THE DISCOVERY OF THE PSYCHOTROPIC EFFECTS OF CARBAMAZEPINE

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Tell me why you decided to enter psychiatry?

For me it was very simple. My father was a psychiatrist. If he were alive now he would be 103 years old. He graduated from Tokyo University. Its hard to say why someone would have done psychiatry almost 80 years ago but he entered the department of psychiatry at Tokyo University and then moved to Okayama University in the Western part of Japan. Finally he moved to Sapporo, where he became a professor of psychiatry in the university there at the age of about 40. Unfortunately he was suffering from diabetes and he died at the age of 44 from a heart attack. At that time I was still in primary school but his pupils suggested to me that I follow in his footsteps. My family also wanted this and so there was little choice. When I graduated from medical school in Tokyo University, I was tempted by paediatrics but finally I decided to go into psychiatry.

If you do medicine here in Japan, I understand you have an option to do either psychiatry or psychosomatic medicine whereas in the West we usually only have a choice between psychiatry and medicine. Why did you choose psychiatry?

I graduated from medical school in 1949 and at that time departments of psychosomatic medicine did not exist. Psychosomatic medicine was introduced into Japan when American medicine came into the country after the Second World War. Before that Japanese medicine was mainly German medicine. In the beginning psychosomatic medicine was mainly done in psychiatric departments. Many psychiatrists were interested in this area and even in the USA most of the pioneers in this area were psychiatrists.

But anyway, I had no choice at that time. Even neurosurgery in Japan was done within psychiatry. In the beginning when I entered psychiatry, I was interested in biological psychiatry. As elsewhere, here in Japan you find that among those who enter psychiatry, one party are psychologically or philosophically oriented and they become psychiatrists to study psychopathology and psychotherapy but I was not so philosophically oriented. I was more interested in neurosciences.

When I entered psychiatry, I was first interested in the EEG for which the new machines had been introduced from the United States and Europe just after the war. Psychosurgery was also very popular at that time. One of my seniors in the department, Dr H Narabayashi, started stereotaxic operations in human psychotic disorders. He did stereotaxic operations on the thalamus at first but they didn't work in psychosis. He switched to Parkinson's disease and discovered that lesions in the globus pallidus produced a remarkable improvement - they reduced the rigidity of the patient. He is very well-known in the study of Parkinson's Disease. Recently, he found that one of the amine precursors L-DOPS (droxydopa) is effective for the treatment of akinesia and the freezing phenomenon of Parkinsonian patients. I was one of his co-workers and at that point I was almost a neurosurgeon. But since neurosurgery began to develop further in the department of surgery, I stopped

doing surgery and concentrated more on the EEG as well as on clinical psychiatry.

I was also interested in psychopharmacology because chlorpromazine had just been introduced into Japan at that time. I went to UCLA in the United States to study some basic neurophysiology in 1958. Chlorpromazine had just been used shortly before that for the first time for some patients in Tokyo University. I studied one year in UCLA in the laboratory of Professor Magoun looking at basic techniques using cats and then I moved to the psychiatric department at Massachusetts General Hospital. I set up a laboratory of neurophysiology there with Dr Frank Ervin. After that I came back to Tokyo University for 3-4 years. Then I worked for 1 year in Jotendo University - a private university - before becoming the professor of psychiatry at Tottori University in the Western part of Japan - I was about 40 then.

In Tokyo University, there were a great number of doctors and separate research groups. Some were working in psychopathology, some in neuropathology, while I belonged to the neurophysiology group. It was difficult to do other things because of the separation of the research groups. But when I moved to Tottori University and became the chairman of the Department of Psychiatry, I had to manage everything from basic research lectures to the treatment of the patients in the University Hospital. And so I started my study of psychopharmacology there.

At that time, chlorpromazine and other phenothiazines were used widely for schizophrenia, mania and other conditions and the problem of side effects, including hepatic disturbances, were very important clinically. I began some studies of this in the San-in Area including Tottori and Shimane Prefectures which is really a very small area - there were only about 1,500,000 in the population and the movement of people was very limited in this area. The size of population made it possible for us to follow almost everyone for clinical investigations. There were about 10 mental hospitals and they were all linked to the University clinic, so that we could ask them for co-operation in any clinical psychopharmacological investigation. At first I started to look at the area of side effects. We also investigated the rate of recurrence of schizophrenia and found that the recurrence was mainly due to the discontinuation of neuroleptics by the patients and their family.

It was at that time also that we started the study of carbamazepine. The first publication on the carbamazepine effect on bipolar disorders was by Takezaki and Hanaoka in Okayama University in 1971. This was for 10 patients with pure mania and 10 with symptomatic mania.

What was your thinking?

Many people have asked me the question why we began to use carbamazepine for manic depressive patients. It is very difficult to answer. One of the reasons was that, as it had been in Germany, in Japan epileptic patients were treated mainly within psychiatry. So we were treating all kinds of epilepsy - grand mal, absences, psychomotor seizures and psychotic disturbances associated with epilepsy. So we had a great deal of experience

with anti-epileptic drugs, particularly carbamazepine. This had been introduced into Japan for psychomotor epilepsy. As you know patients with psychomotor seizures very often had some personality disorder or some psychotic symptoms and many psychiatrists had found carbamazepine useful for the psychotic symptoms and personality disorders of these epileptic patients. So it was quite natural to make the progression to the excited state of other psychoses. At the same time lithium had not been introduced into Japan. It was being evaluated but it took a long time before it was approved. The only other option was neuroleptic drugs, which in mania often had to be used in huge doses causing very severe side effects and even then these drugs were not always effective. So there was an openness to looking at the possibilities of quietening down the excesses of manic patients by other means and because of this we happened to use carbamazepine.

I asked Dr Takezaki who published the first paper about this. He graduated from Okayama University and he was working about the same time - the early 1970s - in a small community general hospital in Okayama Prefecture where they had only an open door psychiatric ward. This made the problem of manic patients even more pressing. They had to try everything they could. Since they had experience of carbamazepine for epileptic psychoses, they tried it accidentally on a manic patient and found it very effective. Our situation was similar. It was not theoretically based. It was driven by clinical needs.

