

**Potential for Human Tissues to Expand Their Contribution in Science and Its Social Applications with Special References to Japanese Topics and Issues:
Text for Health and Science Seminar Section 13**

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Dear Sirs:

Encouraging news from Japan

If you key in the following three words, i.e., Ikee, leukemia, Olympics to an internet search engine, news from all over the world with pictures of a swimming young lady will appear before your eyes. It was only two and a half years ago in February 2019, when she was diagnosed with acute lymphoid leukemia, and received chemotherapy and then allogenic (meaning non-self) hematopoietic stem cell transplantation therapy. After a couple of months of resting and rehabilitation, she started swimming again in March 2020, and recovered so well that she was selected in April 2021 as a member of Japanese swimming team for the Tokyo Olympic in August 2021. Her recovery must encourage people suffering from the same disease that, without modern transplantation therapy, could never be accomplished so well.

Another example showing a high-level achievement in transplantation therapy is indicated in the Japanese Transplantation Society Fact Data (1), where the fifteen years survival rate for heart transplantation cases performed in Japan in 2018 is around 85 %, while it is around 40% for those counted by the World Heart and Lung Transplantation Association (1).

Still another line of encouraging news has been emerging in basic biomedical research field from Japan, whereby human somatic cells, which had widely been believed to proliferate only within a limited number of doublings, and not facilitated with the capability to rejuvenate into stem cells, in fact maintain nascent potential to rejuvenate and to differentiate again into various tissues.

The mechanism for somatic tissue cells to rejuvenate was first discovered by Shinya Yamanaka and his colleagues in 2006 using mouse somatic cells (2), and then using human somatic cells next year (3), and they named these induced pluripotent stem cells (iPS cells). Now many research projects are enthusiastically pursued in biomedical laboratories all over the world aiming at stem cell transplantation medicine where we do not need organs for transplantation anymore, but just a small number of tissue culture cells from skin or other

tissues. There are risks, however, in these lines of study if an attempt at rejuvenation happens to end up with an entire living body, which, in case of rodent iPS cells, has already been attained (4,5).

Here I would like to add one more episode in the production of human protein pharmaceuticals obtained using normal human tissue culture cells, one that was first performed by Shigeyoshi Kobayashi and his colleagues in Japan in 1985. It was human beta interferon.

Legacy of human tissue contribution

The majority of human tissue contributions do not attract the attention of newspapers or TV programs, since they are just working routinely. Day by day human organs, pieces of skin and other tissues have been donated for transplantation therapy. Day by day, cultured human tissue cells are processed for the production of various vaccines and other therapeutic materials, and for devices to detect and quantify infectious viruses.

Not only tissue culture cells, but also human tissues themselves, particularly of liver, skin, intestine, and blood vessel, are contributing in the field of safety and efficacy assurance in the course of development and production of pharmaceutical drugs, cosmetic products, and foods.

According to The International Registry in Organ Donation and Transplantation (IRODaT), the number of actual organ donors, except for that of live organ donors, in many western countries including the U.S., is above 20 per million population (PMP) with Spain (49 PMP) at the top and the U.S. (37 PMP) at the second (6). A survey in the U.S. shows most of all those donated tissues are directed to transplantation therapy, while some, up to 10% of them are directed to basic science and to its social applications as mentioned above (7).

In each of these developments in science and its application there is a story. For example, the first successful establishment of a cultured human cell line, named HeLa, was made from cancer tissue in 1951 by George Gey in Baltimore. Immediately, it was found to be sensitive to poliovirus (8). The first successful series of normal human tissue culture cell strains, established by Leonard Hayflick and his colleague in Philadelphia, were established in the early nineteen sixties, the WI-38 strain among them (9,10). It was found to produce a safe and effective polio vaccine. These two tissue culture cell lines played major roles in suppressing poliomyelitis disease which otherwise would become horrifying pandemic in the world.

