Personal Perspective on Evolution of Neuropsychopharmacology and Currently Emerging Trends

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Contribution to Past Presidents' Statement for the 25th Anniversary of ACNP.
I. Events Critical in the Development of NPP.

The see-saw between the biological and environmental causes of mental disorder has a long history. In the early decades of this century the victories achieved by the discovery of the bacterial origin of infectious disorders encouraged psychiatrists to search for similar etiologies for the mental disorders. The infectious disease model was successfully applied to general paresis by Julius Jauregg von Wagner, (1918) the search for the cause of pellagra with psychosis was undertaken by the epidemiologist, Joseph Goldberger, (1914) and the focal infection theory was proposed by Henry Cotton (1922). Goldberger found the cause of pellagra with psychosis to be due to a deficiency in the diet (later found to be the absence of nicotinic acid) while Henry Cotton's focal infection theory was demolished by the first clinical trial in psychiatry conducted at the New York State Psychiatric Institute by Kopeloff and Cheney (1922). The role of biochemistry in the etiology of schizophrenia was foreshadowed by Kraepelin (1892) in his studies of the influence of drugs on simple psychological processes. He introduced psychotomimetic techniques, regarding alcoholism as a form of temporary artificial "insanity", and under controlled conditions experimented with the effect of alcohol, trional, paraldehyde, sodium bromide and caffeine. However, the impact of these biologically based theories and experiments dissipated in the 20's and only sleep therapy and the ineffective use of barbiturates and similar drugs persisted. The rise of psychoanalysis sideswiped the purely biological methods. Somatic therapies rose
again in the thirties with the introduction of metrazol shock therapy (later replaced by ECT) and insulin therapy and subsequently psychosurgery. These drastic methods seemed to have been acts of desperation in a heroic attempt to utilize them as a last resort in intractable cases. Neuropsychopharmacological methods were less invasive, required no heroic efforts and accomplished results in much shorter time, relatively speaking. The speed of the behavioral changes were so dramatic that it challenged the therapist to provide measures of the degree of change and the corresponding relation to dosage. For the first time in psychiatric history, psychotic behavior could be altered before your very eyes and the need for measurement and evaluation became manifestly apparent. This caught the measurement experts - mostly psychologists - unprepared, since all the available clinical tests and tools provided static measurements like intelligence tests or projective techniques which were geared to trait rather than state measurement. Rating scales had to be produced practically overnight by such pioneers as Malamud* (Malamud et al., 1946) - and more elaborate techniques by Wittenborn (1959) and Lorr (1954).

*There is probably an apocryphal story told about the physiologist, Hoagland, who found some biochemical change in Malamud's patients and asked to see Malamud's data on the same patients. Malamud handed him his voluminous case histories. "Are there no numbers here on their behavior," Hoagland inquired, to which Malamud cried, "No, but if you want numbers I'll make them up for you." That night with the help of Sands he converted his descriptions of behavior into rating scales.
The success of the drug therapies also required better classification of patients in order to obtain more homogeneous groups. To fill this need the free floating clinical interview had to be converted from a blunderbus into a sharpsbooting rifle. Systematic semi-structured and structured interviews resulted (Present State Examination, Psychiatric Status Schedule, etc.) Their use in the US-UK Diagnostic Project (Cooper, et al., 1972) and in the WHO International Pilot Study of Schizophrenia (1974) were the proving grounds in which these instruments were fire-tested. These projects roused diagnosis from its academic lethargy and finally led to the developments of such instruments as the SADS, DIS, Research Diagnostic Criteria, and the DSM-III classification system.

It must be pointed out, however, that the revolution in psychopathology was not due to pharmacological intervention alone. Even before the drug era, the opening of the hospital doors in European hospitals, especially in England, had brought about better outcome results. But, the dramatic effect of the drugs electrified the field.

II. Important methodological and conceptual advances in recent years.

It is clear that the advances in descriptive psychiatry through the improvement in diagnosis and the introduction of neuroleptics stand at the top of the list. Conceptually, the dopaminergic and adrenergic hypotheses are the most striking advances. However, the rise of the diathesis stress model especially in the form of the
vulnerability model has provided a most promising view of the nature of mental disorder, especially schizophrenia (Zubin et al., 1985). It gives promise of altering our view of schizophrenia from a permanent deteriorating condition to a more hopeful view of a state of vulnerability which need not inevitably persist nor lead inevitably to a deteriorated end state.

III. Experimental clinical findings.

The vulnerability model has encouraged the search for markers of vulnerability for identifying vulnerable individuals even before an episode develops and thus raised the hopes of potential prevention of even the first episode and its subsequent repetition. While these markers are not all linked to the neuropsychopharmacological domain, they include such intriguing possibilities as platelet MAO activity (Zubin, 1979). Another contribution from the neuropsychopharmacological domain is the search for episode markers, demarcating the beginning and end of episodes. Among these are the ritalin and apomorphine challenges for schizophrenia and the dexomethasone test for depression (Zubin, et al., 1985).

The role of the immune system as a potential base for measuring stress which may be the agent which triggers episodes in the vulnerable, is another avenue which is potentially exploitable and, of course, the development of CAT Scans, PET Scans and Nuclear Magnetic Resonance techniques for assessing the integrity of the brain are advances which are bound to uncover important new etiological leads.
The role of psychosocial factors such as social networks, premorbid personality in which the development of coping skills are embedded and the ecological niche occupied by the individual are another potential group of factors which, if they do not contribute to etiology, at least determine the triggering of episodes, their duration, relapse and general outcome of illness. The relative role of psychosocial and neuroleptic therapies in outcome of schizophrenia is one of the exciting issues of the day and their interactive use undoubtedly will prove to be superior to each in isolation.

IV. Interdisciplinary Linkage.

There are at least 7 etiological models vying for supremacy in the etiology of schizophrenia (Zubin, et al., 1985) (and of the other mental disorders): ecological, developmental, learning, on the environmental end of the spectrum and genetic, internal environment, neurophysiological and neuroanatomical on the biological end of the spectrum (Zubin, et al., 1985). None of these are necessary and sufficient in themselves, but their interaction may turn out to be so. That is why the future belongs to the laboratories where each of these models are fully represented. Since the vulnerability model provides a place for each of these disciplines in the etiological emporium, it can well serve as an integrating force in the collaboration of all of these disciplines from the environmental and biological spheres.
REFERENCES


