

Clinical research and synesthesiology

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Among medical researches, the clinical research utilizes results of the basic research for society in the form of therapy. President Higuchi of the National Center of Neurology and Psychiatry (NCNP) and Ono, Editor in Chief of *Synesthesiology* discussed the situation of clinical research in Japan. They shared common goals between the clinical research in the medical field and synesthesiology.

Synesthesiology Editorial Board

Participants: Dr. Teruhiko Higuchi, President, National Center of Neurology and Psychiatry
Dr. Akira Ono, Editor in Chief, *Synesthesiology*

Moderator: Dr. Motoyuki Akamatsu, Executive Editor, *Synesthesiology*

(Moderator)

To utilize the results of scientific research in society, we believe the research that pursues a methodology for synthesizing and integrating the elemental technologies is important as well as the conventional analytical and pure basic researches. In the field of medicine, there are basic and clinical researches. Can you explain whether these two are essentially different disciplines, and what exactly is clinical research?

Type 2 Basic Research and clinical medicine

(Higuchi)

The essence of medical research is to develop a new therapy to treat the patient, and to seek new therapy by studying the cause of a disease. In medical research, there is the approach where one becomes directly involved in the disease to understand it, and also the approach where the elements and foundations that comprise the human body and the diseases are investigated thoroughly, and then the actual disease in humans is confronted with such knowledge and technology. Basic medicine studies the functions of normal cells and the workings of normal neurons, while clinical research looks at the pathological conditions and the diseased tissues.

Basic medicine existed throughout the ages. Physiology developed in the ancient times not because people wanted to know the cause of diseases, but because people were naturally curious about “how the human body is composed” or “why does the heart beat on its own”.

On the other hand, clinical medicine is an application of the understanding of how the physiological functions change into a pathological state, using the knowledge and information obtained in basic medicine. There are studies in which humans and diseases are used as direct subjects, to reveal the differences between a normal individual and a diseased individual. In some cases, large-scale clinical researches are conducted using several hundreds or thousands of human subjects to see whether a drug really works or whether it is a placebo effect (where the natural healing effect is observed due to the psychological effect of taking the drug, even though there is no actual pharmaceutical effect).

(Moderator)

There are clinical researches using disease-model animals, but there are also different kinds of clinical research where a large-scale research is done to determine whether it is applicable for human treatment.



Dr. Ono (left), Dr. Akamatsu (center) and Dr. Higuchi (right)

(Ono)

I think that the discussion about the basic medicine and the clinical research may lead to the analogy of the *Type 1* and *Type 2 Basic Researches*. There are dreams in the pure basic research, and the researchers who attained their dreams may win Nobel Prizes and receive research funds fairly easily. There is a great gap in terms of time and technology, however, for the basic research results to become actual products in industry and to be used in society. I think that some synthetic and integrating approaches are necessary for the basic research results to become valuable to society.

(Higuchi)

If *Type 2 Basic Research* is what is called application research, I think the researches that involve animal models and diseased cells can be positioned as such. The large-scale clinical research where humans are used as subjects is close to *Product Realization Research*. I think there is a shortage of research on how to get the products out to society. For example, considering anticancer drugs, one may induce cancer in an animal and prove that the cancer disappears when a certain drug is administered. However, it will not be a “drug” unless it is proven that it really works in humans and that there are no side effects.

(Moderator)

In the sense that it is a way of studying the therapeutic effect using human subjects, can clinical research be categorized as disease-oriented research? Is it like clarifying the disease mechanism?

(Higuchi)

The approach may be a bit different from mechanism clarification. Both pathological research and therapy research use humans as subjects. For example, to study the pathological condition of the Alzheimer’s disease, in the past, we could only look at the brain tissue of the deceased patient under the microscope. Now, with the advancement of imaging technology, we can look directly at the brain image of the living patient to study the pathological condition of Alzheimer’s disease. While this is a pathological research



Dr. Teruhiko Higuchi

using human subjects, it is not therapy research. Therapy research falls in the domain of clinical research.

(Moderator)

Up to the pathological research, the mechanism of a natural phenomenon called the disease is clarified, and that may be close to *Type 1 Basic Research*. When this knowledge is converted to therapy, it turns into *Type 2 Basic Research*.

TMC bridges the pathological study and the therapy

(Ono)

In the field of medicine, does a researcher engage in either the pathological research or the therapeutic one? Or can a researcher engage in all from the pathological to therapeutic researches?

(Higuchi)

Both cases are possible. Let me talk about an example of the study carried out at NCNP. It had been known that muscular dystrophy was a genetically transmitted disease, and a gene called dystrophin was finally discovered by a researcher. After more than ten years we are able to see what kind of abnormal proteins are produced and how they cause the muscles to atrophy. Now the researcher is trying to get to the therapy research.

