ACNP OBSERVED

Joseph Zubin, Ph.D.

VA Medical Center, Highland Drive

and

Department of Psychiatry, University of Pittsburgh, School of Medicine

Prepared for historical perspective article for the 1986 Commemorative Program for the ACNP
Somehow I had always felt as an observer rather than as a full
hearted participant in the College. Not that I did not feel the
impact of the revolution that the drug era introduced or that I did
not become enthusiastic about the potential of chemotherapy for
psychopathology but, somehow I had the feeling that initially it was a
foreign substance introduced into psychopathology by serendipity and
not a natural development. This, despite the fact that long before
the revolution, back in 1951, I, together with my former chief, Carney
Landis, invested considerable effort in a study of the effect of
antihistamines on behavior (Landis & Zubin 1951a; Landis & Zubin
1951b; Cranston, et al., 1952). We had been approached by a drug
company which wanted to determine the side effects of a new
antihistamine, and after the usual negotiations about freedom in
publication, accepted. I undertook this study joyfully since my
undergraduate degree was an AB in chemistry and I savored the return
to an earlier love. It turned out to be quite exciting and we salved
our conscience about engaging in this esoteric work by recalling that
Kraepelin himself had succumbed to the lure of chemotherapeutic
intervention.

We had just emerged from the spell cast by psychosurgery with its
promise to reveal the secrets of brain functioning and its relation to
the mind and had just completed the now classic series of
psychosurgery studies in the Columbia Greystone series of topectomy
operations spearheaded by the late Fred Mettler, (Mettler, 1949 &
Mettler, 1952). Our frontal attack on the frontal lobes was the
challenge of a lifetime and the group of graduate students freshly recruited from returning World War II veterans threw themselves with the same zeal they had exerted during the world war into the new attack on the Brain of Schizophrenia. Little did we know that despite our enthusiasm and increased knowledge of brain function, chlorpromazine was to sideswipe our efforts and reduce us to an anachronism even before our results were published!* It may be that my resentment of having our efforts sideswiped by history is partly responsible for my initial cautious outlook on chemotherapy. Paul Hoch, our commissioner, who was never given to band wagons, Lothar Kalinowsky, who probably viewed neuroleptics as competing with his favorite ECT, Carney Landis and I regarded the claims of the psychopharmacologists with interest and tolerance from the Olympian view provided by the long train of drug therapies that had preceded neuroleptics - insulin, metrazol, barbiturates. But the revolution was of such magnitude, that the mere observer was soon pushed into the fray. I myself, with an interest in evaluation began to feel the need for instruments for measuring the changes observed by the impact of neuroleptics. A review of the available tests indicated that they could not be used to gauge change. They dealt more with basic constant features of behavior and were good enough for the era when

*Dr. Lothar Kalinowsky, on reading this essay, wrote me as follows: "One of the things that will interest you is that psychosurgery is still done with stereotaxic operations in England and Scandinavia. The topectomy project suggested by Mettler, got on the wrong track and helped eliminate psychosurgery in this country."
overt observable changes of the type introduced by neuroleptics were rarely observed. We had to revamp our approach and return to measuring the basic aspects of behavior beginning with physiological responses to stimulation and going on to sensory, perceptual, psychomotor and conceptual (now called cognitive) responses to stimulation. A Mendeleev-like table of the above types of responses under a variety of stimulating conditions was developed and served as a basis for examining the differences between schizophrenic patients and controls in each of the possible rubrics in the table (Zubin & Katz, 1964).

While we busied ourselves in our laboratory, the spread of the drug movement engulfed all of psychiatry and cries of misuse of drugs, warranted as well as unwarranted, filled the air. That is why Paul Hoch sprang into action, convened his cohorts and began planning a strategy for containing the revolution and appealing to the non-nocere ideal. This is how the ACNP started, as a self-defense against the tornado raised by the hopes engendered by the neuroleptics.

It soon became clear that not only instruments for rating objectively changes in behavior were needed, but that the classification of patients which up to then had had a purely academic raison d'etre, now became an urgent need. The reliability of diagnosis was found to be so poor that a need arose for establishing a new biometric unit in the department of mental hygiene which was headed by Paul Hoch as commissioner, to provide not only instruments to measure change, but also to establish objective bases for
diagnosis, prognosis and evaluation of outcome (Zubin et al., 1975). I was given the task of organizing this unit and of formulating its purpose and goals. This need was even more poignant when together with Morton Kramer we noted that not only were our diagnoses unreliable in this country, but they differed from the diagnoses in European countries (Kramer, 1969). This gave rise to the US-UK project (Cooper et al., 1972) to determine the reasons for the discrepancies between the two countries. This is how the systematic semi-structured interviews developed both in the Biometric Research Unit as well as in the Medical Research Council Social Research Unit in the Institute of Psychiatry in London. Biometrics became an important element in the development of neuropsychopharmacology because it provided means for testing the hypotheses raised by drug research and also provided a lingua franca for the multitude of sciences that interacted in neuropsychopharmacology. It provided psychopharmacology with a yardstick and a language as well as a conscience!

