NEUROTRANSMITTER RESEARCH IN JAPAN
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How did you end up in medicine?
My father was an internist and as the first child of a doctor, it was expected that I would do medicine too. I expected to be a doctor from a very young age.

After going into medicine, why did you go on to do psychiatry?
Well I was fond of TS Eliot while I was a medical student. I read 'The Cocktail Party' in which one of the characters was a psychiatrist. He played an important part in this play and that influenced me in part to be a psychiatrist. I was generally interested in the social sciences and literature and this made it more interesting to do psychiatry than other areas of medicine – to see how the mind works. Another reason was that psychiatrists seemed to be good colleagues, to work together with over a long time.

In the West at that time, to do psychiatry would not have been so highly thought of. The cleverest people didn't do psychiatry. Were things the same in Japan?
Yes. At that time, not so many students selected psychiatry for their specialisation. I entered Tokyo Medical and Dental University – TMDU – which was located in the central part of Tokyo, after graduating from Kyushu University. In that year seven doctors went on to do psychiatry from different universities with none from TMDU. They thought that psychiatry would be an important future medicine.

So why was it not very popular to do psychiatry at this time?
When I told my father that I had decided to do psychiatry, he said it was not interesting. He didn't understand why I would be interested. He was a director of a small city hospital for infectious diseases and maybe for him psychiatric patients did not look like they could be cured. I suppose he had never seen neurotic or depressive patients and even acute schizophrenic patients. But I entered TMDU psychiatric department in 1959, just after the introduction of chlorpromazine and reserpine. Among the questions of the National Examination of Medicine in that year were questions on these new neuroleptics already.

Had these drugs begun to make a big change?
I'm not sure because I started psychiatry only after these drugs came on-stream. At the time I could train in psychopathology and psychophysiology but there were no good books in psychopharmacology.

I began my training in April and I was sent to the psychiatric hospital in July, for training in hospital psychiatry, after three months of university training. I met many chronic patients there for the first time. When I had been in the University hospital in TMDU, the psychotropic drugs seemed very effective for the patients we had there. But in the mental hospital, they didn't seem to work. So much so that I went to the pharmacy department and told them they may have used

different or the wrong drugs – that it was not the same chlorpromazine. So there were different patients in the mental hospital – more chronic patients.

How were you trained then – you said the period of training was quite brief
I also did neurology at the same time. At that time in Japan, neurology was not separated from psychiatry, so I was a neuropsychiatrist. I used Baker's Textbook of Neurology. So in the course of 3 months in the department of psychiatry in TMDU, I actually only managed 3 patients and they had neurosis, depression or neurological disease. There was no schizophrenia.

I later saw many newly admitted patients with schizophrenia because I looked after the newly admitted ward. On this ward, there were a lot of things to do other than just psychiatry. You had to look after the medical problems of the patients and also to get involved in rehabilitation. I learned EEG, cerebral angiography and other roentgenological techniques in the university and psychological tests in the hospital during this year. At that time, I had a very great interest in pharmacology especially in the side effects of the psychotropic drugs, the antipsychotic drugs in particular.

When I talk to anyone who comes from Japan, they always mention your work on the side effects of the psychotropic drugs. Why did you get interested in this area?
Its very natural I think to care about the side effects of the drugs. I read about the side effects of chlorpromazine in many American and British Journals. They mentioned things like gastric perforation and the extrapyramidal side effects of course. I intended to be a psychopathologist initially, when I entered TMDU. This was because of the Chairman of the department, Toshiki Shimazaki. He was related to the one of the most famous poets and novelists of the Meiji era. Professor Shimazaki was the best known psychopathologist in Japan at the time. But when I got to see many patients in the mental hospital I began to get more interested in the side effects of the drugs. Initially there was only chlorpromazine and reserpine to think about and one year later imipramine and I suppose I began to think that it was necessary to know more about the psychotropic drugs than it was to know about psychopathology in order to cure patients. So I changed my intention.

