A "Mini-Max": A Research Strategy for Establishing Subgroups of the Schizophrenic Syndrome

by Leopold Bellak

Abstract

It is suggested that a large sample of people exhibiting the schizophrenic syndrome be "repetitively sifted," in an attempt to find etiologic and pathogenic subgroups. For this purpose, epidemiological, biochemical, neurophysiological, psychodynamic, genetic, and other "sieves" should be used. Instead of expecting one factor to hold true for all schizophrenics, one might then hypothesize that a viral factor is the relevant one for a fraction of those born in inclement months, while a pathogenic life history might play the primary role in another fraction. Even within groups, one might find fractions, such as patients for whom the dopamine hypothesis is supported, and others for whom it does not seem to play a role. It is unlikely that one single factor plays the necessary and sufficient role in anyone with the schizophrenic syndrome. Therefore, the method of repetitive sifting should be combined with a "mini-max" model: That is, not only should the group as a whole be sifted, but each individual patient should be searched for different contributing factors, and then a rank-order system of the importance of various factors for each given patient should be established. Such a method of identifying multiple etiologies and pathogeneses would then be a rationale for prevention, treatment, and prognosis.

Having personally reviewed close to 3,000 publications on schizophrenia in 1948, I concluded:

The wide variety of etiological factors reported makes us believe that at least a portion of those have been correctly observed and interpreted and that the clinical psychopathology described conventionally as schizophrenic is actually a syndrome or a reaction type associated with a large variety of etiological factors. [Bellak 1948, p. 444]

In my 1958 review of the schizophrenic syndrome, I wrote:

It is my personal belief that if any findings do prove valid for all "schizophrenics," such findings will be concerned with factors which are secondary to the schizophrenic way of life rather than of a primary nature. I do not consider it impossible, or even unlikely, that various organic factors may be significantly related (even in an etiological way) to some fractions of the vast group diagnosed as schizophrenic. To that end, some systematic break-down of the overall group will have to be effected. . . . [Bellak 1958, p. xvii]

In 1965, I suggested to a Congressional Subcommittee that there existed a need for a schizophrenia research center. My remarks were as follows:

1. I would say there are two basic misconceptions which confound the majority of all work on schizophrenia: one is that schizophrenia is investigated as if it were one single disease rather than a shared common path of a variety of etiological factors. Therefore, research is being done on "schizophrenics," hoping to find a common denominator for all of them, when there is reason to look for specific different causative factors in different groups.

2. The second misconception most generally involved is related to the first one: namely, that often some physiological factor is

Reprint requests should be sent to Dr. Bellak at Department of Psychiatry, Albert Einstein College of Medicine, Bronx Municipal Hospital Center, Jacobi-915, Pelham Parkway South and Eastchester Rd., Bronx, NY 10461.
I went on to say: and, to a certain extent, the pre-integration simply stands in the intervention and treatment of schizophrenia. The current lack of knowledge to answer most of the questions concerning the etiology, empirically speaking; even the knowledge to answer most of the questions concerning the etiology, and, to a certain extent, the prevention and treatment of schizophrenia. The current lack of integration simply stands in the way of solid demonstration of these facts experimentally. It seems, therefore, especially regrettable that such a serious and widespread disorder should not be successfully attacked, simply for the lack of appropriate organization and integration of research efforts. [Bellak, Congressional Record, 1965, pp. 618-621]

I firmly believe that we do already have the hypotheses, empirically speaking: even the knowledge to answer most of the questions concerning the etiology, and, to a certain extent, the prevention and treatment of schizophrenia. The current lack of integration simply stands in the way of solid demonstration of these facts experimentally. It seems, therefore, especially regrettable that such a serious and widespread disorder should not be successfully attacked, simply for the lack of appropriate organization and integration of research efforts. [Bellak, Congressional Record, 1965, pp. 618-621]

Luckily, an administrative change at the National Institute of Mental Health made it possible to translate these suggestions into reality and the Center for Studies of Schizophrenia was established. At a conference of an Ad Hoc Advisory Committee to this new Center, in October 1966, I submitted the following memorandum:

1. The main defect of all etiological or pathogenic studies of schizophrenia is still that one factor is being looked for in all of the patients: be it serum factors, cognitive defects, or family interaction types.

2. Yet, most reviews of schizophrenia end with the statement that it most likely is not a disease of unitary etiology.

In this basic aspect current studies are not more sophisticated than the ones I have been reviewing from 1936 on.

2. The cause of the above is fairly clear: No one group of investigators can very well study a large enough sample for a variety of possible operant factors simultaneously.

We need the type of research that would permit the search for several factors in a large sample simultaneously: serum factors, the contribution of “minimal brain disorder” in childhood toward perception and individuation, family constellation, etc.

The method of repetitive sifting of one large sample is called for, by several teams of investigators working on the data simultaneously, and/or successively. Factor analysis will eventually be advisable.

3. Any of the findings above will probably need predictive studies to establish not only which are the necessary but also which are sufficient factors for the development of schizophrenia: a study beginning in childhood, which at the same time could be a study of the effectiveness of therapeutic interaction, in part of the sample. It might well turn out that the interaction of several factors is necessary to produce schizophrenia, and that none alone virtually ever is significant, though different clusters might combine into the necessary condition.

4. It appears mandatory that the Center formulate hunches concerning the currently thought to be most likely contributory factors and help initiate such studies.

5. These studies should regularly, say, every half year, be reviewed and discussed by the Center and a regularly meeting advisory group.

6. Therefore, fostering of teams of specifically trained schizophrenia researchers as well as the formulation of an advisory group seems essential.