(Moderator)

Looking at the Japanese clinical research statistics that Dr. Higuchi showed us, I am concerned that the number of Japanese papers published in four journals of basic medicine research with high impact factor (2000~2005) is ranked number four in the world, while Japan ranks eighth in the three clinical medicine research journals, and there are less number of papers.

(Higuchi)

Even if there is an accumulation of excellent papers in basic research, we are not getting the application in clinical practice. We are becoming aware that it is not right that we are unable to produce results that are actually useful to people. On that point, I think we share a common concern with AIST.

NCNP is composed of a hospital and two research institutes. In the past, the institutes were mainly involved in basic research, and there was hardly any contact with the hospital that engages in daily clinical practice. However, when we were organized as an independent administrative agency, the consciousness that we should engage in the researches covering “from basic research through application research to clinical research” has risen in the past five to six years. As a move, the Translational Medical Center (TMC) started in 2009. TMC places the importance on linking the research and clinical practice, and to support clinical trials and researches

to promote translational medicine for the clinical research in psychiatry, neurology, myology, and developmental disorder.

Why Japan has fallen behind in large-scale clinical researches

(Moderator)

As in the case of muscular dystrophy you mentioned earlier, there are several basic researches that may offer ideas for therapies. But still there are not a lot of applications to clinical practice. Including large-scale clinical research, why has Japan fallen so far behind in clinical research?

(Higuchi)

A researcher is evaluated for his work of “publishing high-quality, original researches in high-quality journals”. A large-scale clinical research can only be conducted by a team of perhaps 40 people, and it involves extremely careful design and preparations, as well as recruiting many patients. This is extremely unproductive for a researcher. It may take five to six years to complete a single clinical research. Moreover, even if a wonderful result is obtained, there is only one first author. For the other 39 people, considering the efficiency of their energy spent, it is much more efficient to design a trial alone, conduct research in a few months using animals, yield results, and become the first author to publish in *Nature* or *Science*. While it is understandable for the people to think this way, it is one of the reasons that this field has not advanced. In the United States, research funds and human resources are allotted, and there could be multiple authors who are evaluated for participating in the research. I think there are differences, and Japan has definitely fallen behind.

(Moderator)

The background for falling behind in large-scale clinical research seems to be similar to our situation, i.e. the motivation to launch *Synthesiology*. What do you think, Editor in Chief?

(Ono)

Dr. Higuchi mentioned that one of the reasons for being left behind in clinical research is the problem of “paper productivity in research”. At AIST, when we tried to focus on *Type 2 Basic Research* as a bridge spanning between *Type 1 Basic Research* and *Product Realization Research*, we were requested, “Please evaluate us as researchers. There is no journal in this field. What should we do?” That is why *Synthesiology* was created. Although it is still in its dawn, we have been thinking hard how the papers published in this journal are different from the papers of what we called basic science, and what makes them original. Also, we disclose the name of the reviewers. With ordinary academic journals, the tendency is to keep the reviewers anonymous, and the names of the authors are apt to be hidden to the reviewers

to maintain the fairness. We did the opposite. We disclosed what points were given credit and what points were not. We ensured transparency. In fact, this worked positively in terms of fairness. Because the names of reviewers are disclosed, they cannot ask careless questions or make biased comments.

(Moderator)

Are there other reasons that prevent the advancement of clinical research?

(Higuchi)

As a nation, the government has not placed importance on clinical research, has not provided funds, or trained human resources.

The pharmaceutical companies engage in large-scale clinical research, but they are limited to the cases where there are many patients who may eventually use the product. Serious diseases with fewer patients require support of the government. The recently started “clinical trials sponsored by investigators” are conducted mainly by physicians through public research funds, without the direct involvement of the pharmaceutical companies.

In terms of training human resources, the education system is still insufficient. To conduct clinical research, we need specialists in biostatistics and epidemiological statistics, but there are hardly any courses at the universities. Therefore, most people study abroad and return to work at pharmaceutical companies. To conduct large-scale clinical research, one must design it on how many cases are needed to obtain the required statistical significance. However, there are only about five university courses for clinical epidemiology. Even though the researchers may be motivated, there was no environment for clinical research, and its importance was not shared by the government, university, or research institutes. As a result, Japan was left far behind.

(Ono)

Sometimes I hear the phrase “drug lag”.



Dr. Akira Ono

(Higuchi)

It means that the drugs that can be used in other countries cannot be used in Japan, because the system of clinical trial is insufficient here.

(Moderator)

The basic researches for medicine were very active in the United States, and then they started talking about translational research. Was that because the genetic researches came into focus?

(Higuchi)

There was a great breakthrough where suddenly there were potentials for application of genetic analysis. If the genetic studies did not go far, the bioscience researches might not have been stimulated as much today.