Was there any thought in Japan during the 1950s that the drugs might answer psychopathological questions? In Germany when the drugs came out first, one of the interests many psychiatrists had in them was in terms of what they might reveal about the nature of psychiatric syndromes - the answers they might give to theoretical questions - rather than in any cures they might bring about in patients.
I don't think so. Our psychopathologists were very interested in German psychopathology, from Jaspers and Schneider to the anthropological psychiatry of Blankenburg or the Daseinsanalyse of Binswanger. It was a very philosophical way of thinking that was very different from psychopharmacology.

But they gradually began to use psychotropic drugs also, alongside psychotherapy.

I only spent one year in the psychiatric hospital and then I went back to TMDU and entered the neurochemistry group that was directed by Ryo Takahashi. In that group, I studied the neurochemistry of convulsions. I measured ammonia in mouse brains who had convulsions induced. At that time I thought it was important to study the components of convulsions, one of which is anoxia, so I studied anoxia. I devised an apparatus to produce the different stages of anoxia and we measured acetylcholine, ammonia and glutamine.

Can I ask you about glutamate? This was really discovered by the Japanese as a neurotransmitter, which is not very widely known in the West – Takashi Hayashi was involved wasn't he?
Dr Takashi Hayashi, who was the Professor of Physiology in Keio University, found that injection of sodium glutamate into the brain or cerebral ventricle of cats, monkeys or canines induced convulsions. This was in 1954. This observation excited an interest in glutamate and led to Curtiss's findings on excitatory actions of glutamate and other acidic amino acids. Although I never met him I understand Dr Hayashi was an interesting and unconventional professor, who wrote many detective stories under a pen name, Takataro Kigi, which were widely known by even primary school boys. He won the Naoki Prize, a most famous prize for popular literature in 1936.

This initial discovery was connected to future investigations on glutamate in Japan, which turned out very well. Akira Takeuchi found a transmitter role of this amino acid, Haruhiko Shinozaki discovered the excitatory action of kainate and quisqualate, and this was linked to recent cloning studies of glutamate receptors by Shigetada Nakanishi and Masami Mishina.

The fact that a neurochemistry group began in Japan in the mid-1950s is very interesting because at the same time in the West, neuroscience was dominated by the physiologists who were not interested in neurochemistry.
Let me add something here. There was another Hayashi, Michitomo Hayashi. He was a psychiatrist and a famous neuropathologist. When he was in his early 50s, in 1937, he turned his attention to schizophrenia and started to measure blood gas in arteries and internal jugular vein of schizophrenic patients. He presented 10 years worth of results in 1947. This study stimulated a group of young psychiatrists, among them were Shuzo Naka, Hiroshi Utena and Isamu Sano. These were all biologically oriented psychiatrists who thought that there must be some neurochemical change in the brain. So in the following year, M Hayashi organized a 'Schizophrenia Research Group' and this project developed into the Japanese Society of Neurochemistry, which was established in 1958. This was one of the most important research forums for someone like me, until the Japanese Society of Biological Psychiatry was established in 1979.

I wonder if the methamphetamine psychoses made a difference. You had a lot more of them than we had and this must have made it more natural to think neurochemically. How did this epidemic happen in Japan ?
Amphetamine and methamphetamine were used during the War to keep the soldiers awake. Long haul bomber crews used them a lot. After the war, pharmaceutical companies in our country had a large stock of methamphetamine. They propagandized this drug as 'preventing tiredness, stopping sleepiness and activating energy' to clear out the stock. Because the public feeling was unstable in a ruined defeated nation, writers and entertainers first attempted to use the drug and the issue extended to the public in a short time.

Although a Stimulant Control Law was established in June 1951, as of May 1954, 550,000 people were taking methamphetamine among whom 200,000 were in a state of dependence. More than 2 million people had had some experience of this drug. As the numbers of abusers increased, criminal cases of injury, homicide, violence, threat and theft by abusers increased.

