observed at the behavioral level and that which is observed at the molecular—or inferred at the genetic—level. That gap, partly framed by the nature of the questions asked, will have to be

bridged to improve the present rate of progress. More on that later, but first a summary of the currently accepted knowledge.

Twin Studies. It is well-established that there is a higher concordance rate among monozygotic twins (MZ) than among dizygotic twins (DZ), a finding that is often cited in defense of the argument that schizophrenia is a “mostly genetic” disease. In a review of the worldwide literature on twin studies, Torrey and colleagues (1994) report an overall pairwise concordance rate of 28% for MZ twins, and 6% for DZ twins. Thus, it seems clear that sharing 100% of the genes with a schizophrenic twin greatly increases the risk (almost fivefold) of developing the disorder. Furthermore, sharing 50% of the genes, as in DZ twins, provides a risk that is substantially greater than in the general population.

Torrey et al. (1994) reported on twenty-seven pairs of MZ twins discordant for schizophrenia, a research strategy that was potentially revealing about nongenetic causal factors. Perinatal factors were important in at least 30% of affected cases, as were widespread early CNS dysfunctions. Evidence from discordant affected twins sheds some light on the complexity of the genetic evidence from twin studies. Of discordant affected twins, 30% were described as having been different during early childhood (e.g., shy and withdrawn, aggressive, or odd), suggesting possible CNS dysfunction. These twins also showed prominent alterations in brain function as assessed by cerebral blood flow, neuropsychological tests, neurological exam, and smooth-pursuit eye movement. Hypofrontality (reduced blood flow to the frontal lobes), it was demonstrated, is associated with reduced size of the anterior hippocampus. Moderate/severe cognitive impairment in neuropsychological tests was observed in fourteen of the twenty-seven affected twins. The nonschizophrenic co-twins of discordant pairs, though less neurologically impaired than their disordered siblings, were more impaired than a set of control MZ twins where both members of the twinship were considered psychiatrically normal. Comparing schizophrenic persons from discordant and concordant pairs, no significant differences in clinical or potential etiologic variables are found.

What can be made of the findings that changes in brain structure were not correlated with clinical aspects of schizophrenia in the affected twins and that there were significant structural deficits in the

nonaffected twins? It appears that things are more complicated than can be sorted on the basis of this methodology. Although compelling, several shortcomings must be kept in mind. First, despite the apparent robustness of these findings, it remains impossible to predict schizophrenia outcome for individual cases. Second, there are some inconsistencies in these data. In a few cases, the “well” twin appeared more biologically compromised than the affected co-twin. The authors rightly conclude that these data do not sufficiently resolve the most basic questions of the genetics of schizophrenia. However, it does seem that these neurological abnormalities play a role in the chain of causal events that lead to the disorder. We remind the reader of the problems surrounding the definition of the disorder.

Fischer (1971, 1973) extended the twin methodology by reasoning that the genetic influence would rear itself in the offspring of the non-schizophrenic twin, and bore this out in a search of the official records in Denmark. In a follow-up of these offspring, Gottesman and Bertelson (1989) reported age-corrected incidence rates of 16.8 and 17.4%, respectively, for children of schizophrenic and discordant MZ twins. The age-corrected risk for children of schizophrenic DZ twins was of the same order (also 17.4%), whereas that for the offspring of discordant normal DZs was a mere 2.1%. These data constitute, then, a relatively powerful argument that there is some genetic contribution in some instances of schizophrenia. On the other hand, as Gottesman and Bertelson (1989) note, they also show that this presumed predisposition may remain “unexpressed” unless “released” by unspecified environmental factors.

What can be concluded from the twin studies? It must be remembered that if schizophrenia were an exclusively genetic disorder, the concordance rate would be 100%. As we repeatedly emphasize, however, such typological thinking is erroneous when it comes to conceptualizing unfolding biological or genetic influences or factors. As Torrey and colleagues (1994) pointed out, MZ twins are only genetically identical when the original zygote splits. Phelps, Davis, & Schwartz (1997) report that two-thirds of MZ embryos are monozygotic, meaning that they share blood supply, whereas DZ twins never do. Then, it seems plausible that shared pathogens may account for the increased rate. Chronic hypoxia and other obstetric complications are more likely to be shared by

MZ rather than DZ co-twins (Maier et al., 1995). At the very least, the twin studies have provided an important insight that illustrates the lack of clarity between genetic and environmental boundaries. Environmental-biological events that occur during the pregnancy, as will be discussed in greater detail later on, play a role in the unfolding of genetic material and possibly influence CNS development.

Adoption Studies. An additional major approach to examining the genetics of schizophrenia is the adoption strategy. The defining study in this area was carried out by Heston (1966). In a sample obtained from an Oregon state mental hospital, he found a significant difference between the age-corrected incidence of schizophrenia diagnoses among index adoptees (16.6%) compared to controls and a result similar to that for children *not* separated from their schizophrenic mothers. Index adoptees also evidenced an increased range of sociopathic personality disorder, suggesting the possible transmission of a more general sort of psychopathological compromise. Thus, this study provided fairly convincing evidence that enhanced schizophrenia risk was attributable to genetic (or prenatal) causes, and the stage was set to search for genetic causes using the adoption strategy.

The most prominent and extensive of the adoption studies in schizophrenia were initiated by a group of American investigators who were granted access to the exceptionally thorough census and social services database maintained by the government of Denmark. The initial results of this eventually widely reported study became available in 1968 (Kety, Rosenthal, Wender, & Schulsinger, 1968; Rosenthal et al., 1968). The central finding of the original study (Kety et al., 1968) was that a much higher percentage of the biological relatives of the index cases had a schizophrenia spectrum diagnosis than the nonbiological cases (8.7% versus 1.9%, respectively). These results must be tempered because the range of diagnoses included in the schizophrenia spectrum was broad. In fact, subsequent analyses have shown that the finding of heritability specific to schizophrenia does not hold up when more stringent diagnostic criteria for schizophrenia are employed (Rosenthal, Wender, Kety, Welner, & Schulsinger, 1971). Again, the evidence is more supportive for inheritance of some sort of general compromise, a conclusion that is not so surprising in the light of the diagnostic dilemmas reviewed earlier.

Later reports by Kety (Kety, Rosenthal, Wender, Schulsinger, & Jacobsen, 1978; Kety, 1987) have provided results that generally support the original findings. However, one persistent and peculiar finding in which second-degree relatives are persistently more concordant for schizophrenia than those of first degree seemingly disconfirms the genetic transmission hypothesis. Although such an apparent anomaly might be regarded as an important lead to which to devote further effort to unravel the complexities of transmitted—genetic or otherwise—factors, the report by Kety (1987) suggests in narrative format that the balance of first- to second-degree index relatives who show spectrum disorders was “in accord with expectation,” presumably implying a preponderance of the effect in parents and full siblings. Unfortunately, that report does not contain the data necessary to fully evaluate the claim.

Kendler and Gruenberg (1984) attempted an independent replication of the Kety et al. (1968, 1978) greater Copenhagen family study. Using the record data already assembled, these investigators rediagnosed all subjects, adoptees, and family members according to the relatively precise criteria of DSM-III. Of the various results of the project, two stand out as especially important: First, schizophrenia spectrum disorders (now systematically defined to include paranoid and schizotypal personality disorders in addition to schizophrenia) are significantly more frequent in index than in control biological families, and the difference is especially pronounced among the *first-degree* relatives. Second, the risk for a schizophrenia spectrum disorder also significantly increased in biological relatives of adoptees who have a predominantly schizophrenic type of schizoaffective disorder or schizotypal personality disorder. These data are relatively convincing and highlight the systematic strengths of the DSM-III-type diagnostic approach in bringing order to a confusing data set with conflicting reports, notwithstanding the limitations of that instrument as a research tool (see Andreasen, 1998).

An important variation on the adoption methodology is the approach of cross-fostering (Wender, Rosenthal, Kety, Schulsinger, & Welner, 1974). This method examines biologically normal adoptees who are placed in foster homes in which one of the adoptive parents subsequently becomes schizophrenic. The schizophrenia incidence rate for these “cross-fostered” adoptees is then com-

pared with (1) adoptees whose adoptive and biological parents are normal and (2) adoptees who have a schizophrenic biological parent and are raised by normal adoptive parents. The “purified” group incidence rates for at least borderline schizophrenia among adoptees in each of the above conditions were, respectively, 4.8, 10.7, and 19.7%, a statistically significant variation. However, it has been independently reported that the schizophrenic adoptive parent of a large majority of the cross-fostered children had not become seriously disturbed until the children’s late childhood years (Van Dyke, Rosenthal, & Rasmussen, 1975). Hence, they would not have necessarily presented an unremarkable environmental challenge during the presumably more critical earlier developmental period. In other words, the study basically fails to demonstrate that (adoptive) parental schizophrenia is psychopathologically nonnoxious for children exposed to it (barring the implications of prodromal symptoms).

The adoption method was originally conceived as one that would circumvent the serious problems of other pedigree approaches, such as twin studies, with the hope that the answers provided would be more clear-cut. This was not the outcome, however. Beyond the idea that there is clearly a familial link to the disorder, a proposition that one might reasonably surmise purely by conjecture, evidence that sheds light on the nature of that mechanism is lacking. Evidence does exist, in our view, that whatever is being genetically transferred to the individual lacks specificity to schizophrenia *per se* and more accurately relates to a broader type of compromise, perhaps even beyond the “schizophrenia spectrum.” The idea of some sort of general compromise is also consistent with the more recent idea that the most consistent aspect of schizophrenia is poor functioning.

On the other hand, the lack of reports on the environments in which the adoptees were placed is striking. In largely neglecting the environments, a potentially important source of morbidity has been overlooked. This gap has been filled by the work of Tienari and colleagues (1985, 1987, 1994; Tienari, 1991). The design of their study involves a follow-up of the adopted-away children of all women in Finland hospitalized for schizophrenia, beginning around 1960. As these index children grow into adulthood, they are compared with a matched group of control adoptees whose biological mothers were normal. The trend of the results

is already clear and reaches high levels of statistical significance. There is the familiar finding that the index adoptees have developed more, and more serious (including schizophrenia), psychopathology than the controls. Most of this psychopathology, however, is concentrated in the index group reared by poorly functioning adoptive parents—for example, parents who demonstrated high levels of communication deviance. Index adoptees reared by well-functioning adoptive parents had substantially less psychopathology, and control cases reared in disorganized adoptive families experienced more serious psychopathology as adults than their counterparts raised in “healthy” families. We will recall these results when discussing the relationship of schizophrenia to the subculture of the family.

