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ANTIDEPRESSANT DRUGS AND CLINICAL PSYCHOPATHOLOGY


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Dr. Joseph Zubin: I found the papers in this session most provocative and will deal with issues that they raise rather than present the usual conference, since I found little fault with them. I have concentrated on Dr. Klein's and Dr. Goldberg's papers, since they have the common theme of the influence of drugs on classification, while that of Dr. Klerman deals primarily with a survey of clinical practice.

I shall address myself to the first question which Dr. Klein raised: "Do the behavioral changes induced by psychotropic drugs cast light on the bewildering complexity of psychiatric patients?" I will leave to better hands the second question - "How to improve the Statistical Manual so that its categories will be more predictive of response to treatment?"

There are at least three aspects of the behavior of the mentally ill person which need to be kept in mind, even though we do not yet know how to separate them pragmatically: (1) the premorbid personality; (2) the disorder; and (3) the illness.

1. It is obvious that the behavioral repertoire of the patient antedates his psychopathology, i.e., that a premorbid personality exists and varies from patient to patient, even in groups of patients suffering from the same disorder.

2. The disorder from which the patient suffers can sometimes be objectively specified very clearly as to etiology and process, as is the case, for example, with general paresis, PKU, and other conditions of known etiology. But even in disorders of unknown etiology there is provided at least a description of the underlying characteristics which are fundamental to the disorder.

3. The illness from which the patient suffers consists of the focal disorder plus the penumbra of specific situations surrounding the disorder, as well as the idiosyncratic responses of the patient to the disorder and to treatment. This illness will vary considerably from patient to patient, even when the etiology and process of the disorder is known. It will be most variable, however, in disorders of unknown origin, because we still do not know how to

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separate the components of the disorder from the peripheral components of the illness. It is the illness rather than the disorder which provides the "bewildering complexity of the psychiatric patients" to which Dr. Klein refers. Perhaps one of the most important components of the illness is the interaction between the premorbid personality and the disorder.

In considering the effect of drugs on the patient, we may have to consider not only the disorder but the illness, since it is still debatable whether the observed changes in behavior reflect changes in the focal disorder or changes in the peripheral aspects of the illness. Thus, drug effects may cut across the various disorders, if they bring relief from symptoms which, though not germane to the focal disorder, nevertheless accompany them frequently.

Examples of drugs which affect focal disorders are not plentiful, but candidates are lithium for mania and some antidepressants for depression, but there is still considerable controversy over these claims. Whether the major tranquilizers attack the focal disorder of schizophrenia or the peripheral aspects of the illness is also still controversial. No one today would claim that phenothiazines cure schizophrenia in the same way that antibiotics cure infections. Perhaps the closest approximation is insulin in diabetes, but even this may be more of an analogy than a homology.

Faced with the trilemma of separating the effects of drugs on premorbid personality from the effects on the disorder and the illness, Klein, in line with other workers, suggests that only those changes regularly induced by drugs in a group of homogeneous patients be regarded as specific to the syndrome presented by the patients in question. The irregularly induced changes may reflect alterations in the illness or in the underlying premorbidly present personality.

Among the examples Klein gives of drugs which attack specific syndromes are imipramine in "panic" attacks in phobic adults and school-phobic children; and phenothiazines in emotionally unstable character disorders, which are often misdiagnosed as schizophrenia but the drug responses of which separate them from schizophrenia.

Dr. Klein's main contribution ends here, but he proceeds on the basis of some of his previous work and the work of others to the application of psychopharmacological effects to schizophrenia and depression. In the case of pseudoneurotic schizophrenia, he points out that imipramine tended to normalize mood, while chlorpromazine tended to reduce agitation depression in these patients and in this way tended to improve them. Since both of these drugs appeared to alter the afferent rather than the schizophrenic aspects of their disorder, there is some doubt whether pseudoneurotic schizophrenia belongs in the schizophrenic grab bag.

This reminds me of the findings of the U.S.-U.K. project in which a tendency was found for state hospital psychiatrists in New York to label some...
effective disturbances as schizophrenia and of Dr. Klerman’s similar report in his paper in this symposium. The specific contribution that Klein makes over and above the contributions of the U.S.-U.K. project, and perhaps also over Dr. Klerman’s work, is the utilization of drug effects rather than systematic structured interviewing alone to validate the diagnosis of the disorder.

In his final statement regarding improvement in the classification of schizophrenia and depression, Klein moves away from the drug-based components of behavior and leans on premorbid personality characteristics, especially as they relate to prognosis. Here I am fully in agreement with him and with Dr. Goldberg, since I have long felt that prognosis is the key to much of what we observe in the outcome of schizophrenia, even as Kraepelin tried to show, albeit too drastically. To repeat a paradigm which you may have heard only too often, I would categorically maintain the following point of view: The only factor which seems to be prognostic in schizophrenia, and has been so from the very beginning, is that of premorbid personality. Good premorbid trends to improve, poor premorbid do not. All other findings, such as the relation of marital status, education, etc., to outcome can be subsumed under this general heading. Why should this be so? If we assume that the basic feature of schizophrenia is a relatively high degree of vulnerability to stressors, either endogenous or exogenous, and that when an episode occurs it is time limited, then we may conclude that when the episode is over the patient returns to his premorbid personality. If that was good to begin with, he is rated as recovered; if it was poor to begin with, it is difficult to know just when the episode is over and another episode may soon develop because of his inability to cope. Of course, some patients suffer residual sequelae to their disorder — as was the case with Dr. Klein’s phobic patients who, even though their panic was reduced by imipramine, still feared the next episode.