Did anyone know at the start that it was going to cause a problem?
In 1938, there had been a report on 2 cases of Benzedrine (amphetamine)-induced psychosis, which showed delusions during the treatment of narcolepsy. There were few reports on amphetamine-psychosis in Europe and U.S.A. In our country, very soon after the war, psychoses were observed among the abusers. Drs.Tatetsu, Goto and Fujiwara working at Matsuzawa Hospital, published a book 'The Methamphetamine - Psychosis' in 1956, in which they noted the similarities between methamphetamine induced psychoses and both schizophrenia and manic-depressive psychosis. This was in Japanese and for this reason it did not come to attention in the West. Connell in England published the same results but this was in 1958. He emphasized the similarities with schizophrenia, whereas Dr Tatetsu had suggested that there were also similarities with manic-depressive psychoses

Dr Connell's article here suggested that amphetamine produced a brief psychotic reaction whereas Dr Tatetsu's work emphasized that amphetamine could also produce a chronic picture.
Yes this was very important. But to come back to your earlier point, I don't know whether this experience with methamphetamine led to our interest in neurochemistry. Dr Hayashi's work anyway was independent of this. He was looking at oxygen metabolism and found that it was reduced in schizophrenic brain. Dr Utena used methamphetamine injected chronically into guinea pigs. This was the first animal model of schizophrenia. His idea was that this was a chronic model of schizophrenia. They found reduced glycolysis without changes in tissue respiration as observed in the brain tissues taken from the schizophrenic patients. Dr Mitsumoto Sato and his group in Okayama University, later in the 1980s, observed that chronic administration of methamphetamine

increased sensitivity of behavioral stereotypy of rats to methamphetamine. This was called the reverse tolerance phenomenon by Seevers

Dr Utena's work became the focus of student protest in Tokyo University in the late 60s. Why did this happen seeing that he hadn't been doing that kind of work there? And why were things such a problem for psychiatry in Japan?

Dr Utena's study, which later became an issue in the turmoil in Japanese Society of Psychiatry and Neurology, involved the measurements of in vitro glucose uptake and respiratory rates in cortical brain tissues taken from the schizophrenic patients during prefrontal leukotomies. The results obtained from 21 chronic patients compared with 8 controls were published in 1951. Dr Utena became professor of Psychiatry, University of Tokyo in 1966 and became President of Japanese Society of Psychiatry and Neurology in 1967. The student turmoil broke out in February 1968 when the students of the Medical School of University of Tokyo struggled with the director of University Hospital. Medical students had taken a defiant attitude toward the authorities at that time as regards some internship problems. Big and long lasting turmoil sometimes begins following a small accident. In this case, when the Director of the School of Medicine announced the punishment of 12 students and 4 doctors including psychiatrists, disruption spread out in all the campus.

During the turmoil in the Japanese Society of Psychiatry and Neurology, Dr Utena was accused in 1971 of experiments that involved taking brain tissues from living patients. There were mistakes and retractions and also crafty tricks between professors and students as well as between chairmen and young psychiatrists in the departments of psychiatry. There was voting by hands with apparently overwhelming majorities, we had "strong cries" of protest repeated. However it calmed down gradually as the tide of student power throughout the world was ebbing down. New research activities were budding out everywhere in the ruins in the psychiatric departments of universities in 1974, when Dr Utena retired from the University under the age limit.

Why do people not want to think that psychosis has to do with biology – what are they afraid of?

I'm not sure. The psychoanalysts and some psychopathologists mainly think that psychoses are caused by some psychological reason. The brain is not biologically dysfunctional in these people. People like Szasz and Laing, the well-known antipsychiatrists, influenced young psychiatrists. I was in the same symposium as Szasz on one occasion in 1975, I think. I think the struggles and issues were the same in Japan as in other countries. He was saying even then that he didn't use psychotropic drugs.

Why did things get more extreme in psychiatry in Japan than anywhere else?

There was a problem also in paediatrics. It's difficult to be certain but it seems to me that children and psychiatric patients are the most vulnerable groups – they both need some protection.

In Japan is there a problem then in treating hyperactive children with psychostimulants especially seeing that you have had such a problem with methamphetamine in the past.
I'm not a child psychiatrist, so I am a little bit uncertain here but child psychiatrists say to me that children with ADHD can be given methylphenidate now and some of these children show excellent responses.

In the UK at the moment, this is an issue. People saw that children over in the USA get too many pills and they prescribe much less here. The condition is not recognised very commonly in Europe – you have to be pretty severe to get treated.
Whatever the correct balance, it seems to me that it is sometimes necessary to use methylphenidate.