To summarize, the initial promise of the adoption methodology to offer incontrovertible proof of the genetic basis of schizophrenia is now recognized as overstretched. In addition, we would call attention to numerous demonstrations of methodological problems and the erroneously extended conclusions drawn from this evidence (e.g., Benjamin, 1976; Carson & Sanislow, 1993; Lidz & Blatt, 1983; Sarbin & Mancuso, 1980). Aside from methodological concerns, the dichotomization of genetic and environmental components as distinct, assumed to operate in an independent manner *statistically*, overlooks the continual interplay of these factors that actually occurs in reality. It has been established for some time that these methods that treat these components as independent factors are unlikely to elucidate underlying mechanisms of complex traits or disorders (see, for instance, Carson & Sanislow, 1993; Lewontin, 1974; or Wahlsten, 1999). In the light of these limitations, new hope was garnered from the field of molecular biology.

Molecular Genetics. Linkage studies, including the physical mapping of genes, presaged the more prominent contemporary research strategies developed in the biological sciences, leading inevitably to their employment by psychiatric geneticists in attempts to unravel the presumed genetic processes associated with schizophrenia. In the field of genetics, Morgan (1911, 1920) noticed early on that traits could be inherited together, or “linked” on proximal chromosomal locations by the patterns in which combinations of traits were passed on generationally. This idea led to estimating gene distances and locations on par-

ticular chromosomes by triangulation from observed trait coinheritances. More recent advances in gene mapping have occurred at the molecular level with the use of restriction enzymes to “cut” DNA at known repetitive DNA sequences (see Botstein, White, Skolnick, & Davis, 1980), thereby providing a sort of anchoring point for determining relative intergene distances and thus to enable a more direct measurement. The resultant construction of more detailed maps has permitted relatively accurate localization of actual “disease” genes and hence isolation and identification of gene products (i.e., enzymes or other proteins) presumably implicated in various medical conditions. Therefore, it is within the realm of possibility that if certain genes are systematically associated with schizophrenic outcomes, we will one day be able to pinpoint their locations and describe in some detail what proximal effects they have. Bear in mind, however, that it is a long way from there to schizophrenia.

The current consensus is that a “large” and very specific gene effect in schizophrenia is unlikely, and many researchers have recognized for some time that the genetic effects involved with schizophrenia are more likely to involve multiple genes in interaction with idiosyncratic environmental experiences (Moldin & Gottesman, 1997). The result of studies in molecular genetics that intend to establish the loci of genes for complex mental disorders such as schizophrenia and bipolar disorder are consistent with this idea; few of the findings implicating single genes have been replicated. Early results, including the announced identification of a gene location for bipolar disorder on chromosome 11 (Egeland et al., 1987), were seized upon by the popular media and are now known to have been premature (DeLisi & Crow, 1989). In schizophrenia, there has been much interest in a specific region of chromosome 5 that was stimulated by the discovery of a Chinese man and his nephew, both schizophrenic, who displayed a particular chromosome 5 aberration (partial trisomy). Sherrington and colleagues (1988) studied five Icelandic and two British families that have multiple occurrences of schizophrenia and presented evidence for a gene locus on chromosome 5 with a dominant schizophrenic-susceptibility allele. This result, however, is inconsistent with data gathered on American (Kaufman, DeLisi, Lehner, & Gilliam, 1989) and Swedish (Kennedy et al., 1988) families that have high concentrations of schizo-

phrenia. DeLisi and Crow (1989) noted that some data indicated that schizophrenia has higher concordance but milder manifestations in females and suggested that the presumably implicated genes have a sex-chromosome locus, but the argument is entirely inferential. Other studies have examined linkage to a marker on chromosome 6 (Lander & Kruglyzk, 1993; Wang et al., 1995), but other studies of this region that used better samples produced equivocal results (Schwab et al., 1995) or failed to replicate (Moises et al., 1995). In the Irish study of high-density schizophrenia families, there has been some suggestion of a locus on chromosome 8p (Kendler et al., 1996). Other results from the Irish sample suggested a locus on chromosome 6 (Wang et al., 1995). However, those are statistically questionable (Straub et al., 1995; Gottesman & Moldin, 1998). In fact, non-replication for the majority of loci reported is an ongoing problem with linkage studies (Gottesman & Moldin, 1998).

Overall, there has been a general failure to replicate results that identify specific regions in independent samples, and results that implicate a specific chromosomal area are at best suggestive (Moldin, 1997). In the context of these inconsistencies, it has also been pointed out that molecular-linkage strategy simply lacks the necessary statistical power when it comes to testing for anything but large gene effects. We applaud recognition of this limitation, but it seems to us that stacking the deck to detect a small effect size that might be associated with “weak” genetic effects will not ultimately pay off, as in applying alternate strategies such as association analyses (e.g., Risch and Merikangas, 1996). Before leaving this topic, one remaining problem, the fundamental idea of the phenotype, deserves careful consideration.

The Problem of Phenotype. It might be reasonably argued that the cardinal factor limiting the acquisition of knowledge of the “genetics of schizophrenia” is a pervasive blurriness of the concept of phenotype. Definitional problems and the diagnostic heterogeneity that surround the schizophrenia diagnosis notwithstanding, the problem of the phenotype is more basic and involves the intricate complexities of the interaction of genes and environment. To illustrate this fact, the “phenotype” (i.e., the resulting expression of the genotype) in schizophrenia can broadly range from the disorder itself, to features associated with the disorder, to some more basic gene product

involved with structural development that, it is hypothesized, is related to the disorder. Nowhere in the literature can we find any clarity on this matter, although Scher (1999) succinctly stated the problem when discussing the issue more generally:

Phenotypic psychological mechanisms surely arise through a complicated process. The role of genes is likely to be rather far away and indirect. Certainly, our current understanding of the relationship between mind and body limits our ability to understand how genes—which code for physical structure—contribute to psychological development. (p. 436)

We have stressed that genes and environment continually interplay as the process of development unfolds. In this light, the phenotype is an elusive concept. Is the phenotype the disorder? Or is the phenotype one of the hypothesized components of the disorder such as a manifest neonatal complication? The phenotype might also be related to temperament, to neuronal development of receptor sites, or to the language centers. The “genetics” of schizophrenia will be handicapped until there is consensus on the phenotype. Even with some agreement on a meaningful phenotype, there will still be complications inherent in the level at which the phenotype is implicated in the disorder. Consider, for example, that an aberrant gene for a defective receptor site will be limited by our understanding of the way pathological synaptic transmission is implicated in the disorder, something that is, as will become clear shortly, far from settled.

To complicate matters further, exactly what constitutes a gene has varying conceptions that depend on one’s approach. In Mendelian (i.e., in pedigree or family) studies, a gene is a hypothesized construct that is related to a particular phenotype and is isolated based on observed patterns of inheritance. In more modern molecular methods, a gene is the smallest sequence of nucleotides in a strand of DNA that codes for the production of a protein. From a molecular point of view, genes are not necessarily unique; they can be overlapping. In other words, genes produce products that undergo programmed biochemical modification to serve their ultimate function, and sometimes these functions include regulating other genes, sometimes the modification of gene products. Such effects are among intricate, interrelated constellations of events that are complex even for the most straightforwardly seeming diseases. For instance, insulin is originally produced as a protein strand that folds back on itself due to the attraction of

branched amino acids within the protein sequence. Related enzymes cleave off the resulting “folds” to produce the final structure. These related enzymes are coded for by other genes, and the final product is produced by a complex system of interdependent regulation and feedback loops. So what causes diabetes? There is no one sole cause, and at least several mechanisms, more or less “genetic,” can lead to this disorder. These include problems in the synthesis pathway of insulin either blocking the conversion to the final product or leading to a defective final product, abnormal receptors for insulin, or the intercellular insulin-receptor complex that facilitates insulin binding. These varied mechanisms end with the common final pathway of diabetes that appears isomorphic at the level of clinical pathology. Is diabetes a hereditary disease? Some understanding of the mechanism will undoubtedly aid in determining the best treatment. Unlike schizophrenia, however, there is a clear understanding of the pathophysiology in diabetes, thus enabling meaningful study of genetic aspects at the molecular level to determine various gene influences. In schizophrenia, molecular genetic strategies will not be of full benefit until the pathophysiology of the disorder is clearly understood.

The dearth of knowledge about the pathophysiology of schizophrenia obviates the specification of the layers involved in the regulatory processes and their interactions with environmental insults that result in the disorder. In other words, there is not a clear understanding of what bridges the “nature and nurture.” We know that schizophrenia runs in the family and that there is a biological constitution that enhances (creates?) vulnerability to the disorder. It appears that some sort of sequence of traumatic events in the context of development opens the vulnerability, but the role of the timing of such environmental traumas is less clear. It also appears that individuals can undergo traumas similar in magnitude and nature and come out seemingly unscathed, and that not all this can be chalked up to a genetic difference. This has led one of the major thinkers and researcher of the disorder, Paul Meehl (1989), to declare that developing schizophrenia is a matter of “bad luck” in that some idiosyncratic as yet unspecified sequence of traumatizing events opens the vulnerability to the disorder. Finally, evidence also suggests that certain neural pathways function abnormally, but the exact manner of this dysfunction is not entirely clear. Hence, there are many

gaps in the knowledge required to understand the “genetics” of the disorder.

The best illustration of this is MZ twins, where one can assume that the genetic material is identical only when the zygote splits. Subsequent to that time, a multitude of levels between the extremes of “nature” and “nurture” exist, and recognition of these levels underscores the artificial aspect of bifurcating developmental events as either genetic or environmental. Seen in this light, adoption and twin methods are obsolete, or as Meehl (1972) had the good foresight to put it, “we have skimmed the cream; we are near the research asymptote” (p. 368). There can be little doubt that now defunct dichotomous positions traditionally taken in the nature/nurture debate which have for many years effectively driven the research on schizophrenia, have reached a point of obsolescence, and it is likely that without a more complete theory of schizophrenia pathology, the same is true for more modern molecular methods.

In the search for the biological, biochemical, or genetic solution, we believe it will someday be accepted that it was simply asking the wrong question. Is schizophrenia genetic? Of course it is—how could the disorder be devoid of genetic influences? We would go so far as to suggest that, for the most part, there are no inherent flaws in the data. Rather, forces driving the conceptualization and interpretation of the science have been obscuring real progress. As it turns out, current views (e.g., Harrison, 1998) clearly recognize the failure of the promise of molecular genetics—the last bastion for a “genetic solution”—to solve the schizophrenia puzzle. Presently, the new emphasis is on its pathophysiology. We will return to review that area shortly.