(Moderator)

The reductionist explanation now reaches the level that allows synthesis. That is the world of elementary particles in physics, and it's genes in medicine. Because we were able to uncover the element of the mechanism, now people can offer new ideas.

(Higuchi)

How can things be quickly shifted over to clinical research? This is certainly a background for the emergence of translational research.

However, many psychiatric disorders and chronic lifestyle-related diseases such as diabetes are the results of combination of genetics and environment, and they are very complex systems.

What is necessary to promote clinical research

(Moderator)

Although the importance of shifting from basic research to clinical research is understood by society, in Japan, there is no training for the translation part, and there are also issues with the researchers' awareness. Is there hesitation for a



Dr. Motoyuki Akamatsu

researcher or a physician engaging in basic research to shift to clinical research?

(Higuchi)

I'm sure there are interests. However, if one wishes to do so, one must put the main job aside. Particularly, since it is difficult for a researcher to venture out to the site of clinical practice, a team is necessary. Since it is difficult for a researcher to become directly involved in clinical trials, it is necessary to create a team of researchers and clinical practitioners who share a common thinking, mediated by someone in the role of a clinical research coordinator (CRC).

(Ono)

Will that be the role for the national institutes or the independent administrative agencies?

(Higuchi)

I think so. The National Center that harbors large-scale research institutes and a hospital fits well in the role. It is necessary to form a team where the members play their respective roles and work together toward a common goal. The National Center has stated that we are eager to take that role. I think it is difficult for a university to do that since they act by laboratory units.

I don't think there are many organizations that are capable of conducting everything from start to goal, from creating a product in their labs and then verifying the product in clinical situations.

(Ono)

A pharmaceutical company with very large capital can design everything from research to clinical practice, and then conduct large-scale clinical research, can't it?

(Higuchi)

The research institutes of the Japanese pharmaceutical companies are very competent, and have excellent ideas to create new compounds. Yet these compounds cannot be verified in Japan. They are taken to foreign countries, and then are re-imported to Japan as drugs.

(Moderator)

From the standpoint of pharmaceutical companies, are there barriers in conducting clinical trials in Japan?

(Higuchi)

I guess the Japanese clinical trial system is both time-consuming and expensive. For example, when a new drug is taken to the United States, the first step will be completed in half a year, while it takes two years in Japan. In that case, it is better that the first step be completed in the States and the drug be re-imported. In terms of market, Japan has a population of 120 million or so, China has 1.3 billion,

and India has 1.1 billion. That is why people are giving up development in Japan and going overseas. The hollowing out of clinical trial is an issue.

Another point is that the capacity of the medical institution is very small. For example, if one wants to do a clinical trial with 100 cases, about 30 institutions must be contacted in Japan. In the United States or Europe, 10 to 15 cases can be done at one institution.

(Moderator)

Is that a matter of the size of the hospital?

(Higuchi)

Rather than the size, it is a matter of how much effort the medical institution is willing to spend on clinical trials. Now, the CRCs are distributed widely, and they can do all the paperwork while the physicians can concentrate on the evaluation. Before, the physicians had to do the paperwork themselves in addition to their clinical duties. They had to spend lots of time on it, and were limited in the extent they could cooperate.

In 2008, the Science Council of Japan issued a statement called the “Issues of Clinical Trials in Japan and Future Measures”. They indicated the insufficiency of the clinical trial system in Japan as well as the extremely low incentive for the physicians to become involved. Making the situation worse, since the trials conducted overseas are done for the first time ever, they are published in relatively high-quality English-language journals, while the drug lag in Japan forces the researchers to do third-hand trials for which the result can only be published in minor journals. However recently, Japan is participating from the beginning in global trials, and at least the representative researcher is listed as one of the authors in the English-language journals.

Incentive and support system for the researchers are necessary to promote clinical research

(Moderator)

Is writing papers the incentive for doing clinical research for the physicians at the universities and research institutions?

(Higuchi)

It's papers and research funds. However, there are restrictions with research funds and it is very inconvenient.

(Ono)

There seems to be major problems, but how do you think they should be solved?

Do you think the priority is to succeed with the Translation Research Center of the NCPN?

(Higuchi)

That is the priority. And then, we should provide motivation to the people involved in clinical research. A lot of energy is needed to carry out clinical research. To raise motivation, it is necessary to provide various incentives and to build a support system including coordinators. The TMC was created under the concept of transferring the results of the research institute to clinical practice, but the reverse is also necessary. This means that if a physician has an idea or wishes to do certain clinical research, we must be able to provide support, including helping with the design.

(Ono)

What do you think are the originality and interest of the translational research itself?

