TILAK VENKOBABA RAO ORATION

PSYCHOIMMUNOLOGY AND FUNCTIONAL PSYCHOSES: THE INDIAN SCENE

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Mr. Chairperson, co-chairperson, my teachers sitting in this august audience, members of our society, distinguished guests, ladies and gentlemen:

This morning in beautiful city of Lucknow, I have been selected to deliver the "Tilak Venkoba Rao oration" which is indeed a landmark step in my career for a variety of reasons. I am fortunate that I am delivering this oration in the city of my alma mater where I have grown worthy of this oration. I owe a lot to my alma mater and to my revered teachers particularly Prof. B.B. Sethi who brought about a revolution in biological psychiatric research at Lucknow center. I have never met Tilak but as much as I know about him, he was a worthy son of worthy parents Prof. Venkoba Rao and Dr. (Smt.) Parvathai Devi. I pay my regards to Tilak and I am sure that the institution of this award after his name will always encourage behaviorists to research newer areas in the field of biological psychiatry.

Before I deliberate upon the main body of oration, I must thank my parents and my parents-in-law who are also sitting in audience for this prestigious day of my career without whose blessings this achievement could not have been possible. Lastly, I must thank my wife Smt. Shweta Tiwari who is also present here and whose love and constant encouragement and sacrifice has enabled me to see the dawn of this momentous day in my life.

BACKGROUND

My interest in psychoimmunological studies was triggered off by my first research work on the viral hypothesis of functional psychoses, which was principally an immunological study and also because of curiosity to observe etiological correlates of mental disorders in the laboratory test-tube.

The term 'immunopsychiatry' (or psychoimmunology) was introduced by Jankovic to denote the involvement of immune processes, both humoral and cell mediated, in the pathogenesis of certain mental disorders. The term did not appear de novo, but because of certain important observations which made it imperative:

a) in vivo effects of antibrain antibodies on the bioelectrical activity of brain structures and behavior (Mihailovic & Jankovic, 1961);

b) the speculation that schizophrenia is an immunological disorder (Health & Krupp, 1967);

c) the modulation of learning and memory by means of antibrain antibodies (Jankovic, 1985);

d) alterations in immune status following viral infections and the proposed viral hypothesis of schizophrenia (Torrey et al, 1978);

e) the correlation between cerebral atrophy of unknown origin and cell mediated immunity (Jankovic et al, 1977).

The first three experimental and clinical studies have dealt with the activity of antibrain antibodies (e.g. humoral immunity), the fourth with both humoral and cellular immunity, whereas the last one relates to the role of cellular immunity in the pathogenesis of psychiatric disorders (Jankovic, 1985). These findings provided the much needed theoretical basis for immunologic research in mental disorders. Though inconclusive, these investigations have been instrumental in at least heralding a new era of scientific inquiry into the hitherto unknown etiopathogenesis of mental disorders.

The development of immunological research in psychiatry has an uneven history. A preliminary outline of the immune system's capability to resist infections was delineated by the end of the 19th century. However, investigations of the relationship between the central nervous and immune systems began after almost three decades with Sir Thomas Lewis' study of the "Triple Response" in 1920. This was followed in the next two decades by Speransky's (Pavlov's colleague) conditioning studies exhibiting the effect of the CNS on immunopathologic phenomena and by Selye's description of the CNS - pituitary - adrenal axis effects on the immune function at many levels.

This initial period of enthusiasm was followed by a major swing away from the study of the nervous system's possible influence on the immune system, because of the then gathering evidence that the immune system can function independently and
autonomously, and this negative phase lasted for a quarter century or so (Waksman, 1985). However, with subsequent developments in molecular biology and immunology, both in terms of understanding and methodological innovations, a large body of experimental evidence has gathered during the last two decades which points towards the existence of complex interactions between the nervous and the immune systems (Felten et al, 1985). With this knowledge, psychoimmunology has not looked back; since then the development of immunological research in psychiatry has run parallel to that of immunology, reflecting methodological and theoretical advances made in the latter field.

**RESEARCH STRATEGIES**

Immune alterations manifest either into overactive or into underactive immune responses. If the source of immunogen is endogenous, the resultant immune disorder is autoimmunity in the case of an overactive immune response, and malignancy in the case of an underactive response. If the source of immunogen is exogenous, the resultant immunological disorder is an allergy in case of overactive immune response and infection in the case of an underactive immune response. Investigative strategies in psychoimmunology have progressed along these four lines. The majority of research in psychoimmunology commenced in the 1960's, though evidence of a dysfunctional immunological system in psychiatric disorders were already present since the early 1900's. Both immune overactivity and underactivity have been extensively investigated. The 1970’s and 1980’s have seen revitalized activities in this area with the appearance of new centers in which involvement of the immune system in endogenous psychoses has been extensively examined.