While drug therapy flourished, I became more and more involved in determining what changes they brought about and to this end began together with my colleagues in the Biometric Research Unit to investigate how the drugs affected behavior. Before doing so, however we needed to lay down baselines for measuring normative behavior. As a result, we developed a whole host of techniques in the physiological sensory, perceptual, psychomotor and conceptual areas. In order to
prevent drug effects from contaminating our results, we limited ourselves to studies of prognosis of undrugged schizophrenics before drug treatment became universal compared to normal controls. In this way, evoked potentials (P300 was discovered in the process) pupillography, cross-modal reaction time, critical duration in sensory responses were developed as well as verbal conditioning techniques for measuring flatness of affect, interviews for determining friendship pattern, social networks, all of which are now in use in evaluation of drug effects on the one hand, and in determining critical differences between schizophrenics and normal controls on the other (Zubin, 1985).

Among the outstanding contributions of the biometric approach was the provision of a reliability measure that was free of base-rate effects and chance. Jacob Cohen, (1960) one of our consultants had devoted considerable effort in that direction and developed the now classic measure, Kappa, and together with Joseph Fleiss, head of the biostatistics section, extended its application to a variety of needed problems.

While considerable progress had been made in refining the reliability of interviews and diagnosis, it was still necessary to find more behavioral criteria for the validity of diagnosis.

To this end, the Biometrics Research Unit, in addition to developing reliable semi-structured interviews, provided a series of techniques which could serve as "markers" for schizophrenia. These techniques have been presented first in 1979 (Zubin, 1979) at the
ACNP meeting of that year and subsequently in 1984 (Zubin, 1984) dealing with the state of the art as of that year. From the very beginning it appeared to me that the general tendency to regard schizophrenia as a chronic ailment leading to deterioration was negated by the effect of neuroleptics. As a result, I proposed a vulnerability hypothesis rather than a disease hypothesis for schizophrenia on the assumption that the schizophrenic is a vulnerable individual whose vulnerability remains latent unless it is elicited by internal or external stressors. However, the resulting episode is not a permanent state but an episodic one, waxing and waning with the degree of stress to which the schizophrenic is exposed. The function of neuroleptics is to fend off the effect of the stress. The presence of neuroleptics together with the cushioning effect of a good premorbid personality, a good social network and a good ecological niche will prevent new episodes (relapse) from developing and only when the stress increases despite these protective screens, does an episode emerge. Our group is conducting a series of studies to test out this vulnerability hypothesis. (Zubin 1963, Zubin & Spring 1977, Zubin, et al., 1985).

So much for the early history of ACNP and the impact it has had on measurement and biometric investigations.

It might be of interest to inquire whether the progress in neuropsychopharmacology has lived up to its promise. Comparing the success of biochemical interventions attained in such initially baffling mental disorders as general paresis, pellagra with psychosis
and PKU, we must admit that during the last three decades in which neuropsychopharmacology has held sway, the progress has been relatively minimal as far as cure and prevention are concerned. All we have succeeded in doing is maintaining the schizophrenic, for example, in a so-called tranquilized state, but as for cure or prevention, no progress has been made. Why should this be so. Are the functional disorders recalcitrant to neuropsychopharmacology, are our models too inefficient or is there some other obstacle?

Is it possible that our insistence on an exclusive biological etiology may be at fault?

There have been many attempts at answering this question. I believe that one of the most salutary approaches is to widen the scope of potential etiologies by adopting the vulnerability or diathesis stress hypothesis. This permits the entire panoply of scientific models to be considered, ranging from the ecological model, developmental, learning, genetic, internal environment, neurophysiological to neuroanatomical (Zubin, et al., 1985). Neuropsychopharmacology has an important role to play especially in the last four models listed above, but it is only one of the approaches among others. Recognizing this fact, and removing the imperialism which may have characterized some neuropsychopharmacologists, the future developments become easier to consider.

If we adopt the concept of vulnerability and accept the need for a stressor to elicit an episode in the vulnerable, the role of
neuropsychopharmacology in intervening to eliminate or reduce the stress below threshold seems to be a natural option. If the immune system and the neurohumoral system are involved in the development of stress, the neuropsychopharmacologist will have an important role to play in preventing the triggering stress from developing. But it must be remembered that other factors such as social networks, ecological niches and premorbid personality also play the role of moderating variables in lowering, preventing or absorbing stress. The need for collaboration between the disciplines dealing with these factors becomes the goal of the future of interdisciplinary research.

Of late, I have noted, that the early interest and acceptance of biometric contributions to the annual meetings has declined. Why this should be so, is a puzzle. As you look over the list of new members, it becomes clear that biometric neuropsychopharmacologists are an endangered species. When the current generation of Wittenborns, Burdocks, Hardestys, Overalls, Lorrs, Fleisses, Spitzers and Endicotts passes on, who will take their place? I can not believe that the biometricians are no longer needed, that they have worked themselves out of a job! No science can be better than its measurement level. How to attract neuropsychopharmacological biometricians is an important issue. The problem is: Can we make the next generation of biometricians in neuropsychopharmacology less alienated and give them a feeling of belonging to the mainstream of progress rather than be mere handmaidens for analyzing data?
References