How or why did you go on to show that it was prophylactic?
Well as you know bipolar disorders have repeated episodes and so if a drug is found to be effective it is not surprising that it is tried continuously for some time. We did this when the first manic states we used it for responded very favourably and it was therefore almost immediately that we found some prophylactic effects. In these bipolar patients the preceding episodes served as their own controls for the prophylactic effects on subsequent episodes - a kind of cross-over design. After we continued the treatment in this way we became convinced of a prophylactic effect. In some patients both the manic and the depressive phases were completely inhibited, in others there was a partial improvement. The manic episodes disappeared but the depressive episodes remained, or the severity of the manic-depressive episodes was considerably decreased and so on. There are many variations. So we found a prophylactic effect even though at first we didn't expect to have prophylactic effects. The first plan had been simply to quieten down the manic problems we were faced with.

You didn't run into problems of the kind Mogens Schou ran into when he went on to make a claim of prophylactic efficacy for lithium, did you? The world seems to have been more prepared to accept the fact of carbamazepine's prophylaxis than lithium's - is this because the example of lithium made things easier?
The problem has to do with the definition of the word prophylaxis. What is the meaning of the word? Is it just a continuation of the therapeutic effects of carbamazepine, which directly suppress manic or depressive episodes at their early stage of onset, or does carbamazepine act on some other mechanism

that triggers or paces the occurrence of manic or depressive episodes? Many people say that when you continue the drug, the anti-manic and anti-depressive effects will continue but when you stop treatment the problems come back, so there is no prophylaxis. But I am happy with this prophylaxis - if you are having fewer episodes while on the drug. It is possible that the recurrence of manic and depressive episodes is completely suppressed even after the discontinuation of the medication in some cases, and a similar effect had been observed also during lithium treatment.

Well do you think then that any of the antidepressants can be prophylactic if they are used continuously?
Well no, in the case of the antidepressants, in some cases it will suppress the depressive episode for some time but it will often recur even while the patient is on medication. In the case of lithium or carbamazepine, if the patient is a real responder the episode is suppressed completely while the patient is on treatment and I think there are no antidepressants which have an effect like this. I'm not sure whether this is a quality of the drug, or of the pathophysiology of the bipolar state. As you know, if you give carbamazepine to bipolar II patients, who have mainly depressive phases with occasional hypomanias, then the medication may suppress the occurrence completely but if we give it to unipolar depression, carbamazepine will not work in the same way.

When you came to do the prophylactic studies were you aware of any of the claims being made by Pierre Lambert for sodium valproate? He was also saying something similar to you - not just that this anticonvulsant was mood-stabilising but in some sense in some people it seemed to be personality stabilising.
No when we started the study of carbamazepine we knew nothing about this. After our results were published, Professor Emrich replicated them and then I found out from him that Dr Lambert had made similar discoveries with valpromide. But valproate was not available at the time in Japan.

Can you explain what you mean by good for the personality?
In the classic textbooks, an epileptic personality has been described. However, it is said recently that this has nothing to do with epilepsy itself but that it comes from brain damage associated with the organic brain diseases, which cause epilepsy. Anyway in the classical textbooks you can see it described - that these patients may be aggressive, that their mood may be unstable, that they may be circumstantial. Now it is known that carbamazepine could be good as an emotional stabiliser in these patients. The aggression, violence or other emotional instability could improve. So it was not unnatural to think that it might be helpful in some personality disorders also.

After we studied carbamazepine in the double-blind study, and then later after the study by J C Ballenger and R M Post of carbamazepine in mood disorders in 1980, we had a symposium in Japan on carbamazepine in 1983. At that, we found that it had been used by psychiatrists in many kinds of disorders, even before our study. One doctor reported that it was useful in intra-familial

violence - which is a big issue in Japan - many youngsters, particularly boys, become very violent to their parents, they hit them and destroy the furniture, etc. This doctor found that carbamazepine was very good for this kind of violence and he expressed this interestingly. He said that boys who become angry with their parents said that on carbamazepine they still became angry but the feeling of anger stopped at the neck - it wasn't expressed. So carbamazepine doesn't block the occurrence of these feelings it decreases their expression. This doesn't apply to every patient but it does indicate how carbamazepine may be useful in many kinds of emotional disturbances.

Had it been discovered by then that it was useful for trigeminal neuralgia?
That had been described in the attached documents since the drug was approved in Japan. It had been approved by the government for both epilepsy and trigeminal neuralgia. Diabetes insipidus had also been accepted. But the indication for mood disorders was only accepted by the government in 1990, as well as a use in excited states of schizophrenia. It had already been approved by many governments elsewhere for mood disorders but our government was the first to accept a use in schizophrenia.

By excited states of schizophrenia, you mean?
We did a double-blind study in schizophrenia with it, which we published in Acta Psychiatrica Scandinavia in 1989. We had used the BPRS and another scale for mania and we found that it was not helpful for schizophrenia generally but the BPRS items relating to excitement, uncooperativeness and suspiciousness did show a significant difference. Just as with sodium valproate, it is not effective against the process of schizophrenia itself but it is useful for some of the symptoms.

You're very widely cited as the person to have discovered the prophylactic effects of carbamazepine, have you been asked to talk about how you made the discovery or been offered Prizes?
No I have never discussed the story as a whole. I have written the story partially here and there, and I am preparing to write a paper about it all in the near future.

Can you remember the first few patients that went through the study?
Well actually the study was done after I had only a few experiences with carbamazepine in mania. But at that time I was the professor of psychiatry at Tottori University and as I explained I had access to psychiatric clinics and wards of several affiliated hospitals. Every so often I would visit each of these hospitals to act as a consultant on some patients. At that time many of the psychiatrists in our area had difficulty treating manic patients, so when I asked them to join the study and try carbamazepine they were willing to co-operate. So I saw many manic patients in those hospitals and recommended the use carbamazepine to the attending physicians. Thus I was acting more as the co-ordinator. One of my colleagues, Dr Kishimoto, who is a co-author on many of the papers on carbamazepine, was the chief co-worker with me on this project. It was lucky for us that we could get the co-operation of the other doctors in many of the affiliated hospitals. In that way we were able to get 50

patients in one year and in the next 2 years a total of 90 patients for the open trials in the initial stage of our carbamazepine study.

