Lecture and discussion

Ethics of international collaborative research: Perspectives from Brazil *1

Part 1 Selected notes on Paulo Freire
Part 2 Access, Compulsory license, Case Study

(Sunday, December 8, 2019, Keio Plaza Hotel Tokyo, Japan)

Invited lecturer
Dirceu Greco [1], **Professor Emeritus, Infectious Diseases and Bioethics, Federal University of Minas Gerais**

Special guest
Rihito Kimura [2], **Professor Emeritus, Waseda University**

Guest Discussant
Maria Victoria Perottino, Pharmacist; Specialist in Governance, risks and Compliance

Organizers & Discussants
Takeo Saio, Department of Internal Medicine and Psychiatry, Fuji Toranomon Orthopedic Hospital
Chieko Kurihara, National Institutes for Quantum and Radiological Science and Technology

*1 This is a record of an additional meeting on December 8, 2019, following the Presidential Symposium in the 40th Annual Scientific Meeting of the Japanese Society of Clinical Pharmacology and Therapeutics, 2019, held on December 4, and additional round-table discussion on December 5, both are also included in this issue of journal. This meeting was held as the 120th meeting of the Pharmaceutical Study Group with the cooperation of Rinsho Hyoka Kankokai Inc. (Clinical Evaluation). Japanese version is included in *Clinical Evaluation*. 2020; 48(1). Other related articles in this issue: http://cont.o.oo7.jp/48_1/48_1contents_e.html

[1] Chair of the Brazilian Society for Bioethics (2019-2021); Member and Vice-chair of International Bioethics Committee of United Nations Educational, Scientific and Cultural Organization (UNESCO) (2018-2021)

[2] Faculty Affiliate, Kennedy Institute of Ethics, Georgetown University; President, Japan Association for Bioethics (2009-2012); President, Keisen University (2006-2012)

Abstract

Dirceu Greco, M.D., PhD, Professor Emeritus, Infectious Diseases and Bioethics, at the Federal University of Minas Gerais, Brazil, Chair of Brazilian Society of Bioethics (2019-2021), undertook an important role in Brazil during the HIV/AIDS crisis of 1980s to 1990s. He was engaged in taking care of people at risk and living with HIV and in an early phase AIDS vaccine trials as a principal investigator. He directed the Brazilian AIDS Programme from 2010-2013 and participated in the national policy development for HIV/AIDS prevention and treatment in Brazil. During the period of the 1990s to the 2000s, he directly participated in the international debates concerning the revision of the Declaration of Helsinki as well as other UNAIDS/WHO guidelines on bioethics and HIV/AIDS, towards the establishment of the ethics of international collaborative clinical research for developing countries.

This time, we had privilege to invite Prof. Greco to the Presidential Symposium in the 40th Annual Scientific Meeting of the Japanese Society of Clinical Pharmacology and Therapeutics, 2019, and in addition to it, we took the opportunity to have another lecture meeting, to have further discussion in depth on research ethics and bioethics. We learned much from his presentations the essence of Brazilian philosophy, focusing on the topics we requested: (1) Paulo Freire's history and his publications including Pedagogy of the Oppressed; (2) Policies utilizing compulsory licensing to ensure access to drug for the people in the world who need it.

Key words

Paulo Freire, compulsory license, Brazil, HIV/AIDS, fundamental human rights

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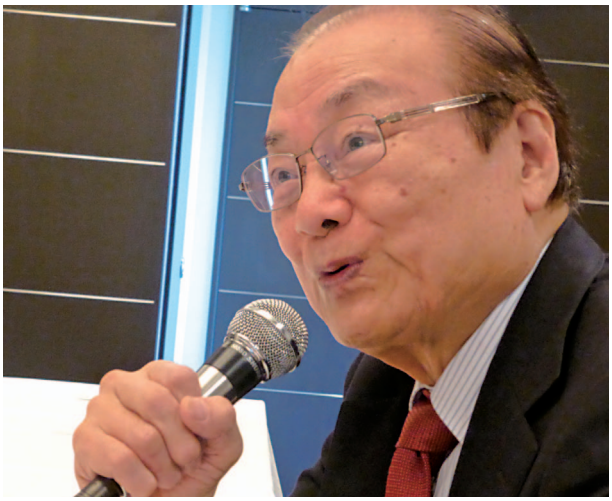
Professor Dirceu Greco, M.D., Ph.D.

Dirceu Greco is Professor Emeritus of Infectious Diseases and Bioethics at the School of Medicine, Federal University of Minas Gerais (UFMG), Belo Horizonte, Brazil. He received his MD degree and this PhD from UFMG, with further specialization in Clinical Immunology at the State University of New York (Buffalo) and at the University of London, England. Dean for Post-graduation, UFMG (1994-1998), Chief, Infectious and Parasitic Diseases Service, University Hospital-UFMG (2009-2011), Chair of UFMG University Hospital Centre for Clinical Research (2005-2010), founding member of the UFMG Research Ethics Committee and member from 2007 to 2010 of the Brazilian Research Ethics Commission (CONEP); member, Brazilian AIDS Commission (Ministry of Health-MoH).

Currently he is responsible for the discipline Seminars in Bioethics at the Graduate Course in Tropical Medicine and Infectious Diseases (UFMG). Main topics of interest include Infectious and Parasitic Illnesses, bioethics, public health and clinical immunology. He has participated in several working groups that gave rise to national/international guidelines related to ethics, prevention, care and treatment of HIV/AIDS and TB. He has frequently acted as temporary advisor to many national/international institutions, such as the Brazilian AIDS Programme, WHO, UNITAID, UNAIDS, UNICEF, UNESCO, CIOMS, the United States Presidential Commission for the Study of Bioethical Issues and The World Medical Association.

He is currently member and one of the Co-Chairs of UNESCO's (Paris) International Bioethics Commission (IBC) and Chair of the Brazilian Society of Bioethics (2017-2019; 2019-2021).

From 2010 to 2013 he directed the Department of STD, AIDS and Viral Hepatitis (Secretary of Health Surveillance, MoH, Brazil).



Professor Rihito Kimura, LL.M., Ph.D.

After graduating from Waseda University's Graduate School of Law in Tokyo, Prof. Kimura taught at Chulalongkorn University, Thailand (1965-69), Saigon University, Vietnam (1970-72), then became an Associate Director and Professor of The Ecumenical Institute of the World Council of Churches and taught at the affiliated Graduate School of Ecumenical Studies, University of Geneva, Switzerland (1972-75). In 1978, he became a visiting scholar at The Center for the Study of World Religions, Harvard University (1978-80). In 1980, he became a Director of International / Asian Bioethics Program at the Kennedy Institute of Ethics at Georgetown University. In 1987 he was appointed as a Professor of Bioethics and Law at School of Human Sciences, Waseda University. He served as an advisor to several international organizations such as CIOMS, WHO and UNESCO etc. He is on the Editorial Advisory Board of The Journal of Medicine and Philosophy (Oxford Univ. Press), and former Chair of Hospital Ethics Committee of Tokyo Metropolitan Government, and a Member of the Council for Welfare and Health Policy Science, Ministry of Health, Labor and Welfare, Government of Japan (1997-2003).

Part 1 Selected notes on Paulo Freire

1. Introduction

Chieko Kurihara　Thank you very much everybody for coming here to have this additional session with Prof. Dirceu Greco, following the Presidential Symposium of the Japanese Society of Clinical Pharmacology and Therapeutics (JSCPT) and the following round-table discussion. Prof. Greco already gave a wonderful presentation and emphatically participated in round-table discussion with Dr. Otmar Kloiber, World Medical Association, who had to leave earlier, and other Japanese colleagues. Now we wish to hear more of his experience and his thoughts and philosophy based on Brazilian experience.

