Proceedings of the 2nd International Symposium on Thalidomide Embryopathy in Tokyo

Date : July 14 & 15, 2019

Venue : Sola City Conference Center
Ochanomizu, Tokyo, Japan

Edited by

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Preface

Fumihiko Hinoshita, MD, Ph.D.

The 2nd International Symposium on Thalidomide Embryopathy (TE) was held in Tokyo on July 14 and 15, 2019. Four years had passed since we held the 1st International Symposium on TE in Tokyo. Research on TE and support for thalidomiders have greatly progressed worldwide during this period. Many research works on TE have been published, not only from European countries, but also from Japan, and a TE-associated law was amended in Germany. Moreover, some new programs to support thalidomiders have been tried in the UK and in some other countries as well. In Japan, we have also tried new approaches to treat and examine thalidomiders, including a nationwide survey regarding the actual life situations of thalidomiders (Birth Defects Res. 2019;111:1633-1642).

Based on these results, this symposium first focused on the clinical and social reports of TE in various fields, next incorporated the special lectures on mechanisms of thalidomide teratogenicity, hip joint surgery and a diagnostic aid to TE, valiDATE as well as on thalidomiders in Brazil, and finally closed with a joint discussion among the oral presenters and a few other moderators. In total, we had 9 special speakers from Germany, the UK, Sweden, Switzerland and Brazil, as well as 7 Japanese speakers and some moderators.

Basically, the babies with congenital deformities which were induced by thalidomide (Contergan) were born in the late 1950's and early 1960's in developed countries. Consequently, many of them survived the physical, medical, social or mental handicaps and hardship, and are now living in their 50's and 60's. The thalidomide disaster was one of the unprecedented human tragedies in medical history. Human society itself is to blame, as it is responsible for the thalidomide victims. Therefore, society should take care of them and treat them as long as they live, even as they would become older and older.

In years past, the anatomical malformations and problems in thalidomiders, particularly in the extremities, and hearing impairment, as well as facial problems, were thoroughly examined and treated. Most patients with TE have become accustomed to handling such physical hardship because they were born with these problems. However, now they face other problems such as persistent pain and more severely impaired ADL, in part due to age and in part due to overuse syndrome progression as well as lifestyle-related diseases which might not have been noticed in their youth. Therefore, researchers, clinicians and healthcare workers of TE are now discovering these problems and difficulties, which thalidomiders are suffering. I believe such an opportunity to hold an international symposium is one of the best chances to clarify, classify, and share those problems and themes. I hope that the experts of TE worldwide will make use of this good opportunity.

Recently, diagnostic aid or criteria are being determined in some countries. In the 1950's and 1960's, TE was diagnosed by some classic methods with physical findings, simple X-ray examinations for systemic bones, hearing tests and evidence of their mothers' taking thalidomide during pregnancy. However, a wealth of knowledge on TE has been accumulated, and image inspection methods have markedly progressed including MRI and CT as well as ultrasonography. Therefore, it might be necessary to newly determine a modern means of diagnosing TE using more sophisticated medical tools. Moreover, we must facilitate the next-generation of physicians to easily diagnose and understand TE, in part because we still find many new claimers for TE in various countries.

Most of the TE experts in clinical fields would mainly consider the clinical, physical, mental health and social problems. In realty, however, we should also think about the pharmacological mechanism which induces TE in embryos. There have been classic theories on the possible reason or mechanism for the congenital abnormalities of TE. Unfortunately, however, more specific or molecular mechanisms remain to be determined. Without the precise elucidation of this mechanism, we cannot truly be freed from this serious human tragedy, TE. Therefore, in this second symposium, we also included the opportunity to discuss the basic mechanism of thalidomide teratogenicity.

Now people throughout the world are facing another human disaster, COVID-19, which started in China from December 2019. I guess there may have been some countries that regarded COVID-19 as something unrelated to them at the beginning. Horribly, however, only a few COVID-19 infected people from abroad easily brought it back to their own countries and it promptly spread to many other countrymen resulting in a serious pandemic with an explosive surge of critically ill cases and deaths. This tragic fact reminds us that our world has become very small and we are living in a truly global society where people from different countries unavoidably connect with other people even though countries did close their border after the initial spread of COVID-19. Unfortunately, the openness, free travel and communication in the world has become a great disadvantage in the case of COVID-19, but it can serve as a good advantage in science and medicine. I think it is very meaningful to directly share the present problems of TE by many experts from different countries and to discuss them together.

We could publish this Proceedings of the 2nd International Symposium on Thalidomide Embryopathy in Tokyo as a culmination of many efforts. I hope this record of the 2nd Symposium will be read and shared by many clinicians and researchers working on TE. I believe the Proceedings will certainly contribute to the development of clinical practice and research on TE, as well as enhancing the social welfare for the thalidomiders; further, it should help to positively stimulate many researchers and clinicians as well as healthcare workers for thalidomiders.

Finally, it is noteworthy that this symposium was supported and funded by the Ministry of Health, Labour and Welfare (MHLW), Japan. I greatly thank Secretary Ms. Chikako Toyota for her assistance and Ms. Chiharu Matsuoka for contributing to the editing of the Proceedings. It was originally planned and managed by "The research group on grasping the health and living situation as well as creating the support infrastructure for thalidomide-impaired people in Japan" which was organized by MHLW. In this Proceedings, you might notice awkward English and grammatical errors. There might be some inappropriately edited parts which are slightly different from what speakers really wanted to say. Therefore, I would like to ask you to overlook such small mistakes and to stress that the most important thing is not to find trivial mistakes but rather to understand the valuable contents each author would like to convey.

Note: This Guide was created under the FY2019 Research on Regulatory Science of Pharmaceuticals and Medical Devices of the Health Labour Sciences Research Grants (under the title of "The research group on grasping the health and living situation as well as creating the support infrastructure for thalidomide-impaired people in Japan") from MHLW, Japan.

Program & Contents

Date: July 14, 2019

Date: July 15, 2019

Welcome & Opening Remarks

Staff: Ladies and gentlemen, thank you very much for waiting. Now, I would like to start the 2nd International Symposium on Thalidomide Embryopathy. We would like to ask Dr. Hinoshita to give the opening remarks.

Fumihiko Hinoshita

Good afternoon. First, I would like to thank everyone very much, especially the speakers from overseas, for coming all the way to Japan during this rainy weather. I also heard it took 2 whole days to arrive from Brazil. I believe that you, Prof. Faccini, are busy and very tired, but fortunately, all of the guest speakers here today look good to me, so I am very glad that you arrived here in Tokyo without too many serious problems.

Moving on, this is the 2nd International Symposium on Thalidomide Embryopathy. Four years have passed since we held the 1st International Symposium in 2015. During these 4 years, I believe that the researchers and specialists in Japan and overseas have conducted a number of new studies. Therefore, more up-to-date information is currently available. We would like to have this information to be shared among everyone so that we can make use of it for the treatment of and further research on thalidomide embryopathy.

We have a lovely audience in this room and wonderful speakers from Brazil, Sweden, Germany, the UK, Switzerland, and Japan. As this is such a great opportunity, we would like to encourage you to have very active discussions and a valuable exchange of opinions.

Now, I would like to begin with opening remarks from our distinguished guests. The first speaker is Mr. Takeshi Annaka, the Director of the Office of Drug-induced Damages of Ministry of Health, Labour and Welfare of Japan.

Takeshi Annaka

Good afternoon everyone. My name is Takeshi Annaka from the Office of Drug-induced Damages of Ministry of Health, Labour and Welfare. Welcome to the 2nd International Symposium on Thalidomide Embryopathy, and thank you very much for coming, especially the speakers from overseas.

I would also like to express my appreciation for the day-to-day efforts made by Dr. Hinoshita of National Center for Global Health and Medicine (NCGM) and all the members of the Thalidomide Embryopathy Study Group.

Thalidomide was approved in Japan in 1957. After that, a teratogenic problem became apparent. From mid-1962, the recall of thalidomide products began, and many thalidomide embryopathy victims were born. In 1963 and after, lawsuits started being filed, and ultimately, 309 victims were officially certified.

The government of Japan paid compensation that provided pension and additional support for these victims, as well as funding for research.

It has been 50 years since the onset of thalidomide embryopathy (TE). Many victims started to experience body pain because of postural problems, subsequently suffering additionally from lifestyle-related diseases with aging.

Dr. Hinoshita and other specialists in the study group have tried to understand the current situation in Japanese thalidomiders by providing medical checkups and conducting questionnaire surveys. As the number of physicians who know TE well is decreasing, the study group provided a guide for the management of TE. We can now share their research on TE with many experts overseas.

Recently, we have also started to see claims from potential new victims of TE. However, for the past 30 years, we have not certified any new victims of TE, so currently, we need to think about how we can deal with newly emerging patients — so-called new claimers. Therefore, we believe that much more experience has been accumulated overseas, and we would like to hear some presentations and comments in regard to this from overseas speakers.

After these opening remarks, we look forward to listening to presentations from prominent specialists and having very active discussions, so that research on TE will progress and be further developed, not only in Japan, but also overseas. With this, I would like to close my opening remarks. Thank you very much.

Fumihiko Hinoshita (Moderator): Mr. Annaka, thank you very much. Next, Dr. Tsugumichi Sato, the Director of the Ishizue Foundation, the Public Interest Incorporated Foundation of Thalidomide Victims in Japan, will give his opening remarks.

Tsugumichi Sato

My name is Tsugumichi Sato from the Ishizue Foundation, the Public Interest Incorporated Foundation of Thalidomide Victims. Thank you very much for your invitation. The Ishizue Foundation is an incorporated foundation under the terms of the settlement of the thalidomide lawsuit for compensation that provides support to thalidomide victims. This organization was established as a welfare center.

When this organization was established, it was operated by the parents of the thalidomiders; however, for about the past 20 years, the organization has been operating in accordance with the initiatives of the victims. Therefore, the victims are now the operators.

I also gave opening remarks in the first symposium, and at that time, I mentioned that historically, holding this symposium for thalidomide embryopathy in Japan is quite epoch-making. And it's been 4 years since then.

I believe that this is another historical epoch-making symposium, and that's great news for me. For many years in various countries around the world, specialists have gotten involved in medical care for the victims of thalidomide embryopathy, and I am really looking forward to listening to their lectures.

Today, not only I but also the thalidomiders currently operating the Ishizue Foundation, have joined this symposium. Nine board members are in attendance, in addition to social workers who provide consultations. We, the thalidomiders, are currently facing various problems, and 'health', one of the themes of the symposium, is quite an important issue for us.

In Japan, many TE victims have died each year, especially the last couple of years. Last year, three victims passed away, so we really have deep concerns about our health. Fortunately, centered around Dr. Hinoshita, we have a MHLW-initiated research group, and this group is very active in terms of research and investigations. We would like to show our appreciation for their efforts. I believe that the efforts of the group will be of great help in maintaining our health.

I am currently 56 years old. Most European victims are probably 1 or 2 years older than me. Anyhow, we are rapidly approaching 60 years of age. Therefore, we have started thinking about our remaining life, and especially if we can receive appropriate care as we age in the future.

Japan provides long-term health care insurance and ensures public support to all residents. However, in our case, we have complications associated with aging and thalidomide-related symptoms, so I wonder if we can receive comprehensive support.

For this as well, we really count on measures guided by research by specialists that can identify the best type of support for older thalidomiders. As Mr. Annaka mentioned, we have recently started to see new claimers for potential TE.

Dr. Kayamori is going to introduce us two new claimer cases, followed by another. This person has a hearing problem. For a long while after the thalidomide disaster, the victims were not registered as thalidomiders, probably because of certain reasons of the parents. But now that they have reached a certain age and began having problems, they have started to make new claims. Therefore, we have to recognize them as new thalidomiders and think about how we can deal with them.

At the same time, there is probably a grey zone or borderline patients, so how we can deal with them is currently under consideration by authorities and specialists. Also regarding this point, appropriate recognition as thalidomiders should be given as early as possible if legitimate.

Again, I am thankful for this very valuable opportunity to listen to presentations by specialists and very much looking forward to it. Thank you very much.

Endocrine and Metabolic Disorders

Tetsuya Tagami

The Medical Checkup Center, National Hospital Organization Kyoto Medical Center, Kyoto, Japan

Fumihiko Hinoshita (Moderator)

Good afternoon. Now let me introduce the first presenter or speaker of this symposium. I introduce Dr. Tagami, the Director of the Medical Checkup Center at National Hospital Organization (NHO) Kyoto Medical Center. He will be giving a presentation on endocrine and metabolic disorders in thalidomiders. Dr. Tagami, please.

Thank you very much, Dr. Hinoshita, for your very kind introduction. Good afternoon to everyone. I am Tetsuya Tagami of NHO Kyoto Medical Center. We've been investigating thalidomiders with a focus on endocrine and metabolic disorders. (Fig. 1)

I will talk about endocrine and metabolic disorders in patients with thalidomide embryopathy (TE) from our hospital in Kyoto. We have examined 46 TE patients, including 15 men and 31 women, at NHO Kyoto Medical Center. Among these 46 patients, 11 (4 men and 7 women) were examined twice at our center in 9 years over a cumulative total of 57 visits (19 for men and 38 for women). Their mean age was 53 years. (Fig. 2)

First of all, some patients are already under treatment with lifestyle-related diseases. Six patients (2 men and 4 women) with hypertension, 3 with diabetes mellitus, 8 with dyslipidemia, 2 women with osteoporosis, and 2 men with gout were under treatment already. Three of these patients who were examined twice were started on medication for a lifestyle-related disease by the second visit. Two patients were treated during this period. There is a possibility the results of the first examination initiated medication. Three patients (1 man and 2 women) were under treatment with more than two different diseases simultaneously from among hypertension, diabetes, and dyslipidemia. Accumulating risk factors, which lead to atherosclerosis, should be addressed through diet and exercise therapy.(Fig. 3)

The second topic is overweight. Ten patients had obesity; 9 of whom were women. The BMI of 1 woman was 34. Another woman had a decreased body weight from 60 kg at the first visit to 53 kg at the second, with a BMI decreasing from 26 to 23. Patients with TE are prone to becoming overweight

Fig. 1

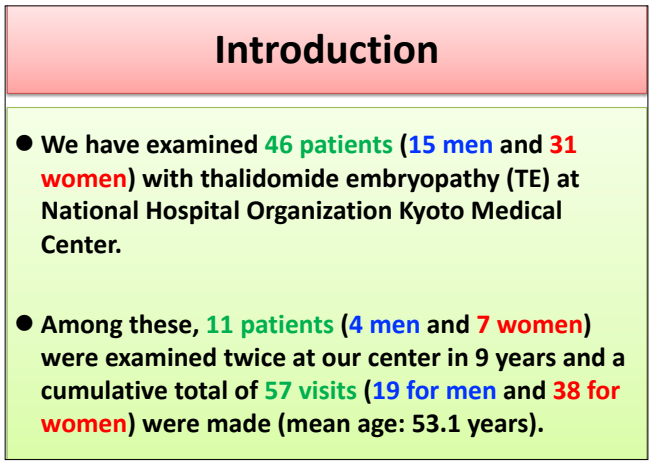


Fig. 2

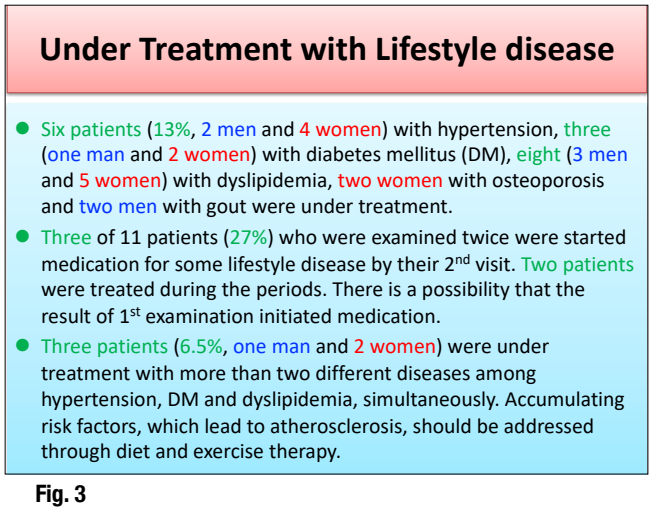


Fig. 3

because of not only developmental limb disorders, but also of finding going outside to be a hassle. As these patients age, they are at increased risk of reduced muscle mass in their healthy limbs, which is called sarcopenia, as well as weight gain, because this reduction lowers their basal metabolism, leading to sarcopenic obesity. Ways must be found to maintain muscle mass in these patients. (Fig. 4)

