biological homogeneity, symptom heterogeneity, and the diagnosis of schizophrenia*

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What follows is the seventh in a continuing series of guest editorials to be published in the Schizophrenia Bulletin. Other readers are encouraged to submit short commentaries on schizophrenia-related topics that they feel merit attention and discussion. Responses to the issues raised in the editorial below will also be welcome. Remarks should be addressed to AT ISSUE, Center for Studies of Schizophrenia, NIMH, ADAMHA, 5600 Fishers Lane, Rm. 10C-26, Rockville, Md. 20857.—The Editors.

Today's biological researcher seeks a laboratory test for schizophrenia that will unequivocally diagnose the disease and at the same time hint at etiology. To do this, he statistically compares a group of schizophrenics and controls on his test. Such a strategy is intended to highlight any salient differences among the groups studied. The diagnosis of schizophrenia, based on overt symptoms, is the independent variable. Neurochemical, psychophysiological, and immunological measures are common dependent variables. Often it is assumed that the more diagnostically rigorous, homogeneous, or pure the groups, the less the error variance and the more clear the dependent variable differences among the groups. For this reason, many researchers regard maximizing the symptom-based homogeneity within groups as a requirement of sound research design.

Symptom heterogeneity within psychiatric diagnostic categories, therefore, is seen as the bane of researchers. Traditionally, many investigators have attempted to achieve diagnostic homogeneity by deriving standard systems of symptom classification. Such systems are limited in their usefulness because the homogeneity they achieve is largely cosmetic.

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Apparently similar symptoms may be caused by radically different etiologies, and a single biologic factor can produce very different overt symptoms. Many biological researchers, frustrated with the relatively weak statistical findings of genetic, drug treatment, or neurochemical studies, agree with Pfohl and Andreasen (1978), who wrote, "It is likely that neurochemists and behavioral geneticists will not be able to achieve much until their clinical colleagues are better able to designate particular homogeneous subgroups of patients for them to study" (p. 197).

We believe that just the opposite may be true. Clinicians need the help of neurochemists, behavioral geneticists, and psychophysiologicalists to define homogeneous subgroups of individuals with psychopathology. Grouping or diagnosing individuals on biological variables instead of symptoms may be a better way to decrease heterogeneity. This reversal of the usual dependent and independent variables, not uncommon in epidemiology research (see Weissman and Klerman 1978), may be illustrated in the example of phenylketonuria and mental retardation. Simply comparing mean blood levels of phenylalanine in groups of mentally retarded and normal subjects yields only the weakest evidence for a role of phenylalanine metabolism in mental retardation and fails to highlight the small group of clinically indistinguishable individuals for whom it is the determining factor.

Similarly in schizophrenia research, theoretically appealing biological variables are tested inefficiently and perhaps prematurely rejected. Bound by the paradigmatic straightjacket of symptom-based diagnostic homogeneity, researchers search for the elusive one-to-one correspondence between specific biological factors and specific symptoms. But if the heterogeneity in schizophrenia reflects diverse multiple etiologies with similar symptoms, as in mental retardation, then this course will not elucidate the biological factors of the illness. Just as contrasting mentally retarded patients with and without psychomotor agitation is not an effective strategy in phenylalanine disorder research, isolating schizophrenic patients with ever narrower definitions of "true" schizophrenia may not pay off in dopamine disorder research. Attempts to reduce heterogeneity through the use of symptom-based schizophrenic subgroups (e.g., paranoid) may also prove unproductive. We already suspect from the wide individual differences in response to psychoactive drugs that a single neurochemical disturbance may produce quite different symptoms from one person to another. Indeed, symptoms could be the worst features for biological researchers to anchor on, since they may be primarily determined by interpersonal psychosocial factors—as many nonbiologically oriented researchers have suggested.

We believe that recent research progress warrants the use of biological variables for developing psychiatric diagnostic systems just as biological measures are used in other branches of medicine. In fact, psychiatrists already bow to internal medicine when biological indicators of tertiary syphilis, lupus, or hypothyroidism are present. Even in areas not yet ceded to infectious disease, immunology or endocrinology, biological factors are used to make diagnoses. Though unsanctioned, the use of lithium carbonate response in differentially diagnosing affective disorder and schizophrenia is not uncommon. In this case, the clinical psychiatrist may be conceptually a step ahead of the biological researcher, because he has identified a diagnostic group homogeneous with respect to a salient biological feature and is willing to ignore the symptom heterogeneity. While he might write "affective disorder" in the chart, the implied diagnosis is really "lithium sensitive behavioral syndrome."

How do we know a psychiatric diagnostic category is valid? Conventionally, in psychiatry validity evolves from the apparent clustering of symptoms. Even for the major categories of schizophrenia and affective disorder, however, the respective symptom clusters are not mutually exclusive (Pope and Lipinski 1978). Attempts have been made to obtain validation from examination of the appearance of symptoms in pedigrees (Kety et al. 1968) and the identification of clinical features of specific drug response (Murphy, Schilling, and Murray 1978), but even these approaches have failed to reduce heterogeneity within categories. Few researchers have identified groups on a biological anomaly or feature and then attempted to validate such classification on the basis of prediction of drug treatment response, pedigree analysis, prediction of clinical course or even symptom clustering.

This strategy of using biological independent variables has a number of advantages. First, it is more efficient for detecting biological etiologies since statistical effects are not diluted by irrelevant cases misclassified because of similar symptoms. Second, many individuals with atypical or less severe symptom manifestations, currently excluded from research studies which rely on strict symptom-based diagnoses, could be studied if they met a biological criterion. A biological strategy that would identify such cases is advantageous since, for example, ge-
Netic studies indicate that "spectrum," mild, or atypical cases predominate among the ill relatives of schizophrenics (Rosenthal et al. 1971). Moreover, since the majority of psychiatric inpatients do not meet strict criteria for schizophrenia yet might well share a particular biological factor, the new strategy allows us to recruit what could be the bulk of individuals with the salient factor. Third, the biological strategy allows the study of nonhospitalized, unmedicated individuals, avoiding the possible artifacts of hospitalization and prior drug treatment which plague reports of biological differences. This allows population screening studies which can identify individuals biologically at risk for psychiatric problems before symptomatic breakdown disturbs and confounds their biology (Buchsbaum, Coursey, and Murphy 1976).

As classification is the first step in science, diagnosis is the most fundamental problem in psychiatry. Biological researchers have an opportunity to develop new modes of psychiatric diagnoses that go beyond the traditional categories and draw upon new knowledge from the neurosciences. Today's biological researcher searching for a laboratory test for "schizophrenia" is not going to find it. Multiple etiologies, false negative symptom elicitation, false positive symptom expression, and the lack of external validating criteria all prevent the identification of a homogeneous schizophrenic group for study. A laboratory test for "dopamine disease," however, is a possibility with current technology. Whether dopamine disease or other biologically based diagnoses are clinically useful diagnoses needs to be determined with new research strategies.

Summary

Much biological research is directed at using biological variables to predict traditional symptom-based psychiatric categories. In this article, the authors discuss the need for a research strategy in which biological variables actually define psychiatric groups.

References

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