Additionally it is great pleasure of us that Prof. Rihito Kimura participate today's session, in addition to the symposium on December 4. He is a special guest, as he is one of the founders of bioethics not only in Japan but also internationally. Prof. Greco is now the President of the Brazilian Society of Bioethics, and member and co-vice chair of the International Bioethics Committee of the United Nations Educational, Scientific and Cultural Organization (UNESCO). And the direct reason why we invited him is that first he contributed much to the international debate of the Declaration of Helsinki (DoH), and secondly he was engaged in the Working Group for 2016 revision of Ethical Guidelines for Health-related Research Involving Humans of the Council for International Organizations of Medical Sciences (CIOMS). Prof. Kimura is engaged in the working group of the first version of CIOMS guidelines. This is truly precious opportunity to learn from both of Prof. Greco and Prof. Kimura. We wish to convey our greatest appreciation.

So we wish to start this session from our self-introduction and our expectation of the kind of things we wish to hear from Prof. Greco.

My name is Chieko Kurihara, National Institutes for Quantum and Radiological Science and Technology. I am very much interested in the international debates on placebo use and post-trial access in the DoH. These topics were well discussed in the JSCPT meeting, so today we wish to learn some other related topics: (1) Paulo Freire's philosophy, because Prof. Greco's important arguments is much based on Freire; (2) Compulsory licensing, as I learned Brazil has unique experience to make use of it during the time of HIV/AIDS crisis.

I am also interested in his private history, not only theoretical issue. Because he was engaged in first-in-human trial of AIDS vaccine in Brazil where he had experienced hard negotiations with communities and he said in his interview article that his protocol had been much improved through discussion with the community people [1]. He is also engaged in HIV governmental policy development process in Brazil and we learned it much in the JSCPT meeting. All of such experience must be strong background of his argument in placebo and post-trial debates in not only DoH but also CIOMS, UNESCO, UNAIDS/WHO documents for which he worked as a Working Group member.

1) Brazil: The ebbs and flows of AIDS vaccine trials. *IAVI Report*. 1999; 4(4): 10-13.
https://www.iavireport.org/vol-04-no-04-sep-oct-1999/1253-iavi-report-04-4

Maria Victoria Perottino My name is Maria Victoria Perottino. I am a pharmacist, working at a private healthcare company in Brazil. I have a master degree in bioethics. My master degree dissertation was on access to drugs. I'm pleased to hear that in Japan approved drugs are immediately incorporated and available. Drug access in Brazil is not like in Japan. When a drug is approved by the regulatory agency, it is not immediately incorporated in the health system.

Maria Victoria Perottino
Maria Victoria Perottino is pharmacist from the Federal University of Minas Gerais (Brazil), master in Bioethics (UMSA, Argentina) a specialist in compliance at the postgraduate degree (Instituto ARC) in health law. Member of the Society of Corporate Compliance and Ethics (SCCE). Exin Foundation certified in privacy & data protection.
Entrepreneur in the health sector for 17 years, left the company to work as a clinical pharmacist in a public hospital, while pursuing a master's degree in bioethics. The inequality in health and the problematic doctor-patient relationship, made me interested in bioethics, which I studied in Argentina, At Unimed-BH for almost 10 years, I worked as a pharmacist and later in the regulatory and Compliance area.

Brazil is a country where there is great social inequality, fundamentally determined by its history of colonization. The 1988 Constitution, wrote under the aegis of democracy, sought to minimize inequities in health, determining the creation of a Unified Health System (Sistema Único de Saúde – SUS), which serves the entire population, regardless of their economic and social condition. This same Constitution, created the National Health Surveillance Agency (ANVISA). This Agency has the aim of acting in all sectors of products and services that could affect the health of the population – so we are talking about food, drugs, medical devices, among others. At that time, the health sector in Brazil was filled with complaints about adulterated and altered medicines. It was essential to create a drug policy to guarantee the quality of pharmaceutical products and calm the population that had lost confidence in medicines and health surveillance. In 2011, a Commission to evaluate the incorporation of technologies (CONITEC) in the SUS was created. Drugs must be previously evaluated by this commission, based on studies of necessity and demands, and only after this approval they may be incorporated to the public health system, that is one of the reasons why there is an excess of judicialization in the health sector, which makes the whole system fragile, time-consuming for the patients and expensive to the state.

Currently, I work for a Brazilian healthcare company in the compliance section. Nowadays a big issue where I work is about privacy, due to a Brazilian new approved law (LGPD, Lei Geral de Proteção de Dados 13.709/2018), based on GDPR. In Brazil, there is no culture of privacy. People do not really know why they should keep their data protected and the risks that the inappropriate use of personal data may cause to its owner. Based on this new law, which is still not in already in effect, companies must have informed consent where the person adheres and opts in or out to the use of their data. It is known that data is a very important asset for any company, improving management, improving healthcare, and helping establish new preventive

programs. All companies have a lot of data and big data banks. In these cases, when we use personal data for management purposes, how can we get informed consent? Is it really possible? Perhaps this action requires so much effort from companies that few will be able to do it correctly. Companies will have to explain to people how they secure their data, but is it really enough? Will people really understand what we are telling them?

Knowing that in Japan the privacy act is already in effect and that Japanese culture is very much prone to privacy, and since privacy is an important ethical issue, especially in healthcare, I would like to listen if possible, a little bit about how it is here in Japan and how was the experience of implementing the privacy act in companies and public institutions. How can we tell people that we use that data?

Kurihara　Thank you very much for your interests in Japanese situation. In Japan Personal Data Protection Law was established in 2003. This legal framework was not sufficient to protect privacy right of individuals. Japanese democratic Constitution was established in 1946 at the time of defeat in the World War Ⅱ, and privacy right is interpreted under the "right to pursuit of happiness" defined in this Constitution. Then in 2016 personal data protection law was revised in order to follow EUGDPR, and legal framework was improved to protect privacy right. The legal framework for private sector got adequacy decision by EU, however, frameworks of public sector and exemption for academic research have not yet got adequacy decision. Through these process, people come to recognize their privacy right, however, actually it is very easy ways or not understandable ways that companies or hospitals provide information about how they use the data of individuals. Number of cases of information leaks are increasing. One of the reason of this increase may be because people's recognition about the legal framework has been expanded, but it does not mean recognition about the privacy right has come to be established. Japanese people very much stuck to "compliance" but not so much care about "human right". Thus I was impressed with your description about privacy right and related challenges in the round-table discussion on December 5.

Takeo Saio　I greatly appreciate this precious opportunity of discussion with Prof. Greco, Victoria, and Prof. Kimura. I proposed to Chieko Kurihara that we should have this additional meeting with Prof. Greco although two days in JSCPT must be plentiful, fruitful opportunity. We wish to learn more about your theoretical framework, more in depth. As for my interest, I have been engaged in evidence-based medicine education. This is in the style of

"workshop", small group learning. I encountered Paulo Freire's philosophy of education, in his great book "Pedagogy of the Opressed". We expanded EBM workshop as grassroots activity, earlier than governmental, top-down scheme comes to be promoted. It is very much important to change the minds of primary care physicians and medical professionals instead of blind acceptance of authority, to be more familiar with EBM methodology and open discussion, free from hierarchy in medical community. It must be "emancipation". So I really look forward to learn from Prof. Greco from Brazilian's experience and perspective.

Rihito Kimura Good morning. It is a privilege and honor to be with you today. I am a human rights lawyer, with a background on law in Southeast Asia. After graduating from the University of Waseda's Graduate School of Law, I taught and did my research work in Bangkok, Thailand, for five years. In the midst of the Vietnam War, I moved to Saigon, Vietnam, where I continued my research on the family law system in Southeast Asia. After witnessing the effects of Agent Orange firsthand, however, I decided to shift my focus from family law studies to human rights issues with the idea of developing a Supra-Interdisciplinary studies of Life and Death issues later to be called as "Bioethics".

After two years in Vietnam, I moved to Geneva for 3 years. In Geneva, I worked with the Ecumenical Institute of Bossey, which has a Graduate Ecumenical School affiliated with the University of Geneva.

Paulo Freire was one of the distinguished professors at the Graduate School of Ecumenical Studies. Freire often came to the graduate school to teach at the Ecumenical Institute of Bossey. At that time, I was the Associate Director and Professor of Human Rights and Ethics in Medicine. Freire was an influential and inspiring scholar and activist. He shifted my perceptions of existence and of the human being. He encouraged me to challenge and tackle the system and the structure of injustice. I truly admired him. I am excited to learn more about Paulo Freire this morning.