To come back to your own work. You went to the USA in the mid-1960s. Why did you go and what did you find?
From 1960, I had worked with Dr Ryo Takahashi on the neurochemical changes associated with various behavioral activities of rats. Dr Takahashi was the first to go to the USA to work with Dr M H Aprison in Indianapolis. When I went there in 1964, I first of all worked on neurochemical correlates of behavior and then I developed a new extraction method to measure acetylcholine in the brain. I did this for two years. From these experiences I became interested in neurotransmitters.

How did psychiatry in the USA compare with psychiatry in Japan at the time?
Well Dr Aprison was in The Institute for Psychiatric Research as a biochemist, so I didn't get to see much of psychiatry in the USA at the time. Shortly before, in 1957, dopamine had been found in the brain. I read some papers in this area. I asked Dr Aprison what he thought about dopamine. He said that it was an intermediate substance to make noradrenaline. Arvid Carlsson had already found some transmitter effects of dopamine in 1957. Nevertheless 10 years later, there were some people who did not recognise that dopamine was of significance. I learnt more about this from Arvid Carlsson a few months ago. I told him about this and he said that after he made his first reports nobody paid any heed to his contribution. Dr Aprison had also the same experience when he and Dr Werman proposed the transmitter action of glycine.

Why had you become interested in dopamine?
Well I was interested in acetylcholine and neurotransmitters generally. After my stay, Dr Tetsuhiko Kariya stayed in this Institute from 1966-1968 and he measured serotonin. Dr Aprison was also interested in noradrenaline. He was

interested in the neurochemical correlates of behaviour generally. It was in the mid-1970s that we started dopamine research in Japan. A clue was the antidopaminergic action of antipsychotic drugs.

When you went back to Japan, you first moved into sleep studies. The whole field of circadian rhythm research has perhaps been more developed in Japan than elsewhere. Is there any reason why this should be?
Our work in this area was quite early in Japan. When I came back from the USA, some animal studies seemed possible to me in the psychiatric field. I looked at the issue of psychiatric illness and noted that most of the patients have insomnia, whether they have schizophrenia, affective disorders or neuroses. It seemed to be a good idea, therefore, to clarify the neurochemical mechanisms of sleep functions and this might lead on to a clarification of the mechanism of psychoses.

So I started to work on sleep deprivation and monoamine measurements. There was a small literature on monoamine mechanisms from Jouvet's group. Dr Junji Matsumoto, who was a physiologist and a Haiku-poet, had published a French paper in 1964 where they had administered 5-hydroxytryptophan to cats and noted that it induced sleep. This gave me a lead and I cited these works. We found that serotonin changed dramatically in the diencephalon in sleep deprived animals. We looked at the reticular formation also and injected radiolabelled tryptophan and found that serotonin metabolism increased in these animals. Later we confirmed increases in tryptophan and 5-hydroxindolacetic acid concentration in the dorsal raphe nucleus and thalamus of rats after sleep deprivation. We also found that tryptophan hydroxylase had a circadian rhythm but only in the pineal gland. Other groups found that there were circadian rhythms in tyrosine hydroxylase in the pineal gland but we were not able to replicate this. In the late 1970s, H Kawamura's group – SI Inouye, N Ibuka and colleagues – established the role of the suprachiasmatic nuclei as a biological clock in rodents. Their papers in Brain Research in 1977 and the Proceedings of the National Academy of Sciences in 1979 were very influential. Later the gene for the period of the circadian rhythm in the Drosophila fly was found in a mammalian species by a Japanese group and it was found that it expressed mRNA in the suprachiasmatic nucleus of mice.

Chronopharmacology seems very important in Japan but its not so appreciated in the West. Why should you be so much aware that drugs given in Japan have different effects if given at different points during the day and we should not be so aware of this?
The Halcion problem is one issue. One of the reports on Halcion amnesia in 1987 came from two neurologists and one neuropathologist who flew from the USA to Europe and took Halcion with some alcohol on the plane. All three reported amnesia after landing for up to half a day. This suggested strongly that the time of taking the medicine could be very important – especially for hypnotics for instance. Chronobiology can be important, I'm sure of it.