In each piece of discovery in the field of modern biological sciences, such as biochemistry, cellular and molecular genetics, immunology, nutrition, biology of development and aging, and neuronal sciences, and applications thereof, one may find

contributions of human tissues in one or other ways. Today, biomedical science is expanding even more rapidly than before, meaning that human tissues continue to play their roles day by day in experimental and industrial laboratories for which they were donated by people of good will.

So, how much Japan is special? Hascross Health Science Seminar No13 (2021) Short Text.

Matsumura, T. Human Tissues The above story may suggest that the early development of biomedical science on human tissues was attained mainly in the U.S., expanded worldwide later, and many countries including Japan are now receiving the legacy of that early development to join in the worldwide campaign for the development of biomedical science and social welfare. There will be nothing particular in this line of story. So, is there anything particular in Japan? Yes, there is! If you turn your head and look at the supply side of human tissues, you will find it.

According to IRODaT 2019 data, Japan is ranked at the 64th among 73 countries in the world with 0.99 PMP in terms of the number of actual organ donors (6). This figure means that domestic supply of tissues is exceptionally small.

Then, how are scientists and those in industrial sectors are coping with this situation? If you look at the paper describing the iPS cell discovery from human tissue culture cells (3), you will find they imported foreskin cells prepared using GMP procedure from a U.S. company. For the production by Kobayashi and his Toray colleagues of interferon beta, again foreskin tissues were imported from abroad, respectively cultivated, a number of seed cultures established, from which one was selected for a largescale culture to make a seed lot system for GMP production.

Another representing case of industrial application of human tissue cells in Japan, i.e., the cultured human skin tissue model (LabCyte EPO-Model) by Japan Tissue Engineering, also uses foreskin tissues (11). Since circumcision is rarely performed in Japan they may most probably be imported from abroad. Unfortunately, statistic data of human tissue importation are not available in Japan. It looks like that many scientists and industrial organizations import human tissues from abroad.

Then, the question is if there are not any public resources of human tissue and cells established in Japan. The answer is yes. The cell bank of RIKEN, the JCRB cell bank of the National Institute of Biomedical Innovation, Health and Nutrition (NIBIOHN), and the JCRB human tissue bank of NIBIOHN are active in supplying material in Japan.

Some of these activities play a global role, such as the supply of iPS cells. Donation of some Japanese human tissues and cells for research purposes, particularly for genetic disease studies have been made occasionally through individual scientists, including us (12). However, overall domestic supply of human tissues for research purpose is very

limited, as is the case for those for transplantation. For example, the NIBIOHN's human tissue bank list does not include cultured human liver cells, which is the most necessary for drug discovery research.

Instead of those Japanese public cell and tissue banks, there are several organizations making up for the shortage. Representative examples are American Type Culture Collection (ATCC), which provides cultured human cell lines of standard quality, and HAB Research Institute (NPO), which provides human tissues for research, particularly for pharmaceutical research, in partnership with NDRI (NGO), a leading human tissue donor organization in the US. It should be noted that these human tissues from abroad are provided free of charge with the consent of the donors, if handed with some handling charges and transportation fees.

Other sources, such as pieces of human foreskin and tissue culture cells derived under the control of GMP procedure have been imported through commercial routes from abroad.

Why is Japan so special?

Basically, Japanese criminal law regards removing a fragment of tissue from a deceased as a constituent of body destruction crime. To be exempted from the criminal law, a law for a special purpose may be essential. Thus, there is an act for organ transplantation and another for pathological examination, in which details of procedures are so described that the action of removing tissues is to be exempted from the criminal law (13,14). What is special here in Japan is that there has never been established a law for tissue removal for research and industrial purposes per se. Discussions continue in the field of medical law if any removal of tissues for research and industrial application might be possible under the present circumstances. In any case, to my knowledge, there are very few cases of tissue removal from the body of the corpse, if not related to limited fields of pathological study.