From Geneva, I returned to Tokyo at the Waseda University Law School. Three years later, I moved to Cambridge, Massachusetts. After my two years work at Harvard, I became the director of the International / Asian Bioethics Program at the Kennedy Institute of Ethics at Georgetown University. I stayed there for 20 years.

In 1987, I was invited by Waseda University to be the first Professor to teach Bioethics in Japan. Throughout this period I was affiliated with both the Kennedy Institute of Ethics and Waseda University. At the same time I was involved with the Japan Medical Association and the Ministry of Health, Labor and Welfare. I also initiated some patient activities in Japan. In 2000, I retired from the Kennedy Institute of Ethics and in 2004, I retired from Waseda University. I then became the president of the Keisen University, a women's university which was established in 1988. At Keisen, I held a seminar on bioethical issues. In 2009, I became president of the Japan Association of Bioethics. I also became an organizing committee members and a board member of the International Association of Bioethics (IAB). Through the IAB, I have met many international bioethics experts and have strengthened my connections to international organizations including WHO, UNESCO and CIOMS etc.

Dirceu Greco It is a pleasure to be with all of you, especially it is great opportunity to be with Prof. Rihito Kimura, as you have profound experience in the field of bioethics not only in Japan but also internationally. You are the living experience of many things that we are going to talk. I am a physician. I started my career in internal medicine. I still do internal medicine like Dr. Saio. Just two years after finishing Medical School I specialized in clinical immunology and pulmonary disease, in the United States and in England.

Upon my return to Brazil after two years abroad, I was very sure that I should work on tropical medicine.

At that time, my university, the Federal University of Minas Gerais, in Belo Horizonte, Brazil, had a lot of experience and research in two of the so-called tropical diseases, schistosomiasis and Chagas disease. At that time, when I returned to Brazil, there was still vector transmission of *Trypanosoma cruzii*. My main focus at that time was with schistosomiasis, which was very prevalent in the State of Minas Gerais, where I live. Besides all the aspects of schistosomiasis (clinical, research and ethics) something else very bad was going on. Brazil was under a dictatorship, which started in 1964. Paulo Freire, I will tell you about that, he had to exile himself due to the dictatorship. At that time, we experienced all the terrible things against human rights, it was almost a duty to discuss and participate in exactly the human rights movements. It is difficult to put in words all the bad things that happened in the 21 years that this dictatorship lasted (it ended in 1985). And almost at the end of it, in 1983 the first case of AIDS was diagnosed in Brazil.

With the spread of the AIDS epidemic, in my university, we opened the first outpatient service to take care of people at risk or living with HIV. Currently our outpatient clinic follows approximately 6,000 people living with HIV. This epidemic, with all its negative impact, taught us a lot. A simple example – we do not name a person with a disease – that is, we should not say *people with HIV* anymore. We say *people living with HIV*, which is very correct and respectful. By treating and supporting those at risk or living with HIV, almost by default, you are directly involved in human rights and bioethics, and dealing with this new disease. I have learned a lot dealing with all the problems of privacy, of prejudice, of discrimination that affected them.

Remember that the first hope for controlling HIV was in 1987, with the drug zidovudine or AZT. The Brazilian Government immediately started the distribution, free-of-charge of AZT, initially produced only by Glaxo and it was very expensive. And I will tell one example of how pharma industries do – approximately two years later, one Brazilian company started producing AZT. Next day, Glaxo reduced its price by 50%. That's just as a background of what we have been seeing with the behavior of drug companies in other simi-

lar situations.

Then, while all the confrontation of AIDS was going on, in 2000, I participated in WMA General Assembly in Edinburgh, where a revision of the Declaration of Helsinki was proposed. The revision was approved with important gains for the participants – the restriction on placebo use and the obligation of providing post-trial access to drugs that shown efficacy in phase 3 trials. Due to pressures by the drug companies and also by the US FDA, two notes of clarification were approved in 2002 and 2004, watering down the gains of the 2000 version. I directly participated against these notes. Unfortunately in the General Assembly of 2008 (in Seoul) the contents of these two notes of clarification where incorporated to the 2008 version – I had the opportunity of participating in this Assembly, with the Brazilian Medical Association, but unfortunately our reasoning was not sufficient to counter these changes. I have also participated in the last meeting of the discussion of the CIOMS ethical guidelines, in Geneva, 2002. And recently I was a member of the working group that prepared the 2016 version of the CIOMS Ethical guidelines. Just after the release of the 2016 document, I was elected as chair of the Brazilian Society for Bioethics and in 2019, I was reelected for a new term of 2 years. And since 2017. I am a member of International Commission of Bioethics of UNESCO. That's my introduction which helps me to explain all the involvement with bioethics and human rights.

2. Biographical sketch of Paulo Freire

I will present to you some selected notes on Paulo Freire. It's taken from what I have read and from Leoncio Soares, a professor of the Faculty of Education at my university, who has been dealing with Paulo Freire's work for a long time. Freire was born on 19 September 1921 and died suddenly on 2 May 1997. He had a heart attack. He was just 75. Born in the northeast of Brazil, in the city of Recife, a beautiful city but very despair. He was born to a middle-class family, but hit by the Great Depression, the family became poor.

He mentions that his father died of hunger and, to make it even worse, he was only 13 then.

His full name is Paulo Reglus Neves Freire. During his childhood and adolescence, he has stated that poverty and hunger severely affected his ability to learn. Like we all know, how we can expect someone to read, to think, and to remember in chronic hunger. Of course, Japan suffered with the same problem during the war. It's almost the same thing, but you have been able to rebuild and recuperate, but for us this is a chronic problem. Maybe this was part of the influence in his decision to dedicate his life to improving the lives of the poor. He says, "I didn't understand anything because of my hunger. I wasn't dumb. It was not lack of interest. My social condition didn't allow me to have an education. Experience showed me once again the relationship between social class and knowledge." This is very true, and we must repeat it every day, because many people think that poor people are intrinsically lazy.

As his family's economic situation got a little bit better, he entered law school and philosophy. At that time, they called it phenomenology and psychology of language. He finished law school, but never practiced. He started working as a secondary school Portuguese teacher. Then in 1944, he married Elza Maia Costa de Oliveira, a colleague teacher. They stayed together for a long time and had five children. In 1946, at 25, he was appointed director of the State of Pernambuco Department of Education and Culture. Pernambuco is the State where the city of Recife is. Then at that time, he started talking and working with the poor.

Working primarily among the illiterate poor, he began to develop an educational praxis that would have an influence on the liberation theology movement of the 1970s. It was together with the Catholic Church's theology of liberation. In the 1940s Brazil, literacy was a requirement for voting. That has been changed now and everyone has the right to vote. In 1962, he had the first opportunity for large scale application of his theories when, in an experiment, 300 sugarcane harvesters were taught to read and write in just 45 days. In response to this experiment, the Brazilian government approved the creation of thousands of similar cultural circles across the country.

Remember the date was 1962, we had just presidential election in 1961, and the new president decided to resign after 6 months in office. At that time, the military didn't want the vice-president, João Goulart to take over. It took some time and only in the beginning of 1963 he was confirmed president.

Then in April 1964, less than 2 years after the João Goulart, there was a coup d'état. It was the beginning of the military dictatorship which lasted 21 years, until 1985. That put an end to Paulo Freire's efforts to revert literacy in Brazil because the military junta did not endorse it. They called him a communist because he was trying to help the poor to learn to read. Freire was subsequently imprisoned for 70 days. Then decided to exile first in Bolivia and then in Chile. In Chile, in 1968 he published his first book, which was published in Brazil only in 1980. It was forbidden because he was exiled. This book was "Pedagogy of the Oppressed". This book got a lot of praise throughout the world. That was very interesting again because he arrived in Chile just before Salvador Allende was elected president, with a very strong social agenda. He stayed president until 11 September 1973 when he killed himself during the siege of the government palace by the military. Then, Chile was also under a military dictatorship. Freire had to move again and this time he went go Boston, to teach at Harvard.