For the double-blind study, we asked several universities all over Japan - Jikei University, Tottori University, Okayama University, Kawasaki University, Hiroshima University, Kurume University and Nagasaki University. The carbamazepine study was done by almost the same group of universities who had done a multi-institutional lithium-chlorpromazine study just before the carbamazepine study. The lithium study was chaired by Prof Ryo Takahashi of Nagasaki University, and published in the Archives of General Psychiatry in 1979.

But there was a problem with our carbamazepine-chlorpromazine comparison study. It started in 1975 and took 2 years during which we collected complete data on 63 patients. The code was broken in 1977, just before the World Congress of Psychiatry in Hawaii, which was in August of that year. I reported the result there. We were unlucky that the results of our double-blind study did not appear in the abstract book because we did not get the details in before the deadline for the abstracts. But we reported it anyway.

After that we wrote the paper in English and sent it to a distinguished Western journal, who rejected it. They rejected it because we had used a dose of chlorpromazine of 275 mg per day and the referee said this was too low - it was no different to placebo and that our study had compared two ineffective drugs and found no difference. We discussed this for 1 or 2 years. You see we had done the lithium study also with a chlorpromazine comparison in Japan, using the same universities, a dose of lithium of 1000 mg and a dose of chlorpromazine of 270 mg per day - exactly the same dose of chlorpromazine. The dose of carbamazepine was 540 mg on average. But the lithium study was accepted and published and we thought that it was accepted because lithium had already been approved and its use was widely known whereas the action of carbamazepine wasn't. We could understand that the dose of chlorpromazine was too low.

But wait a moment, the dose may have been too low for the Americans then, but it would not be too low now for them and it would possibly never have been too low for the rest of the world. Arguably you were the ones who got the dose right.

Well we sometimes used higher doses to treat manic states even in Japanese clinical practice. We looked at many papers in the Japanese literature and found a paper by Prof Toru from Tokyo Medical and Dental University, who is now the Japanese representative on the CINP. He had made a survey of the side effects of neuroleptic drugs taken from double-blind studies. Most of the studies had used chlorpromazine as a control in double-blind trials of new antipsychotic drugs for schizophrenia and according to his study the dose of chlorpromazine varied from 150 to 600 mg. In the West doses were probably twice as high during this period. At that time we were being criticised for having lower doses of antidepressants than Western countries also. Many people have proposed hypotheses as to why this should be but there is no agreed answer at the moment.

About 10 years after the chlorpromazine study, we did a double-blind comparison study of lithium and carbamazepine and found that the dose of lithium we were using was only giving serum concentrations of 0.4 mmol/litre. This was unexpectedly low but we had the same improvement between the two drugs clinically. Again we sent the paper to a Western journal and had great difficulties in getting it published - they argued that the lithium level was too low.

So the low doses of drugs may not be due to a biological factor but more a psychological factor in psychiatrists. Many people argue that Western psychiatrists like to use intensive and aggressive treatment but that in Japan and oriental countries, psychiatrists do not like to go to extremes and we consider the side effect issue very carefully. Also we find here that if the patient gets side effects, the families get worried and doctors like to have friendly relations with the patients and their family. When side effects occur, they don't like to increase the dose.

But its interesting isn't it that we have now realised that the doses of neuroleptics we were using in the West during the 1970s and 80s were far too high and that the optimal dose of chlorpromazine may be as low as 300 mg per day and the optimal dose of haloperidol may be around 3 mg a day - doses which are quite close to what you were using.
I am very glad that the dose of chlorpromazine we used in our carbamazepine-chlorpromazine study, 275mg per day in average, is now recognised not to be a "completely ineffective dose". But recently there is a self-reflection among Japanese psychiatrists that they should increase the dose to the maximum level in a therapy resistant patient before they diagnose the patient as "therapy resistant". Otherwise, we cannot discuss the effect of psychotropic drugs on the international level. Anyway in the case of publication in international journals 10 or 20 years ago it was very difficult to get our findings accepted.

Now can I ask you, did you find things changed when Bob Post came out and began recommending the use of carbamazepine - the Americans have a habit of not accepting anything unless one of their own has had a hand in putting the phenomenon on the map.
Yes I think it is true that Dr Post's paper resulted in an acceptance of carbamazepine's effect. This was even the case in Japan where some psychiatrists did not know of carbamazepine's effect. But when he studied it in the United States, our Japanese studies became very popular. So I often say that carbamazepine was re-imported to Japan from the United States. This happens not just for drugs but in many other areas of life as well. Though Japanese people have become more confident of themselves recently, they often do not appreciate Japanese studies whereas the work done in Western countries is highly appreciated. This has links to the history of Japan. One hundred years ago when Japan was opened to the West after over 300 years of closure of the country to the world, everything Western was seen as good while Japanese things were seen as not so good. This is not so much among the young now but it was true among those who are now

middle-aged or older. It was after Post's paper that the rest of the world began to pay heed to carbamazepine.

Before his article and his theory that it acts by reducing kindling in limbic areas of the brain, what theory did you have as why it was working?

I am also an epileptologist and I knew that the duration of hippocampal after-discharge induced by electric stimulation in cats was shortened but the threshold to induce the after-discharge was not altered by administration of carbamazepine. It means that epileptic excitement can be suppressed by carbamazepine. Therefore, I speculated that some abnormal excitement, not an epileptic process, in the limbic or hypothalamic emotional system, which causes bipolar mood disorders may also be suppressed by carbamazepine and result in the improvement of the symptoms.

In the 1983 carbamazepine symposium in Japan, which I mentioned before, Dr R Akazawa in Juntendo University reported that the EEG of bipolar patients treated with carbamazepine showed a slowing of the background activity, particularly during hyperventilation activation. They showed that cases showing high voltage slow waves during carbamazepine therapy responded to the treatment favourably. Now these slow or delta waves do not originate from the limbic structure but probably come from the hypothalamus or brain stem. So maybe carbamazepine works not only in the limbic structures but also somewhere in the hypothalamus or brain stem. With regard to the chemical or pharmacological process, carbamazepine has been shown to affect various neurotransmitters and neuromodulators such as dopamine, noradrenaline, serotonin, acetylcholine, GABA, and also act on adenosine receptor systems. Prof Emrich and his group in Germany have proposed a GABA hypothesis of mood disorders.