It is interesting to note that this persistence of the conceptual fear even when the physiological component is suppressed by imipramine fits the postulate established by Martin Katz and me in our paper on drugs and personality some years ago. Based on a survey of the work of Maranon, Landis and Hunt, and Stanley Schacter, we postulated that both the physiological as well as the emotional components must be present if a genuine emotion, such as fear, is to be experienced. Since, in Klein’s cases, only the conceptual component of expected imminent recurrence of an episode remains, it alone will not produce a panic reaction. The danger is, however, that once the effects of imipramine subside, the persisting conceptual component itself will kick off the physiological component and a full-blown panic will ensue. I wonder whether Dr. Klein would consider utilizing behavior modification techniques, such as desensitization through imagined episodes while imipramine is still at work, to extinguish the conceptual component. Furthermore, is it possible that since the conceptual component is so strong it might be better to attack...
it directly through behavior modification methods? Or is attacking the physiological component first more economical? Perhaps patients will vary in this respect, depending upon their illness rather than upon their disorder.

It seems, in the light of this analysis, that the primary function of treatment should be focused not so much on dealing with the current episode — although that is important — as on improving the premorbid personality and eliminating secondary effects of the disorder, so that when the episode is lifted, the patient can cope with his problem more effectively.

I heartily agree with Dr. Klein in his comment on Bleuler’s disservice to the concept of schizophrenia when he broadened its boundaries. Science does not become more precise by broadening a concept into vaguer areas.

Dr. Goldberg’s chief concern is to relate drug effects to behavioral changes, as noted in rating scales and in psychological tests. His and Dr. Klein’s stress on prognosis rather than on diagnosis reminds me of the attempt we made twenty years ago, when diagnosis was in the doldrums, to engage in a rather large prognostic study in schizophrenia, in which many of the tests now in use were included. We had hoped to revive diagnosis by giving it a shot of prognosis. This was before the drug era, and though we found correlations in the thirties and forties with some of our tests, we suffered from two major difficulties: the unreliability of diagnosis and the lack of criteria for measuring outcome. In reaction to this debacle, we temporarily gave up the use of the clinical psychological tests and turned to the interview to systematize it and objectify it so that we could have better criteria for diagnosis as well as for outcome. The results are well known to you. There followed the development of the Mental Status Schedule (Burdock and Spitzer), The Psychiatric Status Schedule (Spitzer and Endicott), The Structured Clinical Interview (Burdock and Hardesty), and a whole series of other similar techniques.

Armed with good tools for diagnosis, we then turned to take a second look at psychological tests, just as Dr. Goldberg is proceeding to do. However, we doubted whether using psychological tests merely to buttress clinical diagnosis was desirable. At best the correlations will be of a low or medium order and could not be used except as corroborative evidence. We decided, based on the variety of reasons which Dr. Goldberg has catalogued, that the available clinical range of psychological tests was not satisfactory. We proposed to sample the physiological, sensory, perceptual, psychomotor, and conceptual responses along more rigorous laboratory lines which would meet most of the objections raised by Dr. Goldberg. As a result of this program, we now have some results which we regard as relatively reliable and free of cultural bias and the effects of previous experience — in other words — relatively culture-free indicators of schizophrenia. Among these are (1) bimodality reaction time, (2) evoked potentials, and (3) energy integration.
It is impossible to describe these techniques here, and the reader is referred to where they are described in greater detail. Sutton, S., "Fact and artifact in the psychology of schizophrenia" in Psychopathology: Contributions from the Biological, Behavioral, and Social Sciences, (M. Hammer, K. Salzinger, and S. Sutton [eds.]. New York: John Wiley.) We can, however, indicate that the pattern of physiological, sensory, perceptual, psychomotor, and conceptual responses in schizophrenics is quite different from the corresponding pattern in depressives and in normal controls. It is to be hoped that these patterns may help in differentiating the variety of mental disorders. Beginning with the groupings provided by clinicians, we can further make intragroup differences by means of the above patterns. The new groupings can then be further examined in the light of their interview dimensions and this iterative method can be continued until quite homogeneous groups of patients are obtained.

When interviewing was less developed, psychological tests of the clinical variety were needed to bolster diagnosis. Now, systematic structured interviews are providing a reliable basis for classification, if not for diagnosis. They really resemble psychological tests more than they do interviews, as Dr. Burdock has intimated, and psychological tests would have to demonstrate their competitive value before being accepted. If they are to be of help now, they would have to tap functions which the interview and observational techniques cannot reach. Otherwise, why bother to develop them? Perhaps Dr. Goldberg can produce such tests. One particular characteristic of such tests that would be convincing would be tests in which schizophrenics do not show a deficit, since no matter what test you use, it is usually easy to show that schizophrenics are poorer. We have one such finding — the energy integration finding — discussed earlier.

I believe that one of the chief difficulties of present day diagnosis is the lack of validation criteria. Up until recently only long-range outcome could be used for validation purposes. The availability of drugs like lithium for mania and imipramine for anxiety tend not only to be therapeutic but to validate the diagnosis of the clinician.