In 1974, Pedagogy of the Oppressed book was published in Spanish and English. As I mentioned only in 1980 it was published in Brazil; at the time the military junta started a timid process of political liberalization. After his stay in the United States, he moved to Geneva. There he became a special advisor to the World

Council of Churches. Coincidentally the first meeting of the working group of the 2016 CIOMS ethical guidelines was held there. Paulo Freire helped newly independent ex-Portuguese colonies, especially Guinea Bissau and Mozambique. In 1979, Brazil proclaimed a partial amnesty still during the military dictatorship and he was able to come back in 1980. He immediately started working with his pedagogical process and this was exactly the time that Lula helped with the foundation of the Workers' Party, and Freire was with him in Sao Paolo where the party began. He acted as a supervisor for an adult literacy project from 1980 to 1986. In this period and for the first time a woman was elected mayor of Sao Paulo, Luiza Erundina. He was appointed as secretary of education for the city of Sao Paulo, which already was the largest city in Brazil. This just a glimpse at his history.

3. Human Emancipation

He has said many things on human emancipation. One very interesting quote: "emancipation does not happen by chance, not even by concession, but with being conquest affected by human praxis which will demand unstoppable struggle." That is true. That is the reason I do not like when people use the word "empowerment", because empowerment sounds like a concession and as Freire said it is not – rather people emancipate to fight for their rights. Freire does not advocate liberation as an ideal point outside men to which even they may be alienated. Freedom is an indispensable condition for the search movement in which men are inscribed as inconclusive beings. I also like this quote: "liberation therefore is a birth, and is like a delivery, difficult. The man born of this birth is a new man who is only viable in and through the overcoming of the oppressor-oppressed contradiction, which is liberation of all."

He was very strong in his feelings about this and that's the reason people that were not keen of equality were against him. In the context of his reasonings, the Pedagogy of the Oppressed constitutes the pedagogy of men and women striving for their emancipation. The origin of the Pedagogy of the Oppressed as a humanistic and liberating pedagogy "ceases to belong to the oppressed and becomes the pedagogy of men in the process of permanent liberation."

4. Paulo Freire selected works and quotes

Table 1 lists some of his selected works. The most famous is the Pedagogy of the Oppressed, which I brought to you and that is exactly the 50th year commemorative edition. Another book is Pedagogy of Hope. He called it a return to the Pedagogy of the Oppressed. It was written in 1992. Pedagogy of Autonomy is remarkably interesting too. Then I mention the dictionary of Paulo Freire. It includes most definitions of Freire's terms and several of his quotes.

I have selected some quotes, listed in Table 2. He says that the dominant pedagogy is the pedagogy of the ruling class. Freire invites people to be subjects of their own history. He also says that to people must move from life as biology to life as biography. That is a fantastic thought. Your life is not biology but biography. To promote literacy is equal to raise awareness. To know and to be able to say one's own word, conscience of the world and conscience of one's own self. That is very interesting too because that is what he said many times that when you see someone that comes from a very underdeveloped setting, you think they don't know

Table 1　Paulo Freire Selected Works

- Pedagogy of the Oppressed
  Written in Chile (1964/1968)
  First published in 1970
- Pedagogy of Hope
  A return to the Pedagogy of the Oppressed
  Written in 1992
- Pedagogy of Autonomy
  Necessary knowledge for educational practice
  His last book – 1997
- Paulo Freire's Dictionary - 2008

Table 2　Freire's quotes

- The dominant pedagogy is the pedagogy of the ruling classes.
- Freire invites people to be "subjects of their own history.
  - Passage from life as biology to life as biography.
- To promote literacy is equal to raise awareness.
- To know and to be able to say one's own word.
- Conscience (awareness) of the world and conscience (awareness) of one's own self.
- Reading the world precedes reading words.

anything. He says that frequently these people have read the world much before they could read words. And this must be respected.

I add a last quotation. This is not by Freire. It was a preface by another important philosopher, but not as famous as Paulo Freire. He said, "In a regimen of domination of conscience, those who work hardest cannot say their words, and where huge crowds cannot even work, the rulers maintain the monopoly of the word with which they mystify, massify, and dominate. In this situation, the dominated, to say their words, must fight to take it. Learning to take it from those who hold it and refuse to share with others is a difficult but essential learning, that is pedagogy of the oppressed."

5. Pedagogy of Oppressed and Pedagogy of Autonomy

I am not going to read the following (Table 3), I am going to leave that to you. That is very interesting because in the book if you read, maybe you will remember, he was teaching some people, and in the end, there was a time for them to talk, and one of them said, "I have arrived to this course naively and as I discover myself naive, I start to become critical". First you must know about you. Then knowing about you, you become critical. The second point is very important. To teach is not equal to the transference of knowledge. I must stress what he meant that many times education resembles a banking process. He said many times that it may seem like delivering things like in a bank, you give papers and then you ask for the papers back. He said that is not the way of teaching anyone. It cannot be a banking process. It must be something that both sides participate.

Table 3 Pedagogy of Autonomy

1. Teaching practice: first reflection.
2. To teach is not the transference of knowledge.
3. To teach is a human specificity.

Of course, I am not an expert on Paulo Freire. I have been quoting him frequently in many of my presentations and papers. Changing the subject, Brazil is facing another serious problem – Since the beginning of 2019, Brazil has a new president. He took office in January 2019. It is difficult to define him, as there are many adjectives that one can stick on him. Just after 1 month in office, he said that Paulo Freire was just a communist and that he didn't know anything about anything. He proposed that the Brazilian Congress to take out Paulo Freire's as the patron of Brazilian education. Luckily, the Congress did not agree, and Paulo Freire remains our patron of education.

It is very interesting that Prof. Kimura got to listen to him more than once at the World Council of Churches. I can tell you a story that I think is true. Freire said that people are so different around the world and that Brazilian are people that like very much to touch each other. We, Brazilians, when we greet like to kiss, to hold hands, to embrace. He said that when exiled in Chile, invited as a visiting professor, he was taken to see the university and Freire, as they walk, put his hand on the dean's shoulder and the dean did not like it. Freire, used to the Brazilian custom of friendly touching other people, considered the dean's reaction odd. But then, 3 years later, he had to move to Nigeria and faced a similar situation. On his first visit to an university where he was invited to teach, the dean took his hand while they were walking and now it was Paulo Freire who felt the situation awkward. He said that these two episodes reminded him that we always must respect the differences.

This should also teach us all to think about and understand the differences. Talking about differences reminded me that Brazil is in the other side of the world from you. And we have learned with the Japanese heritage, because the largest Japanese immigration occurred in Brazil. We see a remarkable interracial mixture in my country. Of course, now with the economic slump in Brazil, you are receiving back, tens of thousands of sons and grandsons of the original immigrants.

6. Discussion

Kimura Thank you for your illuminating presentation.

One more impression I had of Paulo Freire was his tendency of speaking very slowly, because in 1972 when I first met Paulo Freire, he was not accustomed to speak in English. He was speaking in his mind, and after some interval, he would start to say something. What he said was very shocking. After returning from Geneva in 1975, I was given the opportunity to teach at Waseda University Law School. During my seminars, I sometimes used English texts. For one particular seminar. I selected some excerpts from Paulo Freire's works and distributed a paper which include his ideas. Previously, Japanese students were not accustomed to raising questions to the professors, as they were educated under the system of Confucius tradition whereby professors are *always* correct. After that particular seminar, however, students began to raise questions to

their professors.

By the way, do you remember what happened 78 years ago today? 78 years ago today, Japan attacked Pearl Harbor. At that time I was only seven years old. As a child, I never questioned the war. I thought that it was a war for justice, and that we are on the way towards victory. It was a sort of brain washing. When we lost the war, I was very much frustrated.

At the Ecumenical Institute in the 1970s, I learned the differences between the Japanese traditional education system and Paulo Freire's idea of education. From then on, I often thought about the purpose of education. Freire changed not only my way of thinking, but also my existence as an individual.