In another piece of work done here in Japan, Dr H Mitsushio and M Toru found that the circadian rhythm of rats in the free-running state, when they were given carbamazepine for a long time mixed with their food, had lengthened periods of their circadian rhythm. This is similar to what was shown for lithium. It is said that in the case of bipolar mood disorders the circadian period is shortened. It might be that the shortened circadian period of bipolar patients is lengthened and normalised with lithium and carbamazepine. Anyway, I understand that the mechanism of action of carbamazepine will be very complex.

With regard to the kindling hypothesis, Dr Juhn A Wada in Canada demonstrated that carbamazepine suppressed the electrical kindling process in the limbic area. It suppresses the propagation of the kindled seizure discharge to other brain areas, rather than suppressing the development of electric kindling process itself. I have no substantial evidence myself to comment on the kindling hypothesis of mood disorders of Dr Robert Post.

One of the things about carbamazepine is that its a tricyclic. Now back in 1961, Professor Haruo Akimoto here was saying that Tofranil could be used to treat both depression and mania. Were you aware of this?

Of course, Professor Akimoto is one of my teachers. I knew his work very well and his demonstration that high doses of imipramine could be useful in bipolar states but at that time no-one confirmed his study. I don't know why not, possibly because imipramine is known to cause a conversion to manic state during the treatment of bipolar depressions.

But ECT can cause some people with bipolar depressions to flip over into mania and yet it is a very good treatment for mania, so perhaps imipramine could be good for both.

At that time many psychiatrists in Japan, I think, probably thought that it could treat mania in certain cases but it was not something that they were going to use in the usual clinical case and eventually most people forgot his work. After we found the effect of carbamazepine, I also remembered his work and wondered if it was something to do with the tricyclic structure of carbamazepine. Dr Akimoto had many good ideas. His group, including Dr Yutaka Honda and others, found the effect of imipramine on narcolepsy. Do you know of any other study using imipramine in mania?

Well I have used other antidepressants, such as mianserin or dothiepin, in mania in some patients with good results. What I think happened was that shortly after he reported his work, the catecholamine theory of depression emerged and this said that depression was about having low catecholamines and in mania there was an elevation of monoamines and that antidepressant treatment raised monoamines. If this is correct, then it would be close to malpractice to give something like imipramine to a case of mania. I suspect it was because of these theories that findings like Dr Akimoto's were ignored.

But, why are the antidepressants used so little here in Japan compared to the West - you use much more anxiolytics here?

I don't know what the reason for the difference between Western and Japanese use of antidepressants is and whether it is a difference in numbers of prescription or the total amount of the consumption of the drug. One reason may be that the makers of the antidepressants have tried to propagate their use through primary care physicians and internists. But these doctors don't like to use antidepressants because of side effects like dry mouth, tremor and constipation and they prefer to use the anxiolytics, which only cause sleepiness or other less serious side effects. As I said before, Japanese patients complain of side effects more often and this inclines doctors to use drugs with less side effects like anxiolytics.

Of the antidepressants that are used, maprotiline is by far the most commonly used. I understand from Tsuneyoshi Yamazaki who was working with Ciba-Geigy at the time that maprotiline was licensed in Japan that in part this was because the marketeers aimed at a psychosomatic medicine market. From what you said at the start of the interview I presume therefore that psychosomatic medicine was just emerging as a distinct speciality at that time. Is there a reason why psychosomatic physicians might be more inclined to use antidepressants and how do you account for the fact that drugs like

Prozac which have been so successful in the West have not made it to the Japanese market?
The relationship between psychiatry and psychosomatic medicine is rather complicated in Japan. As in USA and in Europe, psychosomatic medicine in Japan was developed in the initial stage mainly by psychiatrists in 1940s. Recently, however, most of the psychosomatic physicians start their career as internists and come into the speciality of psychosomatic medicine later. They treat neurotic disorders and mild depression, etc. and the area of interest is very similar to that of psychiatry except for schizophrenia and other severe psychoses. Sometimes psychiatry and psychosomatic medicine are in a state of competition so to speak. Therefore, psychosomatic physicians need to use antidepressants just like psychiatrists and they treat depression and panic disorders. In this, they are quite different from ordinary primary care physicians who are rather reluctant to use antidepressants because of the side effects. However, it is said that, because many of the psychosomatic physicians start their career from somatic medicine, the way of thinking seems to be somewhat different from that of psychiatrists who start their training from psychopathology as well as biological medicine.

I have heard that a pharmaceutical company tried to introduce a SSRI, not Prozac, into Japan and started a trial. But the efficacy was rather unsatisfactory compared with previous antidepressants and they gave up the development of the drug in Japan. Many people said that the reason why SSRIs were not introduced into Japan was mainly due to the policy of the pharmaceutical companies, who thought that the market for antidepressants was not large enough to introduce new antidepressants. If SSRIs are introduced in Japan in the future, they will be used by psychiatrists as well as by psychosomatic physicians.

Do Japanese people become dependent on benzodiazepines? In the West it is clear that not all people become dependent on them and it could be that fewer people here are genetically predisposed to becoming dependent.
As you know, Japanese people, or Mongolian populations, are more sensitive to alcohol and the incidence of alcohol dependence is lower than in Western people, because the aldehyde dehydrogenase 2 which metabolises the aldehyde to CO_2 and H_2O is lacking in about 50 per cent of the Mongolian population. However, I don't know whether or not any genetic studies have been done on the disposition for benzodiazepine dependence in Japan. Recently, so-called low dose dependence or therapeutic dose dependence on benzodiazepine anxiolytics has become a concern among psychiatrists in Japan. Maybe 10 to 20 per cent of patients using benzodiazepine anxiolytics are in the state of so-called low dose dependence, but in most of the cases, the neurotic or depressive state, which necessitated the use of benzodiazepine still exists, so that it is not a state of dependence in a narrow sense. We see very few cases of severe benzodiazepine dependence, which show convulsions or delirium. I suppose that one of the reasons why severe benzodiazepine dependence is rather rare in Japan might be due to the use of lower dose of these drugs compared with that of Western countries. For

example, the usual dose of alprazolam is 1.2mg per day for patients with general anxiety disorder.