Hepatic steatosis. Regarding liver function, seven patients had high ALT levels. The ALT of one man improved at his second visit. The ALT of one woman was as high as 53 IU. High ALT levels were not only liver-related. Ultrasonography revealed a finding of hepatic steatosis. High hepato-renal echo contrast was seen in 21 patients (46%). At-risk patients would benefit from a better diet. (Fig. 5)

Dyslipidemia. More than half of the patients had hyper-LDL cholesterolemia. LDL cholesterolemia had improved in two women at their second visit. Blood LDL cholesterol levels were more than 150 in some patients, more than 170 in two women, and over 200 in two women. One man had hypo-HDL cholesterolemia. Thirty patients had hypertriglyceridemia. Blood triglyceride levels were more than 200 in some patients and more than 300 in one man and two women. Persisting lipid disorders exacerbate atherosclerosis. At-risk patients would benefit from proper eating habits and appropriate pharmacotherapy. (Fig. 6)

Abnormal glucose metabolism. A high level of HBA1c was observed in five patients (2 men and 3 women). The HBA1c level was 7.0 to 8.0 in one person and 6 to 7 in four. Because the HBA1c level increased in almost all of the patients who were examined twice, we have to follow up their health carefully. (Fig. 7)

Hyperuricemia. Ten patients had hyperuricemia, and one male had a blood uric acid level on the order of 8 mg/dL. Hyperuricemia not only causes gout flare-ups, but also is considered a risk factor for atherosclerosis. Pharmacotherapy would be recommended in such a patient if urinary calculus, renal disorders, hypertension, ischemic heart disease, diabetes mellitus, metabolic syndrome or other such comorbidities were present.(Fig. 8)

Chronic kidney disease (CKD) was seen in three patients. A female patient with an eGFR of 17 showed findings of polycystic kidney in an ultrasound examination. Solitary kidney and other deformations are reported in patients with TE. Caution in the form of regular examinations is needed,

Overweight

- Ten patients (22%, one man [6.7%] and 9 women [29%]) had obesity (i.e., body mass index [BMI] > 25 kg/m^2). The BMI of one woman was 34.4 kg/m^2. Another woman decreased her body weight from 60kg at 1st visit to 53kg at 2nd visit (from 26 to 23 in BMI).
- Patients with TE are prone to becoming overweight not only because of developmental limb disorders, but also because many find going outside a hassle.
- As these patients age, they will be at increased risk of reduced muscle mass in their healthy limbs (sarcopenia) and weight gain as this reduction lowers their basal metabolism (sarcopenic obesity). Ways must be found to maintain muscle mass in these patients.

Fig. 4

Hepatic Steatosis

- Seven patients (15%, three men [20%] and four women [13%]) had high alanine aminotransferase (ALT) levels（>30 IU/L）. The ALT of one man improved at his 2nd visit. The ALT of one woman was as high as 53 IU/L.
- High ALT levels were not the only liver-related concern. Ultrasonography revealed findings of hepatic steatosis (high hepato-renal echo contrast) in 21 patients (46%, nine men [60%] and twelve women [39%]).
- At-risk patients would benefit from a better diet.

Fig. 5

Dyslipidemia

- More than a half of the patients (27 of 46 [59%], 8 men [53%] and 19 women [61%]) had hyper-low density lipoprotein (LDL) cholesterolemia (>120 mg/dL). LDL cholesterolemia had improved in two women at their 2nd visit. Blood LDL cholesterol levels were 150–159 mg/dL in three men and two women, 170–179 mg/dL in two women, and over 200 mg/dL in two women.
- One man (6.7%) had hypo-high density lipoprotein (HDL) cholesterolemia (<40mg/dL).
- 13 patients (28%, six men [40%] and seven women [23%]) had hypertriglyceridemia (>150 mg/dL). Blood triglyceride levels were 200–299 mg/dL in two man and three women, and 300–399 mg/dL in one man and two women.
- Persisting lipid disorders exacerbate arteriosclerosis. At-risk patients would benefit from proper eating habits and appropriate pharmacotherapy.

Fig. 6

Abnormal Glucose Metabolism

- The high level of hemoglobin A1c (HbA1c; National Glycohemoglobin Standardization Program) level (>6.2%) was observed in five patients (11%, two men [13%] and three women [10%]).
- The level of HbA1c was 7.0-7.9% in one person (under treatment with diabetes mellitus [DM]) and 6.0-6.9% in four persons (one was under treatment with DM and another was within normal range at 1st visit).
- Because the HbA1c level increased in almost all the people who were examined twice, we have to follow up carefully with their health.

Fig. 7

even where no clear evidence of deformation is present, because such patients may experience age-related diseases associated with renal function more quickly than healthy people. (Fig. 9)

Osteoporosis. Bone mineral density analysis revealed lumbar spine density of less than 70% of the young adult mean in three patients and 70% to 80% in nine patients. Femoral neck density was less than 70 in eight patients and 70 to 80 in 16 patients. Consequently, 10 patients (2 men and 8 women) had confirmed osteoporosis, and 18 had confirmed osteopenia. Endogenous risk factors for osteoporosis include: 1) being a post-menopausal women at least 55 years of age; 2) being underweight; 3) being on corticosteroids; 4) having diabetes mellitus or thyroid disease; and 5) having a family member with osteoporosis. Lifestyle-related factors include: 6) being a smoker; 7) being a heavy drinker; and 8) not exercising or not getting sunlight, which is a particular concern in patients with TE. (Fig. 10)

Finally, endocrine and metabolic abnormalities. Among the 29 patients who underwent measurement, abnormal blood thyroid-stimulating hormone levels were observed in three (slightly high in 2 patients and slightly low in 1). Although we did not perform any diagnostic tests focusing on endocrine function, the adverse reaction to thalidomide listed below suggests that embryonic exposure could possibly affect the development of endocrine tissues. These are secondary effects of thalidomide and the thalidomide derivative, lenalidomide, on endocrine and metabolic function. First, increased insulin resistance; second hypothyroidism; third, thyrotoxicosis; fourth, hypoadrenalism; and fifth hypogonadism.(Fig. 11)

Now, I will summarize the key points. Obesity, which includes sarcopenic obesity, may be the result of limited physical activity. Hepatic dysfunction is often caused by hepatic steatosis. Patients often have dyslipidemia. Some patients have impaired glucose tolerance or chronic kidney disease. Osteoporosis may affect men as well as women. Thalidomide and its derivatives cause thyroid dysfunction and endocrine and metabolic abnormalities. (Fig. 12)

Thank you for your attention.

Hyperuricemia

- Ten patients (22%, seven men [47%] and three women [10%]) had hyperuricemia (>7.0 mg/dL). One male patient had a blood uric acid level on the order of 8 mg/dL.
- Hyperuricemia not only causes gout flare-ups but is now also considered a risk factor for arteriosclerosis. Pharmacotherapy would be recommendable in such a patient if urinary calculus, renal disorders, hypertension, ischemic heart disease, diabetes mellitus, metabolic syndrome, or another such comorbidity were present.

Fig. 8

Chronic Kidney Disease (CKD)

- CKD (estimated glomerular filtration rate [eGFR] <60 mL/min/1.73 m^2) was seen in three patients (6.5%, one man [6.7%, eGFR = 55] and two women [6.5%, eGFR = 17, 59]). A female patient with an eGFR of 17 mL/min/1.73 m^2 showed findings of polycystic kidneys in an ultrasound examination.
- Solitary kidney and other deformations are reported in patients with TE. Caution in the form of regular examinations is needed, even when no clear evidence of deformation is present, because these patients may experience age-related decreases in renal function more quickly than healthy people.

Fig. 9

Osteoporosis

- BMD analysis revealed a lumbar spine density of less than 70% of the young adult mean (YAM) in three patients (one man and two women) and 70% to 80% of YAM in nine patients (three men and six women).
  Femoral neck density was less than 70% of YAM in eight patients (one man and seven women) and 70% to 80% of YAM in 16 patients (five men and eleven women).
- Ten patients (22%, two men [13%] and eight women [26%]) had confirmed osteoporosis, and 18 patients (39%, four men (27%) and 14 women (45%) had confirmed osteopenia.
- Endogenous risk factors for osteoporosis include (1) being a postmenopausal woman at least 55 years of age, (2) being underweight, (3) being on a corticosteroid, (4) having diabetes mellitus or a thyroid disease, and (5) having a family member with osteoporosis, and lifestyle factors include (6) being a smoker, (7) being a heavy drinker, and (8) not exercising or getting sunlight. Risk factor #8 is a particular concern in patients with TE.

Fig. 10

Endocrine and Metabolic Abnormalities

- Among the 29 patients who underwent measurements, blood thyroid stimulating hormone levels were observed in three patients (10%); slightly high in two patients (6.9%, one man [12.5%] and one woman [4.8%]) and slightly low in another woman (3.4%, 4.8%).
- Although we did not perform any diagnostic tests focusing on endocrine function, the adverse reactions to thalidomide listed below suggest that embryonic exposure could possibly affect the development of endocrine tissues.
- Secondary effects of thalidomide and the thalidomide derivative lenalidomide on endocrine and metabolic function:
  (1) Increased insulin resistance
  (2) Hypothyroidism: Incidence of 0.9% (per package insert),
  (4) Thyrotoxicosis (thyroiditis)
  (5) Hypoadrenalism
  (6) Hypogonadism

Fig. 11

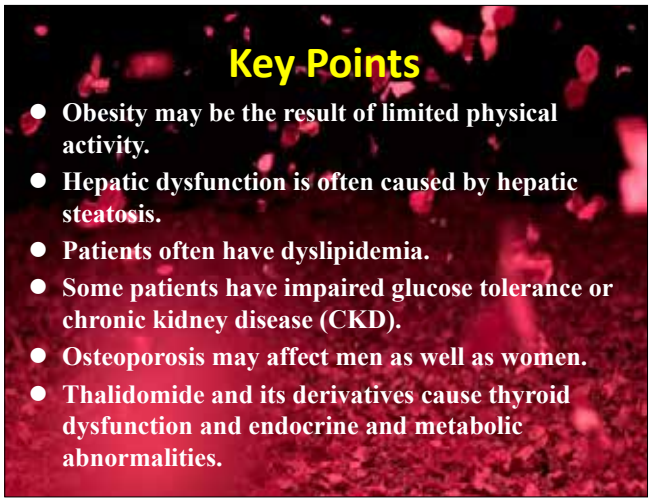


Fig. 12

Q&A

Fumihiko Hinoshita: Thank you very much, Dr. Tagami. Do you have any questions from the floor? Hi, please.

Jan Schulte-Hillen: I would like to know the pathologies you found in the endocrinologic functions of the thalidomiders, are they augmented with respect to the normal Japanese population? For example, as I remember, you found elevated HBA1c in 11% of the patients from Germany. I know that in this age group, the percentage of people who have elevated HBA1c is already something between 5% and 20%. Those numbers seemed very high and I would like to know how the data of thalidomiders compares with that of the normal Japanese non-thalidomide population. Thank you very much.

Tetsuya Tagami: Thank you for your question. We have not directly compared thalidomiders with the normal population in terms of prevalence. But there is, I think, the possibility that thalidomiders engage in less exercise, maybe, which causes obesity, so the prevalence may be higher than that in the normal population, but I don't have any direct comparison data now.

Fumihiko Hinoshita: Next, please.

Christina Ding-Greiner: We have a similar situation in Germany, too. We have a lot of thalidomiders with these kinds of diseases, which are bad for atherosclerosis. I have the impression that they are thinking mainly of thalidomide damage, and that they don't think they may have something as trivial as a high glucose or higher cholesterol and so on. I have the impression that they are not very well informed of what they can actually do for their own health.

If I speak to them and I tell them about prevention, they are astonished and they say, "Well, then, I will proceed like that. I will do that."

So, I think it's very important to think of that and inform people that they have an opportunity to do something against these additional lifestyle-related illnesses as they are growing older. The problem is, they don't think of it. Thank you.

Tetsuya Tagami: Thank you very much. I think our job is to find such diseases, lifestyle-related diseases, and then, we can start a statin or some glucose-lowering medicine. So, that is, I think, very important. Thank you.

Fumihiko Hinoshita: Okay, I can give some additional comments for you. You know, in Japan, there is such a good system to carry out general medical checkups. His hospital also has such a system, you know, the general medical checkup. So we, the Japanese research group, have carried out medical checkups at three medical hospitals or centers on 24 thalidomiders per year.

Then, those patients receiving medical checkups are lucky in the respect that abnormalities such as high glucose levels, dyslipidemia, obesity, and fatty liver will be found; thus, they will be informed early about such abnormalities, which promotes prompt measures or treatment. So, maybe they are lucky. Do you understand, Dr. Greiner?

So, those thalidomiders with lifestyle-related diseases would be treated early because they were examined in general medical checkups and basically, any abnormalities would soon be known by recipients with TE. But it is also practiced in the general population, too. That is, the Japanese medical checkup system.

Christina Ding-Greiner: We do have free checkups in Germany, but for thalidomiders, it's difficult because it's often hard to take blood samples and measure blood pressure. They are not bound to go for a checkup, they are free not to go. Maybe they are not thinking of the hazards. They think more of the difficulty in taking blood and so on, and they say, "Well, I don't want any checkup". That's a great issue, too.

Fumihiko Hinoshita: Oh, I understand. You mean there are some differences in the severity of TE between Germany and Japan. You know, we have only a few thalidomiders with both serious upper and lower limb problems, only two or three.

Basically, they might have short arms and deformities so that we can't take blood from some vessels on the arms in a limited number of cases with TE. So, it is very rare not to

take any blood samples or measure blood pressure. But in your country, you know, there are some thalidomiders with no or very short limbs. Dr. Morrison, do you have any comment?

Dee Morrison: Yes. Two questions. I may need both of you to answer. We have seen some with TE with sleep apnea in the UK, and we know this contributes to cardiovascular disease. Increased risks are obesity, etc., but also jaw problems and abnormalities of the nasal passages. I wonder if you have looked at sleep apnea—we haven't actually done any formal research yet—and whether you have any knowledge of this?

My second question is on CKD. You mentioned that even though they had normal renal function, they might be more at risk as they age. Is there any evidence for this or is it a supposition?

Tetsuya Tagami: I will answer the second question first. I think the obvious abnormality is not present, maybe, but some microscopic abnormalities may be present, but I have no evidence, sorry. Regarding the first question on CVD, I haven't experienced it before. Do you have any experience with this, Dr. Hinoshita?

Fumihiko Hinoshita: Okay, I might roughly understand almost all of the data—clinical data taken at those medical checkups. But so far, I have not found any marked association of high or significant risks for cardiovascular diseases in thalidomiders in Japan. Namely, no marked association so far for cardiovascular diseases. In general, in Japan, there are fewer people who would suffer from coronary problems compared with Western countries.

Next, I should partly answer your question about sleep apnea syndrome. You might have mentioned sleep apnea syndrome, SAS, in short, too. Sorry, I know that in your country you are trying to disclose problems associated with SAS in thalidomiders, right? But in Japan we have not done it.