The name of Paulo Freire was not well-known throughout Japan. In 1975, when I began to teach at Waseda, there were no translations of his works. I felt that the foundation of the Japanese education system has not changed, and that it remained largely ideological. In these times, the Japanese education system support only one-way communication, whereby both students and teachers are restricted. However, the educational situation is gradually changing by the efforts of educational experts who were influenced by Paulo Freire in recent years. Freire's "Pedagogy of the Oppressed" was translated into Japanese and some unique challenges against "Banking System Education" in Japan are going on in the field of "Active Learning"(Prof. H. Kazamaki) and Pedagogy (Prof. M. Satomi and Prof. A. Kusuhara).

Greco　It is very interesting for you to say that because what has happened to your country, especially the impact of the war was terrible. When I think about Japan, I immediately remember of Hiroshima and Nagasaki. Of course, both sides were very wrong, but the atomic bombing of these two cities and the "carpeting" bombing of Tokyo was terrible by themselves and was even worse because this happened at the end of the war. It almost destroyed everything in these cities. Of course, the U.S did not have to do it. The point is that we must remember that education can change that for the present and for the future. In Brazil, the current political power does not want to follow Freire's proposals, because the more people know, the more emanci-

pated they get and then they are going to claim for their rights. The right-wing movement considers that is better that people do not learn anything and thus do not claim for their own well-being. The current situation in my country is bad because, even the insufficient progress we had in education, they are trying to destroy it.

And it is not only with education, they are destroying our public, and also science. The plan is: we destroy education, we back up private health in detriment of adequately financing public health. They say that public health for all is not possible, too expensive. Let us make it private, saying that private companies will make it better. That's not true as private or public, both of them can be very bad and both of them can be good, but having it private health will not be accessible to all, and today in Brazil our Public Health system is a right to everyone, it belongs to everyone. It is even worse because Brazil has a shameful inequity and also has a lot of illiteracy. In Japan, there is always the possibility that people one day are going to know they have rights and they are going to emancipate, ask the right questions to the teachers.

Kimura In recent years, international organizations such as WHO, CIOMS, UNESCO are reporting to the world on issues of anti-illiteracy health education. Paulo Freire was a pioneer for anti-illiteracy and education within the social and cultural system in Brazil.

What are the connections between health and illiteracy issues and the teaching of Paulo Freire?

Greco You are quite right. Health which is closely intertwined with literacy and of course, Freire's teaching in intensely embedded in both. And, thank you, I shall emphasize the aspects of health in his teachings in my talks.

Saio I would be probably only one person in Japan insisting that workshops used in teaching evidence-based medicine (EBM) adopt the andragogical methodology of Paulo Freire's small group learning and this is effective for medical literacy education. In those workshop, the process is not teaching by medical professor for medical student, instead, in evidence-based medicine workshop, groups of participants will learn collective intelligence, using critical appraisal skills program.

Kurihara　I am not a medical professional, and through such kind of process, I learned much about the medical knowledge.

Greco　I was very happy to hear that because when I mentioned Paulo Freire to my hosts, Chieko and Takeo, they were very excited about the possibility of us discussing his work here. And we exchanged quite a few messages on this subject.

At that time I remembered of someone else that I want to mention to you – This is Augusto Boal, born in 1931 and died at age 79, in 2009. The book I presented you is one of his most famous: *the Theatre of the Oppressed*. He was a theatre director, writer, one time politician and earned a degree in chemical engineering in 1952. His writing follows the same lines as Freire and in the late 1960s, inspired by *Pedagogy of the Oppressed*, he began experimenting with a form of a living newspaper theatre. He was also considered a subversive by the military dictators, was arrested and tortured by junta then ruling Brazil, in 1971, and like Freire, he spent 15 year in exile.

Saio　I greatly appreciate that you could present us the book of Boal. I think it is also possible to include his methodology in EBM learning, improving current methodology of role play. We wish to elaborate such theory and would be pleased if we can ask you for your advice in future. Thank you very much.

Part 2 Access, Compulsory license, Case Study

1. Access, Compulsory license, Case Study

Dirceu Greco Responding to your request, I will talk about access, compulsory license, and use a case study to illustrate this. I want to remind you again how far we are. Brazil is located at a 19,000 km distance, just at the opposite side of the globe. I will show some comparisons of population, area, GDP (gross domestic product), HDI (human development index) between Japan and Brazil. When you think about literacy and about respect for people, we are so much far down from you. Brazil's population is approximately 210 million people and 10.8% live on $2 a day. That is almost impossible to think that someone can live on that. I live in Belo Horizonte, southeast of Brazil. From Belo Horizonte, If you go east, that's Rio de Janeiro. If you go southeast, it is Sao Paulo, and Brasilia in the Northwest – My hometown is roughly equidistant from these three cities.

The case study is in Brazil, and I have mentioned this in my lecture on December 4th: "Doctors are forbidden to have any participation in clinical trials where placebo is used as a control when there are efficacious and effective drugs for the disease on trial."(Article 1 of the Resolution 1885/2008, Brazilian Medical Council (CFM). This article was incorporated into the Code of Medical Ethics (2009-2019) and the restrictions to use of placebo are also included in the Brazilian Research Ethics Commission Resolution CNS 466/2012.) If you see the Resolution 1885 date, 23rd October 2008. This was soon after the change of the Declaration of Helsinki, 2008 version. When the Declaration of Helsinki changed flexibilizing placebo use, the Brazilian Medical Council decided to issue a much stringent and protective a resolution immediately saying that this would not apply to Brazil.

2. Brazilian Research Ethics Commission

I have also mentioned that in Brazil we have centralized National Research Ethics Commission, which you do not have in Japan. This commission oversees all research ethics issues in the country. It is worth mentioning that its research ethics directives are applicable to all types of research involving humans, not only for clinical trials. In relation to biomedical research it is a very protective and stringent declaration. It clearly states that at the end of the study, sponsors and the research team must ensure to all participants access free of charge and for all the needed time, to the best prophylactic, diagnostic, and treatment that have been dem-

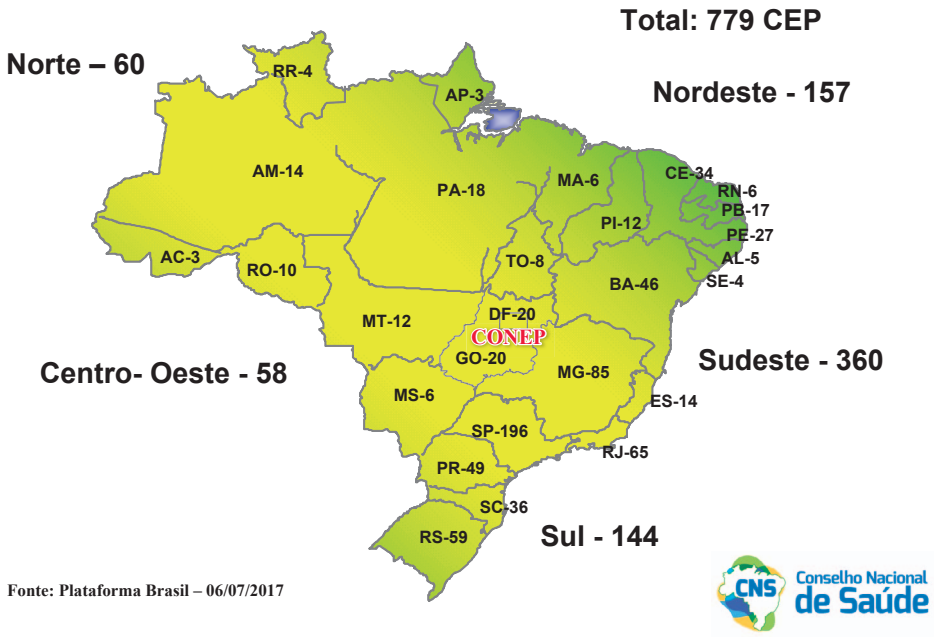
onstrated to be efficacious.