I have heard that the benzodiazepines have been sold in Japan as having mood stabilising properties - Yoshitomi Pharmaceuticals have for instance portrayed Etizolam in this way. This seems to me not the same kind of mood stabilisation that you have been looking at with carbamazepine or what the term mood stabilisation might mean in the West but I can understand a use of this term for this purpose. Can you tell me more about how this use of the term is perceived in Japan?
The use of the term "mood-stabilisers" in Japan is the same as in Western countries, that is, it means a group of drugs which have therapeutic and prophylactic effects for mood disorders, ie for manic and depressive episodes. The mood stabilisers include lithium, carbamazepine, valproate, clonazepam, etc. However, in Japanese, minor tranquillisers or anxiolytics are called "Sheishin-antei-zai" (psychostabilising drug) and mood stabilising drugs are called "Kibun-antei-zai" (mood stabilising drug). The same Japanese word "antei" is used for the translation of two English words "tranquillising" and "stabilising" and it is the cause of confusion. I believe that people in Yoshitomi Pharmaceuticals are using those two words correctly.

Somewhere around the late 1960s, medical students here revolted - this was around the same time as the student revolts in Paris. The odd thing, however, was that it was medical students that were involved, as they are usually very conservative, but also they occupied the Department of Psychiatry - for up to 10 years as I understand it. The Professor as I understand it had to resign - in part because he had been working with psychosurgery and this was thought to be a bad thing. So is or was psychiatry perceived as being an agent of social control.
It is difficult to explain what went on. Tokyo University psychiatric department is described as a redbrick building. It was occupied by anti-establishment forces. This was a similar movement to what was happening all over the world at the same time. It gradually quietened down in other departments around the country but it kept going in Tokyo. Professor Utena, who was a very good psychiatrist and psychopharmacologist, who had made a good study on amphetamine psychosis, was the professor at the beginning of the struggle. He hadn't done psychosurgery by himself but a colleague was doing lobotomies and he took the opportunity to extract a small piece of brain from around the burr-hole, on which he did neurochemical studies. He found some disturbance of glucose metabolism in schizophrenia in this way. So he did studies but not psychosurgery. However the students objected. He nevertheless finished his tenure, as he had not very much time left. The problem then was, with the department occupied, nobody could become a professor of psychiatry in Tokyo university without their tacit approval for a while. The department became an "untouchable" place. In recent years the situation has become gradually better but during all this time very few scientific studies were done in Tokyo University.

This whole period must have put psychiatric research back.

Yes. The antipsychiatrists were particularly against biological psychiatry. At one point only two or three universities such as Hokkaido, Tokyo Medical and Dental, and Okayama universities remained active in biological psychiatry but the situation is much better now. The antipsychiatric movement in Japan is sometimes portrayed as a movement against biological psychiatry but I don't think this was the only reason. Antipsychiatrists were against the establishment itself, not just against biological psychiatry.

In the West the moving forces behind antipsychiatry were not always the same. In France it was an anti-technology and therefore anti-industry movement, of which one of the industries was the pharmaceutical industries, in other countries it was anti-establishment but in other countries such as Holland, the biological approach to man was seen as all but ungodly.

At that time there was a struggle within psychiatry, even within psychopathology, where the antipsychiatrists appeared to be against science itself - they did not want humans being controlled by science. Not just natural science but also cultural science and so they were also against psychoanalytic control. There is still some struggle, although it is much less hostile now. In the case of rehabilitation psychiatry, for instance, there is still some hostility from the antipsychiatrists to the idea of social skills training because training the patient in this way and evaluating the effect of training is not perceived to be a good thing. But, I think, the antipsychiatric movement gave Japanese psychiatrists an opportunity to reflect on the way of treating mentally ill patients humanistically, and it contributed to the improvement of the mental hospitals and rehabilitation system in Japan.

One of the things I've been hearing about here is that there are at present great difficulties in getting clinical trials running whereas 30 years ago you were able to get studies done very successfully. What's gone wrong?

The problem stems from certain scandals such as the blood transfusion episodes - use of un-heated blood preparations, which has the risk of AIDS infection by physicians and pharmaceutical companies. Because of the aggressive ways these have been portrayed in the media, the public began to look at physicians and new drugs with distrustful eyes.

There seems to be a much bigger problem here now than there is in the West. Clinicians seem to have to take a lot more time here to get informed consent than they do in the West.

As far as I understand it, people in Western countries are accustomed to make a written contract in everyday affairs. In Japan, however, we are not accustomed to make a written contract. Many engagements or agreements are done by non-verbal mutual understanding. The written consent is made only in the occasion of very important or serious problems such as receiving a difficult surgical operation. Therefore, when physicians ask patients to sign the document of contract at the time of a new drug trial, the patients and their family tend to take it as very serious, and become anxious that the test drug might be very dangerous one. Sometimes the patients hesitate to give a written consent to physicians.

That seems very strange because in many ways Japan seems more hierarchical than in many Western countries and you might have thought that professionals would be relatively high up the hierarchy
No they are not. Not now anyway. Twenty or thirty years ago doctors were almighty. This was the same as in the West where doctors were often envied because many of them, except for researchers and employees of hospitals, are thought to be rich and are respected by others. But, recently here at least some people are against the authority of doctors - it seems to be a kind of anti-establishment feeling. Journalists in particular have been very aggressive as regards doctors and medicine. This is my impression anyway. The influence of the blood transfusion scandal is very big and the conduct of some doctors relating to that problem is a direct reason why people are sensitive about new drugs - they can't believe doctors anymore. But I think that if we explain what we are doing openly and well, they will agree. I recently was doing some work with new anti-epileptic drugs and if we explained it properly to the patients they agreed because as you know many epileptic patients are still resistant to the available treatments. The quality of the drug is another issue. If it is a good drug, which can lead us to expect an improvement in difficult symptoms, then we can expect the patient to co-operate.