As for as jaw problems, at least at my National Center for Global Health and Medicine, we have been checking abnormalities of the jaw in subjects who were receiving general medical checkups. I'm sorry to say, however, that today, the chief of the dental and oral surgery department at our center could not attend, but he said Japanese thalidomiders do not significantly have any serious unexpected jaw problems. That's all.

Tetsuya Tagami: As Mr. Sato mentioned before, I heard that some patients have already died. Then, do you know the cause of this?

Fumihiko Hinoshita: Maybe, someone is now raising his hand.

Tsugumichi Sato: Well, we don't know all the causes of death for everybody who has passed away, but many of them experienced sudden death. So, sudden death is a mainstay these days. To respond to the question of Dr. Schulte-Hillen, in my memory, Japanese thalidomiders have diabetes, hyperlipidemia, and hypertension at nearly twice the rate of the general population for similar age groups.

And these are the data from a national survey for Japanese thalidomiders.

Fumihiko Hinoshita: You are talking about the second national survey last year?

Tsugumichi Sato: Yes, yes.

Fumihiko Hinoshita: But, as for hypertension, almost the same frequency.

Tsugumichi Sato: Sorry, I mean diabetes and hyperlipidemia.

Fumihiko Hinoshita: I should correct his comment because I myself performed it. Then according to the recent national survey about the present situation and current diseases in thalidomiders in Japan, I don't know why, but the frequency of hypertension in the thalidomiders is almost the same as that in the age-matched general population.

Fumihiko Hinoshita: Are there any other comments or questions? OK. Dr. Schulte-Hillen.

Jan Schulte-Hillen: Yes, I would like to answer whoever asked the question regarding if the cause of death was known. I would like to say that 2 years ago in Germany, 32 thalidomiders died, and there are no scientific data for the cause of death. It is absolutely not known. But, if you ask peer groups, if you ask friends, they say that they passed away without any warning, so we are talking about something like sudden death, like stroke or myocardial infarction, I think.

Fumihiko Hinoshita: Some stroke or cardiovascular events have been reported in your country. But in Japan, maybe no marked causes have been found in most cases with TE, as Mr. Sato said. Okay, anyway, our time is up, so now, let's move on to the next presentation. Thank you very much, Dr. Tagami.

Medical Check-up of Otorhinolaryngology (ORL) for the Patients of Thalidomide Embryopathy (TE)

Nirou Tayama

Department of Otorhinolaryngology, National Center for Global Health and Medicine, Tokyo, Japan

Tetsuya Tagami (Moderator)

The next speaker is Dr. Nirou Tayama, from National Center for Global Health and Medicine, Tokyo, Japan. The title of the talk is "Medical Checkups Regarding Otorhinolaryngology (ORL) for Patients with Thalidomide Embryopathy (TE)". Now, Dr. Tayama, please.

Thank you very much. I would like to talk about ENT medical checkups for ORL (otorhinolaryngology), what kind of results are gained, and what we should do. So, ENT and hearing disorders, as well as malformations, have been studied. CT images are also used to study the situation and with that, we came up with problems likely faced by thalidomiders in the future and what kind of countermeasures or treatments we should provide. This is something we are thinking about.(Fig. 1, 2)

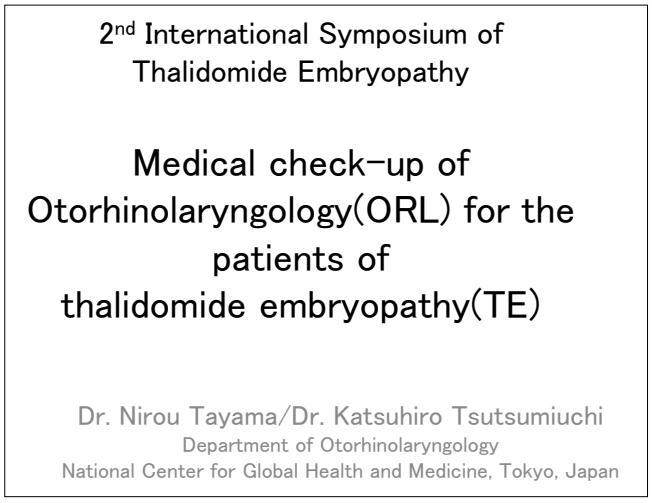


Fig. 1

Fig. 2

In ENT, when it comes to malformations, Dr. Tanaka of Teikyo University has presented a list and a report. As his study progressed, he observed the temporal bone malformation, the outer, inner, and also middle ear malformation and abnormalities within them that make hearing difficult, and he came to find the impact of the site malformation. So, if there is an inner ear problem, nerve deafness would occur, and if there is an outer ear problem, then conductive deafness would occur. And if both, in that case, combined deafness would develop.(Fig. 3)

So, in the nose and oral cavity, abnormalities or malformations have been pointed out. But we haven't really recognized these clearly as symptoms according to our study. So, for about 3 years, the total number is 28 (19 males, 9 females). (Fig. 4)

According to a report by Dr. Tanaka, the number is limited; however, we conducted CT scans on all the patients for comparisons, that's the great approach. So, malformations of

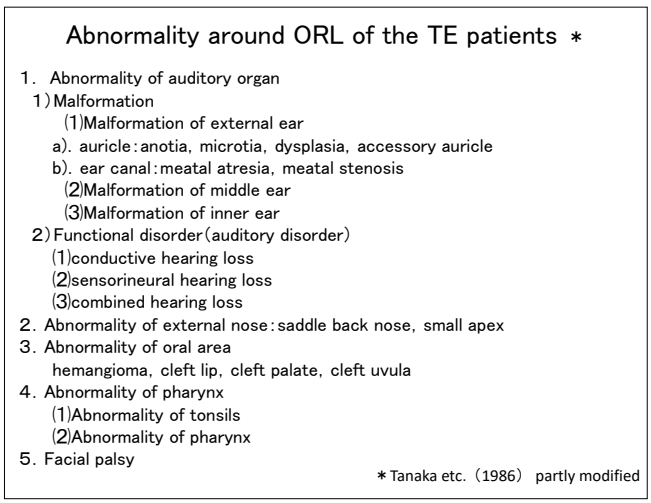


Fig. 3

the inner, outer, or middle ear are quite conspicuous as ORL problems, hearing loss, equilibrium disturbance, facial palsy, and others.(Fig. 5)

Now, the problem is that hearing loss is one problem, but other ear malformations, especially outer ear malformations, lead to other problems, like being unable to wear masks or glasses. Also, if the external ear canal has a malformation, it's very difficult to wear a hearing aid.

These problems increase with age, I believe. So currently, these thalidomiders, their age is right around 60 years, and with aging, they are going to have more and more hearing problems. There might be more such patients exceeding 65 years of age. In that case, how hearing aids can be appropriately used and worn will be a problem that we may encounter more frequently.

So, in the future, we have to of course think about countermeasures for that. This is quite a busy slide, but this is a list that we came up with. Hearing problems, CT findings, and limb disabilities, and how they are distributed, were also studied in a total of 28 cases.(Fig. 6, 7)

Medical Check-up of ORL

Duration : 14, Nov, 2015 – 15, Jan, 2019

Numbers : 28 (M 19, F 9)

Age : 52y.o. – 57y.o.

Evaluation items :

- Malformations in ORL
- Hearing disorder

Fig. 4

Problems in ORL

- Caused by abnormality in ORL organs
  - Hearing loss :
    - Malformations of external/middle/inner ear
  - Equilibrium disturbance :
    - Malformations of inner ear
  - Facial palsy :
    - Malformations of inner ear
  - Unable to wear mask/glasses :
    - Malformations of external ear
  - Unable to wear common HA :
    - Malformations of external ear
- Caused by other abnormalities (mainly disorder of upper limbs)
  - Unable to blow nose
  - Unable to clean ear canal

Fig. 5

In 1986, Dr. Tanaka had already studied many cases with TE. And in the study the hearing test was the main focus. The malformation of the inner, middle, and also outer ear hasn't been really studied by CT. (Fig. 8)

According to the 28 cases we studied, malformations of the inner, external, and middle ear are just like this. And

Full List of our Cases

No.	sex	age	External ear Mal.	middle ear Mal.	Inner ear Mal.	Hearing level	CT	notes	Eye movement	Upper limbs
1	M	52	なし	△	なし	右：15dB、15dB 左：15dB、10dB	両側きめた骨低形成の可能性	軽度の中耳奇形あるが聴力正常	なし	○
2	M	54	なし	なし	なし	右：10dB、25dB 左：15dB、35dB	なし	異常なし	なし	拇指要害
3	M	57	○ 耳介形態異常（術後） 外耳道閉鎖	○	なし	右：90dB、110dB 左：90dB、85dB	外耳道膜様閉鎖 両側つち骨、きぬた骨形成不全	外耳・中耳奇形	なし	なし
4	M	53	なし	なし	なし	右：10dB、20dB 左：10dB、25dB	なし	異常なし	なし	○
5	F	52	なし	なし	なし	右：10dB、10dB 左：10dB、30dB	なし	異常なし	なし	○
6	M	54	なし	なし	なし	右：20dB、55dB 左：20dB、50dB	なし	聴力低下は加齢変化？	なし	○
7	M	52	なし	右真珠腫性中耳炎	○	右：110dB、scale out 左：50dB、scale out	両側外側半規管低形成 右慢性中耳炎	真珠腫性中耳炎 内耳形態異常	なし	○
8	F	57	なし	なし	なし	右：25dB、20dB 左：25dB、35dB	なし	異常なし 軽度聴力低下は加齢変化	なし	○
9	M	52	外耳道狭小？	なし	なし	右：50dB、80dB 左：20dB、45dB	なし		なし	○
10	M	56	なし	なし	なし	右：15dB、10dB 左：15dB、25dB	なし	異常なし	なし	○
11	F	54	なし	なし	なし	右：5dB、5dB 左：10dB、5dB	なし	異常なし	なし	○
12	F	56	なし	なし	なし	右：5dB、10dB 左：5dB、10dB	なし	異常なし	○	○
13	F	54	耳介正常、外耳道狭窄	左真珠腫性中耳炎	○	右：35dB、25dB 左：40dB、20dB	右外側半規管低形成 両側慢性中耳炎 左真珠腫性中耳炎		なし	○
14	F	54	なし	なし	なし	右：10dB、10dB 左：10dB、20dB	なし	異常なし	なし	○
15	M	54	耳介軽度？ 外耳道狭窄＋	なし	○	右：105dB、95dB 左：40dB、40dB	右蝸牛半規管低形成 左外側半規管形成異常 左真菌管無形性		なし	○
16	M	54	なし	なし	なし	右：10dB、10dB 左：10dB、10dB	なし	異常なし	なし	○
17	M	54	○ 耳介奇形（右＞左） 右外耳道狭窄、左閉鎖	○	○	高度難聴	右側頭骨異常 外耳道形態異常 中耳奇形（耳小骨すべて） 内耳形態異常 左側頭骨異常 外耳道無形性 中耳奇形（耳小骨すべて） 内耳形態異常	外耳・中耳・内耳奇形 左下顎頭扁平化	外転障害	なし

Fig. 6

No.	sex	age	External ear Mal.	middle ear Mal.	Inner ear Mal.	Hearing level	CT	notes	Eye movement	Upper limbs
18	M	55	なし	なし	なし	右：10dB、15dB 左：5dB、10dB	正常	異常なし	なし	上肢
19	M	56	右：耳介奇形、外耳道狭窄で耳垢＋ 左：耳介正常、外耳道狭窄、鼓膜異常	○	○	高度難聴	両側内耳低形成 （みぎ蝸牛・半規管低形成、ひだり蝸牛・半規管低形成） 両側中耳奇形 （ツチ骨・キヌタ骨低形成、アブミ骨無形成） 両側外耳道狭窄	外耳、中耳、内耳	外転神経麻痺	重複
20	M	54	右：耳介正常、外耳道狭窄 左：耳介正常、外耳道狭窄で耳垢＋	○	○	高度難聴	両側内耳低形成 （みぎ蝸牛・半規管低形成、ひだり単洞化） 両側中耳奇形 （耳小骨はつとも あり、主にキヌタ骨低形成） 両側外耳道狭窄（軽度）	知的障害	眼球運動障害	聴覚
21	M	55	なし	なし	なし	右：10dB、5dB 左：10dB、10dB	正常	異常なし	なし	上肢
22	F	55	なし	なし	なし	右：10dB、10dB 左：10dB、5dB	正常	異常なし	なし	上肢
23	M	56	右：耳介低形成、外耳道狭窄 左：耳介やや低形成、外耳道狭窄で細く確認できず		高度難聴		両側内耳無形成（内耳道含め） 両側中耳奇形 （ツチ骨・キヌタ骨低形成、アブミ骨無形成） 両側外耳道狭窄	外耳＜中耳＜内耳	眼球運動障害	聴覚
24	M	55	なし	なし	なし	右：15dB、10dB 左：40dB、75(30)dB	外耳・内耳に明らかな奇形は認めない 両側キヌタ骨やや低形成	左鼓膜石灰化	なし	上肢
25	M	58	右：耳介形成術後、外耳道狭窄、耳垢 左：耳介形成術後、外耳道閉鎖	○	○	高度難聴（混合性）	両側内耳奇形なし（ひだりやや低形成？） みぎ中耳奇形なし ひだり耳小骨無形成 みぎ外耳道高度狭窄、ひだり外耳道閉鎖		左顔面神経麻痺	聴覚
26	F	57	右：耳介形低形成、外耳道閉鎖 左：耳介形低形成、中耳術後	○	○	高度難聴	両側内耳奇形 （みぎ＞ひだりで半規管・蝸牛低形成） 両側中耳奇形 （みぎツチ骨・キヌタ骨低形成、アブミ骨無形成） ひだり耳小骨無形成 みぎ外耳道閉鎖、ひだり外耳道閉鎖術後		顔面神経麻痺 外転障害	聴覚
27	F	55	なし（右に耳垢）	なし	△	右：15dB、10dB 左：15dB、10dB	両側外側半規管やや低形成		なし	上肢
28	M	58	なし	なし	なし	右：20dB、20dB 左：20dB、20dB	正常		なし	上肢

Fig. 7

Abnormality of ear

	Our cases	Tanaka(1986)
External ear		
Malformation of auricle	7/28(25%)	43/137(31%)
Malformation of ear canal	10/28(35.7%)	39/137(28%)
Middle ear	8/28(28.6%)	
Inner ear	8/28(28.6%)	
Hearing loss	*12/28(46.9%)	83/137(61%)

(*contains age-related and other diseases)

Fig. 8

when it comes to findings regarding hearing problems, most of the cases have malformations in their ears.

And here, while the number is a bit distant, about 70% of the patients with a malformation had hearing loss.