Schizophrenia and the Intrafamilial Subculture

Research on the family subculture and interpersonal processes within the family that might contribute to the development of schizophrenia reached its zenith in the late 1950s and, with some exceptions, has been in decline ever since. There appear to be five principal reasons for this decline:

1. Such research is very difficult to carry out in a precise and controlled way, far more so than the high-technology-driven research into biological processes so prevalent today.

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2. Relatedly, some early but insufficiently controlled findings of apparent familial aberrancy (e.g., double binding) have proven nonspecific for schizophrenia and indeed somewhat routine in families that have exclusively normal offspring.
3. Dysfunctional behavior in family members, it has been shown, is reactive to the presence of a disturbed family member rather than antecedent to such disturbance; indeed, such circularity in cause–effect sequences in patient–family interaction may be the norm.
4. Research on the possible intrafamilial origins of some schizophrenias has, perhaps understandably, not been popular among parent groups who have (probably accurately) sometimes perceived that they are summarily and unfairly blamed for the disorders of their children.
5. The so-called “decade of the brain” (i.e., the 1980s), for the most part, obviated thinking and research along these lines in mainstream psychiatry.

In the light of the sensitive nature of this topic, we want to be clear about our own position. We find that assigning blame in this area is both counterproductive and based on an oversimplified notion of the way persons become schizophrenic. Parenting is at best an inscrutable task laden with pitfalls throughout the course of child development, and most of the parents we have known, whether they have had the “bad luck” to have raised a son or daughter who became schizophrenic, have done the very best they could to ensure the happiness, health, and success of their children. We have the greatest sympathy for the difficulties faced by the mothers, fathers, and siblings, of schizophrenic persons. Many of these relatives harbor unjustified guilt feelings; we have no wish to induce or augment such feelings—quite the contrary. Nevertheless, we think open inquiry into the developmental process, which necessarily involves attention to the intrafamilial environment, is essential in any comprehensive attempt to discover the sources of schizophrenic outcomes.

Does schizophrenia as a biological disease somehow soften the blow? Admittedly, there seems to have been an impact on destigmatizing the disorder for those afflicted *and* their family members. The downside of the wholesale version

of this view is that personal responsibilities are minimized, thereby creating a steadfast system that excludes that examination of family dynamics, including expressed emotion (EE), and calls into question the contributions of this view to real progress. On the other hand, it is curious that the notion of blame is contingent on the biological–environmental dichotomy. We are skeptical that the biological disease metaphor provides lasting meaningful relief to those exposed to the suffering of schizophrenia. Moreover, it is appalling that the field (either psychiatry or psychology) has yet to find a way to address more kindly the issue of problematic family communication patterns in a direct manner that would foster a posture of curiosity rather than a defensive reaction. We understand that families with a schizophrenic member may well be emotionally volatile, but one only need pay attention to the pejorative nature of many of the family-related concepts about to be discussed for evidence of this shortcoming.

In any event, the heyday of family process research in the 1950s saw the emergence of the double-bind hypothesis of the Palo Alto group (Bateson, Jackson, Haley, & Weakland, 1956), the transmission of irrationality hypothesis of the Yale group (Lidz, Cornelison, Terry, & Fleck, 1958), and the pseudomutuality notion developed by NIMH investigators (Wynne, Ryckoff, Day, & Hirsch, 1958). These and other contributions have been extensively reviewed by numerous scholars (e.g., Goldstein & Rodnick, 1975; Goldstein & Strachan, 1987; Hirsch & Leff, 1975; Jacob, 1975; Mishler & Waxler, 1968; Wynne, Toohey, & Doane, 1979), so we will not repeat the effort here. Suffice it to say that these specific process notions have tended to give way over time to more general ideas that gross intrafamilial communication deviance and a negative affective climate encourages the emergence of schizophrenic behavior. The altered perspective was attributable in no small measure to the success achieved by Singer & Wynne (1965a,b; Singer, Wynne, & Toohey, 1978) in demonstrating that they could postdict the schizophrenia status of offspring from amorphousness and fragmentation in the Rorschach protocols of parents. Subsequent use of a highly similar assessment system in the UCLA high-risk longitudinal sample showed that it could predict schizophrenia spectrum disorders in offspring (Goldstein, 1985). The latter study is particularly significant because the samples of deviant parental communication

were obtained years before the onset of schizophrenia in children, thus ruling out the possibility of parental reactivity to the disordered communication that schizophrenia normally entails.

A nonreactive research design was also employed by Roff and Knight (1981) in a study that related outcomes in diagnosed cases of adult schizophrenia in males to family variables obtained during patients' preschizophrenic childhood years. Data on the latter were obtained from child guidance clinic records that had been prepared at the time these children and their families were seen for various nonpsychotic childhood adjustment difficulties. Particularly interesting was the finding that poor adult outcome was associated with a mothering style remarkably similar to the classic "schizophrenogenic" pattern (Fromm-Reichman, 1948) of rejecting, impervious overconcern, an etiologic concept that had been all but abandoned by researchers by the 1970s. Also in line with the classic notion was some evidence that the effects of such mothering were especially noxious where fathers had been described as critical and noninvolved with their sons. A final instance of this study's rich yield was the confirmation of an association of poor outcome with two particular patterns of parental marital dysfunction that had been described by earlier investigators, in particular, by Lidz, Cornelison, Fleck, and Terry (1957) under the rubrics *marital schism* (extreme distance and hostility between the parents) and *marital skew* (wherein the family subculture is pathologically tilted in the direction of accommodating to serious disturbance in one of the parents).

The notion that familial subcultural aberrancy might promote the development of schizophrenia in offspring must confront at the outset the fact that siblings of the disordered member are usually normal. How have they escaped harm from these presumably relatively constant pathogenic conditions? The answer from proponents of this view is that the subculture of a family is not constant, that it changes appreciably over time, and has its own unique developmental pattern. The early development of the preschizophrenic child just happens to come at a time (Meehl's "bad luck" factor?) of maximum familial pathogenicity. There is some evidence to support this construction.

Taking a direct approach, Stabenau and Pollin (1968; Stabenau, Tupin, Werner, & Pollin, 1965) studied families in which siblings were discordant for schizophrenia and for juvenile delinquency.

They found, in brief, that seventeen of their nineteen “psychopathology siblings” (for schizophrenia alone, nine of ten), compared to only two of twenty-nine controls, encountered periods of maximum family crisis in early childhood identified by the families themselves. The “bad times” included such things as financial disasters, maximum parental strife, and depressive episodes in one or the other parent. A variety of collateral findings confirmed the general picture that these disturbed individuals experienced a world of far less reassuring character in their formative years than their more functional siblings.

Essentially the same type of explanation for normal siblings was offered in the Lidz–Yale family studies (Lidz, Fleck, & Cornelison, 1965). In fact, a criterion for selecting the original families to be studied was that at least one sibling was available who showed no evidence of psychological disturbance. In a series of compelling descriptions, the investigators in this project illustrated how the inherent pathogenicity of a marital dyad can become especially concentrated on a single sibling (owing to gender, concurrent stage of family development, etc), thereby confronting that child with insoluble conflicts and contradictions about the nature of reality that are not necessarily inflicted on other siblings or, if so, at lesser intensity.

As a final entry into this very contracted overview of the extensive literature on family influences in schizophrenia, recall the unique, ongoing project in which independent assessments of child-rearing adequacy were the focus of study by Tienari and colleagues (1985, 1987, 1994; Tienari, 1991) mentioned earlier in the adoption section. There is the familiar finding that the index adoptees have developed more, and more serious (including schizophrenia), psychopathology than the controls. Most of this psychopathology, however, is concentrated in the index group reared by poorly functioning adoptive parents—for example, parents who showed high levels of communication deviance. Index adoptees reared by well-functioning adoptive parents had substantially less psychopathology, and control cases reared in disorganized adoptive families experienced more serious psychopathology as adults than their counterparts raised in “healthy” families. Consistent with their earlier work, these results show a moderate genetic effect—the differential “healthy” and disorder rates of index versus control adop-

tees, irrespective of adoptive family context. However, parental inadequacy and disturbed communication has a substantial impact on the outcome for both index and control cases. Thus, the findings indicate a strong interaction between genetic vulnerability and an unfavorable family environment in the causal pathway leading to schizophrenia. Unfortunately, we cannot be certain that the emergence of odd or psychotic behavior in adoptees did not precede and cause, in whole or in part, the disorganization of their adoptive families. Analyses to examine this possibility are in progress (e.g., Wahlberg et al., 1997), but so far they provide no definitive support for this alternative interpretation. Some independent work reported by Kinney et al. (1997) also fails to show diminished mental health in adoptive parents raising children who became schizophrenic. Despite additional modest evidence for genetic transmission from these studies, the level of integration of the adoptive family into which the child is placed looms as an extremely critical variable. The most disastrous outcomes occur where children whose mothers have been schizophrenic are placed in chaotic adoptive homes.

Because expressed emotion (EE) has usually been seen as related to the course rather than the causes of schizophrenia, we will postpone discussion of it in families until a later section.

Soft Neurological Signs, At-Riskness, and Brain Anomalies

Although we find the genetic evidence pertaining to schizophrenia extremely modest in relation to the amount of “play” it gets and, perhaps excepting the case of monozygotic twinship, by itself virtually useless in predicting individual morbidity (as in so-called genetic counseling programs), we do not discount the possibility that other forms of biological compromise may convey a more substantial risk of schizophrenia. Indeed, it is conceivable that much of what appears “genetic” in the etiology of schizophrenia is mediated in some other biological manner. As it turns out, there is no compelling evidence of progressive brain degeneration in the natural course of the disorder (Cannon, 1998a,b; Russell, Munro, Jones, Hemsley, & Murray, 1997). In those instances where progressive degeneration has been observed, it sometimes appears to have resulted from the iatrogenic effects of antipsychotic medications

(Cohen, 1997; Gur et al., 1998). In other instances, it does not seem that reduced volume in at least some brain areas (i.e., hippocampus) is specific to schizophrenia (Velakoulis et al., 1999). In the light of these findings, it is interesting to note that some studies have suggested that deficits associated with the schizophrenias are the most stable element of the disorder (e.g., Amador et al., 1999; Nakaya, Suwa, Komahashi, & Ohmori, 1999).