During the 1970s, you did clinical trials with sulpiride and then some basic research on the dopamine receptor system and then the excitatory amino acid receptor system.

Our work with sulpiride was very important, I think, especially the work giving sulpiride for neurotic patients. We did this work because I had been in a group for sulpiride research for schizophrenic patients. But at the time, I also used sulpiride for patients with various diseases – depression and other neurotic conditions. I found that some of them did very well. The important thing is the issue of dose. In schizophrenia sometimes up to 1200 mg per day may be needed -–anything from 600 to 1200mg. But in depressive patients we used perhaps 150 mg to 300 mg and for neurotic patients under 150 mg. We found sulpiride to be as effective for neurotic patients as chlordiazepoxide. Because of this I have used sulpiride a lot for neurotic and depressive patients.

While you were doing this, you were also doing basic brain research, looking at dopamine and amino acid receptors. Its unusual is it not to have someone doing both kinds of work?

During this time, we also began to look at the effects of chlorpromazine on adenylate cyclase in the striatum and the mesolimbic area. Then in 1978, I moved to a newly formed institute, The National Centre for Nervous, Mental and Muscular Disorders in Tokyo, where I belonged to the Division of Psychobiology. This was only a division to investigate psychiatric diseases. The institute was built in the precincts of the biggest National Mental Hospital with 700 beds. As the section chief there, it seemed to me that I had to study schizophrenia, so that is how my work in this area started. In 1981 we looked at methamphetamine from the point of view of the reverse tolerance phenomenon. Thus, we approached schizophrenia research.

There was another issue that I got interested in which was the side-effects breakthrough phenomenon. I remember in 1975 I gave a lecture on antipsychotics somewhere and I had a question from the Chairman, who was a famous psychopathologist. He said that they sometimes had the experience that when they injected haloperidol they found that there were no extrapyramidal side effects, did I know the answer? I couldn't answer. If you use large doses of haloperidol for instance, more than 60 mg per day, you can sometimes see that no extrapyramidal side effects occur. Many psychiatrists commented on this. Reading the literature, you can see that this was also true for other neuroleptics. But nobody could explain the neurochemical mechanisms for this.

I found the reason for this. Trying to find out why this might be, I measured everything to do with monoamines using an HPLC. When we used large doses of haloperidol with female Long-Evans rats, we found some interesting results. Usually in rats you use 1 mg per kg to induce catalepsy but when we gave 10mg per kg, we found that on the higher dose there was no catalepsy. This led us to describe a side-effects breakthrough phenomenon. What we found very quickly was that noradrenaline metabolism was increased at these higher doses of

neuroleptics. The ratio of MHPG to noradrenaline was increased in the frontal cortex and the thalamus.

Does this explain why the atypical antipsychotics cause less extrapyramidal symptoms – because they have a greater noradrenergic effect?
Some of them yes. Some atypical antipsychotics cause less EPS due to blocking serotonin-2A receptors. As to noradrenaline, when we disrupted the noradrenergic system, we found it was easy to induce catalepsy. But desipramine on the other hand, used with antipsychotic drugs, made catalepsy much less common. So these clinical phenomena could all be tied into our work which showed that noradrenaline metabolism was increased at higher doses of neuroleptics.

It's very rare for a clinical person to make this kind of contribution through basic brain research
Well I am a psychiatrist using psychotropic drugs and for me it was always important to be conscious of the side effects of the psychotropic drugs. This is one area where it is possible to do good research and at the same time clarify mechanisms of psychosis. This neurotransmitter approach became my way. It was very much a continuation of the kind of work I had learnt to do with Dr Aprison.

After I moved to the National Centre I thought that schizophrenia and the brains of people with schizophrenia were the most important things to study. So I asked psychiatrists around Japan if they were interested to cooperate with these post-mortem neurotransmitter studies. They did. The difficult problem was to collect normal control brains. This is because in the usual post-mortem exam, the brain is not really looked at. They only look at brains when there is some pathology in them. So we had to find a way around this.

