The History of Schizophrenia Research in Japan

by Hiroshi Utena and Shin-Ichi Niwa

Abstract

When schizophrenia research began in Japan in the late 19th century, it mainly followed the German school. Since World War II, however, Japanese research has been more influenced by the developments in American psychiatry. The research in Japan has included studies in epidemiology, histopathology, cerebral metabolism, animal models using amphetamine, postmortem brain chemistry, psychophysiology, psychopathology, and protective intervention from relapses. Principal domains of current studies are subjective phenomena in psychopathology and biological correlates of cerebral dysfunctioning in schizophrenia.

In the latter half of the 19th century the forerunners of modern Japanese psychiatry borrowed heavily from existing European knowledge and practice. Shuzo Kuré (1866-1932), considered to be the founder of modern Japanese psychiatry, became a professor of psychiatry at the University of Tokyo in 1901 and superintendent of Sugamo Mental Hospital (Tokyo) after studying psychiatry in Germany under Professor E. Kraepelin. Thus, the prevailing concept of schizophrenia in Japan was Kraepelinean and remains very much so today (Kuré 1894/1916). Kuré and his students made a pioneering survey of people suffering from schizophrenia and documented the neglect and lack of care for these individuals (Kuré 1918/1973).

Shortly after the establishment of modern psychiatry in Japan, the Kyoto school of thought evolved. It was heavily influenced by French nosology and the ideas of its adherents were far more liberal than those of the Kraepelineans. Theories of the psychogenesis of schizophrenia (Murakami 1946/1971) and the concept of atypical psychosis (Mitsuda 1967) were outgrowths of the Kyoto school. Yushi Uchimura (1897-1980), a student of Kuré, introduced the ideas of K. Jaspers and K. Schneider, translating Jaspers' *Allgemeine Psychopathologie* into Japanese in 1953, before the English edition appeared. The prime concern of most Japanese research psychiatrists of the 20th century was schizophrenic psychopathology because the majority worked with inpatients in hospitals. Thus, Japanese psychiatrists readily accepted *DSM-III* (American Psychiatric Association 1980) with its operational and descriptive criteria.

Post World War II Research

After World War II, the National Institute of Mental Health of Japan was founded and closely followed American trends, with Japanese research also focusing on sociopsychological aspects of schizophrenia. Multidisciplinary studies of interpersonal relationships in families of schizophrenic patients were conducted under the leadership of Tsunero Imura (1906-81). Most noteworthy were his objective assessments of disturbances in empathy and communication (Imura and Kawakubo 1966), which were strongly influenced by the works of H.S. Sullivan.

Epidemiological studies on schizophrenia based upon community surveys, initiated by Yushi Uchimura and Haruo Akimoto in the 1930's, roughly estimated the prevalence rate

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of schizophrenia and the morbidity risk among family members of schizophrenic patients before World War II (Uchimura et al. 1940). Their findings were similar to those obtained by epidemiologists in European countries during corresponding years. This similarity was noteworthy in that the result was obtained in a uniquely non-Western industrialized country. Twenty years later, Hisatoshi Mitsuda (1910–79), known for his pedigree studies, proposed the concept of atypical psychosis, which stemmed from the clinicogenetic studies among relatives of schizophrenic, affective disorder, and epileptic probands (Mitsuda 1967).

Inouye’s (1970) proposals on the three subtypes of schizophrenia were also based on clinicogenetic studies. Comparing clinical characteristics of schizophrenic patients between concordant and discordant twins, he identified the chronic progressive type, the relapsing type, and the chronic mild or transient type. More recently, studies on the incidence and outcome of schizophrenia have been conducted by Ryo Takahashi and Yoshibumi Nakane in Nagasaki in collaboration with a World Health Organization project on the epidemiology of schizophrenia (Nakane et al. 1985; Nakane et al. 1992, this issue).