At this point, item d.1 of the access article is very important because it says that access will be warranted between the end of individual participation and the end of the study. In this specific situation, access will be permitted through a study extension according to a consubstantiated analysis of the participant's attending physician. It says that many times, even before the drug is registered, the participant may be entitled to have access in a compassionate or extension of the study. That was a bold decision. I call you attention to the fact that Resolution 404/2008, was issued 2 months before the 2008 WMA General Assembly that decided to modify the Declaration of Helsinki. The Brazilian decision was that our directives would maintain post-study access and the restriction to the use of placebo, independently of the General Assembly decision. But something else very important was added: it proposes further discussion on the rights of access to health and to the products that have showed efficacy for all, and not only to the research participants. This means a step forward – from clinical trial to real world public health access. The National Research Ethics Commission oversees, as I have mentioned, all the local Research Ethics Committee – as of 2017 we had 840 plus research ethics committees spread throughout the country (Fig. 1). Of course, they are more numbered in regions where there is more research, e.g., Sao Paulo, the State of Minas Gerais, where I live, and then Rio de Janeiro.

3. Factors that affect access to public health

Many factors affect access of products in public health. One is this research and development expenditure. The more research and development expenditure that we have locally, theoretically we have more chance to get drugs and also vaccines, developed and thus accessible. If you see research and development in Japan versus Brazil, Brazil has very little. There are many products developed here, and hopefully most of the time

Fig. 1 Research Ethics Committees in Brazil



it is used in Japan. That is part of the disparity that we talk about. If you speak about Clinical trials, one of the most used databases is the US ClinitalTrials.gov. Most of the numbers here shown are related to phase 3 trials. If you see here, Brazil has a little bit less than Japan at this time. That is total research registered at ClinitalTrials.gov, but it's interesting because when you focus on the numbers for phase 3 and phase 4, Brazil has much more than Japan. That is because phase 3 and 4 are not actually research. What I mean is that in these two phases there is little input from the local researchers – usually the protocol, the methodology and the coordination is not local. This is different in phase 1 and 2, when the real research and development are going on – these 2 phases add up to 47.7% in Japan versus 30.5% in Brazil.

Kurihara I want to say one thing that many of the Japanese clinical trials are registered in the Japanese registry. Not in ClinitalTrials.gov. Another thing is that there are many phase 1 trials in Japan but most of them are not first-in-human study. Japanese companies tend to conduct FIH outside Japan and then after confirming somewhat safety and efficacy then start trials in Japan.

But one point that we Japanese are conducting "research" as you say is that there are many Japanese pharmaceutical companies and academic institutions which have there own pipelines from basic research for discovery to research and development of their own findings.

Greco Yes, that's important and worrisome also – the ethical risks of this outsourcing of phase 1 trials to other countries, but this is not the focus of my presentation. Another thing we should discuss would be that even you register in the American or Japanese registries, all should be included in an independent international portal, such as WHO's. This would allow for one complete database accessible to everyone in the world.

So in Brazil there are many phase 3 studies financed and coordinated by global companies and post-trial

access is critical issue. I have already mentioned to you the intense discussion in 2004 after a note of clarification that really washed down a lot of what was accomplished in the 2000 version fo the Declaration of Helsinki. At that time, the United States Food and Drug Administration (FDA) decided to take out the Declaration of Helsinki from their regulation for the New Drug Applications (NDAs) trial outside the US. The Department of Health and Human Services and the FDA also argued forcefully against the requirement that the effective drugs to be provided to all study participants at the conclusion of the research.

4. Brazil's Universal Health System (SUS)

I mentioned that Brazil has in its 1988 federal constitution that health is a right of all and a duty of the state. This requirement gave rise to the unified health system, giving the right of access to care to all, without out-of-pocket payment. And this is quite unbelievable. With all the economic and disparity problems that we have, this system (the Unified Health System or SUS, in Portuguese) is the sole responsible for healthcare of over 150 million people – actually this, maybe a little bit more now, because many people that had private insurance, with the current economic slump had to give up private insurance, going back to the public system. What the new government is saying is that it is impossible to keep financing this, which is not quite true. They are planning to take as many people as possible out of the Unified Health System saying that anyone who can pay should have their own insurance. It's the new liberal right-wing nationalistic plan. For the last 30 years the public health system has been funded exclusively by the municipal, state, and federal taxes.

We have had successful examples, all of them thanks to the existence of this Unified Health System. One of them is the confrontation of the AIDS epidemic. The Brazilian AIDS programme, especially on the access

to the antiretroviral drugs, has set an example for other developing, and also for the industrialized world. All this may be in jeopardy because, as I have mentioned, as of 2019, a neoliberal, far-right government passed a law limiting health expenditures for the next 20 years. What they are saying is that they are not going to increase it as needed. If you do not increase the needed funds, and the population is increasing and ageing, you are actually lowering them, right?

5. Effects of neoliberal policies on Ebola's confrontation (2014)

This neoliberal policy has had negative effects in several instances and one of them was in the 2014 Ebola outbreak in Africa. Coincidentally, at that time I was in London as a visiting professor to the London School of Hygiene and Tropical Medicine. There were many discussions and seminars on the subject. And an interesting publication at the *Lancet*, Global Health, disclosed, is that a few years before this outbreak the International Monetary Fund advised many countries to curb public health spending. In Sierra Leone, for example, between 1995 and 1996, the IMF required the retrenchment of 28% of government employees, and limits on wage spending continued into the 2000s. This is exactly what they are planning to do in Brazil. When this outbreak hit East Africa, the reduction of community health workers that was intense by 2004, was much intensified by 2008. In 2014 they literally did not have health professionals to take care of the people.

In this connection, what is interesting is that when I was at the London School of Hygiene and Tropical Medicine, the most intense subject of discussion was on the search for a vaccine, but also for efficacious drugs. But it must be said that interest in this was really boosted and financing was increased when it was a real possibility that this outbreak could hit the northern hemisphere. While it was in Africa, it was just another disease affecting neglected individuals in neglected countries. If Chagas Disease would intensely hit the United States, there would be interested in researching for better drugs, like it happened with HIV. This virus, even affecting disproportionately resource-poor countries, also hit the so-called developed world. This partially explains the intense response for the development of efficacious treatments. I remember a cartoon from 2014: In the left side, Ebola was pictured as Africa in a hospital bed saying: My people are dying. Sitting close was the world, sleeping. On the right side, someone saying: "It is crossing the ocean". Currently, the world wakes up, fast. This is very true, and it has to be changed, as people must have rights everywhere.

6. WTO-TRIPS and Doha Declaration

Now we get to especially important issue. We have discussed about the TRIPS flexibilities and compulsory license (Table 1). WTO (World Trade Organization)'s TRIPS Agreement (Agreement on Trade-Related Aspects of Intellectual Property Rights) was signed in 1995. Interestingly, they gave some time for the countries to adapt, it was 10 years. Many countries, such as India and Thailand, used all this time. They were able to establish local production of Active Pharmaceutical Ingredients (API) and manufactured drugs, including generics, of which they are among the largest producers. Brazil, in 1995, keen to please the consensus of Washington, signed almost immediately. That impeded the development of local chemical and pharmaceutical industry.

To counteract TRIPS requirements a meeting was held 16 years later – In 2001, in Doha a new Declaration

Table 1　WTO-TRIPS Flexibilities and Doha Declaration

TRIPS Flexibilities: Compulsory License – article 31
• "National emergency"
• "Extreme urgent circumstances"
• "Public use, non commercial"
WTO/TRIPS and public health
Doha Declaration
(Doha, Qatar - November 2001)
Redefines certain points in the TRIPS Agreement (1995),
Reaffirming that public health prevail over intellectual property issues.
• Primacy of public health
• Technological transfer
• Transition period until 2016
• Permission to export generics

WTO: World Trade Organization;
TRIPS: Trade-Related Aspects of Intellectual Property Rights

was signed, named the Declaration of Doha. It clearly redefines certain points of the TRIPS Agreement in 1995, adding that public health needs should prevail over intellectual property issues. Thus, established the primacy for health. Even with this change and with the possibility of compulsory license for public health purposes, countries were afraid of using it due to pressures from the country of origin of big pharma.

