Psychobiological Measures in Psychiatry:

Discussion

by

Joseph Zubin Ph.D.

Chief of Psychiatric Research (Biometrics)
New York State Department of Mental Hygiene
New York, New York 10032.

A. Introduction

Some years ago when we discovered that the available clinical psychological tests most often used in the clinic (intelligence, personality inventories, projective techniques, sorting tests and some psychophysical tests) did not help in diagnosis and prognosis in a significant way, we turned away from these complex global techniques and returned to the more elementary specific classic categories of responses developed in the experimental psychology laboratories: physiological, sensory, perceptual, psychomotor and conceptual responses (Burdock Sutton and Zubin, 1958). We also classified the variety of stimuli used to elicit these five types of responses into the following: (1) idling state or the state of rest or baseline before a stimulus is applied; (2) energy stimulus in which the energy applied to the receptor organ is reflected in some proportional manner in the response, so that low energy stimuli elicit milder responses and high energy stimuli elicit stronger responses; and (3) signal stimuli, in which the response is not dependent upon the proximal energy of the stimulus, but on prior experience with the stimulus or on genetically wired-in propensities.

This two-way table of stimuli and response constitutes a sort of Mendelejeff table for psychological experimentation, and we have used this paradigm in developing techniques for separating different types of patients into more homogeneous subgroups for research, if not for clinical purposes,
I shall attempt to utilize this Mendelejeff-like table for classifying and discussing the contributions to this symposium.

The Mendelejeff-like table which I described is useful in organizing the techniques which may prove useful in describing behaviors which may characterize homogeneous groups of patients so that experimental results will not be occluded by the inordinate variability which characterizes randomly selected patients, even when they bear the same diagnostic label. However, the variety of patterns which the 5 x 6 Mendelejeff-like table gives rise to when the types of stimuli are classified more clearly, permits a variety of combinations in the 30 rubrics which are practically infinite in number. Some guideline must be sought for selecting among this infinite multitude those which are likely to pay off. Since the descriptive categories provided by this table are only surface deep, we must resort to etiology by way of scientific models and there are at least 6 such models currently under examination by various research teams (Zubin, 1972). They are as follows: (1) ecological, (2) developmental, (3) learning, (4) genetic; (5) internal environment and (6) neurophysiological.

B. Discussion

This session of the symposium is concerned, with only 3 models: (1) the psychological learning theory model as represented by Saarma and Morozov; (2) the internal environment model represented by van Praag, and (3) neurophysiological model represented by Shagass.
Learning Theory Model

Beginning with the learning theory model let us turn to the work of our Russian colleagues.

The theoretical structure provided by Pavlov's first and second signal system constitutes the basis for Saarma and Morozov's contribution to the measurement of changes in clinical psychopharmacology. The tasks they use consist of the usual clinically based approaches of testing. They include in their battery immediate memory and then more remote memory tests for tasks presented during the testing period; a learning task of a list of ten words which the subject has to memorize; word association tests; an addition test; a proofreading test; and a reaction time test to positive and negative (no response required) stimuli. The results of these tests are interpreted in terms of excitatory and inhibitory processes following Pavlov.

One difficulty facing the interpretation of these clinical tests is the question of the effect of motivational factors on performance. The provision of suitable norms, which the paper unfortunately does not provide, is also a difficulty.

The report on the specific nature of the effect of various chemical agents gives information only on the changes (better or poorer performance) on the part of the treated patient, but gives no data on controls. Even the contrast between the different drugs is not treated statistically so that we are left with an eye-ball evaluation of the results of these graphs.
In an attempt to determine the value of the battery of tests as prognostic indicators for the efficacy of various drugs, the entire battery was given to samples of patients undergoing the various treatments. Nothing is said as to whether the research was a series of comparative clinical trials on random samples of admissions. Without some sort of experimental design guaranteeing the equivalence of the various samples, it is difficult to know whether the varying results for the various drugs reflected differences in drugs or samples.

In general, the techniques utilized by Saarma and Morozov are not novel in any sense, since they utilize well recognized testing procedures. The utility of the battery they use does not stand or fall by their interpretation along Pavlovian lines, but it would be most helpful if they introduced more rigorous designs and statistical evaluation. If they indeed used more sophisticated methods, the write-up failed to indicate it.

**Internal Environmental Model**

With regard to the internal environment model, we seem to be on the brink of some great breakthroughs, and even Kety who has served as the critic for most of the earlier approaches to the milieu interieur is beginning to have faith in two of the currently favored hypotheses: excessive transmethylation taking place in the brain and disturbance in catecholamine synapses. Professor van Praag takes as his rationale for biochemical research two goals: (1) the finding of biochemical variables of differential diagnostic significance - the
hope that another 'Wasserman' test will be found, and (2) the hope that by finding the particular biochemical lesion underlying a disorder, it can be expected that its elimination would lead to the disappearance of the behavior disorder or its improvement. With the first aim I agree heartily, with the second I agree only in part. We should search for the biochemical causes but cure and amelioration of disorders of behavior may require more than correcting the biochemistry of the patient. Our wards are full of patients whose biochemistry is probably no longer disordered but whose behavior has become so imbedded in their daily life that further methods involving therapeutic or behavior modification approaches may be necessary.

