PSCYHOPHARMACEUTICALS IN JAPAN
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How did you come to look at the possibility of a career in the pharmaceutical industry?

My father was a pharmacist. I wanted to succeed my father. So I went to university, where I encountered a splendid person, Professor Kase. He had studied pharmacology in the United States, in the University of Utah. He brought back exciting ideas about drug discovery – antitussive and CNS drugs. The story about how Berger developed meprobamate from mephenesin was a really exciting one. This made me interested to be a researcher and drug developer like this rather than just the owner of a pharmacy. So I asked my professor if there was any good company working in the CNS field. He recommended Yoshitomi as the only company already working in this field but he also said that I wasn't suitable for a big company because they have a conservative hierarchy, which distorts the development of young researchers ideas. Excellent advice really.

Can I ask you about the origins of the pharmaceutical industry in Japan? In the West it grew mainly from companies making dyes and plastics.

Before the Pacific War, the Second World War, Yoshitomi Pharmaceuticals was formed as a joint venture between Takeda Pharmaceuticals, which was the number one pharmaceutical company at the time, and Mitsubishi Chemicals, which was the number one chemical company. We were named Takeda Chemicals at first. This was formed as a national endeavour to come up with treatments for malaria because there was a lot of malaria in the Southern Pacific region, where our imperial government had plans to go. This company was asked to supply the treatments - anti-malaria agents such as chloroquine, antibiotics such as sulfathiazole, respiratory stimulants such as vita-camphor and anti-leprosy agents - all useful drugs for this area. Our factory is located in Yoshitomi Town in Kyushu rather than here in Osaka in consideration of possible war damage. Kyushu also had a very good water supply, as well as coal for the production of coal tars. Mitsubishi Chemicals supplied the raw materials - it was in Northern Kyushu. Because it was a national project, the government gave us a special licence to charter any material we needed. Later on in the War we became involved in manufacturing activated carbon for gas masks, for which there was a big demand.

Between one thing and the other by the end of the War, we were the second largest company in pharmaceutical production - we had big facilities and a huge number of employees. After the War, we were renamed Yoshitomi Pharmaceuticals and made independent from the parent companies. We lost our official support and we had to compete in the marketplace. This led us to look for new business and this was one reason to enter the field of mental illness - Takeda was not strong in that sector at that time.

Yoshitomi Pharmaceuticals have the best selling compounds in the CNS area in Japan - Etizolam and Clotiazepam. How did Yoshitomi actually enter the CNS area?

We marketed chlorpromazine in 1955.

That was very early.
The reason why we were interested so early was we wanted to try this compound for the prevention of emesis, caused by the anticancer agent Nitrogen Mustard - N - oxide.HCl. We had originally developed this in the early 1940s - the first cancer chemotherapy agent. Vomiting was a serious problem with this and when we surveyed the literature we found that chlorpromazine had some anti-emetic activities. So we introduced it first as an anti-emetic agent. When the first reports of its antipsychotic activity came through from Professor Deniker and Pichot, from the Sainte Anne hospital, we developed it for this indication also. As you know this was the first effective antipsychotic agent.

Was there any contact between you and Dr Nakajima who was working in the Sainte Anne hospital at that time?
Some of the senior management in the company at the time, Dr Hagihara, might have had some personal contact with Dr Nakajima but this was not critical. We had some personal communications with Rhône-Poulenc because we established a process patent to produce our own method of producing chlorpromazine so that we could produce it independently in Japan. This was the only process patent on chlorpromazine anywhere in the world. Anyway we had contact with Rhône-Poulenc because they sued us but, in a Japanese court, Yoshitomi's method was deemed legally acceptable in this country and we were free to market chlorpromazine ourselves. During this dialogue we developed good relations with Rhône-Poulenc and we exported our own new antipsychotic, carpipramine, to them which they developed with Pharmuka under the name Prazinil. It was marketed very successfully.