Among the good candidates is a somewhat ill-defined syndrome consisting of multiple soft neurological signs detectable in early childhood that has possible fetal or perinatal origins (Lyon, Barr, Cannon, Mednick, & Shore, 1989). Obstetrical complications, such as an unduly short gestational period, in the histories of people who later become schizophrenic are well above normative expectations (Cannon et al., 1997; Gureje, Bamidele, & Raji, 1994; Jones, Rantakallio, Hartikainen, Isohanni, & Sipila, 1998; Torrey et al., 1994), although it is possible that resultant early brain injury contributes to schizophrenic outcomes only among genetically predisposed persons (see Marcus, Hans, Auerbach, & Auerbach, 1993; Mednick et al., 1998). The identification of such a syndrome may turn out to be among the most important contribution of longitudinal high-risk research in schizophrenia. First, we examine the more general aspects of neuroanatomical factors.

The advent of modern computer-dependent technologies, such as computerized axial tomography (CAT) and nuclear magnetic resonance imaging (MRI) have made possible research on the structural properties of the brain in living subjects, and the area of schizophrenia research is no exception. The resulting—and rapidly growing—body of research supports the implication of developmental insults and the possible resultant effects on later cognitive development in the pathway to schizophrenia. The nature of this new thinking is by no means completely developed or uniformly expressed, but essentially it involves the idea that the disorder arises from variable aberrations in brain circuitry. Most forms of the idea include the hypothesis of an early, likely prenatal, insult to the brain that may have detectable neurological effects in early childhood but will not necessarily result in the later development of schizophrenia (e.g., Lyon, Barr, Cannon, Mednick, & Shore, 1989). The latter arises where the initial injury somehow interferes with normal brain synapse development during a period of intensive synaptic

reorganization; for most people, it occurs during adolescence or early adulthood. Conceivable candidates here include neuronal cell “pruning,” cell migration, and programmed cell death, all processes that occur normally during postnatal phases of brain development (see Harrison, 1999, and Weickert & Weinberger, 1998, for overviews).

Pioneering work in this area was done by Fish (1957, 1977) and by Sobel (1961), both of whom stressed that subtly compromised CNS functioning, possibly attributable to birth complications, predisposed to schizophrenia. Fish (1977) describes the pathogenic pattern as one of “neuro-integrative defect” (see Meehl, 1962, 1989, 1990), which leads to “pandepvelopmental retardation” in persons who eventually become psychiatric casualties, especially in the schizophrenia range. The notion of premorbid neurological anomalies has been demonstrated by the high-risk studies (e.g., Mednick & Schulsinger, 1968; Mednick, Schulsinger, & Schulsinger, 1975; Mednick et al., 1978), including the suggestion that obstetric complications may factor in as well. Other support has come from the Israeli high-risk study where two neurological assessments carried out 5 years apart showed that index children (offspring of schizophrenic mothers) were markedly more likely than controls to have various neurological anomalies, most of the soft variety (Marcus, Hans, Byhouwer, & Norem, 1985; Silberman & Tassone, 1985).

Ironically, early twin research made a major contribution along the line of compromising neurological events that had pernicious effects later on. Pollin, Stabenau, and Tupin (1965) intensively studied a group of monozygotic twins and their families who were discordant for schizophrenia. Because heredity is a constant in such a sample, it was hoped that thorough investigation of environmental factors that differentiated the members of the discordant pairs would unearth clues as to the causes of schizophrenia in those twins affected. In virtually every instance, the twin who was to become schizophrenic had a relatively unfavorable intrauterine environment, manifested in lower birth weight at the outset and consistent relative retardation in biological developmental milestones. A significant preponderance of soft neurological signs such as praxis difficulties, abnormal reflexes, and abortive clonus, was found in the index twins. In short, the latter were less “competent” than their co-twins over a broad range of behaviors. These indications of compromised

functioning were of sufficient magnitude to evoke noticeably differential parenting behavior and to lead to a constellation of personality characteristics best summarized as excessive submissiveness in index co-twins, possibly adding a psychosocial impediment to the biological one.

Fetuses or newborns who sustained the earlier insult, according to the developmental view, are at elevated risk for missing or misconnected circuitry that arises during cell reorganization and thus are more vulnerable to developing schizophrenia (Walker & Diforio, 1997). Such deficiencies in neural circuitry would not be directly observable by currently available methods of brain scanning. Certain research findings of recent years are consistent with this type of etiologic scenario.

The so-called "season-of-birth effect" notion is relevant here. Although there is some controversy on this issue (see Bradbury & Miller, 1985; Lewis, 1989a,b, 1990; Lewis & Griffin, 1981), it has been documented and is largely accepted that people who become schizophrenic are more likely than people in general to have been born in winter and early spring months—about an 8% elevation (DeLisi, Crow, & Hirsch, 1986a). This peculiar observation, although possibly open to dispute on the grounds of statistical artifact (see Lewis, 1990), has given rise to a variety of hypotheses including the question of compromised brain integrity in schizophrenia, an idea suggested early by Bradbury and Miller (1985). Accumulating evidence supports these possibilities. For example, Wright, Takei, Rifkin, and Murray (1995) found that maternal influenza in the second trimester of pregnancy is associated with impaired fetal growth, enhanced obstetrical complications, and later-developing schizophrenia. Several studies have suggested that, historically, influenza epidemics are associated at a higher than chance level with the gestation periods of fetuses who later become schizophrenic. The latest of these studies reported by Takei and colleagues (1996) identifies the supposedly critical peak infectious period as the fifth gestational month. Here, risk of influenza exposure in the critical period was associated with enlarged ventricles and sulci among a group of eighty-three schizophrenic patients, relative to controls. Seemingly important and possibly related findings, reported by Torrey and colleagues (1993), establish a strong correlation between the occurrence of stillbirths and schizophrenia risk, presumably some infectious agent; in one of the

cases, according to this hypothesis, it leads to death of the fetus, and in the other to brain changes that enhance vulnerability to schizophrenia.

More recent work using the Finnish registry also demonstrated a relationship between prenatal exposure to polio virus infection during the second trimester and the later development of schizophrenia (Suvisaari, Haukka, Tanskanen, Hovi, & Lonnqvist, 1999). The idea of a virus causing schizophrenia is not new, and simply taken as that, lacks explanatory power in and of itself. However, the relationship between a viral compromise and the subsequent chain of effects in the course of development that might be initiated is something that we find more plausible. On the other hand, work by LaMantia (1999) points to the possible importance of an early insult during the third trimester of pregnancy. This approach focuses on the way the genetic code might be derailed as it unfolds while directing the development of brain areas, including the basal ganglia and hippocampus demonstrated as deficient in schizophrenia.

Despite the promise of findings in this area, it is incumbent on us to conclude this section with a cautionary note. The wealth of findings in this area as an emergent pattern illustrates an impending danger in this promising area of research: Without a clear theory on the way that these neurological insults affect the developmental processes in a manner that relates to identified pathophysiological processes and eventually to the expressed behavior of a taxonomic entity, it is likely that these findings will be merely added to many documented associations with the disorder and will add no real insight to the etiology.

Traumatizing Events

Clinicians who expend the energy and patience necessary to fully understand the developmental background of schizophrenic persons—and, regrettably, not all are willing to do so—usually come away with a powerful impression of traumatizing life circumstances. Perhaps one of the most stark illustrations of madness and associated horrors concerns the Genain quadruplets, all of whom became schizophrenic (Rosenthal, 1963). All four of these monozygotic sisters acquired the diagnosis before age 25. Though the remarkable concordance might suggest the operation of a genetic pathogen, we choose to mention it here be-

cause the sisters were raised in a family context characterized by parental madness of outlandish proportions (e.g., clitoral circumcisions to curb childhood masturbation). Their disorders, moreover, were quite different in respect to course, severity, and relative intractableness, characteristics that in turn were strongly correlated (in the expected direction) with the degree of exposure to pathological parenting. Despite stark clinical examples such as found in the Genain sisters, the yield from studies that compare the backgrounds of schizophrenics and suitable controls has been rather unimpressive in identifying discrete circumstances that differentiate schizophrenics as a group who had particular traumatic experiences while growing up. Perhaps this is another case in which “bad luck” (see Meehl, 1989) such as the occurrence of trauma in particular patterns, sequences, or at key times in development, is more important than the actual events themselves. In any event, we call attention to how little we have to report in this area.

In an early study, Schofield and Balian (1959) compared life history data of 178 schizophrenics with those of a carefully matched normal control group. For even the few significant differences found in the variables that one might assume are critical, the most striking finding was the very considerable overlap of the two groups. Indeed, for the variables of sexual adjustment and “adequacy of sexual outlet,” the backgrounds of schizophrenics were significantly superior to those of controls—certainly not the most expected of findings. Some other results, such as excessive maternal overprotection and domination among preschizophrenics, were more consistent with expectations, but again the large majority of schizophrenic persons had normally affectionate relationships with their mothers. The high frequency of supposedly pathogenic circumstances in the backgrounds of their *normal* subjects led these investigators to suggest the need to study the “immunizing” experiences that may have permitted them to overcome their noxious environments. Although we think that the latter is a good idea, the results of the study are equally consistent with the notion that growing up is normatively hard and that preschizophrenic subjects are somehow excessively vulnerable to its vicissitudes.

Schofield and Balian (1959) included assessments of parental loss through separation, divorces, or death in their schedule but failed to find

this a variable that differentiated their groups. In contrast, Roff and Knight (1981), in the retrospective but nonreactive study described before, did find that parental loss before age 7 was associated with poor outcomes among persons diagnosed as schizophrenic. Similarly, in the Mednick et al. (1978) high-risk study, there was some indication that parental loss (here occasioned by maternal hospitalization) is etiologically significant.

Shifting the focus to precipitating as opposed to predisposing environmental life events in schizophrenia, we now have a fair amount of information on the evocations of schizophrenic behavior among persons who had experienced prior schizophrenic episodes. For example, Ventura, Nuechterlein, Lukoff, and Hardesty (1989), in a 1-year prospective study of remitted schizophrenics, presented strong evidence that negative events (independent of symptoms or personal actions) are associated with relapse. By far the largest body of work in this area has been concerned with familial expressed emotion as a precipitant of new episodes of schizophrenic behavior among recovered or near-recovered persons. We turn now to a brief summary of that literature.