A number of centers across the globe are examining these matters, but the contributions and coordinating activities of the W.H.O. in promoting immunological research in psychiatry deserves special mention. The division of mental health of the W.H.O. has, since 1978, organized one or two symposia each year as part of the World Congress of Biological Psychiatry, at which results of research in this field are discussed. A program entitled 'Antithymic Antibodies in Schizophrenia', involving seven research centers, took place between 1973 and 1978 under the aegis of the W.H.O. The results of this program are set out in a joint publication and have served as the basis for further development of immunological studies at a number of centers (Kozzakina et al, 1980). In recent years, two conferences devoted entirely to 'Viruses, Immunity and Mental Disorders' were organized with the help of the W.H.O. (Louvain, Belgium, 1983; Montreal, Canada, 1984), and the results have been published in two monographs (Morozov, 1983; Kurstak et al, 1987).

In the assessment of over and underactive immune responses, both humoral and cell mediated immunological parameters have been investigated. In addition, other biological parameters which are thought to be linked with the immune system, such as hormones, neurotransmitters, enzymes, etc., have also been investigated. There is an exhaustive list of such investigations, but they have mainly been carried out in Western countries. This reflects the accessibility to resources, methodological and technological advancements etc. In India, these issues have played a detrimental role in research development in almost every field of medical science including psychoimmunology. Isolated studies are available from a few centers and the majority of work in this area has been carried out by us at Lucknow. Only functional psychoses have been investigated in India, though other mental disorders such as stress related disorders, drug addictions, etc. have been investigated elsewhere in the world. What follows is the narration of our activities and future plans in this field.

**PSYCHOIMMUNOLOGICAL RESEARCH: THE INDIAN SCENE**

**Contribution of Lucknow center:**

The very first study in this area in India was carried out at Lucknow center and it reported that all cases of schizophrenia studied had atypical lymphocytes (Sethi & Sethi, 1971). The study did not attempt to differentiate between T and B lymphocytes, nor were their functional aspects investigated. Perhaps, the study was not planned from an immunological perspective.

The second study in the country was also carried out at Lucknow center in 1976-77 by Dr.R.S. Pandey and colleagues. This work had the autoimmune hypothesis in the background and overactive immune response was investigated in schizophrenic subjects employing antigens specifically prepared from different area of brain tissue. A total of 54 schizophrenic and 27 non-schizophrenic medical patients were studied. Antigens were prepared from the frontal cortex, structures of the Limbic system,
and parts of the extrapyramidal system from a 35-year-old man who had died 2 hours after an automobile accident. Antibodies against these antigens (antibrain antibodies) were studied in the serum and CSF of experimental and control subjects.

It was found that antibrain antibodies were present in the serum and CSF of 48.1% of the schizophrenic patients and in none of the control subjects, with high titers of antibrain antibodies being present only in serum. There was no significant difference in the antigenicity of the three antigens. Further, it was found that antibodies were more commonly found in serum and CSF of those schizophrenics who had a longer duration of illness, more episodes, positive family history for schizophrenia, and who received the diagnosis of chronic undifferentiated schizophrenia (Pandey et al. 1981). The study results favored the autoimmune hypothesis for schizophrenia. There is no other report of this nature from the Indian subcontinent. There is an enormous amount of literature on this issue from western countries, but till date the status of the autoimmune hypothesis remains controversial (Ganguly et al. 1987; Koljaskina & Prilipko, 1988).

Psychoimmunology became the area of my interest in the late 1970’s when the viral hypothesis of functional psychoses was regaining ground (Torrey et al., 1978). The first study which I planned was on immunoglobulins and viral antibodies in schizophrenic and depressive patients (Tiwari, 1982). This, my maiden attempt, explored the possibility of an underactive immune response in functional psychoses. I had two objectives in mind, the first being to study the pattern of immunoglobulins and anti-viral antibodies in the serum and CSF of schizophrenic and depressive patients, and the second being to study the relationship between illness variables and immunological parameters.