Carpipramine was first synthesised in 1962. After the big success of chlorpromazine, we needed some backup compound, that would be different to chlorpromazine. We also marketed other tricyclic like antipsychotic agents, fluphenazine, mepromazine but these were all the same - good neuroleptics but as we would say today but they were not active against negative symptoms and we wanted something different. Something that today would be called atypical. Carpipramine was one such agent.

In 1962, one of our chemists synthesised it. At that time, I was the only pharmacologist in the company and I was faced with the problem of how we should evaluate a new atypical antipsychotic compound. At that time, we didn't have any good methods - we didn't have the methods we use now. There was no dopamine hypothesis. This was before haloperidol had been marketed here. I was a new employee. I started with behavioural observations and felt on this basis there was a difference between carpipramine on the one hand and chlorpromazine and the other neuroleptics, as well as a difference between it and imipramine. After the first two years with the company, I went back to medical school for a period and the evaluation was finished by my colleagues. We had the initial pharmacology finished by 1965. From this it was clear that carpipramine differed from imipramine in that it had amphetamine behavioural antagonism and anti-vomiting activity. There was a potentiation of amphetamine group toxicity. So

it was somewhere in between chlorpromazine and imipramine in its profile of effects. It also had anti-tryptamine activity, which means that it was an SDA in today's language.

In 1965, we started clinical trials on the basis of what now would look like very primitive information. At that time it possible to start clinical trials essentially on the basis of toxicity studies - if it was safe. The doctors themselves were interested to test the efficacy of a possible atypical compound. Clinical trial evaluations were not as rigidly established as they are now and one the things was that some of the doctors were prepared to have it themselves to test the safety especially side effects. Of those who tried it, they found that it did not cause parkinsonian side effects. They were also encouraged by the pharmacological differences. When they tried it out on patients first in 1965, they had striking effects especially on negative symptoms. Patients who have been immobilised with negative symptoms for a few years became much less withdrawn. Interestingly we first became aware of what were almost arousal effects, when one very withdrawn patient apparently came up to one of the nurses and touched her on the hip. This led on to nationwide trials, which confirmed our impressions of the drug's usefulness in schizophrenia, including negative symptoms.

But what was the scientific basis behind the drug's usefulness? The clinical evaluations looked very good but we couldn't explain this pharmacologically. At this stage, the dopamine mechanisms involved in hyperactivity, vomiting and gnawing were becoming clearer and biochemical evaluations of dopamine turnover - HVA levels - were becoming possible. But even up to 20 years ago we couldn't explain why the compound was useful for these features. These beneficial effects by the way were confirmed by French scientists in 1978. So the clinical trials were led the pharmacological evaluation. Nowadays especially with the progress of binding assays it is clear that carpipramine has D-2 and S-2 antagonist properties - it was an SDA earlier than risperidone. This compound was really good clinically but its problem was it was borne too early and the pharmacological background was not there to support it.

It was born at the same time as clozapine; did it have similar effects in the clinic?

Very similar. Doctors preferred it to clozapine at that time. Clozapine was developed in this country by Dinippon Pharmaceuticals but they stopped because of ripples from the problems with agranulocytosis overseas. Other side effects were found in this country - fever especially. This led to a caution about clinical trials in the face of such a side effect.

Carpipramine still sells in this country but there has been a problem with Japanese pharmacoeconomics - here, we have a system where the price of pharmaceuticals reduces year by year. This affects older drugs in that there may be no return on the investment. Recently a company that produces the general anaesthetic pentobarbital wanted to stop it but the government obliged them to continue. The reason they wanted to stop was that the return on its use was so poor. We also have an ultra-short acting anaesthetic, which

we would like to stop producing because every time it is used we are almost giving money to the people who are taking it. But doctors and patients need reliable and safe drugs for this purpose so under the terms of a "prestigious obligation" we continue to supply it. But because of this there is an incentive to develop new drugs that will be safer and more effective but also that will get a better price. This is good for us but for the economy it may not be for the best. For this reason we developed mosapramine and clocapramine but they were not as distinctive as carpipramine. The dopamine-blocking effects were more prominent - so that they had much fewer atypical properties.