In some cases, the surgery was already done, the ossicle chain was generated, a hearing aid was worn, or an external ear canal was established. But in such cases, earwax tends to be accumulated, so this has to be well taken care of. (Fig. 9)

So now, this one is the microtia, and also there is atresia for the outer ear canal, and you hardly see anything at all. Then, there are various inner ear abnormalities. The malformation takes place in the case of the inner ear.(Fig. 10, 11)

This is case #3, which involved very severe hearing difficulties. This part of the auditory ossicle is malformed on the right and left, causing a malformation of the inner ear. (Fig. 12, 13)

This is case #7. Towards the right, there is the otitis media and cholesteatoma. We have seen other similar cases.(Fig. 14, 15, 16)

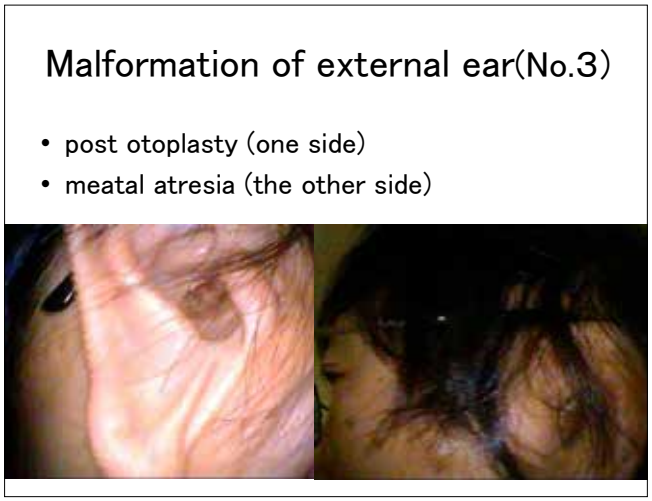


Fig. 9

Fig. 10

Fig. 11

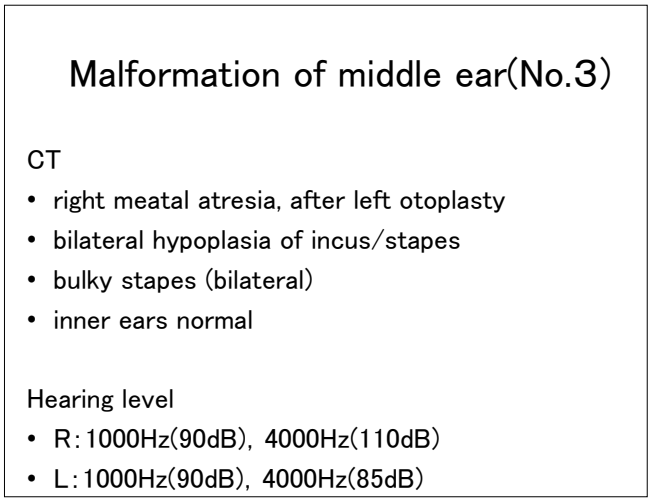


Fig. 12

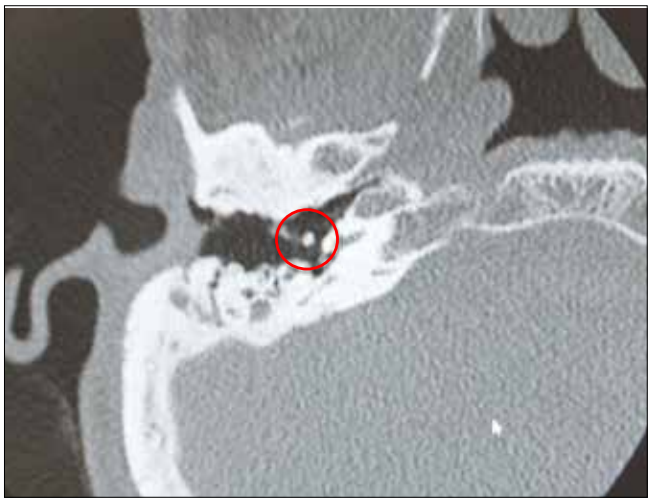


Fig. 13

And in this case, the semicircular canal has a malformation. So, to what extent is this temporal bone malformation and otitis media cholesteatoma correlated? The number of cases is limited, so we don't know the relation between those two. Here is the auditory ossicle and here you can find the lesion.

Case #17. Malformation of inner ear. Here you can see various abnormalities, and the auditory ossicle is also malformed. In this case, a very severe hearing difficulty developed, so hearing capability was almost lost. Then, other known otological disorders. Well, these are limited. Five cases of ocular motility disorder and facial palsy due to malformation of the temporal bone. Nose, larynx, pharynx, no abnormalities. And the malformation of limbs and ORL abnormalities are correlated based on Dr. Tanaka's study. (Fig. 17, 18)

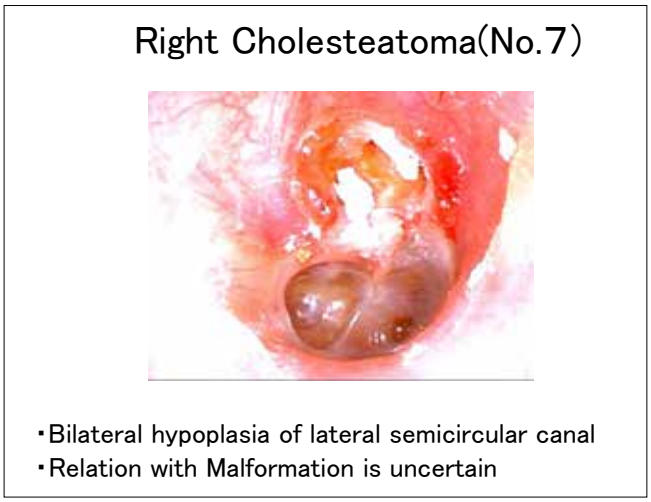


Fig. 14

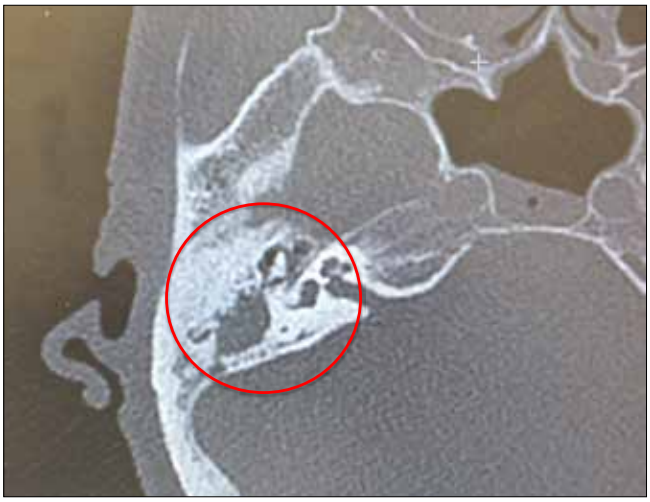


Fig. 15

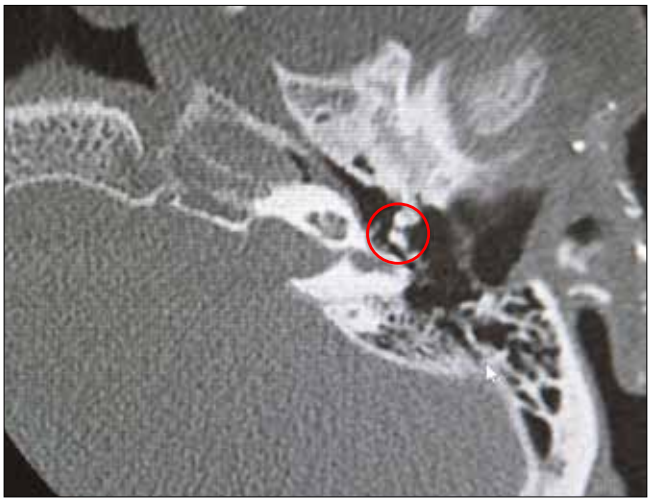


Fig. 16

The malformation of limbs and ORL abnormalities were concomitantly found in seven cases, and 15 cases had malformation of limbs only and no ORL abnormality. Hence, six cases had ORL abnormalities without any limb abnormalities. (Fig. 19, 20)

The hearing and CT results regarding the malformation of the inner ear are not always in concordance, and there are some differences. Even though there is mild hearing impairment, and in some of them, no anatomical abnormalities are clearly shown by CT. Therefore, it cannot be clearly identified what actually causes hearing loss in such cases. (Fig. 21)

Well, so what are the main problems in relation to ORL?

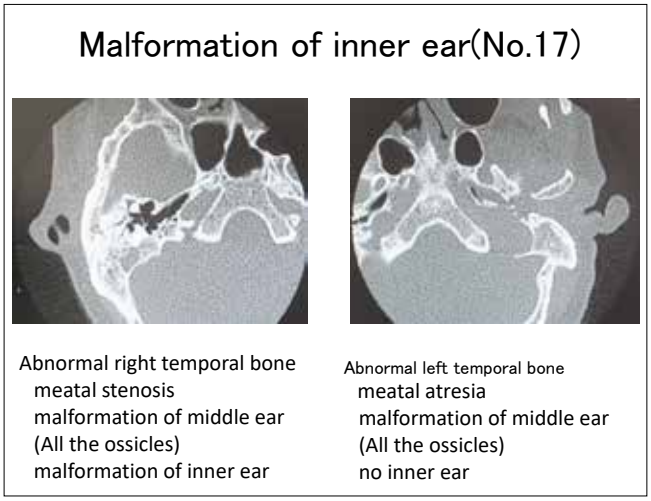


Fig. 17

Relation between malformation of limbs and ORL abnormality

Tanaka etc.(1986)

Malformation of limbs	ORL abnormality		total
	yes	no	
yes	50(7)	46(15)	105(22)
no	32(6)	0(0)	32(6)
	91(13)	46(15)	137(28)

( )shows our cases

Fig. 18

Mostly, some patients need regular ear treatment, like those who have stenosis in the ear—external ear canal stenosis. In such cases, it's very difficult to clean up the ear canal to remove the earwax. Also, some had ear surgery in the past. Then, due to the deformity, the ear canal becomes very complicated in terms of shape. In order to treat such a complicated structure, we need a doctor who is quite used to that kind of treatment, otherwise, it would be very risky. If they have otitis media, this should also be treated.(Fig. 22)

In addition, as for deformities in the external or internal ear, patients have difficulty in self-care of the ear canal because of upper limb deformities. Regarding the future, TE victims will have hearing problems due to aging, so they will need to wear a hearing aid. However, they also have some deformities in the ear, so it will be very difficult for them to wear a hearing aid. And also, hearing aids require adjustment. However, if they have an upper limb deformity, they will have difficulty adjusting their hearing aid. Therefore, even though they are not so old, in 10 or 20 years, the hearing loss due to aging will be a huge problem for TE victims.

This is also the case of patients with upper limb disorders, who have an accumulation of earwax and cannot clean it on their own because of limb disorders. Of course, sometimes there are people who have difficulty cleaning their ears even without a limb disorder. Thalidomiders, however, certainly have limb disorders, so it would be even more difficult for them. (Fig. 23)

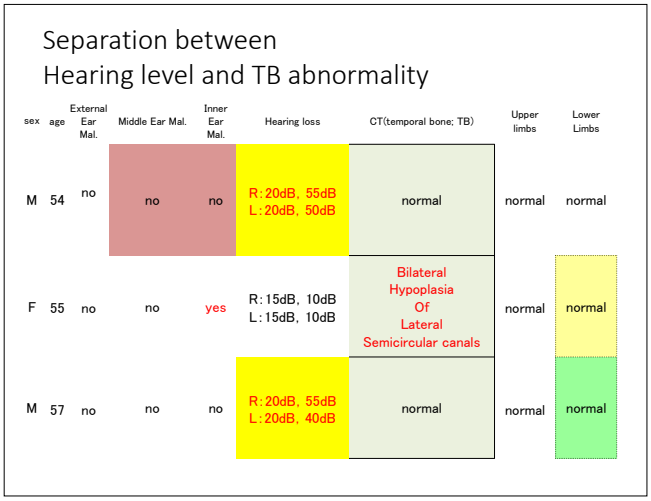


Fig. 21

Non ontological disorders

- Ocular motility disorder : 5 cases
- Abnormality in nose : 0
- Abnormality in larynx/pharynx : 0
- Facial palsy : 2cases

Fig. 19

Malformation of limbs	Hearing disorder		total
	yes	no	
yes	7	15	2
no	5	1	6
total	12	16	28

Malformation of limbs	abnormal temporal bone		total
	yes	no	
yes	6	15	21
no	7	0	7
total	13	15	28

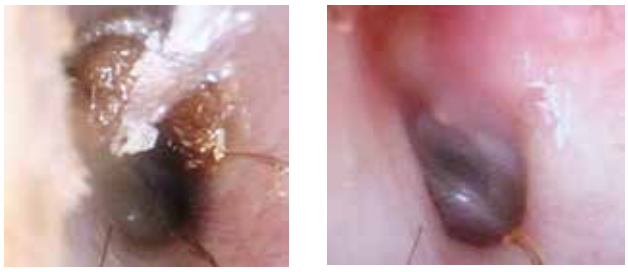
Fig. 20

Problems

- Need regular treatment of ear
  - Meatal stenosis
  - Post ear surgery
  - Otitis media
  - Disorder of upper limbs
- Age-related hearing loss → HA
  - Problems the same as above

Fig. 22

The case of upper limb disorder



Ear wax

Fig. 23

This is a person who had surgery and whose ear canal is quite complicated in terms of shape because of the surgical procedure. Here is the earwax. Actually, it took me more than once to clean it. It's very difficult, even for experienced doctors.(Fig.24) Again, here is an accumulation of earwax. The earwax has become very hard and difficult to remove. In my general impression, we see this in many such thalidomiders. (Fig. 25)

This patient has otitis media. I recommended this person to be treated by a nearby ENT doctor.(Fig. 26)

Again, we find an accumulation of earwax that gets very hard. Removal requires some extra treatment.(Fig. 27)

This is the ear post-surgery. A very wide area of the external ear canal is seen after the otitis media surgery. In this cavity, we found lots of accumulated earwax that took more than 1 day to remove.(Fig. 28)

Moreover, the entry is very small. However, there is a huge cavernous area or cavity. I am quite used to cleaning earwax, but this actually took me more than once; therefore, I requested the patient to go to the nearby ENT doctor for cleaning, but there are not many ENT doctors who treat TE victims on a day-to-day basis. Therefore, we made a special petition to the Oto-Rhino-Laryngological Society of Japan. I was actually a member of the Welfare and Medical Committee of this society. (Fig. 29)

Fig. 24

Fig. 25

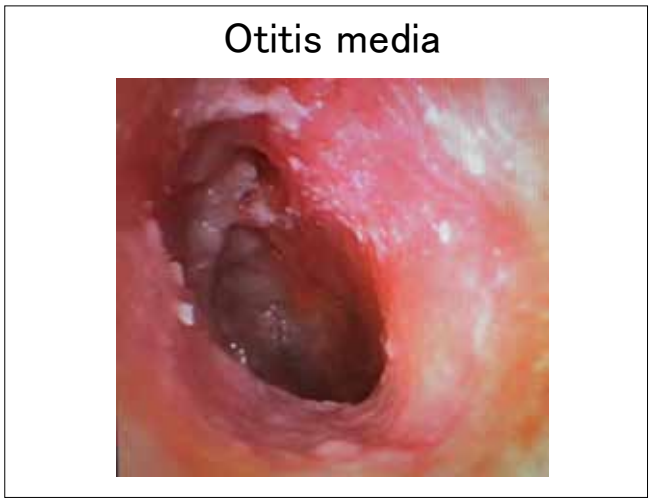


Fig. 26

Fig. 27

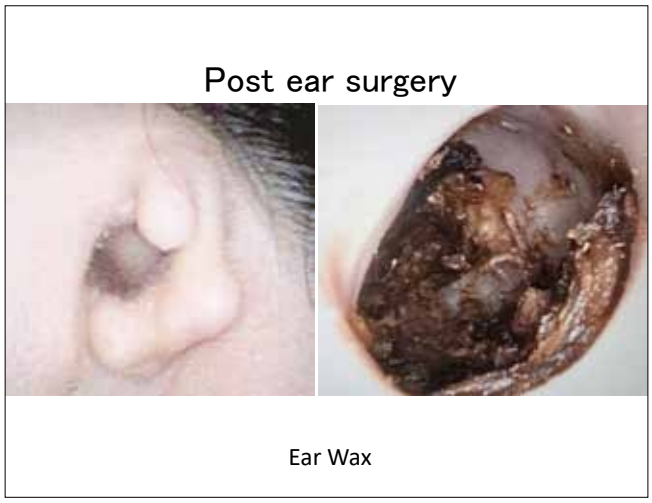


Fig. 28

Advanced skills are required in the future to treat these people; therefore, we have requested the society to take special measures and considerations. We have specialists who are consultants for hearing aids, and there are many designated consultant doctors all over Japan.