Dr Ryo Takahashi had moved at this time to Nagasaki. Did he move because of the troubles in Tokyo?
He had been the associate professor with Professor Utena and had been involved in trying to defend research. But when the previous professor who had been in Nagasaki retired, he was keen to have Dr Takahashi replace him. When Dr Takahashi went to Nagasaki, it was in the midst of the turmoil. He put a lot of effort into getting research happening again and he did a lot of research on chronobiology and affective disorder. He also developed international links – he established a WHO Collaborative Centre in Nagasaki.

One of the things you seem to have been able to do in Japan better than people in the West has been to do cooperative research. Dr Takahashi had a role in getting this going, didn't he? He did some early CT scan work but where in the West we were reporting on 20 subjects, whereas he reported

on 200 to 300 subjects, which suggests that you were all cooperating more than we do here.
Well he was a particularly good organiser. He also had good friends everywhere. Co-operative research of this kind also tends to be supported by grants from the Ministry of Health and Welfare

Can I ask you about drugs from Japan that we haven't had over here – carpipramine, clocapramine, mosapramine – some of these look like what we now call atypical antipsychotics over here.
These three antipsychotic drugs were produced by a Japanese Pharmaceutical Company, Yoshitomi. They have a similar structure. The idea was to link up the iminodibenzyl of tricyclic antidepressants to a butyrophenone structure. They blocked dopamine D-2 receptors but they have an iminodibenzyl nucleus like imipramine so they also have some atypical features perhaps. Mosapramine was most interesting because it had some activating effects.

Clozapine didn't cause agranulocytosis in Japan but it did cause hypersalivation and fever. Maybe there are racial differences here. Agranulocytoses are much less common in Japan generally. Remoxipride was discontinued worldwide because of blood problems in Europe but there was no problem in Japan.

Would other Japanese psychiatrists, like you, try the drug out to see what the side effects are like and would this explain why Japanese psychiatrists use lower doses of psychotropic drugs than are used in the West?
I have used sulpiride for many neurotic patients. It can, however, be risky sometimes even in a dose as low as 150mg. I have seen people get tardive dystonia although I have not seen Parkinsonian problems. I have tried it myself to see what the side effects are. I don't know whether all Japanese psychiatrists would try these drugs themselves but also I am not sure we use lower doses, when you take into account body size.

Well my impression is that the doses we were using have been shown by clinical trials to be too high and we are now revising our doses down to your levels. I think people here haven't been as concerned about side effects.
Twenty years ago we were asked to determine the appropriate doses for some of our trials and as a result came out with a set of recommendations for dose levels that people have kept to since.

Recently there have been concerns expressed by Western pharmaceutical companies say that they cannot get into Japan – for instance there are no SSRIs on the market with you. On the other hand I hear some Japanese psychiatrists say that some of these drugs we haven't got are ones we don't really want. And you use more anxiolytics than are used in the West. Why is it that drugs are slow to get into Japan.

Well there is not such a big benzodiazepine abuse problem in Japan and psychiatrists are maybe happier to use them for general neurotic patients. But we need SSRIs because they seem to have less side effects and to be less dangerous than the tricyclics. It is difficult to get them on the market because the clinical trials all take time and psychiatrists haven't got this much time.

Well is there a problem with clinical trials then – I understand there is an informed consent problem.

It becomes more and more difficult to develop new psychotropic drugs in our country. In the USA the patients are recruited by mass media because they expect to gain economically by participation. In our country, the medical insurance system is well organised and no one gains by participation. Written consent is difficult to obtain, because our society is not familiar with these ideas of contracts. There are few people who are prepared to volunteer to participate in new drug trials. Psychiatrists are all too busy to take the time seeing patients needed to do a trial and they do not want to use inert placebo for their patients. Besides, if a psychiatrist writes a paper on a clinical trials of a new psychotropic drug the value of the paper is assessed not to be high. For all these reasons, we still do not have either clozapine or the SSRIs' at the present time.

When you look back at Japanese neuropsychopharmacology, who have been the most important people?