Research on expressed emotion (EE), usually defined as a pattern of behavior involving both high intrusiveness and high levels of criticism directed toward the former patient, began in England (Vaughn & Leff, 1976, 1981) and was in due course transported to the United States (Hooley, 1985; Vaughn, Snyder, Jones, Freeman, & Falloon, 1984; Butzlaff & Hooley, 1998; Hooley & Hiller, 1998; Linszen et al., 1997; Miklowitz, Goldstein, & Falloon, 1983). At this point, there can be no doubt that it is associated with rehospitalization of schizophrenia; it occurs in conjunction with familial communication deviance (Doane, Falloon, Goldstein, & Mintz, 1985; Miklowitz, Strachan, Goldstein, Doane, & Snyder, 1986), and its reduction is associated with relapse prevention (Falloon, Boyd, McGill, Williamson, & Razani, 1985; Hogarty, Anderson, Reiss, Kornblith, & Greenwald, 1986). There remains, however, some question of the direction of the effect (i.e., the more disturbed the former patient, the more likely is rehospitalization, *and* the more provocation of EE in family members). Basically, this argument was made by Parker, Johnston, and Hayward (1988), who presented evidence that EE was significantly associated with a poor posthospital course only in one-parent households, where the

impact of disturbed behavior would be maximally likely to lead to high EE.

However, this construction is inconsistent with data from the UCLA high-risk study indicating that high family EE (in association with other variables already mentioned) *predicts* schizophrenia spectrum disorders that have their onset much later (Goldstein, 1985), suggesting a causal role in the relapse process (Nuechterlein, Snyder, & Mintz, 1992). Given that attempts to reduce EE and associated behaviors in family members have been very impressive in relapse prevention (e.g., Falloon et al., 1985; Hogarty, Anderson, Reiss, Kornblith, & Greenwald, 1986; Leff, Kuipers, Berkowitz, & Sturgeon, 1982; McFarlane et al., 1995), the time has come to gain a fuller understanding of these processes, as Hooley & Hiller (1998) suggest.

Aberrations in Pathophysiology

Pathophysiology represents the favored model for an attempted integrative view of the interaction of biochemical, biological, and genetic findings relating to the supposed disease processes of schizophrenia. The history here is characterized by a multitude of hypotheses. The earlier ones involved the idea of autointoxication by substances, sometimes unknown and exotic ones (e.g., “taraxein”; Heath, Martens, Leach, Cohen, & Angel, 1957). The idea of a single, pathognomic agent is now for the most part duly recognized as extremely unlikely, given the complexities of such processes, and so we would assume that the days of searching for a single causative agent are over. The current tack usually entails an “integrative approach” that emphasizes the interplay of different neural systems, which is pretty much the only way to account for the massive and sometimes seemingly contradictory array of findings. Despite these presumably well-accepted cautions, however, a tendency to focus on a specific area as causative of the disorder remains. Along these lines, the dopamine (DA) hypothesis has occupied the attention of researchers for the longest period of time. There has also been some emphasis on neurons that are rich in gamma-aminobutyric acid (GABA) that, it is thought, mediate dopaminergic functioning. With the advent of the “atypical” antipsychotics, there has also been renewed interest in research on the serotonergic mechanisms. It also appears that the latter interacts with at least

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some aspects of the dopaminergic system. The often disregarded caveat here is that a therapeutic role does not imply etiology (Harrison & Burnet, 1997).

Receptor-Site Theories. Hypotheses related to various receptor sites in the brain have been proposed primarily on the basis that therein lies the site of action for drugs used to treat schizophrenia. Among them is the dopamine hypothesis (e.g., Meltzer & Stahl, 1976) that has sustained the longest period of empirical attention. For interested readers, the lengthy history of this hypothesis is revealed in some detail in an earlier edition of this chapter (Carson, 1984). The basic etiologic hypothesis is that schizophrenia is the product of excess activity in dopaminergic brain pathways, caused by either increased levels of dopamine or by increased sensitivity of the receptor sites. The evidence supporting this hypothesis rests mainly on the observation that the original antipsychotic drugs used to alleviate symptoms of schizophrenia are dopamine antagonists (Creese, Burt, & Snyder, 1976; Seeman, Lee, Chau-Wong, & Wong, 1976). Of the several DA neuronal tracts known to exist in the brain, probably the most attention has been focused on one that originates in the mesencephalon and terminates in the limbic system (hence called the *mesolimbic* tract). In fact, however, the site of action of therapeutic DA blockade—if that is the principal mechanism involved in symptom moderation with neuroleptics—has not yet been precisely determined. It is likely that DA in some way plays a role in schizophrenia, as is the case of other receptor-site theories, but its causal significance is far from clear (Davis, Kahn, Ko, & Davidson, 1991; Joyce & Meador-Woodruff, 1997; Seeman, 1987).

Several basic and well-identified problems with the dopamine hypothesis persist, and it is curious that adherents are reluctant to relinquish the DA hypothesis despite these problems. First, dopamine-blocking drugs are by no means specific for schizophrenia, and their use to treat other psychotic and neuropsychological disorders, affective disorders including mania, and severe personality disorders is relatively commonplace. Second, it has been known for years that the dopamine receptor blocking effect occurs within hours of administering the drug; however, clinical effects do not emerge in some cases for several weeks. Further, the therapeutic effect is obtained not by achieving “normal” levels of dopamine functioning, but at rather

abnormally low levels, as evidenced by the correlation of clinical outcome with symptoms of Parkinsonism and more seriously of tardive dyskinesia. Finally, the newer “atypical” neuroleptics exert their symptom-alleviating effects in a wholly different manner, suggesting that the dopamine system plays a complex role in multifaceted sequencing of neurochemical events associated with the expression of schizophrenic psychopathology. Overall, these problems suggest that what is known about the involvement of dopaminergic systems only partially reveals its place in the mechanism of schizophrenia.

Increasing complexities have been discovered regarding DA receptor sites. Snyder, Burt, and Creese (1976) first proposed the idea of two types of dopamine receptors in the brain, now indexed as D₁ and D₂. D₁ receptors stimulate production of the enzyme adenylate cyclase, implicated in the enhancement of cell responsivity, whereas D₂ receptors inhibit adenylate cyclase production. The “blocking” effects of neuroleptics, it is now thought, involve binding to the D₂ site, thereby in some manner inhibiting DA neurotransmission, possibly by preventing transmitter binding on the D₁ site or by a more direct route of inhibiting adenylate cyclase. These DA receptors can exhibit different states of high and low affinity for the reception of neurotransmitters. The dual and bidirectional high–low conversion represents another puzzling variable in the DA regulatory process. The discovery of dopamine receptor subtypes did not stop there. In 1990, a D₃ receptor site was identified (Sokoloff, Giros, Martres, Bouthenet, & Schwartz, 1990), and, at this time, no fewer than five dopamine receptor sites have been identified (D₁ to D₅).

Another source of complexity in the dopamine hypothesis concerns locations of the dopamine neurotransmitter systems. Dopamine is pervasive throughout several different areas of the brain. One study found a decrease—not an increase—in dopamine D₁ receptors in the prefrontal cortex of those diagnosed schizophrenic and suggested that this might explain some of the cognitive impairment of the disorder (Okubo et al., 1997). The anterior cingulate cortex, which plays a role in the function of attentional processes, is another area where pathological neuroprocesses associated with dopamine have been investigated. Several studies have implicated the cingulate cortex in schizophrenia psychopathology (e.g., Andreasen,

Paradiso, & O’Leary, 1998; Tamminga et al., 1992).

There is some evidence that the dopamine systems of schizophrenics are fundamentally different. Using challenge methodology, the demonstration of abnormal reactivity of dopaminergic transmission in response to amphetamine in schizophrenic patients appears robust (Abi-Dargham et al., 1998; Breier et al., 1997). However, it has also been suggested that a more accurate model of schizophrenic-like psychosis is gleaned from the more specific action of phenylcyclohexylpiperidine (PCP), a drug that effects the channel that down-modulates glutamatergic processes. It is believed that PCP, which can induce psychotic-like states in normal individuals that last up to three or four hours, can, in schizophrenics, unleash much longer periods of psychosis by virtue of lack of a means to turn the system off (Grace & Moore, 1998).

In one study, subjects were administered a non-selective dopamine agonist, apomorphine, or placebo, and then performed a verbal cognitive task. PET scans were then obtained for two groups—schizophrenic and controls. In schizophrenic patients but not controls, administration of apomorphine enhanced cognitive activation of the cingulate cortex during the verbal task. The results provided *in vivo* evidence that an impaired cognitive-task-induced activation of the anterior cingulate cortex in schizophrenic patients can be modulated by dopaminergic manipulation (Dolan et al., 1995). By studying the interaction of manipulating the dopaminergic system with a verbal task and the effects of the activity of a specific brain area, the authors were able to demonstrate a *systemic* difference in schizophrenic patients. Rather than enabling conclusions in terms of etiology, such an approach begins to recognize the complexity and importantly attempts to bridge mind (i.e., verbal task) with body (i.e., cingulate cortex activation). Still, no doubt, there are many missing pieces to this puzzle.

The “atypical” antipsychotic drugs (e.g., clozapine, olanzapine, risperidone) further complicate the dopamine puzzle. So-called “atypical” because they do not produce the side effects associated with the traditional neuroleptic medications, notably, tardive dyskinesia, these drugs, it is assumed do not impact the same dopamine receptor sites as the traditional ones. However, the demonstration by Nyberg & Farde (1997) estimated that extrapyramidal symptoms (EPS) are not evident

until approximately 80% of the D₂ receptor sites are occupied. In other words, it may be that the new antipsychotic medications exert a clinical effect before the number of D₂ receptor sites required for extrapyramidal symptoms have been affected.

Unfortunately for the dopamine theory, these newer drugs are apparently just as effective as the older neuroleptics, although the more dangerous of these (clozapine) is reserved for those who do not respond to the more traditional drugs. Perhaps due to a desire to preserve the potential for the dopamine hypothesis, it is sometimes concluded that patients who do not respond to the traditional antipsychotics represent a subgroup of schizophrenics who have a variant dopamine pathology. However, Valenstein (1998) has pointed out the inconsistency of this line of reasoning because those patients who do respond to traditional neuroleptics respond to the atypicals as well.

It is clear that the newer antipsychotic medications that exert their effects primarily in systems other than the dopamine system pose particular problems for the dopamine hypothesis. The "atypical" antipsychotics, olanzapine and risperidone, primarily affect serotonergic receptors by decreasing transmission activity, in particular, the subtype receptors that have been labeled "5-HT₂." Interestingly, it is believed that these receptors sites are where LSD exerts its hallucinogenic properties (Pierce & Peroutka, 1989; Wing et al., 1990).