Thus, the only openly accepted source of human tissues for research use is of biopsies removed from live donors with informed consent, those removed from discarded materials after surgical operation, such as umbilical cords, skin tissues cut and removed at a cosmetic surgery, peripheral fragments of normal tissues obtained after a surgical removal of malignant tissues etc. when accompanied with appropriate ethical arrangements.

Now the readers may understand that these tissues above are the main sources of Japanese public tissue banks. Unfortunately, they cannot satisfy many of the current demands for human tissues for research and industry.

Recently, the domestic transplantation law was revised in response to the international criticism of transplantation travels, which were often accompanied with organ trafficking (15). Japan was nominated as one of the countries with frequent transplantation trips (16).

With this revision of Japanese law, however, no legal measures have been taken to address the imbalance between supply and demand of human tissues for research and industrial purposes.

Then why not change the laws so that they fit the modern situation? Unfortunately, I have no definite answers to this question. One point that I may mention is that this might be one of the boiling frog phenomena, like in the case of global warming, so that a slow environmental change tends to be ignored by people at large until it becomes a catastrophe.

For instance, if importing human tissues one-sidedly and ignoring accumulation of negative feelings in donating countries continues, the situation may worsen and lead to a sudden break of international ties, which may not easily be recovered afterwards.

I understand that to maintain good international relationships, Japan must keep it in mind that human tissue supply is not something like "Ask and it shall be given to you." It must develop its own supply of human tissues to fill at least a major part of its domestic demand, and must try to maintain international exchange of the tissues in a fair balance, or to reduce its domestic consumption so that it may meet with their domestic supply.

Are there any possible fears among Japanese on tissue donation?

I would like to list up a few points as below:

- Tendency for unanimous decision

Japanese people tend to appreciate a unanimous decision more than decisions taken by one's self (17). This tendency might have been inherited since the ancient Japanese ethical codes established by Prince Shotoku (AD604), a devoted Buddhist, of which the first article is 'Respect for harmony'. In the case of organ donation, Japanese law requests family members' agreement, even if the candidate donor is giving consent (14). This respect for harmony principle reflects the strong ties among members within a family, and works as a barrier against the social isolation of individuals and for family members to share any risk that might happen.

The tendency for unanimous decision in Japan is becoming weaker in recent years, and the autonomy principle more appreciated. Apparently, family ties are becoming weaker in city lives where people tend to live more individually than before, so that stressing family-based unanimous decisions may work less effectively than before.

However, on the other hand, it appears to me in Japan that the autonomy principle tends wrongly to mean taking the responsibility for all the risks that could be associated with an action which has been taken by one's own decision.

It may be difficult to return to the 'old' Japan where members of a family or other groups were tied strongly among them and shared any risks among them. Therefore, it may be important to develop social mechanisms that protect individuals from social isolation and from accusations of irresponsibility when they adopt autonomy principle in making their

own decisions on matters such as organ transplantation and tissue donation.

- Extending longevity of donated tissues

Tissue culture cells once preserved frozen may keep their lives for at least tens of years, meaning that the donor and/or his/her bereaved family members may not be able to maintain their right to withdraw them from any works that they do not want, or to discard the once donated tissues.

- Tissue lives outside of a human body

Nowadays, there are numerous ways in which a tissue can be handled and used once removed from the donor's body. It may reside in a foreign body as a transplanted organ, tissue or cells, in a research laboratory for the study of cancer or other diseases, or in the processed form of a tissue sheet or others ready to be exposed in testing procedures. etc. Therefore, it is becoming hard for donors or their families to trace where their tissues are, and how it is being used.

- Effectiveness of informed consent

Tissues and cells, which come into a research laboratory for the first time, being accompanied with a sheet of informed consent, for cancer research for example, might happen to be investigated with an unexpected discovery, for example, of their sensitivity to a certain virus, and then transferred to an industrial factory where they are used to produce a test kit for detecting the virus in foodstuff etc.