So we began with carpipramine, which we came across serendipitously and now we are trying to reproduce something like it using a much more rational approach. We have been doing a lot of work in this area comparing the effects of haloperidol and clozapine, pharmacologically, electophysiologically, behaviourally, biochemically and in terms of their molecular biology in our research departments in Kyushu and Tokyo, in order to come up with a new agent that will be distinctively different to both haloperidol and risperidone - that will have a broader spectrum of action - an ideal drug. We have also recently established a very advanced research facility YRING - which stands for Yoshitomi Research Institute in Neuroscience in Glasgow - involving Glasgow and Strathclyde Universities, aimed at coming up with a novel antipsychotic.

A great deal of research in this area hinges on the fact that clozapine is still mysterious. People have hypotheses about its critical properties, such as the D-4 or 5HT-7 receptor action but no-one has cleared this up yet. So using molecular biology techniques we have been trying to establish what exactly it is that brings about clozapine's benefits, especially on negative symptoms. What proteins and enzymes are affected. We have invested a lot of money in this and hope for good returns from the investment in a few years. We have already found a specific inhibition of Rho-kinase, which we reported in Nature in October of this year. This may be involved in the brain in its action and may shed some light on its action on brain functions. This kind of approach looking at signal transduction or c-fos activity will yield an answer at some point.

So we concentrated on CNS first but now we compete in other fields as well - the gastro-intestinal field is our second biggest area. The more we find out, the more it seems that the brain and the gut are very closely linked, in terms of sharing a range of common neurotransmitter - dopamine, 5HT, acetylcholine, CCK etc and in terms of their influence on each other. Many pharmaceutical technologies therefore are applicable to either the CNS or the GIT and we were well placed to enter this field of research - GI motility etc. We developed S-3 antagonists for anti-emesis ourselves which brings us back to where we started from - working with anti-emetic agents.

Can we also talk about your anxiolytic research programme? Roche, I thought had the benzodiazepine market very well controlled. There are stories about them having patented all possible derivatives of diazepam and yet you have had with Etizolam and Clotiazepam the first and

second best-selling psychotropic compounds in Japan. How has this situation come about?
We have always had a very strong medicinal chemistry department, who have been able to manipulate structures. The first idea was to chemically manipulate diazepam. As you say the patent on that was fully covered. We wanted to escape from the Roche's prison. This led us to clotiazepam, a thienodiazepine. This was a unique compound but its properties were not unique, it was mild but very similar to traditional benzodiazepines. We tried to improve this - not necessarily in terms of effects but we worked on the potency aspect of clotiazepam. This led to etizolam, of which 1 mg of this is equivalent to 10 mg of clotiazepam.

Our first screening method was an anticonvulsant method, as well as alcohol potentiation. These were not pharmacological methods for pure anxiolytic agents. You have to wonder if this kind of behavioural evaluation is not more a method of evaluating side effects rather than anxiolytic effects proper. We were using conditioned avoidance and punishment models. These are strong fears that we have given the animal but is that the same as anxiety? This is not a pure anxiolytic effect. The barbiturates clearly have effects on some of these methods also but in their case there is sedation and clear memory disturbances. People, I think, have misunderstood what an anxiolytic evaluation should be about.

Anyway neurosis has been a target for us but so also has psychosomatic disease. In this country, hypertension has been a big market, for instance. etizolam has been quite effective in this area - in the symptomatic management of hypertension. It is not anti-hypertensive in its own right but ten years ago it was jointly prescribed with anti-hypertensives, during a period when there were no beta-blockers, no calcium channel blockers, no ACE inhibitors. It was a similar picture in the treatment of ulcers. But now with the H-2 blockers and proton pump inhibitors - we are marketing Astra's omeprazole - and other drugs the market is changing. This has been changing over the past ten years but 15 years ago we gave much more emphasis to the management of somatic diseases.