Of the atypicals, clozapine is a bit of an anomaly because of its far-reaching and varied effects. Clozapine affects the dopamine system as well as the serotonergic system, and also a wide range of other receptor types (Nyberg & Farde, 1997). There is evidence that clozapine achieves its effects through D₄-mediated GABA modulation (Bergson et al., 1995). GABAergic neural systems are another area that, it is thought, plays a role in schizophrenia based on evidence from postmortem and functional imaging studies that demonstrated abnormalities (Akbarian et al., 1995; Benes, Vincent, Alsterberg, Bird, & SanGiovanni, 1992; Busatto et al., 1996; Meltzer, 1994). Further complicating matters, it appears that 5-HT₂ receptors have a role in controlling GABAergic neurons (Harrison & Burnet, 1997).

In connecting these systems to behavioral output, there is no more specificity, although some brain areas have been broadly related to either negative (e.g., amygdala) or positive (e.g., the prefrontal

cortex) symptoms, mainly on the grounds of speculative reasoning. The serotonergic systems are related to affect, cognition, motor behavior, hormonal, sleep, and body temperature regulation (Cowen, 1991; Stephenson, 1990). Clearly, dopamine and serotonergic systems play critical roles in the schizophrenic process, but where they fall in the cascade of events that undergird the classic psychotic and thought-disordered clinical picture is much less clear (Nyberg and Farde, 1997). It may be that role of neurochemicals will have to include other influences, such as the aberration of neural circuitry, before the role of biochemical abnormalities will more completely elucidate the schizophrenic process. In any event, the limitations of psychopharmacological technology are not unlike those of some forms of cancer treatment, where cellular production of all types, not just cancerous cell growth, is stopped by some chemical interventions and produces well-known iatrogenic effects, an accepted cost given the present limitations of treatment in this area. Similarly, psychotropic drugs used to treat schizophrenia have far-reaching effects such as tardive dyskinesia.

Although perhaps painting too optimistic a picture, Nestler (1997) clearly recognizes this in emphasizing that pinning schizophrenia on a simple increase or decrease of a neurotransmitter is unlikely to pan out and that some sort of integration of brain structures and the various pathways and systems connecting them will be implicated in the emergent etiology of the disorder. Impressive work done by Grace and Moore (1998) makes a comprehensive attempt along these lines. Noting that the nucleus accumbens demonstrates a functional interdependence of the various brain areas that have been implicated in schizophrenia (e.g., the prefrontal cortex, amygdala, and hippocampus), they developed a model of pathophysiology that focuses on the *regulatory* aspects of this brain area on the other areas. Although speculative, they go on to suggest that the development of the various brain systems (including the physiological mechanisms) may be impacted by aberrant processes in the nucleus accumbens. Such an approach takes into account the interrelationships of the various systems, but we suspect that there will be limitations in the knowledge that will be acquired. Specifically, the idea persists that there is a *localized* dysfunctional brain area ostensibly responsible for the dysfunction in other brain areas (i.e., the nucleus accumbens). Simply put, there is

no a priori reason to necessarily assume a single causative agent that leads to the malfunction.

Biology and Disease Commentary. The idea that “chemical imbalances” in the brain cause serious mental disorder is for some reason an appealing proposition these days. Perhaps the complexity of these physiological processes in some way eludes careful scrutiny by those most involved with the *behavioral* pathology of the disorder. Yet the disease metaphor persists largely based on evidence that has been obtained in a sort of backward fashion. The essential strategy, now commonplace for more than a decade, has been to implicate sites in the brain known to be affected by drugs that are employed to attempt treatment of the disorder. More sophisticated approaches are being attempted with the recognition that multiple brain systems interact *as part of the pathological process*. However, the idea that there is a primary pathological factor or site in the brain persists, even in the most sophisticated of models such as that described before by Grace and Moore (1998). Focusing attention on the nodal areas where the other brain areas connect to each other is a reasonable idea, but it is still driven by the idea that there is a *single, fundamental causative agent* (or area) in the brain that is responsible for the disorder. At the present level of knowledge, such a reductionistic approach is quite possibly an unwarranted step—at least as far as etiology is implied. Observations of brain pathology are merely another level of clinical description. As such, they are important and valid descriptions, but for some reason it seems that they are accorded causal status.

We would not suggest that results from such studies are not worth pursuing, especially in the context of a richly developed theory such as that by Grace and Moore (1998). Indeed, this level of information will be a vital piece of the schizophrenia puzzle. Those models which acknowledge the complexities of interaction in brain systems in the *process* of the disorder will be especially important. For all the pieces to fall into place, however, will require relating these systems to behavioral output, and doing so will require consideration in the developmental context. Importantly, the idea of identifying a primary lesion may be one the field is ready to discard. The unfolding development of these systems, and the accompanying events (molecular and otherwise) will be key to developing an understanding of the etiology of the disorder. Our main contention here is that

brain pathology should not be accorded status above clinical description for its explanatory power. Perhaps the results of the varied attempts to treat schizophrenia can serve as a reference point for integrating the molar aspects of the disorder.

Treatment Perspectives

We cannot attempt here to approach adequately a comprehensive review of research on the treatments and outcomes of schizophrenic disorders. Therefore, we will limit our review here to treatments of historical significance and to those treatments that will hopefully provide some insight into the schizophrenia phenomena. We will be brief with—roughly speaking—the two classes of therapies: the biological approaches because we leave it to the others who present the biological view to provide a comprehensive overview, and the psychosocial therapies because, quite plainly, there is not a lot to report. The essence of our focus is also intended to shed light on the fundamental nature of the psychopathology involved. Before proceeding, we call upon the reader to reflect for a moment that schizophrenia has been a disorder, more so than any other mental disorder, that has consistently *required* multiple levels of intervention.

Biological Approaches

With the widespread introduction of the phenothiazine drugs, beginning with chlorpromazine, in the mid-1950s, the more drastic forms of biological intervention underwent a rapid decline in use. Psychosurgery, hydrotherapy, and insulin coma, all of them once fairly routinely employed, are for the most part rarely considered today for any form of mental disorder. Electroconvulsive therapy (ECT), still widely used to treat severe mood disorders and once a mainstay of “therapy” for schizophrenia to the point of abuse (e.g., “regressive” ECT involving multiple administrations per day), is now regarded at best as an improbably useful last resort for schizophrenic patients whose disorders have proven persistently refractory to other therapeutic measures, although there is some evidence to suggest that the threshold for this approach may be relaxing somewhat (e.g., Fink & Sackeim, 1996; Kales, Dequardo, & Tandon, 1999). The fact that these appallingly primitive

techniques were still in widespread use only a generation ago speaks to the desperate level to which psychiatry had fallen immediately before the present era of neuroleptics. What sometimes seems to outsiders as an excessive attachment to these drugs among many psychiatric practitioners may be more understandable when viewed in this light.

Nevertheless, that attachment—insofar as it involves a sense of delivery from helplessness by the advent of the neuroleptic era—may be misplaced to some extent. Notwithstanding the seemingly unrestrained advertising claims of pharmaceutical companies about the role of their products in bringing about an alleged mental health revolution, many forces other than the availability of neuroleptics were in operation by the 1950s that were helping to modify views about the hopelessness of severe mental disorders and therefore to transform the previously wretched and iatrogenic environment of the average mental hospital. These positive attitudinal changes were doubtless aided and accelerated by the new drug therapies, but we do not know that they would not have happened anyway.

A look at resident schizophrenic population figures of state and county mental hospitals for the period under consideration is instructive in regard to the general point we are making here. These figures, assembled by Mosher (1989) from data gathered by the National Institute of Mental Health, show that the national peak for resident schizophrenic patients in public hospitals was reached in 1960–1961 at about 269,000. This was 5 years after neuroleptics became readily available and 2 to 3 years after their use had become practically universal, clearly demonstrating that the turnaround from ever-increasing resident schizophrenic hospital populations was not primarily attributable, as is commonly supposed, to the direct clinical effects of these drugs but rather to some other factor or factors. The drop in hospital populations remained modest until 1963, the year when the federal Community Mental Health Centers Act was passed. Thereafter, the rate of decline accelerated dramatically, a trend Mosher attributes primarily to continuing federal legislation (e.g., extension of Social Security benefits to the young mentally disabled) that made community living for the seriously disturbed an increasingly feasible alternative. He points out, interestingly, that in western European countries, with equal

access to neuroleptics but with the pertinent social legislation already in place, the sharp decline during the 1960s in hospital residency for schizophrenia did not occur.

There is no denying the relief that can be brought about by neuroleptics—for both the patient and the doctor. Anyone who had seen a mental ward before neuroleptics were introduced can attest to the apparent inhumanity and suffering. But any patient will clearly inform you that the humanity is not fully restored, and the suffering is not fully relieved by drug treatment. Why else would medication compliance be such a preponderant issue in the treatment of schizophrenia? To be clear, drug bashing is not our intent. However, reservations that run counter to the widespread enthusiasm for this type of intervention need to be voiced, especially when some psychologist colleagues want prescription writing privileges. Viewed objectively, the actual record of accomplishment for neuroleptic intervention in schizophrenia is quite modest, especially where unpredictable, serious, and intractable side effects like tardive dyskinesia are factored in.

We have become accustomed in recent years to looking seriously at the results of meta-analytic studies in trying to assess treatment effectiveness. Though it has been largely overlooked in relation to schizophrenia, the original Smith, Glass, and Miller (1980) meta-analysis of the benefits of various therapies for various diagnostic groups included an assessment of drug therapy for schizophrenia. The drugs-alone average effect size (essentially the mean magnitude of the treated group's deviation from the mean of the control group, in control-group standard deviation units) in this assessment was +0.51, a figure that is decidedly on the low side for the many effect sizes reported in this remarkable work. Its basic statistical meaning is that the average functionability (as variously assessed) of exclusively drug-treated schizophrenics was at approximately the 70th percentile of that of untreated controls. By comparison, the average effect size for psychosocial interventions with "psychotics" was +0.68 (75th percentile of controls), whereas the drug-plus-psychotherapy combination for schizophrenia resulted in a very respectable average effect size of +0.80 (79th percentile).