Thus, it is becoming hard for donors or their families to trace where they are and what they are doing now. Particularly when they are handed to researchers through a cell and tissue bank, there is no way to know if the tissues are directed to any further research project of what kind. A family may thus feel that the form of consent is insufficient to control all potential uses.

A prerequisite for the future expansion in Japan of tissue lives outside a human body, therefore, may be to formulate ethical principles (tentatively called "human tissue ethics") that are supported by the majority of the Japanese people, internationally acceptable, and to develop social mechanisms to ensure those ethical principles once established, are maintained for a long time.

With the aim of resolving these long-standing issues, I have been trying to propose a private set of ethical principles and application for human tissues by discussing with colleagues who share the same interests in Japan and other countries (17-19).

Historical Development of Bioethics and Legal Systems

Nowadays, it is reasonably accepted that the safety of medical technology and pharmaceutical drugs cannot be guaranteed without any clinical experimentations on human subjects, nor without laboratory studies on those human tissues that have been removed from human bodies. On the other hand, the ancient ethical statement of Hippocrates that "no treatment should be performed that does not benefit the patient" has also been appreciated highly up to the present. To find a solution to harmonize the two conflicting ideas has long been the central matter of discussion in bioethics.

At the core of the current code of ethics, there are the 10 articles of the Nuremberg Code (1947), which were extracted at the international tribunal against human experimentation during World War II. The first article, "The principle that the informed consent of the autonomous individual is indispensable," has played a central role in subsequent ethical decisions. This principle was succeeded in the Declaration of Helsinki by the International Medical Association, and has since been accepted internationally.

Unfortunately, however, scandals that do not conform to the principle have occurred in various countries since then. To cite a representative example, experiments with no treatment for syphilis infection were exposed in 1972 (Tuskegee Syphilis Study, U.S.), and in response, the U.S. Congress quickly enacted the National Research Act, 1974)(20).

The report submitted in 1978 by the advisory committee established by this law (the Belmont Committee) proposed three basic ethical principles to be followed when conducting research on human subjects: i.e., Respect for person, Beneficence, and Justice. The U.S. legal system was structured in a way to ensure these three ethical principles.

The Belmont Report added "the principle of protection of persons who have lost their autonomy" to Article 1 (the principle of respect for autonomy) of the Nuremberg Code in consideration of the fact that the Tuskegee Study involved human experiments on indigenous people who lacked language comprehension.

Another trend was triggered by the discovery in the late 1990s of the existence of a large number of specimens obtained from infants and children and stored for a long period of time without the consent of their parents in the UK (Alder Hey Hospital case etc.). In order to restore the public's trust and to prevent the recurrence of such incidents, a system for the approval of institutions handling human materials and a system for the management of the location of human materials were established (Revised Human Tissue Act, U.K. 2004) (21), and the British Human Tissue Authority was established.

What these trends clearly show is that even if ethical principles are stated and many countries and their citizens agree with them, this alone does not guarantee the viability of the ethical principles. Violations may lurk and one day may explode into a major incident. In order to avoid this way of progress, there has been a movement in developed countries

to ensure ethical principles through laws.

It is understandable that legal restrictions should be minimal in the field of science where freedom of idea and action is highly appreciated, and in medicine where that most appreciated is the trust between a patient and his/her doctor, and any interference outside this core framework should carefully be avoided.

Thus, in this article, the point of discussion is on the establishment of ethical principles and minimal legal requirement to ensure the ethical principles.

Proposal of Five Principles of Human-Tissue Ethics

- First principle: Respect for autonomy, respect for human beings and human tissues

In the Belmont Report, the respect for human being principle was added to article 1 of the Nuremberg Code (1947), i.e., the respect for autonomy principle. Here in the Principle 1 of human-tissue ethics, it is proposed that human tissues should be respected as objects accompanying humanity.