There have been many basic pharmacologists. Some of them have been world famous. For instance in the peptide area there was Masanori Otsuka, who found the actions of Substance P and GABA, which was very important research. Dr Otsuka ironically did not agree for a long time that glutamic acid was a transmitter. Dr Shigetada Nakanishi was also important. He was a biochemist who cloned glutamic acid receptors.

Clinically the important people have been Dr Teruo Okuma as well as Dr Saburo Otsuki from Okayama University. He was the successor of M Hayashi. He educated many psychiatrists. Dr Hiroshi Utena was also important. He is still working even though he is in his 80s. He worked in many fields in psychiatry. Dr Sadanori Miura and Dr Mitsukuni Murasaki have been involved in developing new psychotropic drugs. Dr Hajime Kazamatsuri is interested in side effects of psychotropic drugs.

In the early days, the late Dr Isamu Sano was important. He found reductions of dopamine in the striatum of Parkinsonian patients even before Dr Hornykiewicz found this. He had a woman patient with Parkinson's disease in his department and after her death, they got the brain and measured the dopamine in the striatum. Dr Kazumi Taniguchi measured it. Dr Sano wanted to publish the results immediately but Dr Taniguchi stopped him – its too preliminary he said. So they only published in Japanese. This was in 1959, one year before the European neurologists found the same fact. Dr Sano was also one of the first to use 5HTP for depressed patients but unfortunately he died young – in his 50s.

Then there was Dr Hirotaro Narabayashi was important for his stereotactic surgery of Parkinsonism. He is a good friend of Arvid Carlsson. Dr Yasuo Kakimoto was a psychiatrist who discovered many brain substances. Dr Nozomi Suwa was a psychiatrist and a psychopharmacologist, who was the first to use chlorpromazine in Japan. Dr Itaru Yamashita was also very important. His research was mainly endocrinological. He was the Japanese delegate to the CINP for a long time. He worked with Dr Tsukasa Koyama who is his successor.

There was an early co-operative group called the Clinical Psychopharmacology Research Group. How did this get going?
This was the style of Japanese developments in psychotropic drugs. The late Dr Hitoshi Itoh was very important in this area. He studied methods of evaluation and he got this group going with the late Dr Ryo Takahashi and Dr Yovio Sato. They were a good group. I think they may have had support from some company like Ciba-Geigy. They have been very influential in Japan.

Coming back to your own work, is neurochemistry as important now as it once was?
The age of post-mortem neurochemical studies is over now. They contributed to our understanding at the time. But brain imaging is now more important. There have been discrepancies between these two approaches. Our post-mortem work showed increased dopamine D-2 receptor density, which we did not find in recent imaging work. This may have something to do with the younger age of the patients we can look at now with imaging machines. Also schizophrenia is only a set of syndromes that may involve a heterogenous group of disorders and those who come to post-mortem may be quite different to those we get to image. I think genetic studies will be very important in this area in the future from the viewpoint of heterogeneity. Different family pedigrees will be important.

So do you think we should do more studies on the neurochemistry of symptoms such as delusions that occur across syndromes or the neurochemistry of temperamental differences?
I can say there are many kinds of positive symptoms. Some are very easily cured by even small amounts of antipsychotic drugs. It gets more difficult where these are mixed with negative symptoms. It's difficult to know how to treat these kind of auditory hallucinations for instance. These can be very treatment resistant. I used perphenazine, nemonapride, sultopride, pipamperone, bromperidol and so on.

Are there differences between the antipsychotics that haven't been explored fully.
Yes. We have 30 different antipsychotics. Maybe if you've got too many it becomes difficult to systematically research the differences between them although we have found some differences between them. On the issue of treatment resistant schizophrenia, especially those cases that have positive

symptoms, I sometimes succeed, sometimes not. I think we need more investigation of the neurochemical correlates of symptoms of schizophrenia in order to establish the precise pharmacotherapy of this disease.

You have an interesting study on the use of mianserin for delirium. Where did you get that idea?
My colleagues Dr Kunihiro Isse and Makoto Uchiyama found that this effective. I am now the head of the research group on mianserin for delirium. It is very effective. It's very difficult to explain why, but one possibility is its blocking action on serotonin 2A receptors.