Thus, we petitioned the society so that those consultant doctors would also be ready to examine TE victims. I am sorry, this slide is shown in Japanese, but it explains more about the hearing aid consultant doctors. They are of course doctors who have a good understanding of hearing aids and hearing impairments. (Fig. 30)

And here we have a list of consultant doctors in each locality. We have requested and made a special petition through the society to take special care of thalidomiders. (Fig. 31, 32)

We have also explained to otolaryngologists that thalidomiders have limb problems and complicated hearing problems, and that this will increase further in the future with aging. TE victims can also contact our research group directly or through the Ishizue Foundation. (Fig. 33)

Then, in the course of the discussion, we can introduce them to key persons for hearing aids who are consultant doctors located near the patient's residence. We can thus recommend that they visit such consultant doctors. (Fig. 34, 35)

Fig. 31

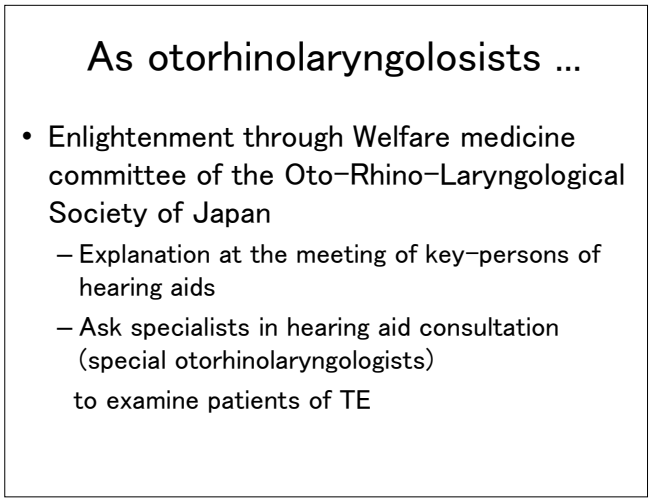


Fig. 29

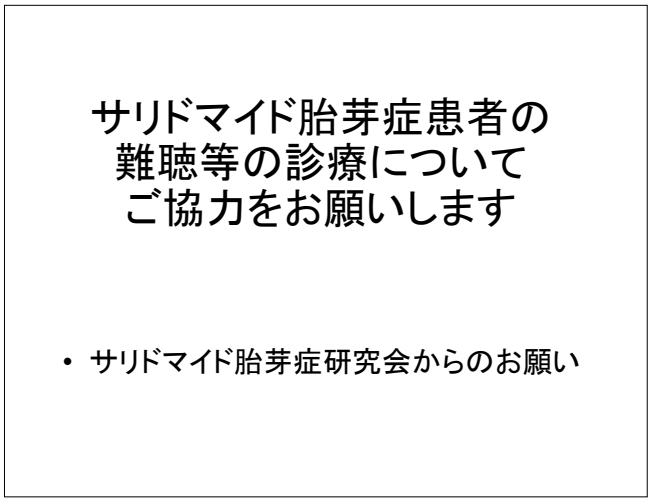


Fig. 32

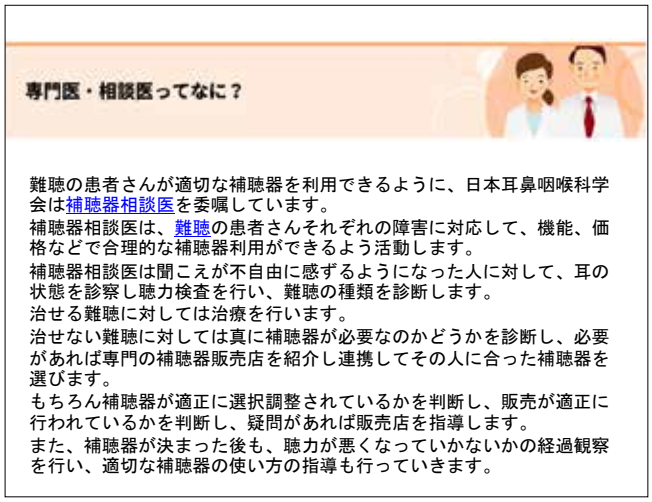


Fig. 30

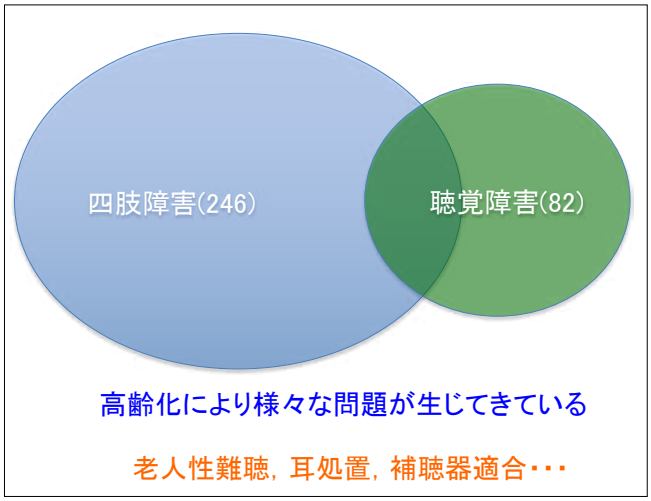


Fig. 33

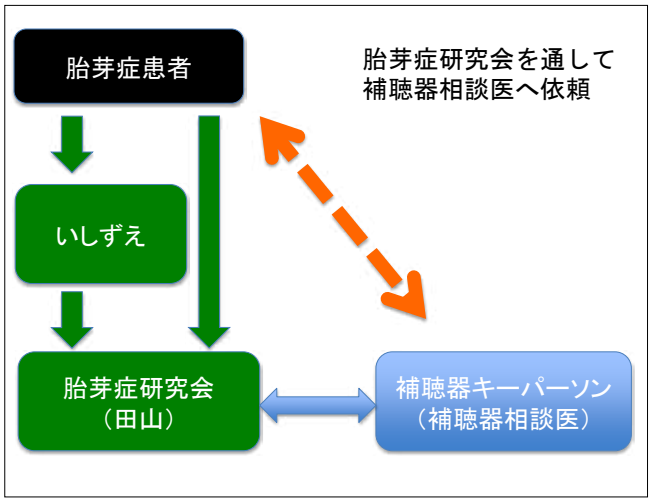


Fig. 34

Fig. 35

When TE victims visit a general ENT doctor, the doctors sometimes don't know how to treat them, so they just decline. Thus, in order to avoid such situations, we recommend TE victims to come to the Ishizue Foundation or to our research group so that we can make appropriate recommendations for and introductions to hearing aid specialists. We would like to aid the treatment of TE victims in the future from the standpoint of ENT doctors. Thank you very much for your attention. (Fig. 36)

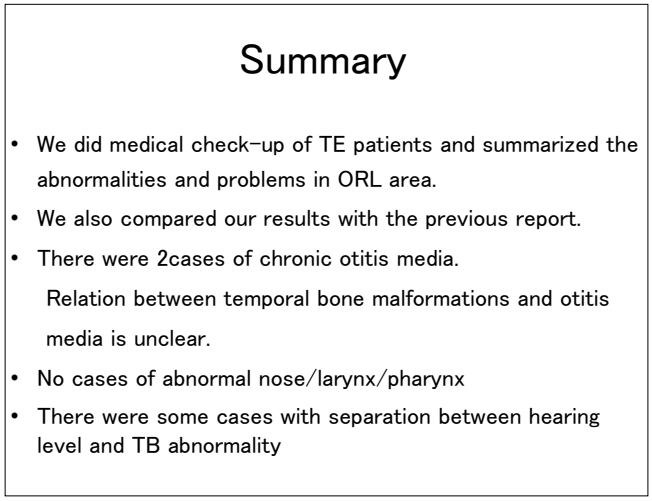


Fig. 36

Q&A

Tetusuya Tagami: Thank you, Dr. Tayama. Now, we would like to have the Q&A session. Any questions or comments?

Fumihiko Hinoshita: Thank you, Dr. Tayama. Very interestingly, we heard about your examination results in the otorhinolaryngological area. I was surprised to find that there were so many thalidomiders, even those with upper limb deformities, who have hearing impairments mainly caused by serious earwax or some other reason.

Nirou Tayama: Well, the overlapping (mixed) type is the main cause of the hearing difficulties because of upper limb malformations. Generally, there are a lot of patients without malformations, but with an accumulation of earwax. However, the number of patients who have hearing difficulties because of earwax is not so large. As you know, hearing difficulties occur because of age, that is, physiological symptoms. Therefore, I think we will see more and more such problems in the future.
So, if they receive treatment or periodical consultations with ORL specialists, then most of the cases with hearing difficulties can be prevented or delayed. Hearing loss cannot be prevented if it's the result of aging, especially in thalidomiders 65 years of age and older, and then, hearing problems will progress. Among those aged over 80 years, 80% have hearing problems or hearing difficulties. Hearing problems due to aging could increase, and are very difficult to stop. Thus, otitis media should be avoided to preserve hearing function. Or, if it occurs, it should be well treated.
So, those are the countermeasures for such a disease, but when the cause is aging, it's difficult to handle. Thank you.

Christina Ding-Greiner: In our first survey, we had the impression that one thing is hearing loss and another thing is deafness. We had in our sample, which was about 900 persons, 47 who were deaf, and only about 50% had malformations of the limbs; the other 50% had normal limbs, normal long arms and legs. Among people with hearing loss, we have many with damage to the upper and lower limbs, and they have the same orthopedic problems as the general sample. So, we had the impression that it is a different thing to be deaf and to have hearing loss. Deafness is an early type of fetal damage, which includes eye damage, too.

Nirou Tayama: Well, absolutely, the deaf tend to have a very strong malformation from birth. And such people actually don't acquire language at all. But in the cases in Japan, and with my own survey, of course it's limited, but I usually don't find such severe people in Japan; therefore, they are moderately impaired. And in the case of inner ear malformations, they have some conductive hearing problems; therefore, we can give them a hearing aid.
Those without any hearing loss may have a problem in the future; therefore, we might be able to classify them into three groups: those with very highly marked hearing loss, those with hearing loss due to age, and those with good hearing who may have hearing loss in the future. Those with moderate hearing loss may have severe hearing loss in the future.

Tetsuya Tagami: According to Dr. Tanaka's survey, you didn't find anybody who was completely deaf?

Nirou Tayama: There were, yes, there were some of them, but they were very small in number.

Tetsuya Tagami: Any other questions or comments? No questions? Thank you very much. So now we would like to close this session. Thank you very much.

Two New Claimers in Japan

Ryoji Kayamori

Department of Physicotherapeutics, Teikyo Heisei University, Tokyo, Japan

Junko Fujitani (Moderator)

Hello, my name is Junko Fujitani. I am a rehabilitation doctor at National Center for Global Health and Medicine (NCGM), and I am very honored to introduce Dr. Kayamori, a Professor at Teikyo Heisei University. He is one of the legends among thalidomide embryopathy (TE) doctors. He has been involved in the treatment of thalidomide patients for many years. He was a good clinical doctor for thalidomide victims in childhood, and he is still a very active clinical doctor and researcher. Today, his presentation is about new claimers in Japan. Please start.

Thank you, Dr. Fujitani. Ladies and gentlemen, good afternoon. I am so glad to have you here, even on this rainy day. I am going to introduce new claimers in Japan. These two cases of thalidomide victims were referred from the Ishizue Foundation. The first case is a 54-year-old man born in 1962, and the second is a 46-year-old woman born in 1971. They wanted to know whether their malformations were due to thalidomide. However, they were too modest to ask their mother that question. They could not ask their mothers whether their mothers had taken thalidomide during pregnancy before their mothers expired or became senile. (Fig. 1)

This is the number of new claimers in the United Kingdom from 2013 to 2018. Overall, 276 people applied for new claims. Four cases were accepted, six cases are in trial, and the others were rejected. This is the number of new claimers in Germany from 2009 to 2017. Overall, 105 people applied for new claims, 10 were accepted, 43 were rejected, and 49 remain unsettled. (Fig. 2, 3)

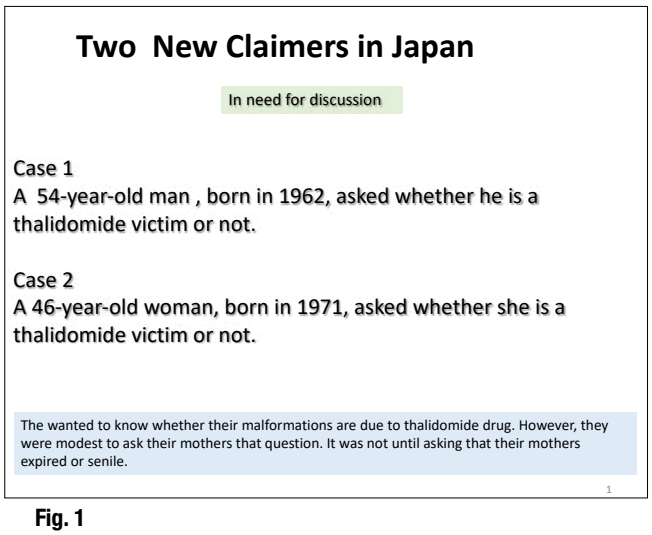


Fig. 1

So, this is the first case, a 56-year-old man born in Osaka in 1962. You can see a bilateral triphalangeal thumb with hypoplasia of the thenar muscles. Triphalangeal thumb can be seen on X-ray. Compared with the normal control, these thumbs have three phalanges, which is considered not a real thumb, but rather, a form of pre-axial polydactyly. There is

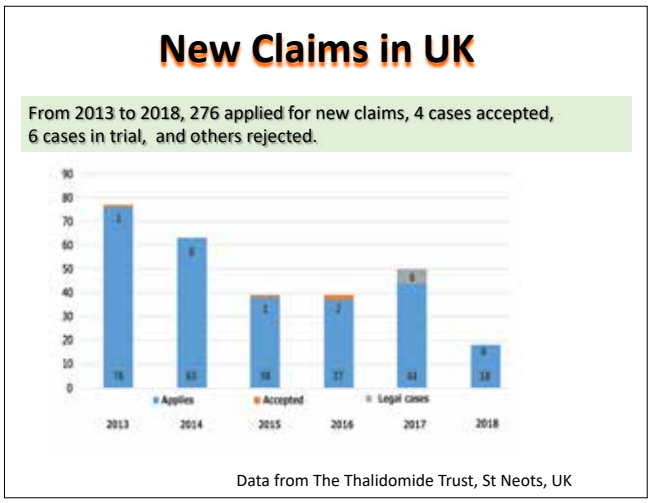


Fig. 2

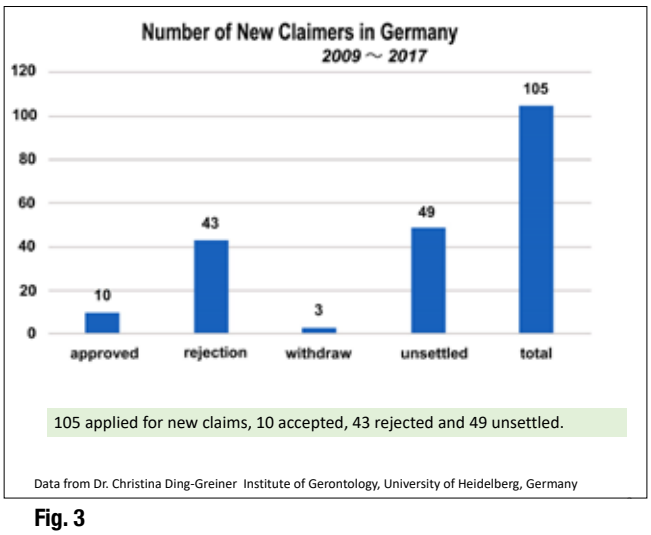


Fig. 3

also hypoplasia of the trapezium and scaphoid bone, in addition to minimal hypoplasia of the radial styloid process. (Fig. 4, 5)