Michitomo Hayashi (1885–1973), who was a student of Professor Kuré and a highly respected neuropsychiatrist and neuropathologist, pioneered research in cerebral metabolism. In 1948 he organized a schizophrenia research group supported by a grant from the Ministry of Education. At that time he was able to measure the cerebral arteriovenous differences in blood gas concentrations of schizophrenic patients. He correlated these differences with the course of schizophrenic episodes and found that in times of symptom remission there was an overproduction in the venous carbon dioxide concentration, indicating an increase of the respiratory quotient (Hayashi 1950).

Stimulated by the work of Hayashi, Utena measured the in vivo glucose uptake and respiratory rates in cortical brain tissues taken during prefrontal leukotomies, a common treatment of the time. Using control groups of mentally ill and severely neurotic patients, Ut ena found that chronic schizophrenic patients demonstrated a significant reduction of glycolysis, with no change in oxygen uptake or carbon dioxide production (Utena and Etoz 1951). Two subjects with methamphetamine psychosis with deleterious course also displayed reduced glycolysis. This finding triggered the formulation of the chronic amphetamine intoxication animal model of schizophrenia.

Studies of Amphetamine Psychosis

In the 1950’s there was a sharp increase in the use of illegal amphetamines in Japan, which led to an epidemic of amphetamine psychosis with symptomatology strikingly similar to that of schizophrenia. The report by Tatetsu and his colleagues (1956) on the phenomenology and clinical course of amphetamine psychosis provided the foundation for subsequent studies and was substantiated by a similar report in Britain (Connell 1958). However, unlike Connell, Tatetsu pointed out that some amphetamine-abusing patients demonstrated a chronic and relapsing course of the psychotic state even after abstinence. This finding opened the way to the development of the chronic amphetamine intoxication model of schizophrenia. Ut ena and colleagues initiated animal studies of amphetamine intoxication (Ut ena et al. 1959; Ut ena 1961), administering methamphetamines to guinea pigs for long periods and measuring their brain metabolism. Alterations similar to those found in schizophrenic patients were seen in vitro metabolism of the brain tissue of the guinea pigs, that is, a reduction in glucose uptake with normal tissue respiration. Although the functional significance of this finding was then obscure, the behaviors of the intoxicated animals were indeed abnormal, suggesting that an animal model of schizophrenia had been discovered (Ut ena 1966).

In acute animal experiments, amphetamines produced stereotyped motor excitement (Randrup and Munkvad 1967, 1968) which appeared to result from stimulation of the dopaminergic system. Experiments with rats documented that chronic administration of amphetamine elicited a prolonged and stereotyped behavior pattern in which rats became supersensitive and intolerant to amphetamines (Sato 1979). Sato and colleagues (1992, this issue) described this process in terms of chemical kindling. Stereotyped behavior patterns could be elicited by stressful events, even when the animals were not given amphetamines but were in supersensitive states. Hada and colleagues (1979) reported that the behavior could be easily conditioned by using a buzzer. In addition, Ut ena (1978) found that motor retardation, indifference to surroundings, and impoverishment of behavior patterns also lasted for prolonged periods after stereotyped excitement had been observed. These dysfunctional “autistic behavior” patterns were observed after long-term administration of amphetamines in guinea pigs, mice, cats, and monkeys (Machi yama et al. 1970).
The validity of the amphetamine model of schizophrenia has been strengthened by similarities between the neuropathology of postmortem brains of schizophrenic patients and human and animal brains intoxicated with amphetamines (Palma and Sotelo 1952; Tatetsu 1964; Senitz and Winkelmann 1981). The research conducted by Utena and his colleagues on the amphetamine model of schizophrenia has had repercussions on the delineation of positive and negative syndromes in schizophrenia. These are illustrated in Machiyama’s article (1992, this issue). Furthermore, experiments with monkeys dependent on amphetamine highlighted the role of premorbid behavioral traits as determinants of the model psychosis, a finding that is consistent with the vulnerability-stress conceptualization articulated by American researchers (Zubin and Spring 1977; Nuechterlein and Dawson 1984; Liberman et al. 1987).