Can I ask you whether scales like the Hamilton rating scale are appropriate in Japan - I understand when you submitted your work in the first place, you hadn't used the Hamilton rating scale - perhaps this was one of the reasons why the paper wasn't accepted.
We used a scale devised by the Clinical Psychopharmacology Research Group in Japan, the CPRG scale, which was not known abroad. The reason we used this in our carbamazepine study was that, first, the CPRG scale was developed with co-operation of leading clinical psychopharmacologists in Japan at that time. Ryo Takahashi had also used the CPRG rating scale in the multi-institutional double-blind lithium-chlorpromazine comparison study, which preceded our carbamazepine-chlorpromazine study. We thought that the use of the same rating scale would give us the chance to make a better comparison of lithium and carbamazepine by means of meta-analysis, etc. We used chlorpromazine as a control drug to carbamazepine because at that time lithium hadn't been accepted by the government and they didn't accept that we could use it as a control for carbamazepine. This was why we used the CPRG scale.

Do you think the Hamilton is less useful here in Japan than in the West - do we need more culturally specific rating scales?
I'm not a specialist in rating scales, but recently in Japan, the Hamilton rating scale for depression has been used widely as a standard and first choice rating scale for depression. I don't think we have any inconvenience in applying this rating scale for Japanese patients. I don't know there have ever been any comparisons between the two scales, CPRG and HRSD. Would you expect cultural differences on rating scales like this?

Well I would be interested to see how the scales compare because there are conditions which you have here like social phobia or Taijin Kyofu,

which until quite recently it seemed we didn't have at all in the West but in fact I'm sure that for ages in the West we called a proportion of these cases neurotic depression. Now if you see the condition as neurotic depression on the one hand and social phobia on the other, you are going to use different items if you are trying to rate treatment effectiveness.

Since the operational diagnostic systems as DSM-IV and ICD-10 became prevalent, comorbidity of depressive disorder and anxiety disorders (panic disorder, social phobia etc) is an important problem. As far as I understand, we use HDRS rating scales for anxiety and other necessary rating scales together in such cases.

One of the things you have here which we don't have is a very big market for anti-dementia drugs so called and also a huge market for private MRI scans - people regularly go for "brain checks" - this is unheard of in the West.

It is not true that Japanese people regularly go for "brain scan" by MRI, but we use MRI very frequently in daily practice. It is very useful for diagnosis of organic brain diseases, particularly for diagnosis of multi-infarct dementia and Alzheimer's dementia as you know. But it is our regret that we have still no good way to treat the condition even if we make a correct diagnosis. One of the reasons why the development of anti-dementia drugs is so prevalent in Japan may be that the increase in the aged population has been very rapid in Japan and, in 2020, about one fourth of the population in Japan will be over 65 years old. So pharmaceutical companies are very eager to develop new drugs because they are expecting to have a very large market for the anti-dementia drugs in the near future.

But I understand that so many people go to have MRI scans here that you have begun to realise that there are very many normal people who have changes in their brain. This is intriguing - that you can have a lot of brain change without changing the person too much.

The problem of asymptomatic MRI changes in senile and presenile subjects is very interesting. This can have several meanings. The first is that the symptoms of the infarction are too subtle to be detected clinically. The second is the small defect symptoms will be compensated very rapidly before they are detected as clinical symptoms. The third will be that it is difficult to differentiate between the symptoms of small infarctions and slight physiological degradation of mental function. Well all I can say is that I wouldn't want to have an MRI done myself, while I am asymptomatic because who knows what my ventricles would look like. I think MRI however has been very useful in the diagnosis of depression because as you know some of the depression in the involutional period correlates with vascular changes on the MRI. Some people say that people with vascular changes are resistant to antidepressant drugs - indeed there are a number of studies showing this.

Can you tell me something about Professor Shimoda's ideas about a depressive temperamental style - the immodithymic temperament as it has been called?

Because I worked in Tottori University I knew Dr Shimoda very well. He was the Professor at Kyushu University for a long time. After he retired he moved to Tottori and he became the president of the university as a whole and also the founder of the department of psychiatry. So we have been interested in his theories and we have done work on what we call in Japanese "Shuchaku-kishitsu". This is very difficult to translate - some people call it cohesive character type. The behaviours are very similar to the Typus melancholicus that was described by Tellenbach in 1961. This personality has been proposed as a premorbid personality by Shimoda in 1941 beside the cyclothymic personality of E Kretschmer, and the idea had been generally accepted as such in Japan, particularly with regard to the initiation of endogenous non-bipolar depression. The personality type is characterised as orderly, perfectionist, meticulous, conscientious, reliable, zealous and persistent. Most of them have no hobbies except work. They are inflexible, and unskilled at coping with difficult live events - their only response to this situation is to work harder and more persistently, but finally they become exhausted and depressed. Many people say that twenty or thirty years ago when the computer had not been introduced and society was moving at a slower pace, that kind of melancholic personality, if they worked hard, would be respected and get promotion but that recently the pace of change has increased and the cohesive person is less well adapted because they cannot adapt to change and they are more likely now to get depressed. It is interesting though that the idea of a melancholic personality is not accepted in American psychiatry - it is only accepted in Japan and Germany.

Well what's the difference between this and anankastic personality?
I think there are several differences. The anankastic personality is concerned about small, useless and sometimes absurd things, and, these symptoms are experienced in many cases as ego-alien experience and, in many cases the patients try to overcome the symptoms but cannot succeed. The symptoms will disturb the thinking and behaviour of the patient. In the case of the melancholic personality, in contrast, they are not concerned about absurd things. Their focus is with normal behaviour, their work, but they just cannot adapt to their situation flexibly and rationally. The patient with melancholic personality believe that their way of thinking and conduct is right and they try to pursue their way with all their might and become exhausted. The development of personality may depend on both genetic factors and social conditions so the personality outcomes may change in different settings.

Well I'm sure there are genetic inputs to traits like introversion and extraversion and to neuroticism but as for personality types, it seems more difficult to pin down a genetic contribution there.
Yes my teacher, Professor Yushi Uchimura, who was the predescessor of Dr Akimoto as Professor of Psychiatry at Tokyo University - we celebrated what would have been his centenary if he had been alive recently - he studied in Munich, under Professor Spielmeyer, the famous neuropathologist. He came back to Japan and took many German ideas with him. One of the things he did was to inaugurate a twin study of psychiatric disorders in Japan and they collected family trees from all over Japan. According to their study, features

such as mood appeared to be genetically determined but features such as punctuality seemed to be more socially determined.