(Higuchi)

For the muscular dystrophy research I mentioned before, the first clinical application will be done at our hospital. The hospital is very cooperative because it is an original effort of the Center. The researchers are highly motivated because the research does not just end with discovery and they can be involved in the actual clinical application. However, when this study goes well, I wonder how many places will cooperate if we want to do research using several hundred cases throughout Japan. This will depend on the results of the clinical research sponsored by investigators.

(Ono)

So, in this clinical research sponsored by investigators, things can be taken from small-scale to medium-scale. Do you turn it over to the pharmaceutical company after that?

(Higuchi)

Yes, exactly.

Research accepted and supported by society

(Moderator)

Since clinical research is a process where something is verified in society, I think the awareness that “it must be supported by the entire society” is necessary. If one behaves according to the values of the researcher alone, no one will help any large-scale trial. Don't you think a shift in awareness of society is also necessary?

(Ono)

Also the attitude toward risks is important. The Japanese robot research is at quite an excellent level, but the last frontier is safety. The robot manufacturers become hesitant about product realization, because they think, with any accidents, “How much liability must we take?” or “Is it entirely the manufacturer's fault?” I think it is similar for clinical trials. Is the risk taken entirely by the provider, or does the receiver or society agree to share the risk?

That part is still insufficient, and that's why the robots aren't being sold widely. Robotics is left behind in the clinical trial.

(Higuchi)

Oh, I see.

(Ono)

Therefore, we decided to create safety standards for robots, although it may not be at the level of standards of ISO or JIS. We want to consider safety as much as possible from a public standpoint, and show that such and such safety standards have been cleared. We called this "pilot certification". We make a social agreement for the safety, and then ask the customers to try it out.

(Moderator)

In Critical Path Research and Education Integrated Leading (CREIL) Center of Tsukuba University, we seek help from the network of general practitioners in Ibaraki Prefecture when they conduct translational research. The private-practice doctors can enjoy the opportunity to have hands-on experience with state-of-art medical technology by helping out the clinical research.

For robots, we can say, "There may be risks, but please evaluate them." Then, the people can enjoy the opportunity to work with the state-of-art technology, and perhaps things will turn around well.

(Ono)

It's one of the ways for people to contribute to society. I feel we need such attitudes in medicine and amongst our disciplines, too.

(Moderator)

Those were the general users and doctors, but I think the patients have a different mindset.

(Higuchi)

Comparing the patients in Japan and the rest of the world, there are differences because of the differences in systems. First, the insurance system is different. Japan has the universal insurance coverage, and anyone can receive medical treatment. In the United States, although President Obama is trying to change it, each individual must pay expensive insurance fees. Since the clinical trial is free, people flock to participate.

I think the essence is the spirit of volunteerism. In the United States and Europe, I feel there is strong enthusiasm for volunteering, where people want to do good for others and contribute to society. In Japan, the willingness to participate in a clinical trial is low.

(Moderator)

I feel that there is a tendency for the Japanese to seek benefits

but not want to take the risks.

(Ono)

Certainly, I think there are many cases where people cannot judge the balance between the risks and benefits. The universal insurance coverage is an excellent Japanese system, and we attained a society with the highest longevity in the world. Many people feel that we've been successful so far, so we can continue this way, but actually it won't be a smooth ride from here on.

(Higuchi)

I think this also leads to the subject of organ transplant and ODA. We must carry our share of the burden.

(Ono)

I think Japan has attained a safe and secure society quickly. That was very good and a happy thing, but because we attained an ideal society, we cannot take the next step. We cannot muster the energy to go on. Perhaps we are at such a stage. I think the good things about Japan should be left as it is, but some things must eventually change.

(Moderator)

When we are suddenly aware that the earth environment itself has changed, we may find that we can no longer adapt to it. There were times when researchers could do whatever they wanted in the past, but now is the time when the entire society must get involved. Under a social consensus, we must think and act. Thank you very much.

(This interview was held at the AIST Akihabara Office in Chiyoda-ku, Tokyo, on July 2, 2010.)

Profile of Dr. Teruhiko Higuchi

Graduated from the School of Medicine, The University of Tokyo in 1972. Worked at the University of Tokyo Hospital; Saitama Medical University; Psychiatry and Human Behavior Department, Graduate School of Medicine, Gunma University; and as the professor of the Department of Psychiatry and Neurology, Showa University Fujigaoka Hospital. Became the deputy director of the Kohnodai Hospital, NCNP in 1999, and its director the following year. Became the director of the Musashi Hospital, NCNP (currently National Center Hospital) in 2004; the president of the NCNP from 2007 to present. Member of the Science Council of Japan. Also member of the Japan Society of Clinical Neuropsychopharmacology (vice president), Japan Society for Occupational Mental Health (permanent director), Japanese Society of Mood Disorders (director), and others. Specialties are pharmacology and biochemistry of mood disorders, clinical psychopharmacology, and clinical research of depression.