Psychosocial Treatment Research

In 1958, Utena and his colleagues in the Department of Psychiatry at Gunma University started a 5-year project aimed at preventing relapse in schizophrenia. A combination of neuroleptic drug therapy and counseling and support for development of living skills was administered to protect patients from the noxious effects of stress superimposed upon vulnerability. Results of this project were not promising in terms of actual reduction of relapses; however, the project produced a Japanese version of social skills training called “Seikatsu Rinsho” or clinical work in daily living (Yuasa 1972). The patients participating in this project followed up more than 20 years later; half of them were self-supporting (Ogawa et al. 1987).

These encouraging findings were paralleled in similar long-term follow-up studies from Europe and the United States (Harding et al. 1987). Clinical researchers in Japanese psychiatry have long been interested in the phenomenology of subjective experiences and the sense of “self” of schizophrenic patients, hoping to use such understanding to develop better therapeutic approaches. Toshiki Shimazaki (1912–75) opened an anthropological vista to studies of thought and experience in schizophrenia in the 1940’s, which was beyond the contemporary descriptive psychiatry. His book “Illness and the Person” was published after his death (Shimazaki 1976). The Kyoto school of phenomenology, deeply influenced by Japanese and German existential philosophy, popularized the view of a transcendental “other” merging with the “self” of schizophrenic patients (Kimura 1975). Nakai (1974) delineated naturalistic stages based on longitudinal studies of schizophrenia. A comprehensive framework of the mental functioning of schizophrenic patients in terms of spatial conceptualizations was formulated by Yasunaga (1977), who named his work the “phantom space theory.”

Recent Biological Research

Japanese psychiatry suffered a period of confusion and stagnation from the latter half of the 1960’s through the 1970’s. The younger generation of psychiatrists joined the counterculture, participating in radical activities and occupying hospitals and clinics. The antipsychiatry movement was fueled by Maoism and an upsurge of sociopsychological interests in psychiatry. The Japanese Psychiatric Society was thrown into near chaos and laboratory research activities ceased at many universities. The phenomena clearly demonstrated the frailty of Japanese psychiatry, which contrasted with the psychobiological trend that was concurrently rejuvenating psychiatric research in the United States. Research activities slowly resumed in the late 1970’s, influenced by developments in cognitive psychology, neuropsychology, and information-processing theory. Psychophysiological studies using biological markers were introduced into psychiatric research activities. Summarizing the renewed interest in biological theories of schizophrenia, Utena (1979) suggested that relapse liability was a type of “hysteresis” with a biological background that created a vulnerability to disconnection of basic psychological functions.

Initiating psychophysiological studies of schizophrenia, Shimazono and colleagues (1965) recorded eye movements during resting states with eyes closed, a decrease in small rapid movements, and an increase in slow movements as the arousal level lowered from the alert to resting to drowsy states. Using this measure, chronic schizophrenic patients were shown to be hyperaroused, displaying slow habituation to stimuli in galvanic skin responses as well. These findings were compatible with those of Venables and Wing (1962), and were replicated frequently by European and American investigators (e.g., Frith et al. 1982).

These eye movement studies have been extended to fixation-point recordings during eyes-open studies of schizophrenics, depressives, and patients with amphetamine psychosis and frontal lobe damage (Ando et al. 1979). Kojima and colleagues (1992, this issue) report recent results from Japan on eye movement abnormalities in schizophrenic subjects. In ad-
dition, studies of the smooth pursuit eye movement abnormalities in schizophrenia initiated by P.S. Holzman (1987) have been replicated by Yoshihiko Matsue and Teruo Okuma (1984), particularly in relation to lateralized dysfunctions. Many studies of the electroencephalograms (EEGs) of schizophrenic patients have been undertaken in Japan as well; however, in recent years, EEG studies have focused on information processing in the brain in relation to attentional and cognitive disorders of those with schizophrenia. Event-related potentials, particularly P300s, have attracted much attention. Niwa and his colleagues (1992, this issue) reported on this topic.