With regard to the cohesive personality, Prof. C Ogura in Ryukyu University, Okinawa, recently examined the event related potential and found a decrease in the amplitude of miss-matched negativity (MMN) and increased amplitude of N2b. The former represents a hypofunction of automatic processing of stimuli and the latter hyperfunction of conscious processing. Because those changes were observed both in depressed and remitted periods, Dr Ogura suggested that those changes could represent a trait marker for unipolar depression.

On the personality question can I reintroduce the issue of social phobia. Until 15 years ago we had no social phobia in the West but now we have an epidemic in the making it seems.
I suppose that Western people have also had social phobia more or less but social phobia has not been recognised or diagnosed as such before the era of the operational diagnostic system. Taijin-kyofu or social phobia is rather prevalent in oriental countries as Japan, China and Korea. In China, Morita therapy for social phobia is very well known because, even under the communist society, people seem to suffer from social phobia. The low incidence of social phobia in Western countries, and the high incidence in oriental countries has been explained by the cultural differences between the East and West. It is said that, in oriental countries as Japan, China and Korea, where Confucianism is prevalent, people are more concerned about "shame" and are afraid that they might fail in public and be criticised by fellow people in the society. On the other hand, in the Western Christianistic culture, people may be more sensitive to the feeling of sin and guilt, that is, when they fail they think that they could not accomplish the obligation and feel guilty to God. Therefore, the Japanese people are usually more sensitive to the evaluation of their counterparts and become vulnerable to social phobia.

Well the issue I think is that we are now recognising that you could say that some people who in the past we in the West have labelled as having neurotic depression could be said to have this condition, but I have to add that some of the drug companies have an incentive to help this recognition because they think they have treatments which will be useful.
I don't know what kind of incentive for pharmaceutical companies helped the recognition of the social phobia in Western countries. It is true that anxiolytics such as alprazolam and etizolam and antidepressants as clomipramine and SSRIs will be useful for the treatment of social phobia. It may be possible that some pharmaceutical companies try to promote the detection and diagnosis of social phobia as the subject for pharmacotherapy. By the way, another reason why social phobia is not so prevalent in Western countries may be that, in your societies, that kind of person is trained in a way that means they are less symptomatic. Children are trained to express their opinion much more in the West. This was much less so in Japan until recently. In primary school, in my age in Japan, children learnt passively what their teacher said and there was no training to express their opinion or to debate in public,

whereas in the West children are trained to debate and express their ideas. This kind of training will alter the expression of the condition. Recently the number of people suffering from social phobia among young people in Japan seems to be decreasing somewhat, probably because of the change in education.

I think that the nature of humanity is not very different among the countries and races. I have been engaged in the sleep study, and as I am a psychiatrist I am interested in the study of dreams. When I was in Tottori University we did a systematic study on REM sleep dreaming. I was surprised at the fact that the contents of the dreams of young Japanese students at that time were quite similar to those published by Freud in 1900 in "The Interpretation of Dreams". The incidence of what for Freud were "typical dreams" such as "object endangered", "falling through space", "being chased or pursued", "taking tests or examination", etc were high also among the youth in the present time. So it seems to me that human beings don't vary so much in the depths of their minds even though the times and cultures may change.

Well that links up to the question of circadian rhythms. Japan has been one of the most active countries in the world for the study of circadian rhythms.
I am surprised to hear that people in other countries are less interested. Sleep studies is actually quite a new science in Japan. The reason why psychiatrists are interested in this and circadian rhythms has been because of hypotheses that depression is caused by some dissociation of circadian rhythms - the phase advance hypothesis. Recently, delayed sleep phase syndrome (DSPS) was introduced to public through the mass media and this promoted the study of sleep medicine. There were many students who could not go to school in time because of the sleepiness in the morning due to DSPS. They have been treated as lazy students before but the recognition of DPSP changed the situation and now those students are treated as patients with a sleep disorder, which should be managed medically.

Certain sleep/circadian rhythm manoeuvres also seem to get built into Morita therapy as a hygiene measure it seems.
I don't know whether Professor Morita intended to control sleep/circadian rhythm during the procedure of Morita therapy. The period of "absolute bed rest" which is the stage of introduction to the Morita therapy, during which the patient is asked to stay in bed all day long for a week, may exert a strong influence on the circadian rhythm of the patient. It also gives the patient the opportunity to reflect on oneself.

In Japan, the so-called Confusianistic way of living is still prevalent as a tradition. The idea of taking a daytime nap is not supported usually. The idea that you should get up early, go to work early and work hard during the day is preferable. This way of living is quite rational from the stand point of "sleep hygiene" - to potentiate the amplitude of circadian activity-sleep rhythm. People with delayed sleep phase syndrome have great difficulties adapting to this society. The sleep-wake schedule in modern life is becoming more and more irregular and people feel it difficult to adapt to the society. This is partly

why many people have been interested in the circadian rhythm problems. It is also clear that the pharmaceutical companies here have an interest in developing drugs such as vitamin B12 and melatonin to control the circadian rhythm in this kind of patient.

This leads into the area of chronopharmacology - the idea that you can give a cardiovascular drug at a certain point in the day and it will have no effect but then if you give it at another time it will have dramatic effects. Companies here are more interested in this than the companies in the West.

In the case of neuropharmacology there are several researchers here who have done good work on predicting when to give drugs. But this kind of work is not very well known and not applied among psychiatrists yet. One of the reasons why psychiatrists are less interested in the chronopharmacology will be that most of the antipsychotic drugs have fairly long half-lives. In the case of hypertension, the knowledge of when to give drugs has become very common among internists but this has not happened in psychiatry. Recently, however, many psychotropic drugs have been given in one dose last thing at night to reduce side effects such as sleepiness, weariness and dullness. Do you know whether there is a basis for this with regard to the efficacy of the drugs?

I don't know for certain but it is clear that many of them work just as well given once a day and that is not because of their half life - even with a short half life they will work given once a day. Also a group in Pittsburgh some years ago gave clomipramine by intravenous pulses with several days between pulses and showed it worked as well that way and of course ECT is a treatment that is given in a pulsatile fashion. So at least in the case of depression there seems to be something there but whether there is a right time to give the pulse is less certain. Can I ask you are seasonal mood disorders of interest here?