Again, I make sure that triphalangeal thumb is considered a form of preaxial polydactyly. (Fig. 6)

It means a lack of a thumb and polydactyly affecting five fingers on both sides. The pisiform bone is really prominent. (Fig. 7)

One of the basic principles in TE is preaxial longitudinal ray hypoplasia including the thumb, radius, and humerus in the upper limb. (Fig. 8)

Fig. 4

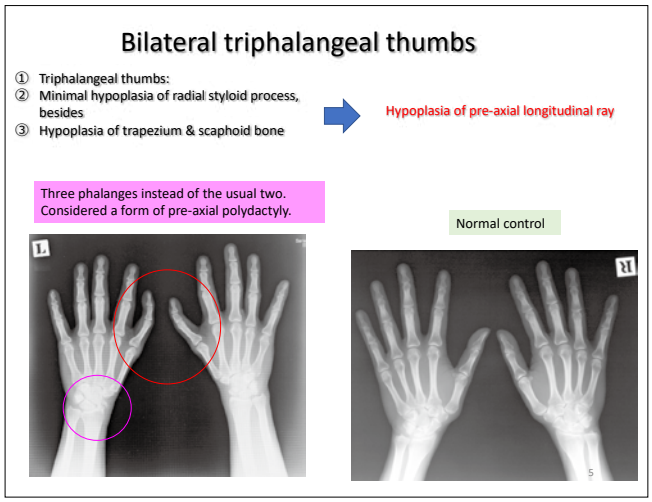


Fig. 5

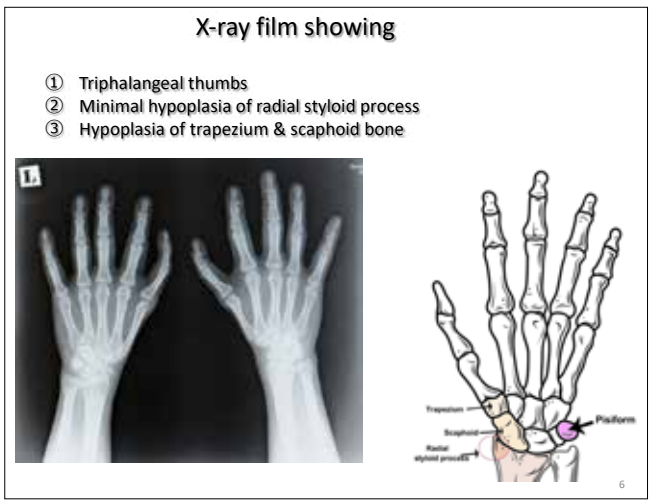


Fig. 6

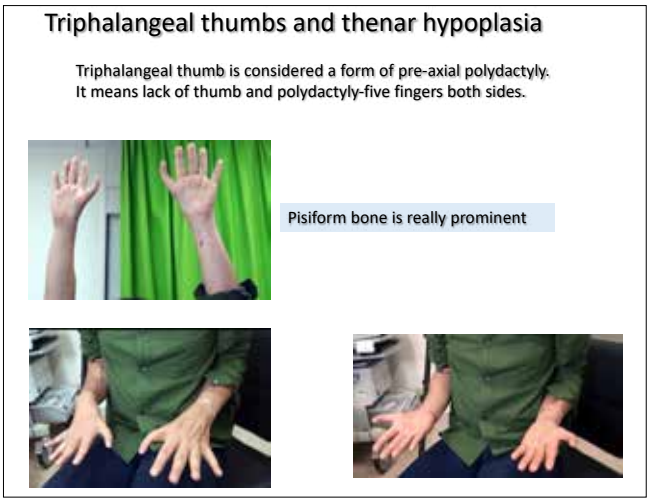


Fig. 7

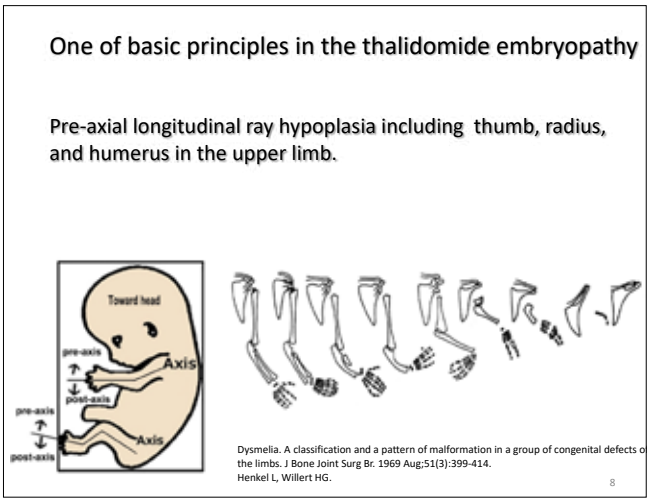


Fig. 8

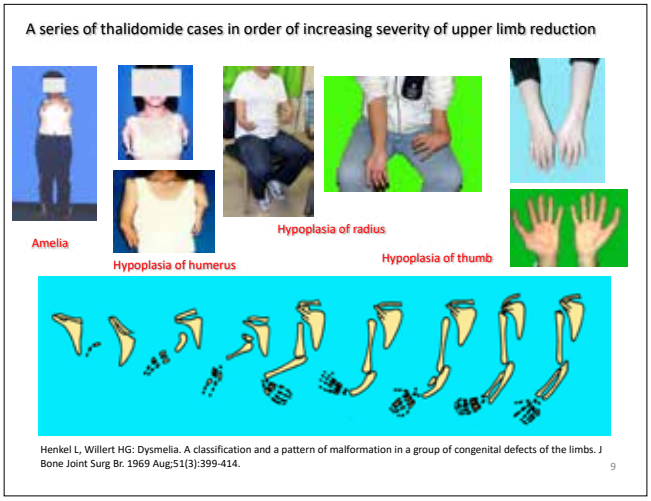


Fig. 9

Here are a series of thalidomide cases with upper limb reduction in the order of severity. Amelia and hypoplasia of the humerus, radius, and thumb are arranged in the order of severity in the upper limb from left to right in the slide. The last picture shows bilateral triphalangeal thumbs. (Fig. 9)

Congenital malformations are classified into hereditary and embryopathy in etiology. There are lots of similarities in morphological malfunction between the two to make a diagnosis of TE, and no family is indispensable, although they share preaxial longitudinal ray hypoplasia, for instance, triphalangeal thumb or Duane syndrome, in common. Malformations are inherited in cases of hereditary or familiar etiology, but cases with embryopathy are not inherited. (Fig. 10)

This is a picture of an old case. Dr. McBride in Australia, one of the heroes of the thalidomide scandal, published a paper reporting that TE could be inherited, and reduced the anxiety of many thalidomide victims. Around 1990, without genetic analysis, it was difficult to differentiate between hereditary and embryopathy with almost the same malformations. (Fig. 11)

Regarding triphalangeal thumb, there are many hereditary syndromes presenting as trigeminal thumb. They show autosomal dominant genetic transmission. The differential diagnosis is shown below. Duane radial syndrome, so-called Okihiro syndrome or Holt-Oram syndrome are so famous. In embryopathy, there are a couple of syndromes showing triphalangeal thumb. (Fig. 12)

Again, let's return to the first case. His disabilities consisted of grip and pinch without the thumb. The grip is not between the thumb and finger, but between the fingers and pisiform bone. The pinch is not between the thumb and index finger, but between the index and middle fingers.

Whenever he grips, he has to use the pisiform bone instead of the thumb, which is the reason why that bone has become prominent. (Fig. 13)

I will show you an abdominal CT. He does not have a gallbladder and the right kidney is markedly atrophied. (Fig. 14)

This is an MRI. I will show you the right kidney, which is severely atrophied with benign cystic lesion or vascular anomaly. This area shows a cystic neoplasm or vascular

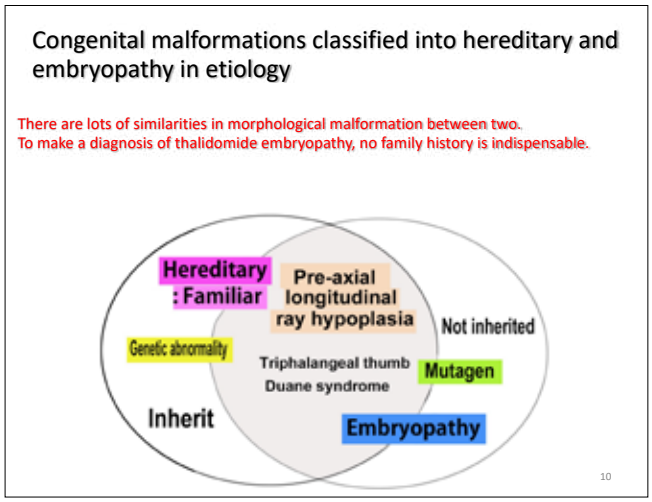


Fig. 10

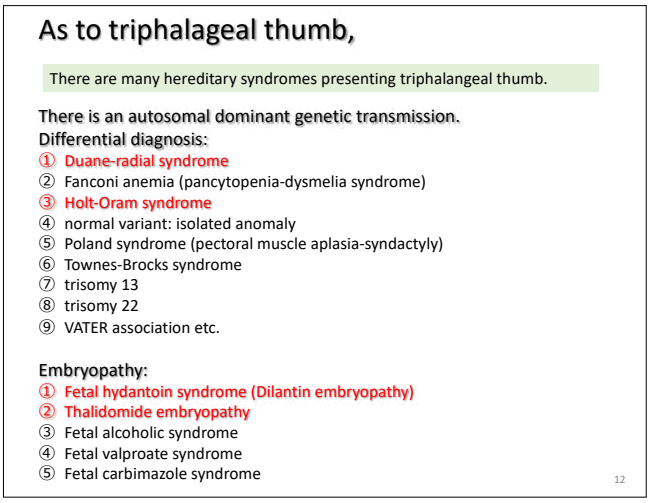


Fig. 12

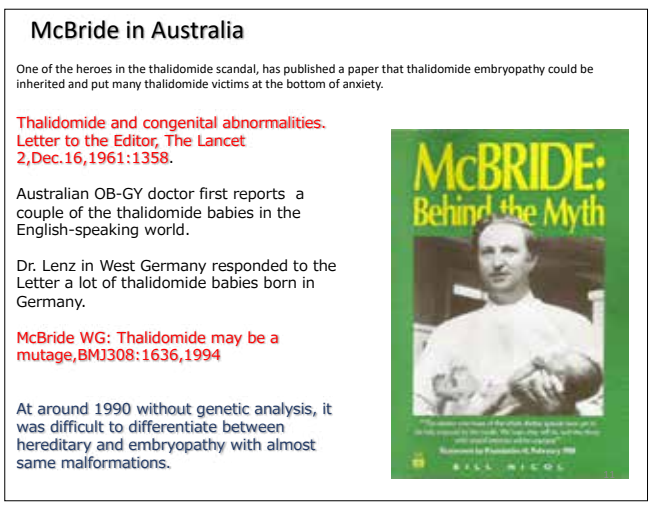


Fig. 11

Fig. 13

anomaly, but I don't have any knowledge about this. The right kidney is severely atrophied, but no agenesis is seen. (Fig. 15)

This is the second case, a 46-year-old woman born in Kagoshima, the southern part of Japan, in 1971. (Fig. 16)

She has a short club hand with a rudimentary thumb on the left. On the right, her thenar muscle is hypoplastic. (Fig. 17)

On X-ray, she has hypoplasia of the radius and thumb. The carpal bones are not clearly separated on the left. Unfortunately, the hypoplasia of the thumb and carpal bones is not clear on X-ray because of technical problems on the right. (Fig. 18)

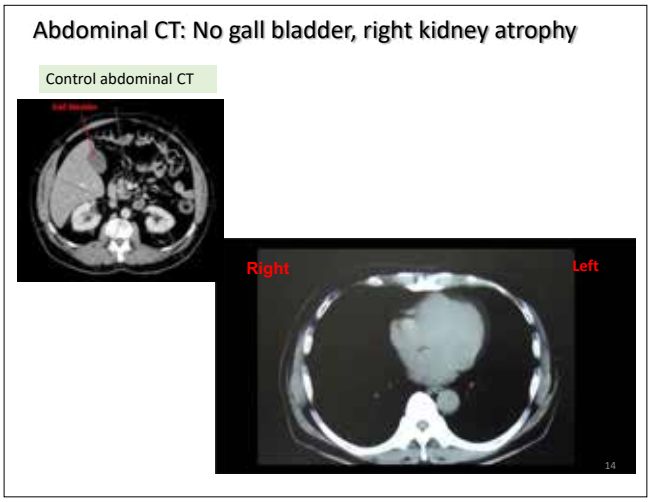


Fig. 14

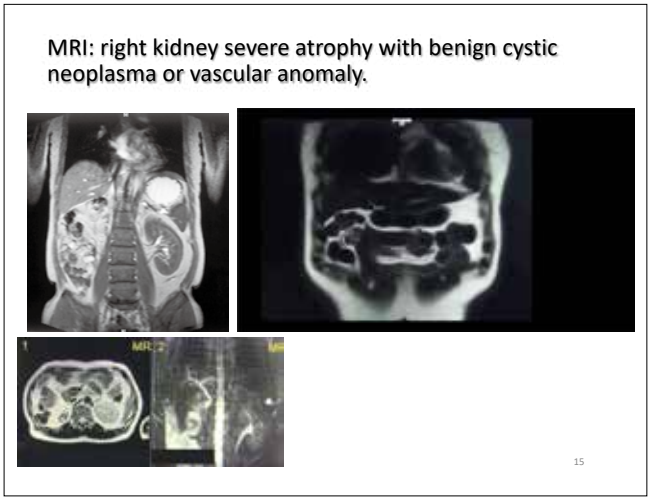


Fig. 15

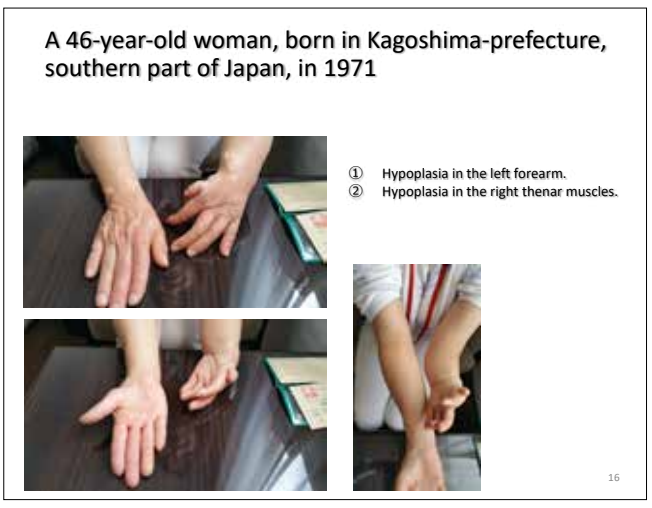


Fig. 16

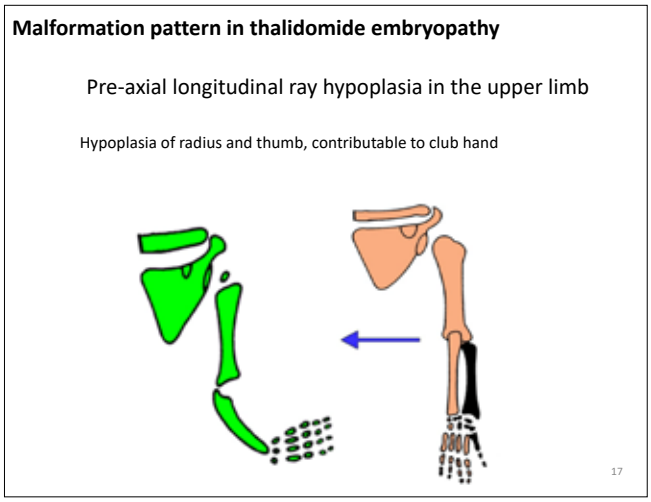


Fig. 17

Fig. 18

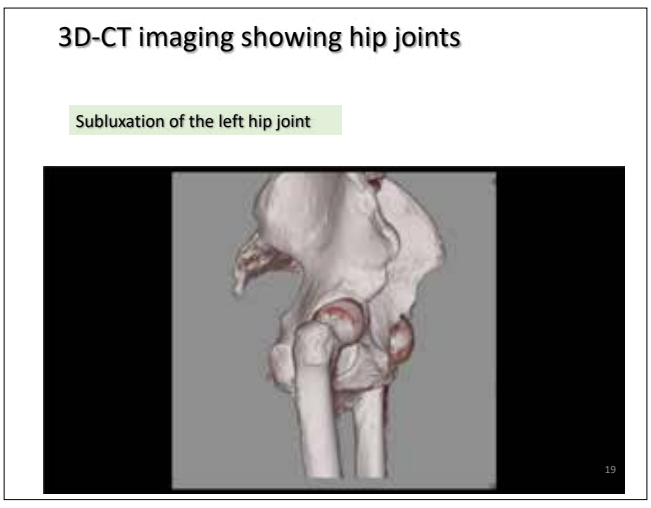


Fig. 19

This is a 3D-CT image showing the hip joint. Her left acetabulum is small and shallow, resulting in subluxation or osteoarthritis deformans in the left hip. (Fig. 19)