This has been further complicated as industrialized nations are trying during bilateral negotiations on trade, especially with less affluent countries, to impose what is called TRIPS-plus obligations. These are provisions on intellectual property protection that go beyond what is originally requested by TRIPS. It extends patents longer than 20 years or introduce provisions that limit the use of compulsory license or that restrict generic competition. Of course, this will restrict the use of public health safeguards and flexibilities available in TRIPS and it is many times difficult for some countries to say no as they are afraid of the cancellation of all negotiations.

In 2007 Brazil was still capable of issuing a compulsory license of a drug using the flexibilities allowed by the Doha Declaration. This was in 2007, Lula was the President of Brazil and he signed a decree sanctioning the compulsory licensing for efavirenz. In the decree it was stated that this decision was taken in "absolute compliance with international requirements and with Brazilian legislation." Efavirenz, if you are familiar with the treatment of HIV, was for many years a staple medication, which was used in combination with other antiretrovirals. This drug was produced by Merck. At that time, Brazil was buying it for $1.59/tablet. Prior to issuing a compulsory licensing, you have first to ask the producer for a discount – Merck offered a 30% rebate, reducing the price to US$1.11 but efavirenz could be found as a generic for $0.45,

At that moment 38% of AIDS patients were on efavirenz. By the end of 2007, 75,000 of Brazil's 200,000 AIDS patients would be taking this drug. Annual cost/patient was US$ 580.00, representing an annual expenditure of US$ 42.9 million. Prices charged for the generic product decreased the annual cost/patient to US$ 163.22 or US12.1 million/year.

They estimated a saving of $236.8 million by the year 2012 when the patent would expire. They decided

to go ahead with the compulsory license only after ascertaining that the drug could be produced in Brazil. Just after the compulsory license, efavirenz was bought form India, while production procedures was started at a public laboratory in Rio de Janeiro (at *Farmanguinhos*).

Brazil was subject to a lot of pressure: first Merck officials declared that if Brazil proceeded with the compulsory license, they would stop all research in Brazil. The Brazilian AIDS programme found out that they were not really investing anything in research in the country, so it would not make any difference. The other pressure was, of course, just lip service, no one wrote about it. It was rumored that if Brazil signed the compulsory license, there would be an increase in the taxes for orange juice, exported into the United States. By the way Brazil is the largest producer in the world of orange juice. Luckily, this was a bluff. They just found out that they could survive with this licensing, no problem for Merck, no problem for the United States. The only thing they were probably afraid of is that this example could spread to the world. It did not happen often. Thailand did the same for another HIV, tenofovir. Even Brazil never repeated it for many reasons and one of them was again economical pressure- it went like: don't do it again because if you do, then we are really going to retaliate. As a matter of fact, that was not the first time that Brazil entertained the idea of issuing a compulsory license – the precedent was in 2005, and the drug was lopinavir/ritonavir (Kaletra®), also for HIV, but it did not go through because there was no local technology for producing it. But in 2011, the patent application for tenofovir was not granted and we started producing it locally with estimated savings of $400 million in 5 years.

7. Recent case: post-trial access

I will present a case study - Recently there was a case in Brazil concerning post-trial and the judiciary. During the discussion on December 5, we talked a lot about informed consent procedures. We all were very critical on the way that most informed consent procedures occur. In many situations, the informed consent is not truly informed, and the participant has many difficulties in understanding what has been presented and just sign it. Even when used as a kind of protection for the researcher (and not for the participant) it may have the power of law, so to speak.

This was the case in a recent situation in Brazil. As it is the norm in Brazil, the informed consent included an item stating that the drug company was supposed to provide treatment after the end of the trial, but they did not do it. They said, no. Added that the patient could receive the drug through the public health system, so just go there and get it. The father of the child read about the right to post trial access in the informed consent document, where he found that, "sponsors doing research with human being are responsible for providing the drug that was developed even after the end of research." He then went to the Judiciary claiming for his rights. The Justice agreed with him and in his sentence condemned two international laboratories associated in a joint venture to give back to the state of Rio Grande do Sul, where the research took place, the money spent with medication for the child that was born in 2003 and had already died of cancer at the time of the sentence. The company, Genzyme should refund the state the equivalent of US$ 50,000.00, which was the amount paid by the public health system. Thus, this case is an example that what is included in the informed consent document may have the force of law. Coincidentally a few years later Takeda tried to buy Genzyme but it seems that their bid was not successful.

8. Discussion

Kurihara　Thank you very much for your very interesting presentation. I learned so much on these issues of placebo, access and compulsory licensing. I would like to ask you, how was your personal involvement in this process of compulsory licensing to provide drugs to the HIV infected people? After that, there must be hard pressure from outside.

Greco　In 2007, the Director of the Brazilian AIDS Program was a woman, Dr. Mariangela Simão, who is currently Assistant-Director General of WHO in Geneva. She directed the programme from 2007 to 2010, and I succeeded her in 2010. She went through a very difficult discussion in relation to a compulsory license of an antiretroviral drug, efavirenz. This drug was produced by Merck and Brazil decided to use of the articles of Doha's declaration which permits compulsory licensing to protect public health. When I got to be director of the department, this issue was already set and things were almost all set. They started producing generic in Brazil. At the time while I was director, we did not issue patent for tenofovir. That was my experience during this time. Afterwards, the economic situation of Brazil was particularly good. During Lula's time in office, growth was at 4% per year, which is considered extremely high for us. But then it started to slow down after Lula left his presidency. We are still producing in Brazil all 11 of the 22 HIV medications, most of them produced by public laboratories, but these are not protected by patents.

I have frequently participated in the process of acquiring HIV drugs, first sitting with pharma company representatives and in Brazil these drugs are bought centrally. All the drugs for HIV, for hepatitis are bought by the Minister of Health and distributed throughout the country, so the leverage is much higher than buying smaller amounts in different places (hospitals, for example), as it happens in many European countries. How is it in Japan? Who buys drugs for HIV, for hepatitis, for cardiac disease, for psychiatric drugs?

Saio　Each hospital negotiates with distributer company about the amount and if applicable discount price, but In Japan price of the drug and reimbursement by public money is defined by the government, according to some rules of calculation.

Greco　If each hospital does it, it is much harder to negotiate because the amount that you are buying is much smaller. If you have a large amount, there are two things that may happen. One, is the risk politicians are going to make money in that, because negotiation is going to be in the hands of a few people. On the other hand, there is a big advantage as the country will have more leverage as they are buying large quantities. In Brazil, to mitigate corruption risks the Ministry of Health has a department negotiating price, but the actual payment is through another department, both open to scrutiny. This make it more difficult to corruption.

The negotiating price table, in which I participated many times, was incredible because pharma representatives would come with a price set, and when we said it was too expensive and we would not buy. Usually they would leave the room to supposedly call the CEO, and 10 minutes later, they would return and say – yes, we have got a better pricing and many times this would repeat again and again. It reminded of price waggling in a shopping mall. But even with all this negotiating power, patented drugs are usually awfully expensive. If you cannot produce or buy generics, you may be lost. It is worth mentioning the price of the new antivirals for hepatitis C treatment. These new drugs offered real hope for hepatitis patient, reaching a cure rate as high as 90-95%. But in the beginning, the price for Europe, it was the same for Japan, it was $80,000 per treat-

ment. Who could really pay for that – of course it was impossible for individuals in resource-constraint countries, right?

Saio In Japan generally 70% is paid by the government and 30% is paid by patients. But there is a monthly ceiling about ＄800. The drug for hepatitis C produced Gilead is over $500 per pill.

Greco Yes, at the time it was released it was too expensive in Europe, North America and Japan. Brazil negotiated the price for treatment, and it went down to $2,500,00 per patient, which is still above the reach of most developing countries. So, it is about half as much what is paid in Japan. In 2019 the price in Brazil went down to U$1,750/patient but this is still much higher than the cost of a generic. In India one of the most effective antiviral for hepatitis C costs $300.00/treatment. This price disparity must be confronted, and nations could start using the Doha declaration to circumvent patent rights for better access to essential medicines. This is a good fight for all. The problem is that, as I have mentioned before developing countries are afraid of using the flexibilities allowed by the Doha Declaration or have already signed the TRIPS Plus agreements.