One of my colleagues Dr Kiyohisa Takahashi in the National Centre Hospital is working on Seasonal Affective Disorder (SAD). He organised a multi-centre study on SAD and found many cases all over Japan, and studied the effect of bright light therapy. He is also a researcher on circadian rhythms and they are testing the effect of Vitamin B12, methylcobalamin, for DSPS and other circadian rhythm disorders. They found it is effective for non-24-hour sleep-wake syndrome but the effect for DSPS was less clear.

Dr Takahashi seems to have been a very active figure. Can you tell me something more about him - what was his thinking, what was his training and his background?

Takahashi is a very common family name, and there are many Dr. Takahashi's even among Japanese psychiatrists. I will tell you here about Dr Ryo Takahashi. He is already deceased since 1988 from liver cancer at the age of 60. He had been 2 or 3 years younger than I. We were studying together in the same department of psychiatry in Tokyo University. While I was working on neurophysiology, Dr Takahashi studied neurochemistry. His research was first on the neurochemistry of anticonvulsants. He later moved to Nagasaki University and became the Professor of Psychiatry there. He did

many epidemiological studies in psychiatry there because Nagasaki was the city where the atomic bomb was dropped and all the people in Nagasaki area are registered in order to follow-up the effects of the bomb. He investigated the incidence of depression and schizophrenia prospectively. This way Nagasaki University became the WHO collaborating centre for epidemiology.

He served as a chairman of the multi-institutional study on the comparison of lithium carbonate and chlorpromazine in Japan, which I mentioned before, and published the result in 1979. Professor Ryo Takahashi served as the Japanese representative in a number of forums. He was involved in Paul Kielholz's International Committee for the Prevention and Treatment of Depression (ICPTD) and later a Japanese Committee was also established. Dr Takahashi was the first chairman of the Japanese Committee and I succeeded him when he died. After several years in Nagasaki, he came back to Tokyo and worked as professor of psychiatry in Tokyo Medical and Dental University. He served also as a chairman of the multi-institutional study on the brain CT-scan of schizophrenic patients.

Yes a huge one. Where other groups world wide at the time were reporting results from 20 or 30 patients, he had something like 240 and in a sense he was the first one to cast doubt on the theory that schizophrenia was caused by enlarged ventricles.
The multi-institutional study on CT-scan picture of schizophrenia in Japan was preceded by the pneumoencephalographic (PEG) study of Prof Yushi Uchimura in 1934. When he was the professor of psychiatry in Hokkaido University, Prof Uchimura performed a large scale systematic study on the PEG of schizophrenic patients and found abnormalities such as enlargement of lateral and third ventricles in 45 per cent of the patients.

Professor Yamashita was another figure from Japan who used to go to early CINP meetings.
Yes, Professor Itaru Yamashita was the professor of psychiatry at Hokkaido University. His predecessor Prof Nozomi Suwa, in the mid-1950s, had studied in Harvard and helped to introduce psychopharmacology to Japan. Prof Suwa opened a WHO Collaborative Centre of Psychopharmacology in Hokkaido University, and Dr Yamashita succeeded him in the department there. Prof Hitoshi Itoh also used to go to CINP. He was associate professor at Keio University, one of the largest private universities in Japan. He died from leukaemia. Historically speaking, he was one of the founders of clinical psychopharmacology in Japan. He was one of the members of Clinical Psychopharmacology Research Group in Japan (CPRG), and he did many clinical studies including on the side effects of psychotropic drugs.

Did Nakajima who had been working in the Sainte-Anne with Delay, Deniker and Pichot have any influence here?
Not really. As a researcher he was not very active while he was in Japan. When he came back to Japan from France, he worked in Roche and I helped him at the time of development of bromazepam in Japan. But he later went on to become the head of WHO

Can I ask you about the amphetamine psychoses that happened here after World War II. I've heard two versions of the story - one that the Americans flooded the market with amphetamines and the other that they leaked out of the Japanese army where they had been used during the war to combat sleep and increase aggression

I'm not sure. People say that during the War the army did use it and, after the war, that amphetamines were released from the army and circulated among the people. The increase in amphetamine psychosis was just after the War and so there probably was an amount of the drug in Japan but I don't have substantial data. They then became controlled and any waves of drug use since then have been because of imports from South East Asia or illegal synthesis in Japan.

Did people here think amphetamine psychosis was a model for schizophrenia and did they think this before chlorpromazine?

Yes they did. The study of amphetamine psychosis was undertaken by Professor Hiroshi Utena in the early 1950s. He also succeeded in making an animal model of amphetamine psychosis in mice, cats and monkeys and used them as an animal models of schizophrenia. The importance of amphetamine psychosis had not been recognised at this stage in Europe. We were seeing far more patients. At that time, up to about several percentage of schizophrenic pictures were due to amphetamine, so it was very important to differentiate between real schizophrenia and amphetamine psychosis. Amphetamine psychosis mimics the positive symptoms of schizophrenia but not the negative symptoms. At that time we used the presence or absence of negative symptoms, a flattening of the personality, or "Praecox-feeling" when we tried to differentiate between schizophrenia and amphetamine psychosis from clinical symptomatology. The psychotic picture usually clears up very quickly in the case of amphetamine psychosis after withdrawal of the drug. However, Prof Seijun Tatetsu in the Metropolitan Matsuzawa Hospital at that time reported that amphetamine psychosis could show recurrence without the use of amphetamine. That is, he found that the patients with amphetamine psychosis who had become asymptomatic after discontinuation of amphetamine could relapse if they later took alcohol or encountered stressful situations. There could be flashbacks. We could not believe this at first, but now we respect his penetrating observation.

Are we training people now to observe clinically in the right way - to be able to distinguish adequately between superficially similar pictures?

This is a very difficult problem. Some of the older psychiatrists are against DSM IV and that kind of operational approach. They worry that if the young psychiatrists are trained by this approach only, they won't learn to observe and understand the patients in any depth. Anyone can make diagnoses in this way, they say, but we should also know something about the pathogenesis, psychodynamics and everything else about the illness. Of course, the standardised operational diagnostic system is very important and useful. Before standardisation came in though, there was endless discusssion at cross purposes. The two approaches need to supplement each other.

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