Although these figures on the effectiveness of standard drug treatments in schizophrenia are sobering when viewed against the backdrop that they

are often the only treatment offered, they do not convey to a full extent the limitations of an exclusively pharmacological approach. These limitations reside in the virtually complete ineffectiveness of these compounds in enhancing those energies, awarenesses, and skills that form the basis for effective engagement of the social environment, a vital set of personal resources that are strikingly deficient in the behavioral repertoires of the large majority of persons who acquire the schizophrenia designation. Consider in this regard the following remarks of the distinguished Harvard social psychologist Roger Brown, reported on his attendance at a local meeting of Schizophrenics Anonymous:

[The group leader] began with an optimistic testimony about how things were going with him, designed in part to buck up the others. Some of them also spoke hopefully; others were silent and stared at the floor throughout. I gradually felt hope draining out of the group as they began to talk of their inability to hold jobs, of living on welfare, of finding themselves overwhelmed by simple demands. Nothing bizarre was said or done; there was rather a pervasive sense of inadequacy, of lives in which each day was a dreadful trial. Doughnuts and coffee were served, and then each one, still alone, trailed off into the Cambridge night.

What I saw a little of at that meeting of Schizophrenics Anonymous is simply that there is something about schizophrenia that the antipsychotic drugs do not cure or even always remit on a long-term basis. (Brown & Herrnstein, 1977, p. 641)

Brown's observations remind us that perceptive and articulate "laypersons" can often tell simple truths about mental patients in a way that jaded mental health professionals often cannot. We question only his circumspection in suggesting that the antipsychotics "do not ... always remit" the devastating social deficits that normally accompany schizophrenic disorders. We hold that they probably *never* do, and that it is unreasonable to expect that they, or any other currently conceivable drug, might have such an effect. In this sense, we see the pharmacological approach limited indefinitely to a merely palliative role in therapies for schizophrenias. The empirical evidence indicates that long-term rates of *social* recovery in schizophrenia have not improved since the advent of neuroleptic drugs (e.g., Harding, Brooks, Ashikaga, Strauss, & Breier, 1987a,b). The ambitious study by Hegarty and colleagues (1994) mentioned earlier provides compelling evidence. Moreover, a smaller scale but similar study by Warner (1994) confirms the main findings reported by Hegarty and colleagues. It seems obvious to us that our

profession is going to have to look elsewhere for the "cure" to this type of problem.

On a more optimistic note, the disappointing performance of the antipsychotic drugs in the study described relate only to the older "typical" compounds such as chlorpromazine and haloperidol, and may conceivably be overcome with further advances in pharmacological therapy. Sheitman et al. (1998) identify a number of newer "atypical" antipsychotics in various stages of development and use; any of them might produce a better record in terms of social recovery. A primary advantage of the atypical antipsychotic medications is that they are less pernicious in side effects, supporting the hypothesis that the iatrogenic effects of older psychotropic medications may play a role in limiting social recovery. In any event, these newer compounds have yet to be thoroughly evaluated along these lines.

Psychotherapies of Schizophrenia

Perhaps as a backlash to the days of the "double-bind" and other family approaches that resulted in uncalled for parent bashing and undoubtedly owing some influence to the recent "decade of the brain" that included a heavy emphasis on biologically based research at the National Institutes of Mental Health, there has been a very serious dearth of psychosocial research in schizophrenia. It should not go unnoticed that earlier forms of psychotherapy did not position themselves well in being subjected to empirical evaluation, and this inadequacy likely set the stage for the so-called biological revolution. So dominant became the latter that some extremely promising alternative approaches that appeared in the decades before the 1990s were quite simply ignored by the majority of the professional mental health community. These examples include a therapeutic community-based program of "self-help" for patients moved from the hospital to a commercially failed motel with minimal professional oversight (Fairweather, 1980; Fairweather, Sanders, Maynard, & Cressler, 1969), and a rigorous token economy "social learning" program for chronic state hospital patients (Paul & Lentz, 1977). There was also the report of a well-designed study that demonstrated the superiority of specialized individualized psychotherapy conducted by highly experienced therapists to antipsychotic medication in treating schizophrenia (Karon & Vandenbos, 1981). These studies produced ex-

citing results in patient progress without, for the most part, extensive use of medication. The randomized clinical trial (RCT), ironically borrowed from the medical field concerned with pharmacological efficacy and now a mainstay of psychotherapy research, allowed a more recent examination of the efficacy of some very specific forms of psychotherapeutic intervention for schizophrenia. We now review the various psychotherapies.

“Moral” and Milieu. Such “active” (as opposed to prophylactic or maintenance) treatment as occurs in cases of schizophrenia is probably most often conducted in inpatient settings. Even where drugs are the primary mode of intervention, therefore, it is important to ask whether the psychosocial context or milieu of the hospital or ward has any therapeutic significance. A variety of evidence indicates that it does, beginning with the apparently pronounced successes of “moral” (i.e., psychosocial milieu) therapy asylums during the earliest decades of this country’s founding.

The era of moral therapy in the United States lasted only roughly through the first half of the nineteenth century, following which it succumbed to paradigmatic social, cultural, and population changes (e.g., a huge influx of non-English speaking immigrants) that, during the subsequent century, produced the disgraceful, overcrowded, “snake-pit” conditions of public mental hospitals of the 1940s and 1950s. The rates of hospital discharge of persons suffering serious mental disorders fell precipitously during that period and resulted in the accumulation of “chronic” cases, most of them doubtless schizophrenic, in the human warehouses that mental hospitals had become. According to the old hospital records unearthed by Brockoven (1972), mental health professionals ironically had done a much better job *before* 1850, lacking as they did access to the subsequent dramatic but evidently largely irrelevant advances in biomedical science that were shortly to begin. In fact, general adoption, for all mental disorders, of the organic model suggested by general paresis, whose connection with syphilis was discovered in 1857, probably contributed significantly to the demise of the moral therapy movement.

The idea that effective treatment of schizophrenic persons should include the planned creation of a benign psychosocial environment surfaced again in the late 1920s with the establishment by Harry Stack Sullivan (1962) of a special ward at the Sheppard and Enoch Pratt Hospital for treating

young schizophrenic males. In all probability, Sullivan himself had earlier had some sort of brief personal experience with this type of disorder (see Alexander, 1990, for a detailed examination of this possibility). Whatever the case, he had some insights not widely shared among his professional peers. Revolutionary for its time, this small ward was run with tight control by Sullivan (e.g., he personally selected and trained the nursing attendant staff), and in due course it achieved considerable fame for its innovative philosophy and for the therapeutic results achieved. It was one of the factors that first catapulted Sullivan into a position of prominence in American psychiatry (Chapman, 1976). Unfortunately, few hospital directors were willing to follow his lead in treating schizophrenia, and his influence in this respect seems to have been confined chiefly to the local area around Baltimore, notably including the famed Chestnut Lodge in Rockville.

The notion of milieu therapy (alternatively, therapeutic community) did not really catch on again until approximately the 1950s, undoubtedly aided, as we have seen, by the advent of neuroleptic drugs. Subsequently, the record it compiled (reviewed by Mosher & Gunderson, 1979; Neale & Oltmanns, 1980) may be termed encouraging, although the results achieved are, of course, strongly confounded with drug effects in most settings. In one remarkable study, that of Paul and Lentz (1977), they are not; in these authors’ exceptionally well-controlled experiment, chronic patients treated with milieu therapy (in comparison to those who received standard hospital care) fared much better in outcome measures such as release to the community. We shall return to this study shortly in the following section to consider the behavioral aspects employed. In a later report, Mosher and colleagues described the “Soteria Project” and reported the results of milieu treatment, in most cases without neuroleptics that were on a par with treatment as usual for acute psychotic episodes (Mosher, Vallone, & Menn, 1995).

The beneficial effects of a psychologically wholesome milieu for chronically schizophrenic patients can apparently be gained even without hospital confinement. Fairweather and colleagues (1969) with consummate boldness, moved a substantial group of such patients out of the hospital into a commercially defunct motel (“The Lodge”) where, after a brief orientation period, the latter were left for the most part on their own with only

minimal supervision or medical coverage. The guiding principle was that of self-help. Contrary to the dire predictions many made, after a somewhat rough start, this small society began to organize itself, established a division of labor, and created various other formal arrangements essential to social living. Within a surprisingly short time, it became a truly viable and for the most part sustaining community. In due course, in fact, these “psychotic” citizens established a profitable janitorial and landscaping business! The patient cost per day to the state of California dropped to a fraction of what it had been, although that is perhaps the least of the benefits realized.

The Lodge project was eventually terminated formally, although the expatient community successfully continued on. Despite the evident promise of this approach and the considerable efforts of Fairweather and his associates to promote its consideration on a national scale, the path proved difficult (Fairweather, 1980). Although a few similar projects have been undertaken at scattered locations with comparably impressive results, support in official state or local government budgeting has been rare, as have enthusiastic expressions of interest among members of the traditional mental health disciplines. Why? We can only conjecture that this innovative concept ran so thoroughly counter to institutional bureaucracy and the prevailing professional zeitgeist that it was the victim of a destructive type of cognitive inflexibility or (more sinisterly) of political assassination. Obviously, it still deserves a serious, comprehensive, and extended trial.

Behavioral. A similar fate overtook the extraordinarily promising “social learning” program that was part of the large Paul and Lentz (1977) project mentioned before. In this treatment condition, patients were subjected to a closely monitored and continuous token economy, one whose contingencies were unusually rigorous both in behavioral expectations and the range of reinforcements meted out as a consequence of good or substandard patient performance (token acquisition). The outcomes for patients in this program exceeded by a considerable margin the very respectable ones achieved with milieu therapy (which, as noted, were notably superior to standard hospital care), again without significant contribution from drugs. Of a control-matched sample of these chronic patients, 11% achieved wholly independent functioning without readmission during the course of a 4½-

year follow up, whereas 96% of them managed continuous community living for at least 90 days. As we have learned to expect, there was modest postdischarge behavioral deterioration for many of these patients, but nondrug aftercare services were generally effective in reversing this trend. We are baffled by the practically uniform absence of response to these challenging findings—for example, among state mental health authorities—over the years since their original publication.

Although we have yet to see the potential realized in bold and imaginative therapeutic programs, our own conviction is that the real promise of behavioral intervention in schizophrenia resides in the programmed establishment (reestablishment?) of those skills essential to independent adult functioning in an increasingly demanding and complex social environment. As pointed out by Bellack, Morrison, and Mueser (1989), a dearth of significant progress in this area is attributable at least in part to misdirected effort and a related failure to analyze adequately the tasks to be accomplished. The deficits that need to be addressed, for example, are in the main at a more basic level than “problems solving.”