As mentioned, it has been established that human somatic tissue cells, once left from the body maintain their capability to proliferate and to express many functions outside the donor's body, as an existence capable of helping human society. Therefore, I understand that these tissue cells once removed from body may be regarded as "components of biological diversity important for its conservation and sustainable use" as stated in Convention on Biological Diversity UN, 1992. (Japanese law 'Basic Act on Biodiversity 2008 was enacted according to the convention (22).

In addition, somatic cells taken outside of body are now known to retain the capability to be rejuvenated into pluripotent stem cells, from which a number of differentiated tissues and organs can be generated again in appropriate conditions. The possibility is even suggested from animal experiments that they may regenerate an entire live body of a human being. Since these somatic cells apparently lack autonomy, the responsibility of protecting, nurturing, and managing them so that they remain within the framework of ethical existence ultimately rests with autonomous individuals.

- Second principle: The beneficence principle with an extension of its application to human tissues

In human experimentation, which cannot be performed without any possible risk, the beneficence principle states that, in order to maintain humanity, there must be efforts to minimize risk and maximize benefit. This principle is easy to understand when participating in a clinical experiment. In many cases of transplantation medicine and tissue research, however, the direct benefits accrue to the recipients of human tissues, while the direct risks are directed to the donors. Therefore, in order to minimize the risk while

gaining well being in accordance with the beneficence principle, it is essential for the donor and the recipient to build a strong partnership within a social framework, and to construct a system that disperses the risk and shares the benefit evenly among the participants.

- Third principle: The principle of justice with consideration of its application to human tissues

Justice in the Belmont Report was strongly linked with equality and equal opportunity, and calls for a break with racism. In the enactment of the Organ Transplant Law in Japan, justice was concerned with the suitability and fairness of opportunities for organ transplantation. The establishment of a Japanese nationwide distribution system was an achievement.

Now that the handling of human tissues has changed from being limited to organ transplants and pathological autopsies to medical treatments through various in vitro processing, basic biomedical research, manufacturing medicines, and provision of testing methods, I propose that justice for a piece of human tissue should be based on equal opportunities for any of the benefits that may accrue to society.

- Fourth principle: Principle of respect for the humanity of human tissues

Human tissues must be respected and cared for, because they are of human origin, they bring great benefit or even harm to society, and they are living organisms with the possible potential to reproduce human individuals. However, unlike humans, they are not required to be autonomous. Nevertheless, in order for these tissues to continue to contribute to the welfare of society without causing harm, this principle states that the tissues should be granted the right to be watched and protected throughout their lives. While the first principle is from the standpoint of human beings confronting human tissues, the fourth principle calls for the rights to be protected as a right of human tissues themselves. Here, the way of treating genetically modified organisms in Cartagena Protocol on Biosafety, as enacted in Japan as a law (23) may be helpful.

- Fifth principle: Principle of the free nature of human tissues

This is a principle that states that the human tissue itself, which is separated from the living body, is neither the property of the donor nor the property of the recipient, but is a living organism with its own dignity, and that ownership of the human tissue is not recognized. However, in principle, payment for the expenses required for handling and the added value that results from the processing of the human tissue should be recognized as compensable, separate from the free nature of the human tissue.

Mechanisms to Apply the Five Ethical Principles for Human Tissues

In order to ensure the viability of the above five ethical principles, at least several agencies will be needed to implement them. It is not meant here that these agencies should belong to the government, but they may be private and located in many places as much as they are tied to each other exchanging necessary information among them.

- **Service agencies**

They provide both donors (and hospitals with donors) and recipients (and research laboratories or factories with recipients) of, and all who are interested in, human tissues with information and service concerning advances in transplantation medicine, science, technology, ethics, social welfare and industry, and current managements system thereof. For this purpose, they may make arrangements for educational seminars and publications, meetings to know each other among people concerning human tissues, and other events.

They may also provide those people who have already donated tissues with specific information as to the fate of the tissues as much as available and those who are going to receive tissues with the current ethics and legal systems to follow. At the request of those who want, they may provide second opinions or advice on specific terms on donors' or recipients' requests.