Were you aiming more at the psychosomatic market than the psychiatric market? In the West we don't have psychosomatic medicine in the sense you have it here in Japan.
In Japan, there is a guideline for the development of anxiolytic agents. Both neurosis, including general anxiety, and psychosomatic disease are indications and we are obliged to investigate both. Just as with an anti-inflammatory agent, we have to investigate arthritis and frozen shoulder and for a calcium channel blocker we must look at both angina and hypertension, so also if we concentrated on neurosis only, the health authorities, when they examined the new drug application, would ask us why we had not investigated the psychosomatic area. The reason why the health authorities stick on this point is that we have a long history of using anxiolytic agents as a first line drug for psychosomatic diseases. Things are changing though with the introduction of DSM-IV or ICD-10.

We are also changing. We have begun developing benzodiazepine partial agonists. We have some original work in this area with this compound, Y-23684. This is a compound, which is free of the benzodiazepine structure. This is an idea that has been developed by Professor Akaike, who was one year behind me in school. He developed a new electrophysiological patch-clamp method, using one single neurone, in which he clarified that our compound is a partial agonist of the chloride channel compared to diazepam. This gives us a new therapeutic horizon - this compound may be free of sedation, addictive potential, memory impairment or alcohol potentiation, while still having sufficient anxiolytic activity on sophisticated tests of anxiety such as the elevated plus maze and social interaction model - these are not punishment models. The problem with diazepam and older benzodiazepines is that the anxiolytic efficacy increases with increasing dose but so too does the sedative and other side effects.

In the West the whole area of anxiolysis has become a problem because of the benzodiazepines and dependence to them. For this reason people prefer "antidepressants" to "anxioytics". The word "anxiolytic" is a problem word at the moment. It seems that people here don't become as dependent as in the West - is this correct and does it explain the much greater use of benzodiazepines over here.

I partly agree with your opinion. People have very few problems with addiction over here. There is a strict control of prescribing. But also genetically the Japanese seem to have less mental disease than in the West. In the West people are always pre-occupied with themselves, whereas the Japanese system is much more modest and co-operative - people work together much more. Against this background amphetamines are much more of a problem than are the benzodiazepines - we are much more sensitive to the changes, the exaggerations of behaviour, produced by the amphetamines. The behaviour of people in the West is already more exaggerated so amphetamine induced problems are less obvious but here amphetamine abuse is a big social problem and it interacts with criminal activities. Sedative agents are seen as much less of a problem in Japan. But with some of the strong sedative agents such as Halcion, we have seen similar problems with paradoxical hyperactive reactions. Halcion has become famous in underground society here on the drug market. Having said all this, the benzodiazepines as a group are not without some addictive potential and that is why we are very interested in our new partial agonist.

You have been working on the antipsychotic agents and anxiolytics but what about antidepressants? The antidepressant market here seems very small - it seems amazing that Prozac isn't even on the market here.

We are working with Bristol-Myers' nefazodone at the moment but we have been having problems enrolling patients into clinical trials. Both patients and their families hesitate to enter into trials in this area at the moment. We explain that the problem of tricyclic antidepressants is their anticholinergic properties, which give a dry mouth, blurred vision, urinary hesitation and other effects. In the case of the SSRIs there have been the problems with nausea as you know and this has been a particular problem for in Japan - urological and gastro-intestinal side effects are very unpopular here. So far among the

SSRIs, only fluvoxamine have applied for a licence. So if it comes to a choice between anxiolytics and antidepressants, the anxiolytics still win out. Also, there is something of a preference for an agent that will be sedative rather than arousing, like perhaps Prozac. Maybe there will be some change in the future but it won't be very soon - it could be 20 years time.

There is another issue. The Japanese dislike visiting neuropsychiatric hospitals or being thought of as having a neuropsychiatric disorder. In Japan, the terms neurosis and depression are used mainly by psychiatrists. Doctors from other departments, such as internal medicine, don't use them. Depression, neurosis and schizophrenia are not clearly distinguished by the population. They are rather regarded as a single disease. To visit a psychiatrist therefore is sometimes understood as to be suffering from schizophrenia. Therefore patients with mild depression and anxiety prefer to visit other departments and to be diagnosed with a psychosomatic disorder and anxiolytics are prescribed for such patients, whereas antidepressants are more apt to be limited to psychiatrists. Anxiolytics also have an immediate onset of action and very reliable effects unlike antidepressants. Finally there is the fact that the major companies targeting the psychotropic market don't have antidepressants in their product line, which may have affected the low sales in Japan.