Family. As in other areas of psychosocial intervention in schizophrenia, research in family therapy has waned substantially in recent years, although its past record is quite respectable (Mosher & Gunderson, 1979). Our reading of the etiologic evidence is that the neglect is a very serious mistake. The primary exception to the pervasive inactivity in family therapy concerns work on the reduction of EE to prevent relapse among persons who have already had one or more hospital admissions. Not surprisingly, such interventions appear quite promising (Faloon et al., 1985; Hogarty et al., 1986). There is some suggestion that intervention to reduce EE may make it feasible to reduce neuroleptic drug dosages, with attendant benefits in instrumental and social role functioning (Hogarty et al., 1988), not to mention reducing the risk of tardive dyskinesia. Family therapy would be an excellent medium for identifying instances of EE and for teaching family members how to avoid it (Tarrier & Barrowclough, 1990).

Individual. Though the work of several gifted psychotherapists of schizophrenics, such as Sullivan, Freida Fromm-Reichmann (1950), Green (1964), and John Rosen (1953) is an important part of the history of the field, it must be acknowledged that we lack good data on long-term outcomes for

the patients that they treated. The bases for their short-term success are also obscure, although in various writings each of these individuals articulated the principles that supposedly guided their interventions. Because the “principles” are not readily transmitted to others with the assurance of comparable results, our suspicion is that the critical element in each instance was some combination of personality factors that made for facile communication with psychotic persons. Conceivably, they are factors that share some commonality with those identified by Whitehorn and Betz (1954) in isolating a group of psychiatric residents who achieved excellent results in work with schizophrenic patients in the years before neuroleptic drugs washed out the effect.

In the not so distant past, Karon and Vandenbos (1981) published a book on the psychotherapy of schizophrenia which they unabashedly subtitled “The Treatment of Choice.” The recommended techniques, ample and fascinatingly illustrated, bear the unmistakable impress of John Rosen. The book ends with a complete report of a research project designed to compare the outcomes of psychotherapy administered by “experienced” and less experienced therapists, neuroleptic drug treatment, and a combination of the two for thirty-three randomly treatment-assigned patients during an effective project period (including follow-up) of 44 months. The multiple-outcome-measure results (which include rehospitalization data) are thoroughly analyzed and discussed. In summary, they showed a strong superiority in the long-term outcomes for the psychotherapy-only treatment group. The drug-plus-psychotherapy group had outcomes only slightly superior to the drug-only group, an effect the authors ascribe chiefly to drug-induced interference with the psychotherapy process.

The report just described also includes a valuable discussion and critique of earlier and probably better known comparative treatment projects of this general type, to which the interested reader is referred (they are omitted here because of space considerations). Overall, the results of these projects are less favorable to the psychotherapeutic approach in schizophrenia than those reported by Karon and Vandenbos (1981), although more encouraging than some secondary reviews have portrayed them. There is a persistent tendency in this literature, by the way, not to recognize the multiple ways in which drug treatment and psycho-

therapy differ that make direct, competitive comparisons of the two more problematic than superficial analysis would suggest. An excellent discussion of some of these considerations was offered by Stiles and Shapiro (1989).

It is striking how relatively little current research on the individual psychotherapy of schizophrenic persons is currently underway, compared to other treatments (i.e., biological) or other disorders. One wonders whether the impact of negative opinions about psychotherapy issued by some has declared the issue moot (e.g., Klerman, 1984). Coursey (1989) expressed this attitude by suggesting that we need a new type of psychotherapy for schizophrenia, one that recognizes the global inefficacy of standard psychotherapy and that accepts schizophrenia as a “biological distortion,” the biological revolution in psychiatry, according to Coursey, having “won.” As described, this desired form of psychotherapy, which hardly seems new, would be akin to case management for a defective organism. Apart from wondering what research literature Coursey reads and how anything has been won, we are distressed by the unrestrained condescension of his position, as we suspect many intelligent schizophrenic persons would be. Katz (1989) offered a suitable admonishment for this line of thinking.

On the other hand, the tide may be turning. The American Psychiatric Association’s (1997) *Practice Guideline for the Treatment of Patients with Schizophrenia* that contains expected comprehensive recommendations on managing medication of patients in various phases and at differing severities of disorder also makes a host of recommendations relating to the desirability of vigorous psychosocial interventions. In making these recommendations, the *Practice Guideline* takes notice of the development in recent years of a number of relatively new psychosocial initiatives demonstrably effective in ameliorating the problems of schizophrenic patients, particularly those problems that seem largely unresponsive to antipsychotic drugs (Kopelowicz & Liberman, 1998). Ironically, it may be that the current scientific standard for demonstrating efficacy in the field, that of the randomized clinical trial or “RCT,” is making it possible to gain a foothold in demonstrating the importance of psychotherapy for schizophrenia. In contrast to effectiveness studies (i.e., how treatment interventions hold up in the field under less controlled circumstances), RCTs aimed at efficacy

seek to demonstrate how well an intervention works under controlled conditions, thus making it possible to identify a potent treatment. A number of "psychotherapy trials" conducted in this manner reaffirm the role of psychotherapy for schizophrenia.

Hogarty and colleagues (1997a,b) report on a controlled 3-year trial of "Personal Therapy," a form of psychotherapy specifically aimed at schizophrenic individuals. This treatment was very effective in enhancing the social adjustment and social role performance of discharged patients. Personal therapy is described as a staged, nonpsychodynamic approach oriented to learning coping skills for managing emotion and stressful events. In favorably commenting on this program, Fenton and McGlashan (1997) assert the need for a flexible individual psychotherapy component in virtually all treatment packages for schizophrenia.

Training in social skills (see, e.g., Bellack, Mueser, Gingerich, & Agresta, 1997; Dilk & Bond, 1996), as has been demonstrated, has a positive impact on overcoming the embarrassment, ineptitude, awkwardness, and attentional "cluelessness" displayed in social situations by many persons who have undergone episodes of schizophrenia. A broader aspect of social relations concerns integration into a community. Many schizophrenic patients, sometimes abruptly discharged into the community, have great difficulty in marshaling resources and organizing their lives. Included here is some propensity to become involved in substance abuse, often as self-medication for unpleasant antipsychotic drug side effects (Kosten & Ziedonis, 1997). Therefore, there is considerable need for persistent and vigorous community-based follow-up and aid in managing life problems (e.g., Mueser et al., 1998), including coordinating continuing antipsychotic medication (Kopelowicz et al., 1997).

One final, less optimistic point concerns the problem of system inertia. These psychosocially based efforts to compensate for the shortcomings of antipsychotic medication in treating schizophrenia are not at present generally "in place" and functioning up to speed. An intensive effort to assess the degree of conformance of actual practice to a set of previously issued treatment guidelines similar to those described before in the mental health systems of two states found that conformance was generally less than 50%, especially to the psychosocial enhancements recommended

(Lehman et al., 1998). We suspect that a national compliance assessment effort covering all fifty states would not produce a more encouraging picture at this time. Actual mental health practice, it seems, fails to keep pace with what is known to be maximally effective in restoring schizophrenic patients to active and productive citizenship. In this sense, we have continued a very long-standing pattern of limited horizons for and neglect of this portion of the population.

Conclusion

Some behavioral scientists (e.g., Whitaker, 1992) dispute the idea that schizophrenia is caused primarily by biological factors. It is unfortunate and counterproductive that biological and psychosocial research are often conceived as mutually antagonistic and that they rarely make contact with one another. Importantly, although much lip service is paid to the evidence of interaction between biological and psychosocial variables in schizophrenia, studies that actually examine the interaction are rare. Hopefully, interest (and funding) for such endeavors will increase in the near future.

As a good illustration of this type of integration, consider an innovative project that involved rating childhood "home movies" obtained from schizophrenic patients conducted by Walker and colleagues (Grimes & Walker, 1994; Walker, 1994; Walker et al., 1994). The preschizophrenic children showed less—and less positive than negative—emotionality, had poorer motor skills, and showed a higher rate of peculiar movements, such as tic-like muscle contractions, suggestive of neuro-motor abnormalities. Bear in mind that the manifest nature of these problems would all but certainly impact the child's social environment negatively. It is extremely likely that the (presumably) neurologically based behavioral deficits observed in the then preschizophrenic children would be noticed and responded to negatively by others who come into contact with them. The child who rarely manifests joy (even on celebratory occasions such as birthdays), whose emotional expressiveness is prevailing in the bland to negative range, who is motorically clumsy or awkward, and who may evidence peculiar involuntary movements, is likely to have a far less stress-free early life than the child endowed with the opposite characteristics. Mini-

mally, such a scenario suggests that the occurrence of stressful life events may affect social and personality development and is not independent of a potentially pathogenic biological “diathesis.” In fact, this idea has been a central element in the important contributions of psychologist Paul Meehl (1962, 1989, 1990) in tracing the developmental course of schizophrenic outcomes. Berenbaum and Fujita (1994) offered a similar conceptualization.

Meehl’s (1962, 1989) concepts relating to the genesis of schizophrenia are in broad outline—if not in their details (e.g., we find implausible the notion that a single dominant gene controls vulnerability)—refreshingly closer to what we envisage as a more ideal approach to finding the answers. It seems inescapable in our reading of the evidence that the connections of causal links from the molecular to the molar (behavioral) levels, from the endoenviornment to the ectoenviornment, are both lengthy and intricately interlaced. To unravel the mysteries will require the talents and skills of many different kinds of scientists, from the molecular biologist to the specialist in the social development of children, working in a framework in which some minimal level of collaboration will be essential. Divided research camps devoted primarily to furthering of ideologies are a decided hindrance that we can ill afford in this type of scientific context. Until we can move beyond the clash of genetic/biological *versus* environmental/psychosocial paradigms, we will be limited to a vision holding that the etiology of schizophrenia resides in some imprecisely specified combination of “bad luck.”

The simple fact is that in much of the contemporary literature, the psychosocial dimensions of schizophrenia are denied at intensities that approach religious fervor. We fear that the “great and desperate cure” mentality (Valenstein, 1986), the magic-bullet fantasy now embraced by much of psychology as well as our sister discipline of psychiatry, is a step backward in time, one that retards scientific progress and deprives untold numbers of persons designated as schizophrenic of the demonstrable benefits of soundly planned and executed psychosocial intervention. Meanwhile, an egregiously imbalanced allocation of scarce research resources deprives the mental health professions of opportunities to develop vitally needed knowledge that could lead to psychosocially based techniques enhanced in cost-effec-

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tiveness, possibly even ones that would enormously potentiate the now rather limited horizons of the growing catalog of antipsychotic drugs.

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PART III

Personality Disorders

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