This is a coronal section of the abdominal cavity on CT that shows prominent scoliosis and agenesis of the right kidney, in addition to subluxation of the left hip joint. (Fig. 20, 21)

Fig. 20

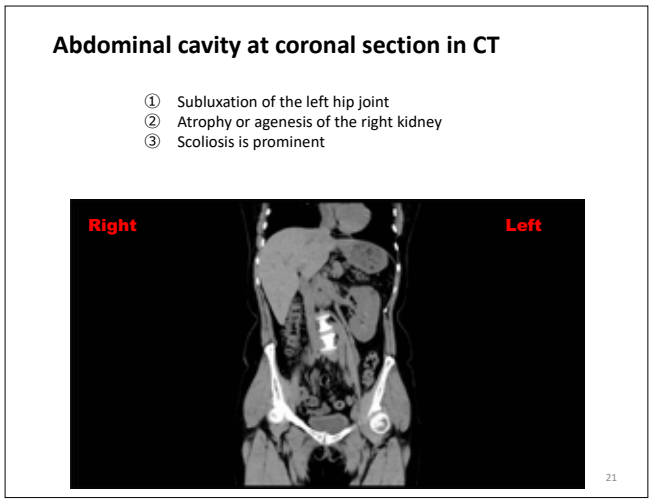


Fig. 21

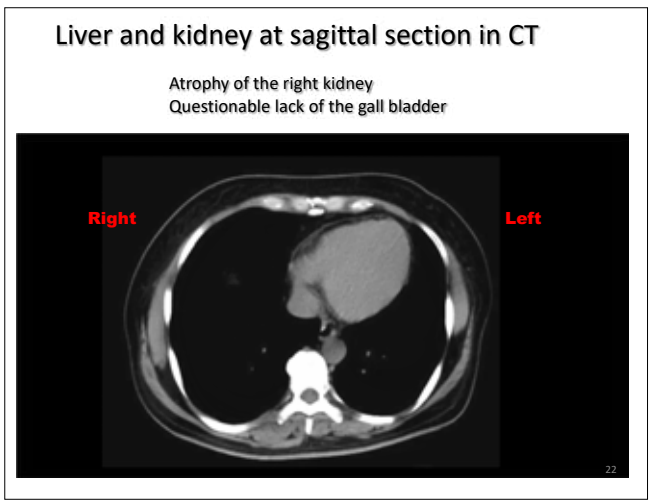


Fig. 22

As to the kidney anomalies in TE, intravenous pyelography is showing a crossed non-fused renal ectopia on the right in the other thalidomide victim. The ureter is located on the left side of the bladder in contrast to the kidney on the right. It might be likely to migrate to the right. Thus, it is indispensable to survey abdominal malformations using abdominal CT and/or MRI in thalidomiders. (Fig. 22, 23)

Now, we have the discussion. Both cases are almost the same in morphological malformations with preaxial longitudinal ray hypoplasia in the upper limb and atrophy or agenesis of right kidney. The only difference is the birth date. The first case is 1962 and the case is 1971. The difference seems to be crucial.

The first case may be a thalidomider, but not the second, judging from the perspective of the diagnostic algorithm for so-called DATE. (Fig. 24)

Most thalidomiders in Japan were born between 1959 and 1964. The recall of thalidomide began in September 1962 in Japan. On the other hand, it started in November 1961 in Europe after Dr. Lenz's warning. Dr. Lenz is known as the

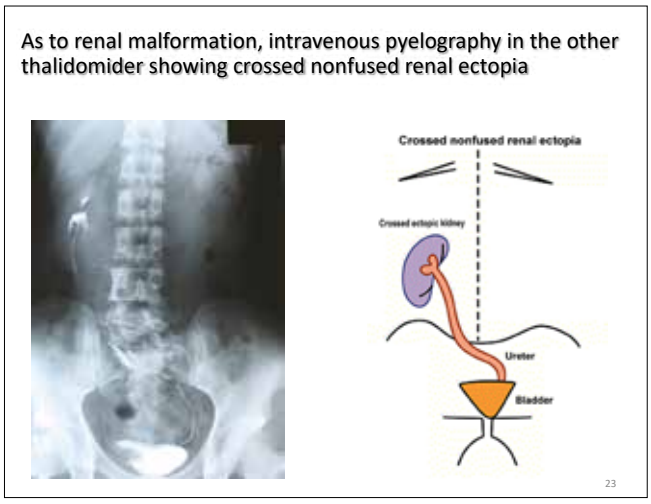


Fig. 23

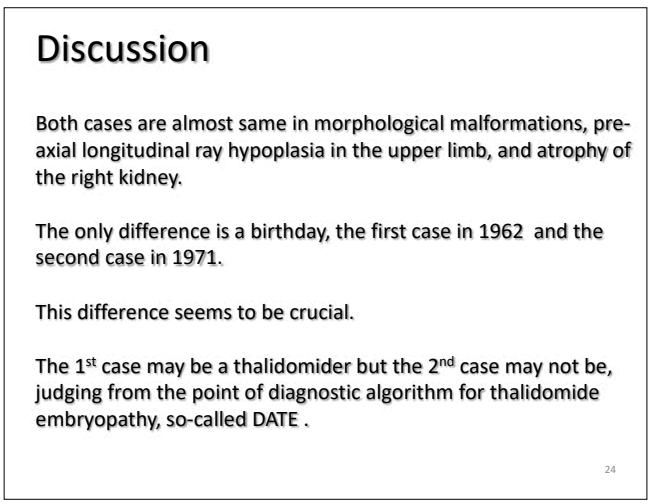


Fig. 24

father of thalidomiders in Japan. (Fig. 25)

This is one victim who was born in 1969 in Okinawa, where the United States ruled at that time. The notification of thalidomide recall from the Japanese government might not have reached the family of this victim. (Fig. 26)

This patient was born in 1969 in Okinawa. This is a rare exceptional case. The prohibited sale of thalidomide was not fully communicated, and that's the reason why he was born 7 years after the ban. We are happy that Okinawa returned to Japanese rule in 1972. (Fig. 27)

Epidemiology in the thalidomide scandal taught us a lot, and this was the starting point of academic epidemiology, so no more thalidomide victims would be born after the banning of thalidomide sales. This illustration shows the relationship between thalidomide sales and the incidence of TE. Thalidomide victims began to diminish 8 months after recall. (Fig. 28)

This is the diagnostic algorithm for TE (DATE) by Dr. Mansour, Dr. Baple, and Dr. Hall from St. George's University of London. We are looking forward to hearing the lecture on DATE by Dr. Baple. Thank you very much for your attention. (Fig. 29)

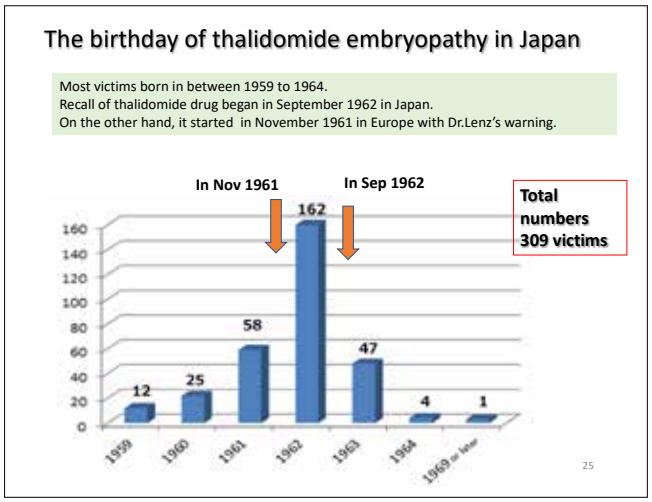


Fig. 25

Fig. 26

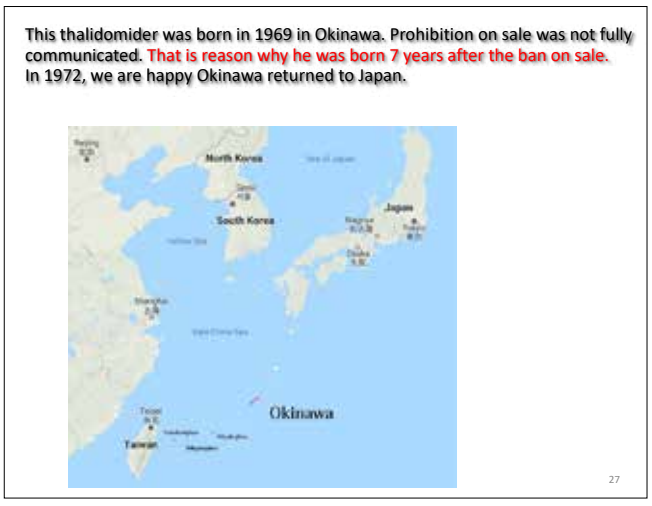


Fig. 27

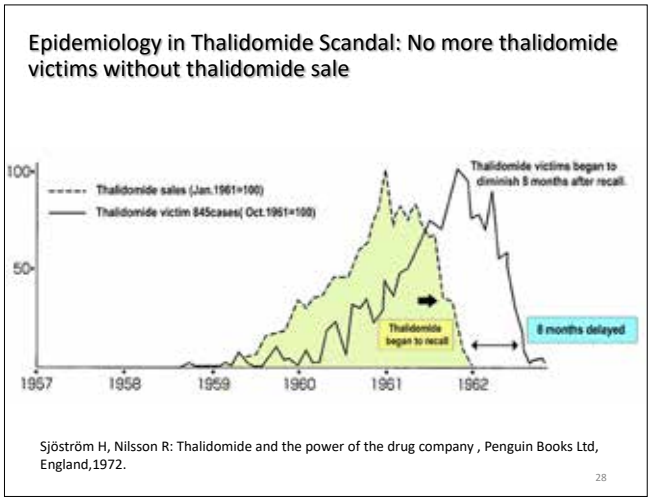


Fig. 28

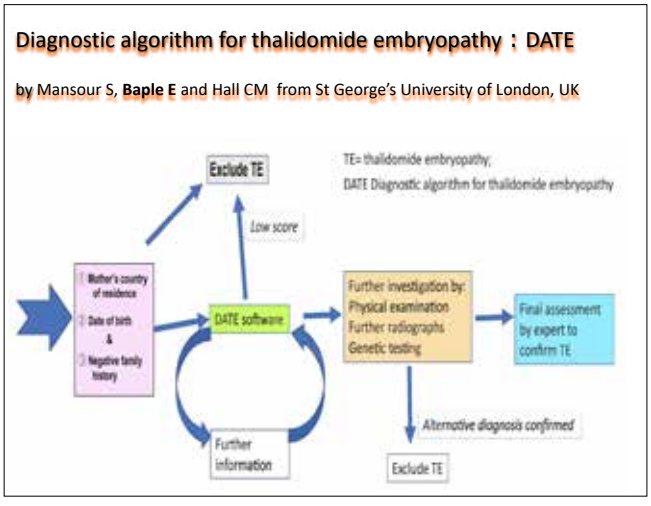


Fig. 29

Q&A

Junko Fujitani: Thank you, Dr. Kayamori. Do you have any questions or comments?

Lavinia Schuler-Faccini: Okay. Thank you for your beautiful presentation. And, as I am from Brazil, I'm going to talk tomorrow, but in Brazil, thalidomide never went off the market. It was not really commercialized, but it was provided by the government. So, we are facing lots of questions from people. And it's very difficult sometimes, as you have shown, to reach a diagnosis based on the clinical presentation. I think one of the saddest parts is that lawyers have discovered a way to make money from people, so they sell the history of the mother who took a drug that she didn't know about, and thus, it's really difficult to help these people. Thank you so much.

Ryoji Kayamori: We are looking forward to hearing your lecture tomorrow.

Junko Fujitani: Any other comments?

Jan Schulte-Hillen: Thank you very much. I would just like to say that a late birth of somebody with typical birth defects should not be used to rule out a thalidomide condition automatically. When I was working as a physician in Munich, the last time I saw thalidomide in one of the medical cupboards of a patient at their home was only 7 years ago. So old people don't throw drugs away, and perhaps the drug was still working when taken.

Ryoji Kayamori: Thank you, Jan.

Female Participant (Unknown Speaker): Thank you very much for your very nice presentation. I just have a question about the two new cases. Do you know, I mean, if there was any kind of malformation like those in other members of the family, it's my first question. And if you ask the parents, I mean, obviously, it may not be the case in Brazil, but they might actually have a history. Have you asked about this, because it's so late, I mean, 1971 is quite late. Thank you.

Ryoji Kayamori: Yeah, it is one of the most important things. But I have not heard from the Ishizue Foundation, a welfare foundation for thalidomide victims, that there is any family history so far. But I didn't examine this in detail. Family history is very, very important.

Junko Fujitani: Any other questions or comments? Okay, so thank you very much, Dr. Kayamori.

Ryoji Kayamori: Thank you very much.

A Diagnostic Aid to Thalidomide Embryopathy

Emma Baple

Royal Devon & Exeter NHS Foundation Trust, Exeter, UK

Ryoji Kayamori (Moderator)

The next speaker is Dr. Emma Baple. She earned her MD from St. Bartholomew's and the Royal London School of Medicine and Dentistry in 2002. She earned her PhD at the University of Exeter Medical School in 2014. Her specialty is Clinical Genetics. Her current position is Clinical Senior Lecturer specializing in Genomic Medicine at the University of Exeter. She has won numerous prizes, awards, and research grants, and has many publications. It's difficult to detail everything. We are very looking forward to hearing her lecture especially on DATE. Could you start?

Thank you. Thank you very much for the kind invitation. I want to tell you today about what we have now actually renamed ValiDATE, which is a diagnostic aid for thalidomide embryopathy (TE) that I have worked on with a team from St. George's Hospital, where I undertook some of my Clinical Genetics training. This work is done by myself, Professor Sahar Mansour, who is a professor of Clinical Genetics and a Clinical Geneticist at St. George's Hospital, and Professor Christine Hall, who is an internationally renowned radiologist who previously worked at Great Ormond Street Hospital. Even though she is retired, she is still often asked to help with difficult cases and has led a lot of the work that we've done on this.