You mentioned that there might be a change to antidepressants in future but if there is a change like that, in say 10 years time or more, I expect that in the West by then we'll have gone back to prescribing anxiolytics.
Yes, I think if you find an anxiolytic with less side effects it will change Prozac's market. Depression is not one of our targets at the moment but panic and irritable bowel syndrome are. At the end of August we broke the trial code and found that our partial agonist, Y-23684 is superior to placebo in the treatment of panic, so we have decided to go on to further double-blind trials. Irritable bowel syndrome is one of the psychosomatic areas for which there is still no good other treatment and so we are targeting it also and in mid-Sept last in our trials we broke the code and found that Y-23684 was superior to placebo in double-blind trials. This is a first demonstration that any anxiolytic agent is superior to placebo in IBS, so we are very excited.

The Japanese literature generally refers to the prophylactic effects of carbamazepine whereas the Western literature often refers to it as a mood-stabiliser. Now I mention this because I read in your literature on etizolam that it is seen here as having mood-stabilising properties. I can understand why it is described this way but this would be very unusual in the West. Can you tell me how things are seen here?
There must be some misunderstanding here. We would see etizolam as useful in the depressive state of an anxiety disorder but this is distinct to a mood-stabiliser.

Its very unusual in the West for a company to have been interested in the CNS so early - in the West, the attitude was that psychiatry is not real medicine in the way that respiratory and cardiac medicine is

The way I see it, Western people are very rational and mechanistic and this suits research in some areas of medicine but not in the CNS so much. Brain research is still at a very primitive stage with few good hypotheses. Japanese people are much more emotional and sensitive and are much more likely to take gambles. The story of carpipramine illustrates this. It came about by serendipity. We had no supporting hypothesis but we didn't let it go because of that. We believed that it was something new and that it showed important new characteristics and properties and so we went ahead and asked the doctor what the response to this agent was. It is more difficult to take an intuitive approach like this these days and because of this we need to link up more with rational technologies, with for instance pure selective agents coming from a well worked out theoretical and rational framework.

Has there been any impact of Japanese pharmaceuticals on the Asian market - Western companies until recently have largely been looking at the West. I don't know how much they understand the markets - the health concepts - in East Asia. Your company must be at some advantage here.
Yoshitomi have not yet established a place in East Asia generally but from April 1998 we will be linking up with the Green Cross Company, who have branch offices and products throughout East Asia - Singapore, China etc. So I can see an Asian business develop but the markets are very different. Sophisticated drugs have not been of great interest in many of these countries until recently. They have been much more interested in traditional approaches and traditional remedies. They still have serious nutritional problems and they also have had much more urgent matters such as Malaria, Shigella and Cholera to deal with. Once these issues are not so big a problem anymore, then they may get to the stage where some of the products we have may be of greater interest. For instance, even in China, there are now in places great discrepancies between rich and poor and among those who are wealthy there is considerable demand for our S-3 antagonist anti-emetic agent. For the majority of ordinary workers, a short course of this would cost more than one month's wages but there are people for whom this is not a problem. So the marketplace is changing but a poor country cannot support a large market for these new compounds.

In the case of psychiatric disorders, if the country is rich, these disorders are usually covered by the government because schizophrenics have no monies. This kind of social system has to come in a country before it is possible to develop a psychiatric market.

Is health seen as important here? - Let me explain, in most Western countries, until about 1960 health was not as important a thing as it is now - there were no separate departments of health for instance. It almost seems now that as people lose religious belief they have been replacing it with concerns about their health so that health is almost a central value now in Western societies. How are things here?
Japanese people are very careful about their health. After World War II, there was a lot tuberculosis infection. Nutritional improvements led to decline in tuberculosis but an increase in cardiovascular disease. The Japanese people

at this stage are very sensitive to information on health related matters. This is particularly so for the current middle-aged generation. But I'm not so sure about the younger generation, who don't hesitate about smoking. But health is very important here to the extent that companies ask their employees to check their health twice a year. All people over the age of 40 have to check for gastro-intestinal and respiratory cancer and there are no charges for this.