The sample for the study comprised of 30 schizophrenics, 30 depressives, 20 controls (non-psychiatric, non-neurological surgical patients scheduled to be operated under spinal anaesthesia), and, in addition, 20 neurological controls of either unknown, multiple, or doubtful etiology. All patients and controls were recruited following stringent inclusion and exclusion criteria. Total CSF protein, humoral immunoglobulins G, A and M antibodies against rubella (hemagglutination inhibition antibodies) and against cytomegalovirus (complement fixing antibodies) in the serum and CSF of all subjects were investigated. Part of the results have been published (Tiwari et al., 1984, 1989 & 1990). Essentially, it was a negative study and the results were neither in favor of an underactive immune response, nor in favor of the viral hypothesis of schizophrenia and depression. Instead, part of the results favored an overactive immune response and thus provided some supportive evidence for the autoimmune hypothesis. Nonetheless, some of the observations deserve special mention.

Of the depressives in this study, 33.7% had raised total CSF proteins - a pattern also noticed in neurological patients. Serum IgG was significantly higher in depressives and in neurological controls, whereas serum IgA was significantly higher in schizophrenia, depression and neurological controls. IgM was within normal limits. In the CSF, IgG was detected in all subjects, and was significantly higher in schizophrenics, depressives and neurological subjects, whereas IgA was detected in the CSF of only 23% depressives and 25% neurological patients and IgM was detected only 25% of neurological patients.

The hemagglutination inhibition (HI) antibodies against rubella virus, tested in the lowest and highest dilutions of 1:20 and 1:1280 respectively, were found in the serum of all the subjects and the incidence of seropositive cases and the geometric mean of antibody titres were found to be higher (but not statistically significant) in schizophrenic, depressive and neurological subjects as compared to surgical controls. HI antibodies were not detected in the CSF of any of the subjects. The complement fixing (CF) antibodies against cytomegalovirus, tested in lowest and highest dilutions of 1:8 and 1:256 respectively, were found to have a pattern similar to HI antibodies and these two were not detected in the CSF of any of the subjects. The immunoglobulin levels were found to be significantly higher in the serum of schizophrenics and depressives and had a direct relationship with the total duration (longer duration) of illness, number of episodes (more episodes) and positive family history.

When an infectious agent, such as a virus, is suspected to be the cause of a particular diseased state, the immune response is usually expected to be hypoactive. However, in this study, an almost opposite trend was noticed, thus apparently refuting the viral hypothesis of schizophrenia and depression. However, it is known that certain viruses in certain circumstances trigger an autoimmune response either by affecting the B lymphocyte or the T lymphocyte regulatory function. Do, then, the increased
immunoglobulins in this study indicate the presence of viral infections? As anti-viral antibodies were not detected and T cells were not investigated in this study, no conclusions can be drawn. Do these observations, then, favor the autoimmune hypothesis? For an autoimmune disease, there should be, besides elevated immunoglobulins, presence of various auto-antibodies, depressed levels of serum complement, immune complexes in the serum, depressed levels of T suppressor cells, etc. None of these variables were investigated and, therefore, any inference about autoimmunity will be far fetched.

The results of the study, however, did indicate that depressives in many immunological aspects resembled neurological patients who were of either unknown, multiple, or doubtful etiology (Guillian-Barre syndrome (6), motor neurone disease (4), idiopathic epilepsy (5), cerebellar ataxia (3) and Parkinson's disease (2) (a total of 20 patients). This was the most important finding of the study and provides enough ground for future immunological research.

Our second major work in the area of psychoimmunology was the result of our previous work and the unconfirmed reports in the literature that psychotropic drugs have an adverse effect on immune function. The work was carried out in 1987-88 and was entitled, 'A study of the effects of psychotropic drugs on humoral and cell mediated immune responses in schizophrenics and depressives'. The work was carried out by Dr. D.K. Agarwalla, a postgraduate psychiatry student, under my co-supervision and part of the results have been published (Agarwalla et al, 1991). Thirty subjects (12 drug naive and 18 total drug free for 3 months) each of schizophrenia and depression were recruited along with 15 healthy volunteers (controls) for the study. In all of these subjects, quantitative assessment of the immune system was done by assaying the humoral (IgG, IgA and IgM) and cellular (T and B lymphocyte) fractions in peripheral blood. Qualitative assessment of immune function was done in vivo by the PHA (Phenyl hemagglutinin) skin test. Both the quantitative and qualitative assessment was done at base line, and after 2 and 4 weeks of treatment. To test whether clinical improvement in patients was the result of immunopotentiation by psychotropic drugs, the improved schizophrenics and depressives were compared with non-improved groups and it was found that the immunological profile of the two groups did not differ.