Kurihara I always argue that there are many people in the world who cannot access to necessary drugs, meanwhile, as I sent you my paper on valsartan, the companies have invested so much money to "seeding trial", no social value. You showed that there are many phase 3 or phase 4 studies in Brazil. It is unethical if the company invest much money to seeding trials and save their money for the budget for post-trial care and post-trial access for all in the community. Did the case of Genzyme change the attitude of companies?

Greco They keep trying and really are doing the same thing that they have done all the time. For instance, they conduct specifically phase 3 trials in many countries, because these have many advantages – of course the good side is that the efficacy phase will be tested in different populations, but the downside is that knowledge is not really transferred. And another risk is that by involving reputable scientists in different countries there are evident risks of conflicts of interest – for instance when the tested drug is approved for marketing.

The point is that we must join efforts to invest resources to tackle the diseases that affect neglected populations and to ensure access to many other treatments that affect these populations. We should do more to make countries invest also in phase 1 and 2 trials – that is invest not only in doing the trials but on the development of needed products. Even in the United States, if you check all the developed drugs, they most of the time have started with money from NIH. Most of the basic development is paid by the public. It is after it gets to phase 2 or 3 that the drugs companies get in, usually getting also all the profits by charging unacceptable amounts for the developed drugs.

Kurihara That is a very interesting point because in Italy, there are so many seeding trials which cause publication bias, and people proposed some system to fund money from pharmaceutical companies and allocate to researchers through some public system. It is like the case of Brazil that the government buy the drug and allocate it. Japanese hospitals buy much drugs getting reimbursement from public money and this causes polypharmacy. As for the clinical trial, as I mentioned in the December 5 meeting, Professor Masanori Fukushima worked so much to develop academia-oriented drug development, Phase 1 study, utilizing academic discovery and organize all the clinical trial to reach to product approval. Furthermore, his recent argument is academic-oriented marketing. This is very important proposal. Marketing should be for public health, not profit making. At the starting nobody in Japan believes such kind of academic-oriented development will come to be true, but at this moment, it comes to be the fact. Then, marketing for all who needs in the world would becoming the fact. He is one of our team to make proposal of Human Subject Protection Bill, which was not realized but included in the "additional resolution" of Clinical Trial Act recently established responding to pharma-granted inappropriate trials.

Greco One way out not only for Japan, but also for other countries, is for the essential medicine list from WHO. It's well prepared and up to date. Many times, if you see in our specialty, you have so many different drugs to pick up from. Everyday there is a new one which they claim to be little bit better. With that, you pressure the hospital to buy it as it is there in the directors of the American Gastroenterology Society and we don't know who made them. There is a lot of conflict of interest. People who participate are financed by the laboratory. One thing that happens that's good is we talked about vaccine. Brazil has a very large vaccine program and almost everything is in public health. Many of them are brought through the Pan-American Health Organization fund. They check everywhere what is cheaper. They buy bulk and then sell to Brazil. That is the way that we can get better pricing.

The point that is very important is that the WMA mandate is exclusively with physicians. Anything they say about other profession is not their mandate. The particularly good thing that happened is that declaration became possession. All the health-related people, they use, but their mandate is only physician. As I mentioned to you, we do not know exactly what CIOMS is. It is not WHO. It is in collaboration with WHO, it brings people from WHO, but it is a separate thing. UNESCO theoretically should be a good place, but people are saying the document is too vague. It does not set points. My point is that maybe we needed the document that is international that does not have to be from the United States or the UK. It should not be from those countries. It must be from one international institutions, such as WHO, in which all countries participate.

Kurihara I completely agree with you that UNESCO is theoretically ideal. Also, I think as people say that the document is too vague. It should be improved. Or otherwise, "additional protocol" such as the ones

Left: CIOMS guidelines 2016 version and its Brazilian translation; right: the first version of the CIOMS guidelines

for European Council's Convention on Human Rights and Biomedical Research (Oviedo Convention) may be good to be added. UNESCO is very important because its declaration is based on, as core document, the Declaration on Human Rights in 1948. And more ideally, such document should be international treaty based on International Covenant on Human Rights.

WMA's achievement is great, as it is almost gold standard of medical research community notwithstanding disagreements with some paragraphs. However, its value and limitation is to be "addressed to physician only". Non-medical researchers would of course adhere to DoH, and the WMA very much welcomes it, but it is theoretically impossible to include the issue of "responsibility of us, citizens/bioethicists". UNESCO must be able to involve us.

CIOMS represents 42 members/associate members of medical science societies and medical research councils/national academies of science. WMA is a member, IFAPP is also a member. CIOMS says it represents substantial proportion of the biomedical scientific community. But to make it truth, more societies, e.g. JSCPT should be a member. However, it is not limited to physician, thus new version of the CIOMS guidelines talk about responsibility of ethics committee, government, community, not only researchers.

I would like to ask Prof. Kimura how is the situation in the CIOMS at the time of starting the guidelines for research. It is for developing countries but at that time not so many of the developing countries where human studies were conducted had not yet established democratic government.

Kimura During the beginning stages, some of the representatives from authoritative governments attended the meeting. At the meeting, the representatives expressed an urgent need for guidelines within in

their regions.

By the way I would like to ask Prof. Greco about a general organizational system for ‘patient safety’ in Brazil. In Japan, we have recently developed a medical safety organization, though it focuses on ‘medical safety’ rather than ‘patient safety’. One of the keywords of the conference we held last week was ‘Patient-Centricity’. Dr. Kloiber from the World Medical Association mentioned ‘Patient Centricity’. Some cases were also mentioned in Brazil as well as US’s ABCC’s (Atomic Bombs Casualty Commission) research in Hiroshima and Nagasaki in Japan. Do you know of any general patient safety legislation in Brazil?

Perottino　I will give you some related information. There is a resolution from National Health Surveillance Agency (ANVISA) – the agency responsible for issuing guidelines on everything related to health, that addresses patient safety. All hospitals and all clinics must have a Nucleus for patient safety (NSP), and they must report to this agency any perceived irregularity.

According to ANVISA, NSP is “the health service body created to promote and support the implementation of actions aimed at patient safety”. It is an extremely important component in the search for the quality of activities developed in health services. The objective is to support all activities related to patient safety through the implementation of risk management in health facilities, public, private, philanthropic, civil or military, including those engaged in teaching and research. The NSP must consist minimally of a doctor, a pharmacist and a nurse. According to article 13 of one of their directives (DRC no. 36/20137), the non-structuring of the NSP constitutes a health infraction, and under the terms of Law no. 6,437/1977, it is also liable to civil, administrative and criminal penalties.

Kimura　We used the word at the beginning, in the 1980s, ‘patient-centered medicine’ initiated by myself as a first Bioethicist Lawyer in Japan together with an eminent physician Dr. Shigeaki Hinohara. Now the word ‘patient centricity’ became the keyword.

Greco　That may be more than a change of wording. We discussed on the December 5th meeting about

implications of "paternalism". The patient centered is the opposite. There are two international institutions that we should consult more frequently on these topics, one is "Slow Medicine" from Italy and "Choosing Wisely" from the United States. Slow Medicine is more patient-centered because it says much more about what the patient should receive. Choosing Wisely is more from the institution, but they complement each other to the extent of saying that the patient should be the center of our efforts and care. Actually, this is the first thing that is written in the Declaration of Helsinki - our mandate is to take good care of the patient, but again, there it all about the physicians, as they are under the mandate of WMA.

Kurihara Thank you very much Professor Greco, for your great talk. It's very nice to learn about two important topics today. We wish to continue discussion with you after returning back to home in Brazil. We appreciate Prof. Kimura, it is great opportunity to invite you, on the day of "Pearl Harbor", following discussion by Prof. Greco providing his deep concern about the Hiroshima observational study. Ethics of this kind of study just observing people, not providing care must be continuously discussed. Thank you Victoria to provide your profound insight of bioethics, especially focusing privacy protection and patient safety. We learn much about the strong theoretical framework of human rights enhancement of Latin American people. Thank you very much.

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