Let me chase the health-religious issue. When chlorpromazine came out in 1952, along with the all the other new agents, the pharmaceutical industry was seen as a good thing in helping tame the diseases that come from Nature. But by 21968, when the students went on revolt in the West, one of the targets was the pharmaceutical industry. There were mixed views about the benefits of the pills and the pollution of the environment associated with pharmaceuticals. The view emerged that Nature is Good and diseases in a sense almost come from man. Here in Japan, how are the industry viewed? Are all the pills you produce viewed as a good thing or is the industry viewed with a certain amount of caution? Is the industry viewed as making too much money?
This is very philosophical. Things are changing here. Everything is changing especially health problems. Up till recently people trusted the drugs. There was a great reliance on and reverence for doctors, nurses, medical systems and drug treatments. But after a number of drug disasters, there have been newspaper campaigns about the risks of drugs, about price differences, how doctors are getting unreasonable amounts of money. They say that the companies are more interested in profits than in safety aspects. I am sure this has been overemphasised by newspapers and television campaigns. But anyway it has led to a change of attitudes among people, so that they now see the drugs as very dangerous and doctors and pharmaceutical companies as not very good. Because of this our Association of Pharmaceutical Manufacturers is campaigning on the importance of drug development to our national life and also on how proper drug treatment can actually save money. This campaign, however, has only just started. We are still concerned that we may lose some markets and more important lose the capability to develop new drugs. Some of the companies have begun to downsize because of this. Hospitals have too. This is the latest development. We will have to wait and see how the nation wants to go in the future. It is impossible for us here in Japan to go back to Nature - we have no land.

There is a great deal of confusion and depression, which is part of the reason why the Japanese stock price has gone down. We have had discussions with the government about the situation. We have also begun to look at future developments on a global basis, including the marketing. This means we are facing a new situation.

Its interesting to hear that things are the same here as in the West. In the West, there has a criticism of psychotropic drugs as agents of social control. I understand that when you had student unrest here in 1968, the students occupied the department of psychiatry in Tokyo for 10 years. What did this do to research and how did the industry view it - did it

make you feel that the CNS was perhaps not such a good area to be associated with?
This was a great pity, especially in this field, which is so sensitive. For this reason we established the Pharmacopsychiatric Research Foundation, which gives researchers a chance to do work and report their findings. This Foundation gave money to almost all the major hospitals and University Institutes. But as you say the Professor of Psychiatry in Tokyo was criticised because of an association with experimental therapy. This had a big impact on research. It slowed it down, especially new drug research. Psychiatry is still the field that is the most slow moving for new drug research. Younger clinicians seem more interested to use conventional drugs and psychotherapies and they are particularly worried about new drugs because of the issue of informed consent.

Yes more than in the West, this issue seems particularly complex here at the moment. Why is that?
My personal view is that there should be an independent organisation, which decides what is the theoretical rationale for prescribing this compound to this particular patient. At the moment, the system is that each university hospital decides how consent is to be obtained. I think patients and their families would trust an independent legally recognised group, who would have the responsibility of informing the patient fully. At the moment the situation in this country is that clinical trials have almost stopped because of this issue of consent.

Another difference between here and the West at the moment is that when clinical trials began in the West, clinicians participated in them for free because of their interest to answer scientific questions, whereas now they charge very hefty fees for each patient put through. In Japan, I understand clinicians are not paid for putting patients through trials.
It is strongly prohibited to give money to doctors for recruiting patients to trials. Some money goes to the goverment - to the nation's budget - and some of that comes back to the university but few incentives are given to the clinician. This is another factor in making trials difficult. A small incentive would be helpful. Clinicians are losing the enthusiasm to do trials. They are also afraid of criticism from the national newspapers.

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