Such an agency needs expert volunteers and administrative staff, and substantial economic support from those who have been receiving benefits from human tissue activities.

- **Expanded matching agencies**

One may imagine this category of agency as an expanded form of current organ procurement organizations, which mediate needs and supply of organs. In an expanded matching agency, the need for tissues comes not only for transplantation therapy, but for research, development and industry, and tissues to be supplied may be in the form not only of organs, but forms including skin pieces and intestinal tubes. Best matching should be aimed on the bases of a carefully designed algorithm and individual case-by-case decisions justifying the ethical principle for equal opportunity to access a tissue among multiple possible destinations. For prompt decision making, efficient use of computer may be essential, while a donor' s wish and conditions for tissue donation should carefully be considered in the match making process. It will be essential for this matching process to be free of charge.

- **Tissue banks**

Many tissues for research, development and industrial uses may be initially stored in tissue banks before being directed to individual scientists or technologists. There in a tissue bank, tissue culture cells may be obtained from pieces of tissues, and frozen-stored for a long time before directed to their final destination.

It may not be a prerequisite for such a tissue bank to be governmental, but any independent tissue banks should be approved with a certain requirement for it to operate in an ethical and a safe manner.

- Agencies watching over and protecting human tissues

An agency of this category watches over the handling of human tissues at each organization including research institutes, hospitals, industrial companies which may be engaged in medical treatment, research, or welfare industry, examines research plans and documentations as necessary, conducts audits as appropriate, and monitors the status of compliance with the principle of free of charge and the return of economic benefits generated by added value based on the principle of humanity. They will be expected to work for the respect to humanity of tissues as well as for the beneficence principle in intimate ties with service agencies. The activities of watching and protecting agencies may have to be overseen by an appropriate committee independent from the organization.

If not all, at least some of these executing agencies as proposed above may need to be accredited in order to ensure their quality. In addition, some organizations and services may have to be funded by the national treasury in order to ensure free handling. If a watching and protecting agency is to be given responsibility for executing audits and examinations, legislation will be needed to guarantee their authority to fulfill these responsibilities. The content of the work that would require such legislation is considered in some details elsewhere (19).

To begin with, what may we be able to do for future advancement?

There may be number of ways. The following two possibilities are just initial thoughts:

In the first place, one may write an organ donation card as freely as he/she wants. As in many countries, examples of several organ donation cards are presented in Japan. They are printed in accordance with the current Japanese law of organ transplantation. One should know however that these cards are only examples, and one is totally free to write his/her wishes in any possible way as he/she wants.

Thus, if a card does not mention any choice for your tissue to go to research field, you may write your choice, for example. With the card so written, your tissue may not be sent to research field, since the present Japanese cabinet order, as recognized by the Japanese organ transplant law, does not permit it. However, your card will give attorneys the power to ask the court to evaluate if the cabinet order is violating the constitution or not.

In the second, one may be encouraged to ask questions or to extend your own thought on human tissue issues to a candidate representative of either parliament, city council or of whatever democratic bodies. As much as we are in a democratic society, where any ethical principle needs to be ensured by law, it cannot be done without the participation of those representatives.

Concluding remarks

Mankind has an uncanny ability to treat things that are not there (or that we are not sure are there) as if they were there. The words and concepts that we use without any doubt in our daily lives, such as God, zero, paper money, and corporation, are the products of this mysterious ability. I hope that giving dignity and authority as a living organism to a part of the human body that had once been regarded as a personal property will lead to a leap of social richness into the future.

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Supplementary notes

There is a plan of Web meeting to discuss the matter of mutual interests on the future advancement of human tissue world. If you want to join in the meeting either as an audience or a discussor, please leave your e-mail address in the communication site of health and science crossroad (<https://hascross.yokohama/contact/>). When fixed, we would like to send you further information.

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