As to the structural abnormalities of the brains of schizophrenic subjects, an old but significant work of Uchimura and Oyama (1934) should be noted. They reported ventricular enlargement as revealed by the pneumoencephalography, mainly of the third and lateral ventricles, which progressed in the early stage after the onset of the illness. A morphological computed tomographic (CT) study of brains of schizophrenic patients was conducted as a multicenter collaborating project, the results of which were reported by Takahashi and colleagues (1982). They observed the following: (1) an enlarged ventricular system and atrophy of the frontal and temporal cortices; (2) a cerebral atrophy in some patients with a short duration of the illness, particularly in the frontal lobe and the Sylvian fissure; and (3) no significant relationship between CT abnormalities and treatment history.

Using \(^{11}\)C-glucose positron emission tomography (PET), Kishimoto and his colleagues (1986) identified three groups of schizophrenic patients showing different topographic patterns of regional amino acid pools—hypofrontal, hypoparietal, and normal. Gyoju and his coworkers (1988) obtained an intriguing result in an examination of patients with auditory hallucinations by single photon emission computed tomography (SPECT) using N-isopropyl-p-[\(^{123}\)I] iodoamphetamine (IMP). Hallucinating patients displayed a high concentration of IMP in the early scan at the left temporal area.

Biochemical investigations of postmortem brains of schizophrenic subjects have been conducted by two groups in Japan. Toru (1985) found higher tyrosine hydroxylase activity, dopamine metabolites, and D\(_2\) receptors in the basal ganglia of the brains of schizophrenic subjects. Toru and his colleagues (1986) also found an increase of kainic acid binding in the frontal lobe cortices of schizophrenic subjects and a decrease of glutamic acid in other brain regions that correlated inversely with the finding for kainic acid binding. These findings also suggest a hyperdopaminergic state in the brains of schizophrenic subjects (Toru 1985; Turo et al. 1986). Meanwhile, Mita and colleagues (1986) reported decreased serotonin \(S_2\) and increased dopamine \(D_2\) receptors in the frontal cortices of chronic schizophrenic patients.

Japanese psychiatry has also contributed to the development of pharmacological therapy in schizophrenia. There are 26 antipsychotic drugs of 7 chemically different categories now available in Japan. Among them, timiperone (a butyrophenone derivative), zotepine (a thienepin derivative), caripipramine, and clozapipramine (both iminodibenzyl derivatives), have been developed in Japan. To develop effective pharmacological agents for symptoms such as alogia, affective flattening, anhedonia, and avolition of chronic schizophrenic patients, Kazutoyo Inanaga and his colleagues (1975) administered L-dopa (300–500 mg per day) in combination with antipsychotic drugs to 105 hospitalized schizophrenic patients. They concluded that L-dopa was effective for diminishing withdrawal symptoms in chronic schizophrenic patients.

Lending impetus to current schizophrenia research in Japan was the 1986 International Symposium on Cerebral Dynamics, Laterality and Psychopathology, which provided a forum for the presentation of many articles, including those on brain imaging studies (Takahashi et al. 1987).

Research grants are awarded by the National Center of Neurology and Psychiatry (NCNP) of the Japanese Ministry of Health and Welfare. Most grants are for 3 years and have supported such projects as “Studies of the Etiology and Clinical States of Schizophrenia,” “Biological Studies of Schizophrenia and Mechanisms of Chronicification,” and “Biological Studies of the Pathogenesis and the Onset of Schizophrenia.” The results of these studies have been published in the two monographs “What is Schizophrenia?” (Shimazono and Inanaga 1984; Inanaga and Toru 1987).

While psychoanalytically oriented psychiatrists are a minority in Japan, one influential analytical leader, Takeo Doi, interpreted the difficulties of schizophrenic patients as a failure of “amae,” which can be translated as “to depend and presume upon others’ benevolence,” similar to the passive object love of M. Balint and viewed as a peculiar preoedipal characteristic of Japanese personalities (Doi 1972/1981). Japanese psychiatrists interested in psychopathology and psychotherapy have organized annual workshops on schizophrenia for 16 years, the proceedings of which have been published yearly by
the Tokyo University Press (1972–87). These books have made valuable contributions to the understanding of schizophrenia and have given impetus to Japan's psychotherapeutic movement. The endeavors of psychopathologists have filled the vacuum created during those years when biological studies on schizophrenia were forcibly halted by the antipsychiatry movement.

References


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