Professor van Praag's chief concern is to determine whether mood and motor disturbances are accompanied by disturbances in the central monoamine (MA) metabolism and if whether these disturbances are nonspecific or specific to a given syndrome or nosological entity, and whether this disturbance is the cause or the effect of the behavioral disorder.

The fact that HVA increase goes along with the factor of motor agitation rather than with 'real' psychotic symptoms such as delusions and hallucinations is somewhat of a puzzle, but perhaps delusions and hallucinations are not such good criteria for psychosis, since Bleuler regarded them only as secondary signs.

While I am in no position to assess the biochemical side of the story, I did get a statement from one of my colleagues, Dr. David Dunner, who has been active in this field.
He points out that the development of the probenecid method at the hand of van Praag has aided considerably our understanding of amine metabolism in depression and in Parkinson's disease. The method employed, however, has been criticized as not producing sufficient blockade of active transport of acids out of the CSF. The values of HVA and 5-hydroxyindoleacetic acid, 5-HIAA, that van Praag reports, are considerably lower than those reported for the probenecid method used by the NIMH group (Goodwin et al., 1973). Secondly, at these lower concentrations of 5-HVA, the methods for assay of these acids have been questioned in terms of what is actually being measured (Perel et al., 1973). Although the results reported are in line with other studies, there is a question as to their actual predictive value since we do not know what chemical compounds beside HVA create the fluorescence in spinal fluid assays which is termed "HVA".

It is interesting to note that Dr. Sutton in our laboratory (Bruder, Sutton, Babkoff, Yozawitz, Gurland, & Fleiss, preprint) found a psychophysical measure which differentiate the same group of patients that Professor van Praag differentiated — the retarded depressives. Apparently this group of patients, and no other groups tend to benefit more from the addition of a 10 dB click after a 25 dB click separated by 15 msec in so far as their reaction time to this stimulus pattern is decreased. The other groups do not change in their reaction
time to this stimulus pattern. It is to be hoped that
the probenecid method and the auditory test can be applied
to the same patients to verify that the two types of reactions
actually occur in the same patients

Neurophysiological Model

Some of the striking findings in the neuro-
physiological model reported by Shaçass are the considerably
higher incidence of excessively stable and well regulated
EEG's in the "process" type of schizophrenia as contrasted
with the reactive type.

There were no other strikingly new facts
brought out in this area, but I was glad to see that the
sedation threshold is still operative and that interest
is still strong in photic driving which was a great interest
in the 40's and is now experiencing a revival. The big
breakthrough in quantitative
EEG work of the last decade and the finding that the coefficient of variation, CV of the integrated EEG amplitude in schizophrenics, is smaller than in normals — the only function I know of in which variability is less in schizophrenics — seems to have been brought into question. Shagass' failure to replicate this finding and the reversal he observed in females i.e. that female schizophrenics have a higher rather than a lower CV casts some doubt on the value of the original findings. The results yielded by comparing recordings from the two hemispheres also seems at the moment quite confusing.

In contrast with the global EEG findings which reflect the overall electrical activity of the brain, the evoked potential field has made definite strides forward. Shagas' early classic work on somatosensory responses seems to have held up, and now the evoked potential work has spread to the auditory and visual modalities in work with the mentally disordered. The problem of augmentors and reducers — Petrie's perceptual dimension — which were found in the visual evoked response, is somewhat baffling. I have often wondered whether expectancy may not play a role, since in at least some of the earlier experiments the stimuli were not presented randomly but sequentially in blocks. However, the finding that bipolar manic depressives are augmentors while the unipolars are reducers, is indeed a challenging finding.

The AER up until recently was studied for its mean amplitude only. Now that several automatic devices for measuring variability have come on the market we should expect
a spate of variability studies.

Shagass' finding of smaller SER variability in chronic schizophrenics than in normals during the first 0 msec is indeed striking. It speaks for greater rigidity or stability in the responsiveness of the evoked potential to sensory input, which occurs during the first 100 msec of the recording. In the subsequent portions of the AER, which deals with information processing, the variability of chronic schizophrenics increases over that of normals.

Shagass' recovery function of the SER is continued to be a useful method. The findings that not only depressives but schizophrenics and personality disorders also show reduced recovery in visual evoked potentials seems to make the recovery measure less unique. The problem of the reliability of the diagnoses may be one factor here, but beyond that, the clinical variables that covary with the recovery function need investigation.

The fact that clinical recovery is accompanied by normalization of the AER leads one to suspect that somehow this measure reflects the disordered process itself.

**Mixed Model**

Dr. Peter Venables' paper has presented me with a problem, because of its challenge as well as because it forced me to rethink the application of my models. His paper is concerned with two aspects — genetics, and with the state of arousal propagated by the autonomic nervous system which had not figured in my previous taxonomy. As for the genetic intrusion by way of high risk populations, this fits the models well.
As for arousal via the autonomic nervous system, I had reserved the neurophysiological model for information processing via the central nervous system. The autonomic nervous system and its state of arousal really belong to the idling state category—indicating the state of the organism before a stimulus hits it. In other words it conditions the reception of information but does not involve the processing of information. It is more like the carrier wave underlying all behavior on which various loads are imposed. However, if I were to find a place for variation in arousal in my models, I don't know whether the physiological basis for responding provided by the level of arousal may not be better regarded as part of the internal environment, closely tied up with the release or inhibition of metabolic energy. At all events, it's a puzzler. Furthermore, not all workers have taken the concept of arousal to their bosom, and the data in the area, though challenging, are far from very generally accepted.