How did anyone think to use this drug for this condition?
Yes, the usual practice had been to use small amounts of haloperidol as most people do worldwide. The Japanese government also allow us to use the benzamide, tiapride, but it isn't used so much. Their group used to use a small dose of amitriptyline for the insomnia of patients with delirium tremens. A second hint came from ritanserin. At a sleep research meeting in Europe in 1987, Dr Uchiyama heard about the effectiveness of ritanserin for the insomnia of aged patients. Because they had been troubled by the side effect of urinary retention in this age group and ritanserin was unavailable in Japan, they decided to use mianserin. This led to the discovery and in Japan many psychiatrists now use it for this reason in an approximately 30 mg dose.

There are big differences between the West and the rest of the world as regards prescribing antidepressants. In Japan for instance you prescribe more anxiolytics and less antidepressants than us. You hear lots of people in the West justifying their position by saying you in Japan are unhappy to diagnose depression – that anxiety is more socially acceptable. I find this hard to believe. It sounds more like a rationalisation of our confusions as regards anxiolytics if you ask me. Have you any thoughts on this?
I prescribe anxiolytics or sulpiride to mild depressive patients because antidepressants have a lot of side effects. But do not misunderstand us. We use antidepressant to the maximum dose to the depressive patients. There is no problem making a diagnosis of depression to the patient and family.

Using an "antidepressant" for delirium is a conceptual turnaround that makes you wonder if we are right to pigeonhole these drugs the way we have been doing. For instance you have also been using sulpiride as an antidepressant
Yes, and also to reduce auditory hallucinations we often use carbamazepine, which sometimes can be very effective. Carbamazipine decreases the blood concentration of haloperidol, so its efficacy is not explained by some pharmacokinetic effect. I think we need to try different things out for different conditions. Of course there are many different diseases in psychiatry but the aetiologies of none of these are known and the psychotropic drugs we have at the moment are symptomatic treatments rather than anything else. For this

reason we should be prepared to try everything for instance for tardive conditions such as tardive dystonia or tardive dyskinesia. For instance, I recently had a patient with facial coenesthopathia, which was long standing. I thought this might be related to tardive dystonia which had been triggered by neuroleptics in the past given for a depressive condition. So I tried oxypertine. This is related to reserpine and it cleared up this very debilitating condition the next day. He was very glad.

Recently neuroleptic malignant syndromes NMS are increasing in Japan. We have assumed this is because knowledge is improving. We used to use dantrolene. I know ECT is used in the United States but at the moment I would be too nervous to try that. My hunch is that NMS is caused by strong blockade of dopamine receptors after an abrupt increase of antipsychotics or a withdrawal of anti-parkinsonian drugs.

In genetic studies of schizophrenia, recently, we found a missense variant in dopamine D-2 receptors. Dr Gershons' group in the NIMH found the same variant the following year. In our research program we also found an increased frequency of cystein variants in schizophrenia. A mutation had caused serine to be replaced by cystein. We found that patients without negative symptoms were more likely to carry the variant. If schizophrenic patient has this variant then, the prognosis is good. This finding has not been replicated consistently but I think this is because people are analysing different patient groups – chronic patients.

What I think this leads to is this. Dopamine receptors are sequestered, internalised in response to dopamine. This is part of what modulates the response to dopamine. These variants mean that there are different rates of internalisation. Some of these variants delay internalisation, so that the receptors are much more exposed to dopamine. We also found that there was substantial heterogeneity in tyrosine hydroxylase levels. Those with high levels of this enzyme are more likely to get schizophrenia it seems. We also found increased excitatory amino acid receptors especially in strychnine - insensitive glycine binding sites, along with glutamate receptor variants. We hypothesized that there is glutamate hypofunction in the chronic schizophrenic states and that we should be thinking of glutamate agonists in this condition.

I retired this year and Dr Toru Nishikawa will succeed me. He is now working on the genetics of schizophrenia with some new strategies. He found that d-serine exists in the brain. This is an agonist for the glycine binding sites on the NMDA receptor. I hope that our research will open up new treatments for antipsychotic resistant schizophrenic patients.

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