7. Different problems will have to be studied in various “contract institutions,” much as the Psychopharmacology Branch of NIMH arranged to have different drugs (and sometimes the same, for control purposes) studied in different hospitals. Synchronized, interlocking, and methodologically, centrally supervised research is essential at this stage of our knowledge of schizophrenia.

A publication, similar to Psychopharmacology Bulletin is advisable, to decrease the publication lag.

The social importance of schizophrenia alone makes such a Center a very important institution and demands that it be enabled to play a major role in the primary, secondary, and tertiary prevention of schizophrenia.

The suggestions in my memorandum are, of course, entirely consistent with my previously stated multiple-factor psychosomatic theory of schizophrenia and its later elabora-
The proposed research aims at the simultaneous investigation, with a single population, of genetic, neurophysiological, and psychological factors, all of which are believed to be implicated in schizophrenia. To date, they have been examined primarily as isolated factors. The goal of this program will be to reveal interrelationships among these areas through representative measures from each. In addition, the relationship between ego function patterns and the selected measures is to be investigated by Bellak's current ego function assessment scheme. More specifically, the researchers will strive to:

(a) Determine whether any of the three factors—the neuropathological, psychogenic, and genogenic—is a primary factor . . . in different subgroups of schizophrenics; 
(b) Establish whether any two or more of these factors coexist in a sample of schizophrenics where a single factor does not play a primary role, and in what variation;  
(c) Examine the relationship between these three factors and different (possibly specific) ego function patterns in any of the above subgroups; 
(d) Further study ego functions in a broad random sample of a schizophrenic population in order to reveal any possible subgroups based solely on ego function patterns;  
(e) Differentiate the schizophrenic group from diagnostically normal persons with regard to pathogenic measures and ego functions.

A multidisciplinary approach to a problem as complex as schizophrenia and its presumed pathogenesis requires a broad research strategy. The relationship between measures of pathogenesis and ego function patterns should lead to more refined hypotheses concerning the etiology of schizophrenia and should also suggest programs to improve specific diagnosis, prognosis, and treatment. [Bellak 1971, p. 27]  

In later attempts to conceptualize this particular research strategy, I came to speak of it as the mini-max model1: the attempt to identify for a given schizophrenic patient the etiologic and pathogenic factors that might play a maximal role and then, by rank order, others that would play a lesser and finally a minimal role. Actually, even this model is, in the light of current research, still too simplistic and coarse. 

More than ever, the method I referred to in 1966 as "repetitive sifting" needs to be combined with the mini-max method. In fact, repetitive sifting on one large sample for subgroups should come first. Every schizophrenic patient in a large sample should be examined for the existence of neurological, biochemical, experimental, genetic, and infectious factors of different nature. When subgroups among these subgroups have been found, a rank ordering of factors contributing to the phenotype schizophrenia by the mini-max method should almost automatically result. A diagnosis might then involve hierarchical statements such as:


It is very likely that there are several subgroups within the larger subgroups mentioned. Within the neurophysiological group there are some in whom a childhood encephalitis may have played an important role (Bellak 1948). Data supporting the possibility that season of birth may play a  

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1 Mini-max is a term used in mathematics, which is unrelated to my use of it in this article.
role in schizophrenogenesis are sometimes interpreted as possibly due to a greater incidence of viral infections in winter months. It remains unclear why this plays a greater role in male schizophrenics (Torrey 1979). In another splinter group of the neurophysiological subgroup, the delayed evoked response potential may play a major role. In yet another subgroup, the dopamine hypothesis may be shown to be the best explanation of schizophrenic disturbances, while in others, to judge from the diversity of data for and against the dopamine hypothesis, dopamine disturbances may not play a role at all.

It is very likely that in some schizophrenics individual history plays the primary role in the illness, while in others the family network may be the main matrix for schizophrenogenesis. Anthony presents persuasive evidence for the existence of different subgroups of schizophrenic children (Anthony 1969).

Summary

From the history of failures in schizophrenia research in general and the fact that some investigators found data that seemed bonafide but could not be reproduced for another sample of schizophrenics or all schizophrenics, it should be clear that the greatest likelihood is that various different factors play a role in a percentage of schizophrenics. It should thus also be quite clear that no single approach, no search for a single factor by a single investigator with a relatively limited sample is likely to be successful.

I want to call for a large multi-hospital study, similar to the very successful combined study of psychotropic drugs (Casey et al. 1960) to study a large sample simultaneously and repetitively for several factors, attempting to establish several subgroups and sub-subgroups.

For this purpose, a heuristic dragnet has to be designed. Each patient must be studied from a multiplicity of standpoints—all the ones enumerated here and many more. Eventually, a cluster analysis should demonstrate that one set of factors holds primarily true for one sub-subgroup and another one for others, with considerable overlap.

Once such subgroups are tentatively identified, we need to study each individual within each group, as well as the group per se, for clinical characteristics, historical characteristics, genetic characteristics, and others, and then attempt to correlate various forms of therapy for each of them. Similarly, their prognosis must be studied for critical differences.

Eventually, we might be able to undo the work of Kraepelin and Bleuler, who did such a splendid job of trying to establish a disease called dementia praecox or schizophrenia out of the confusing welter of many different psychiatric conditions. We must hope to substitute specific etiologic subgroups for the catch-all that the present term "schizophrenia" or "schizophrenic syndrome" embraces.

References


The Author

Leopold Bellak, M.D., is Clinical Professor of Psychiatry, Albert Einstein College of Medicine, Bronx, N.Y.