The fast recovery rate—or slow habituation proneness characteristic of high risk populations presents Dr. Venables with a problem which he attempts to solve on the basis of the schizophrenic inability to gate out irrelevant responses or to being even more goal directed than the normal. There is, however, a more parsimonious simpler option. Why not apply Salzinger's (1973) immediacy hypothesis? If the schizophrenic is more bound to the immediately prior stimuli in time—or more contiguous stimuli in space—then it would follow
that he would appear more irrelevant, because paying attention to a stimulus just because it is present and not because it is important only makes for irrelevancy.

C. Summary

I have tried to summarize the outstanding contributions to this symposium and have tried to provide a framework for their classification. But I cannot leave this discussion without indicating the overall state of the art — that is, what place does measurement of psychobiological functions, as defined here, have in psychopathology and what is the role of changes in these functions. If one were to make ex cathedra statements regarding the state of the art, they might take the following form:

Generally speaking, subjects who are capable of changing under the load of a drug or some other type of intervention, usually change for the better under therapy. In the behavioral field, as an example, Salzinger (1973) has shown that the patients who increase the rate of emission of affective utterance tend to be released more quickly from the hospital. Any number of psychophysiological measures tend to be normalized with improvement, indicating that those who are flexible enough to change, also benefit from therapy. In most of the neurophysiological and psychophysical measures also, improvement in clinical status is accompanied by normalization of the measure
under consideration. Thus, Ritalin tends to normalize the $P_3$ component of the AER in hyperkinetic children, and the greater effect of uncertainty on the evoked potential disappears with improved clinical status (Pritchp, 1974). This tendency towards normalization presents an interesting question. Are the anomalous behaviors noted in mental patients traits which are invariably characteristic of their behavior or, are they state-dependent, occurring only when the patient is ill and disappearing towards normalcy when the patient recovers? If we assume that all mental disorders represent time-limited episodes induced by life stressors and that all patients recover from such episodes, then the behavioral indicators which we have found indicative of mental disorders may be of no significance when the patient is well, for they might disappear with improvement, as some of those we have discussed here, do.

Only those indicators which are independent of the presence or absence of an episode would remain of value for prognosis; the others might be used for detecting or confirming the presence of an episode when it does occur, and be used as an indicator of improvement when it disappears. However, it may be possible that for prognostic purposes, we may still use these indicators, by challenging the patient with a manageable stressor which would induce a mild reversible reaction, in order to determine the degree of vulnerability present. Thus, since about 10% of patients
treated with reserpine develop a depression (Harris, 1957), a screening technique has been developed for selecting the depression-prone so that such patients will not be subjected to reserpine. By challenging the patient with the mild challenge of the screening test, the presence of depression-proneness can be determined. This type of stressor can serve as a paradigm for testing the role of life-events in the "spontaneous" production of an episode of a disorder. Just as certain drugs like reserpine elicit depression, certain life events may also serve to trigger depressions or other mental episodes in a given patient, and the determination of which life events are a threat to the well-being of the person should eventually be detectable by some screening device. Whether the life event triggers the episode through biochemical interacting variables based on genetic predisposition or, whether the triggering occurs in some other fashion, is not so crucial at this point in time as is discovering which life events do the triggering.

**D. Proposals**

Having reviewed the field of psychobiological measures of change, it would be well to indicate what path the future work in this area should take. Unfortunately, there is no clear road ahead, and for this reason, I thought it best to outline for you the path our Biometrics Research Unit is taking in line with the descriptive categories of our Mendelejeff-like table we developed, and in line with the etiological models we have proposed.
Because of lack of time we shall single out the neurophysiological model, but these or similar techniques are equally applicable with some necessary adaptation to all the other models.

In order to develop techniques which would prove useful in diagnosis of mental disorders and in assessing change with treatment, such techniques should have the following characteristics:

a. They should be as simple as possible -- finger lift in RT for example -- and should involve the least number of options in performing the task. It is preferable to have a technique in which there is only one way to respond, so that we can pinpoint whether the subject was performing the way we thought he would perform, or not.

b. The patients should be described operationally in terms of their dimensional profiles based on structured interviews and pitted against specified criteria for diagnostic classification.

c. The techniques selected should not be subject to the criticism that they might reflect criterion differences (motivation and attitude) rather than sensitivity. For this reason, techniques in which patients "excel" normals in performance are highly desirable.

d. It should be possible to move iteratively from interview findings to laboratory findings and vice versa. In this way, laboratory findings on patients can help make better diagnostic differentiation, and this in
turn might rebound to better differentiation based on laboratory techniques. By thus interchanging independent with dependent variables, we might improve the precision of both.
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