This study raised some important questions. Is immune profile unrelated to schizophrenic and depressive psychopathology? Is immunopotentiation a non-specific phenomenon, particularly in terms of clinical improvement? Is immunopotentiation in any way related to the course and outcome of schizophrenic and depressive pathology? These issues remain unanswered by our study. It may be speculated that there is a non-specific immunopotentiation by psychotropic drugs used in the study in the initial phase of treatment which might return back to the preexisting state during the later course of therapy, or else, if the elevation persists, it is simply non-specific. Perhaps, a long term study might answer some of these questions.

These findings indicate that neuroleptics and antidepressants cause immunomodulation, more specifically immunopotentiation. This observation and reports of immunomodulation in the literature (Vertanian & Koljaskina, 1987) inspired us to take up the third work in the field of psychoimmunology in 1989-90. Dr. Sanjay Agarwal, another postgraduate student, carried out the work entitled 'Role of an immunomodulator in the treatment of schizophrenics', under my co-supervision. It was based on the observation that there is a hyperrespon-
sive B cell functioning (increased production of humoral immunoglobulins) in schizophrenics due to diminution in regulatory activity of T suppressor cells, secondary to a reduction in the number of T suppressor cells. This led to the hypothesis that by use of an immunomodulator, T suppressor cell functioning can be corrected which will eventually correct the hyperresponsive B cell functioning (Vertanian & Koljaskina, 1987). This work of ours was the result of this hypothesis, and we attempted to study the efficacy of an immunomodulating agent, levamisole, using the agent as adjunct to neuroleptics in the treatment of schizophrenia.

Thirty four schizophrenics, recruited following rigorous inclusion and exclusion criteria, underwent a six weeks trial in which eighteen patients (experimental group) received levamisole and chlorpromazine alone following randomization. Chlorpromazine was given in a dose of 15 mg/kg body weight per day for the study period, and levamisole in the dose of 150 mg twice a week throughout the study. Immunological parameters (IgG, IgA, IgM and C3, C4 complements, T cells, B cells and T suppressor cells) were studied on day 0 (baseline) and on days 21 and 42. These observations have been very encouraging. The study revealed that T suppressor cells are decreased in number in chronic schizophrenics. On treatment with levamisole, this decrease is corrected and the schizophrenics showed corresponding clinical improvement as well. Moreover, the coefficient of correlation revealed that this increase in T suppressor cell number is significantly correlated with the improvement in the psychosis. The observations thus indirectly support the autoimmune hypothesis of schizophrenia and also provide evidence that chronic schizophrenics respond better to conventional neuroleptics when treated in combination with levamisole. The only limiting factor in the study was a small sample size, and there is obviously a need for a larger study.

OTHER INDIAN CONTRIBUTIONS

Only a few other workers have attempted psychoimmunological studies in schizophrenia. Rao and associates at NIMHANS, Bangalore, studied serum immunoglobulins in schizophrenics as compared to controls (Rao et al, 1985). The investigators studied the effects of treatment and illness profile on immunoglobulins. It was a negative study and no association / correlation could be established. A similar work has been carried out at the Department of Psychiatry, Institute of Medical Sciences, BHU, under the supervisorship of Dr. I. Sharma (personal communication). The results are yet to be published. I am not aware of any other work in this field by any other center in the country.

CURRENT ACTIVITIES AT LUCKNOW CENTER AND FUTURE DIRECTIONS

Another study which has been planned is about the genetic aspects of psychoimmunology. Schizophrenic and depressive probands with family history of illness in their first degree relatives are to be investigated. In particular, T suppressor cells are to be studied which have almost conclusively been shown to play a role in autoimmune diseases.

Till date, inspite of concerted and sincere efforts, no definite direction could be delineated, except that in our most recent work, we could detect decreased T suppressor cell numbers. This observation and findings of increased levels of immunoglobulin does indicate the possibility of an autoimmune aetiology of schizophrenia. Further, in our first study, we found similarities between depressives, schizophrenics, and neurological controls of unknown, doubtful or of multiple etiology, particularly with Guillain-Barre syndrome for which a viral etiology is proposed. With these findings we stand at a crossroad, and are eager to pursue both roads, i.e. that of autoimmune and of a viral hypothesis.

No doubt, the future of psychoimmunology is promising and several avenues are open for further research. Besides autoimmunity and infection (viral?), the other roads which could be travelled are that of immunogenetics and allergic / hypersensitivity reactions in the understanding of the complex aetiopathology of functional psychoses. Internationally, this area is being pursued vigorously and all aspects of immune function including genetic, biochemical, endocrinial etc., are being investigated. India is rich with fresh and untreated patient populations with adequate climatic variations and, therefore, the country should provide the most fertile ground for psychoimmunological research.

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