So, I'm only going to talk to you very briefly about the background of this work because everybody in this room already knows a lot about thalidomide and TE, but a brief overview helps to put the work we have done in context. (Fig. 1)

In summary, I am going to talk to you about our diagnostic algorithm, how it came to be, describe DATE or ValiDATE as we are calling it now, the WHO Conference which helped to inform its development, and how we hope it might be useful. (Fig. 2)

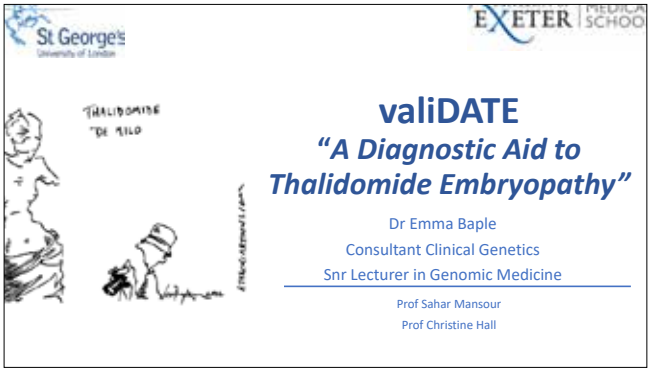


Fig. 1

So, first, a little background. When we were initially doing this work, we were looking at thalidomide from the UK perspective. As people know, thalidomide was available in the UK between April 1958 and November 1961. The majority of births affected by TE happened between 1959 and 1962, so that was where the majority of cases and clinical information that we have been able to collect date from. (Fig. 3)

So, TE is a diagnostic dilemma as many people in this room already know, and the two cases previously presented today make this apparent. Part of the reason for this is the lack of evidence of exposure. And I recall, when we initially went to speak with The Thalidomide Trust, Dr. Claus New-

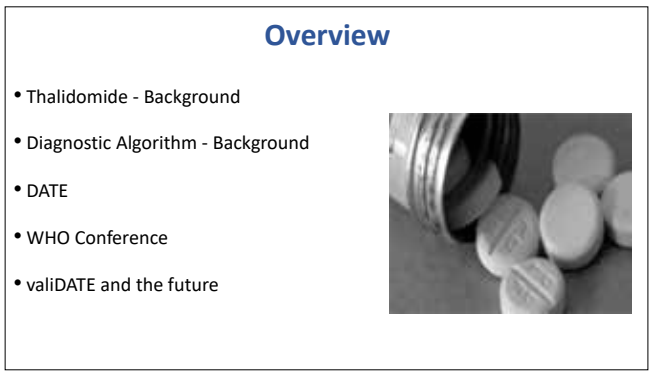


Fig. 2

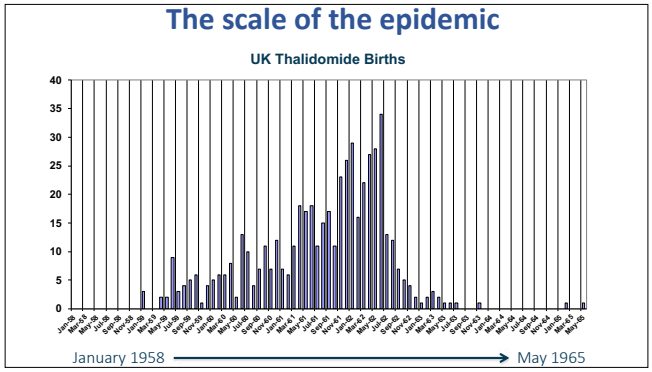


Fig. 3

man, who has worked with the Trust for a number of years, told us that there's only probably about 50% of individuals whose mothers actually recall even taking thalidomide, and those are TE claimants who were certainly affected by TE. (Fig. 4)

Part of the problem is that particularly in Germany, but also elsewhere, thalidomide was included in some medications but not listed. So it wasn't always obvious what people had taken and when.

Birth defect records were nonexistent or incomplete back in those days, and only very severe limb defects and other severe physical defects were recognized because they had previously been rare. And as we know, as all the clinicians here would know, patients' memories are very unreliable, so recalling exactly what happened is difficult.

So, in 1964, the Ministry of Health in the UK produced the document shown here about the deformities caused by thalidomide. And they said what I think is a very pertinent quote. "It's impossible to say with any certainty what constitutes a thalidomide deformity. There seems to be little evidence of a typical thalidomide deformity." So that's really the question that we were trying to address with ValiDATE.

The timeline shown here has been extremely useful. And Lenz, whose picture I show here, was one of the pioneers that really helped us to understand the deformities associated with thalidomide and its relation with the time of exposure during pregnancy. Lenz did this work with Knapp. They investigated the records for 86 women looking at the time, at the precise time, at which they took thalidomide, and the dose that they took.

Their work showed that it was the time of exposure and not the dose that was important. They showed that around half of TE-affected babies were born with upper limb defects only, one-quarter had upper and lower limb defects, and one-sixth had anotia or microtia, so an absent or small ear. Their work defined this timeline, which actually still stands today, so this is a very important piece of work. (Fig. 5)

The additional text on the timeline, which is in italics, comes from the excellent work that was done in Sweden looking at the facial and ocular abnormalities seen with TE.

So, thalidomide as we all know is a teratogen, and all of the birth defects shown on this slide will be familiar to people in this room. It was also suggested in the 1990s that thalidomide might be a mutagen; in other words, that defects could be passed from one generation to another. What we now know is that those cases have subsequently been shown to be a genetic disorder, a genetic variant that was passed down through the generations that caused a genetic syndrome that mimicked TE, or what we call a phenocopy of thalidomide. (Fig. 6)

There has been very robust work done demonstrating that thalidomide is not a mutagen.

I'm not going to dwell on this now though, because I am sure that this will be covered by Lavinia Schuler-Faccini

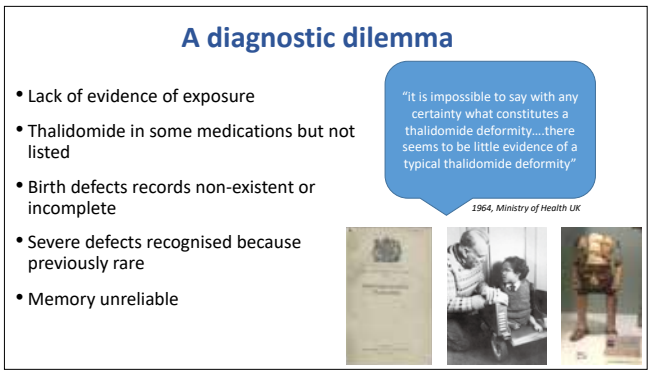


Fig. 4

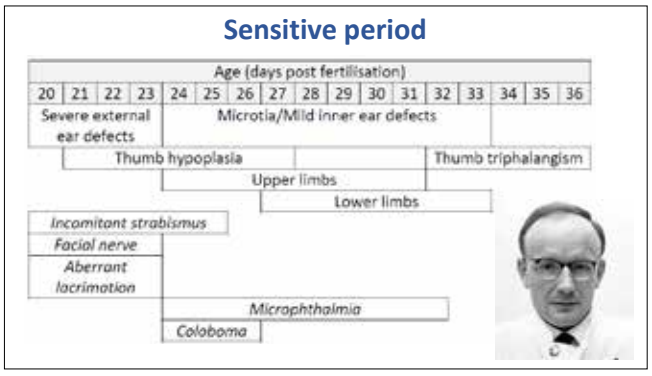


Fig. 5

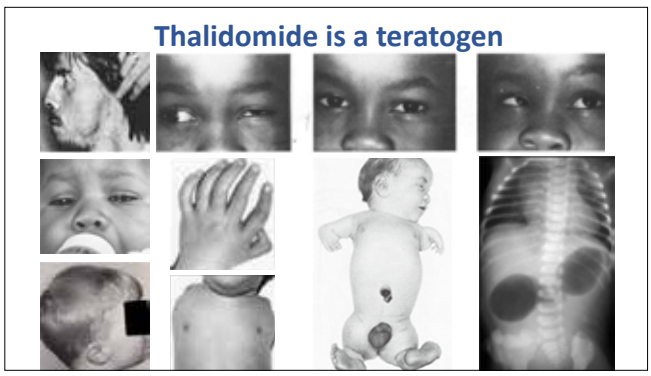


Fig. 6

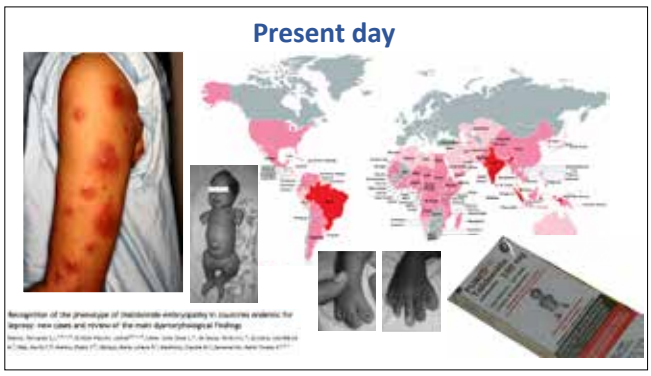


Fig. 7

tomorrow. Thalidomide was reintroduced in 1965 in the UK as a treatment for multiple myeloma in individuals over the age of 65. But it is also still used to treat the cutaneous manifestations of erythema nodosum leprosum. (Fig. 7)

The current use of this drug in countries like Brazil has led to a large number of individuals being born with TE. (Fig. 8)

So, this is just to remind us all of the scale of the TE problem globally, which is actually still growing in certain parts of the world like Brazil. So, many people, when you tell them you work on or are interested in thalidomide, say well, all those individuals must be getting older now and the problem must be decreasing. But actually, all those older individuals still have problems that resulted from this drug, as we'll hear more about tomorrow. In addition, there are still more individuals being born today. (Fig. 9)

So that really was where we started from in terms of the background when we were thinking about this diagnostic algorithm.

So, how did it really come to be? Well, we were invited by The Thalidomide Trust in the UK to write an independent review of TE, and this work has been done intermittently by St. George's University over the years. The brief was to cover the historical facts and the proposed teratogenic mechanisms and to look at whether there was any new knowledge that might help inform the diagnosis, the characterization of the phenotype, and the differential diagnosis and genetic tests that might help. There were no financial links to the trust in any of the work that we'd done other than the production of the software, which I'll come to. (Fig. 10)

When we first started this work, we were trying to think how we might best try to solve this diagnostic dilemma. If you look at the pictures of these children here so I am a clinical geneticist, and any clinical geneticist would recognize the facial features of these children as indicating that they had a condition called Kabuki syndrome. And this excellent paper here, which looked at only a very small number of individuals with Kabuki syndrome, identified mutations in the coding region of gene MLL2 as the cause of the disorder. (Fig. 11)

What that work teaches us is that if you diagnose a condition accurately, it enables you to characterize that phenotype even more clearly as time goes on and to identify the underlying cause and mechanism of the disorder. Once you understand the underlying cause, you can really get at what's

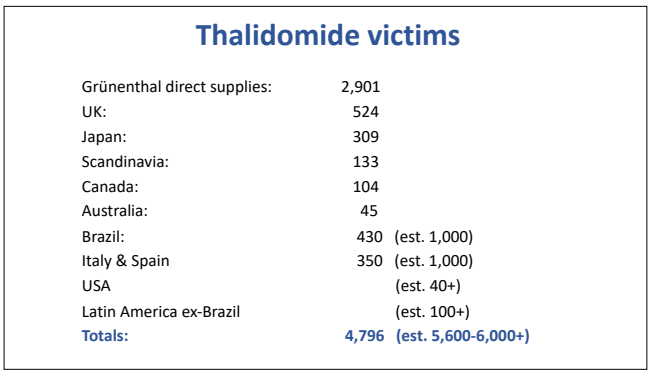


Fig. 8

Fig. 9

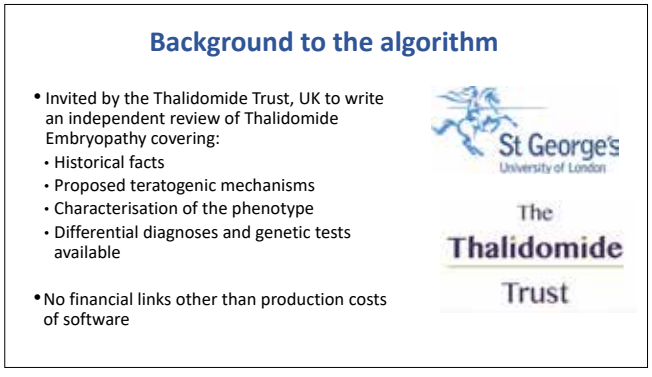


Fig. 10

Fig. 11

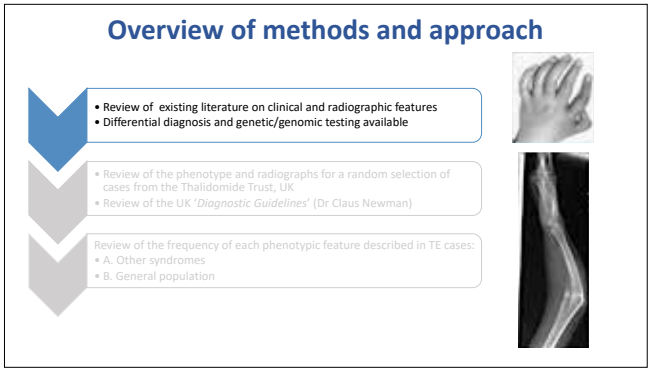


Fig. 12

going on in the body. So, this was our goal. (Fig. 12)

So, what did we do to tackle this issue? Well, we reviewed the existing literature on the clinical and radiographic features, and there is quite extensive literature available on this. We then looked at the potential differential diagnoses for TE and the genetic and genomic testing that was available. So, this was all back in around 2012–2013 when we started doing this. (Fig. 13)

So, since TE was initially a problem we have recognized a huge number of genetic syndromes over that time, and that list grows daily. So, there's an extensive list of differential diagnoses for TE, one of the most important being Okihiro syndrome, which is caused by mutations in a gene called SALL4 and is one of those phenocopies I mentioned earlier that can be passed down through generations. We looked at all of the potential TE phenocopies and any condition with phenotypic overlap with TE. We looked at the aspects of the condition that were absolutely indistinguishable from TE and those that were more variable.

So, individuals with Okihiro syndrome can have something like a Duane anomaly and radial ray malformations. They can have those features in isolation, and those are both features seen in TE. (Fig. 14)

Other abnormalities seen in Okihiro syndrome that overlap with TE but are perhaps less common in one or the other condition include anal stenosis or imperforate anus, renal anomalies, other ocular abnormalities, external ear anomalies, and abnormalities of the lower limbs, although these are much, much rarer in Okihiro syndrome than in TE.

And so then, we looked at the differentiating features. (Fig. 15)

So, you never see phocomelia or amelia in Okihiro syndrome. The lower limb defects that you do see on occasion are tibial hemimelia and syndactyly of the toes. The external ear anomalies are also very different. So, we did this work for all of the disorders we felt were phenotypically overlapping with TE.

What did we do next? We reviewed the phenotype and the radiographs for a random selection of cases from The Thalidomide Trust, and we also reviewed the UK diagnostic guidelines that the trust was using at that time, which were written by Dr. Claus Newman. (Fig. 16)

When we looked at these cases, we wanted to look at the radiology again. Christine Hall did this work. So you'll have to excuse the fact that I am not a radiologist. I will point out those things that she has taught me.

So, amelia, we would all recognize as an absence of a limb, and phocomelia, which is a term we've used in medicine, but is not actually always that well defined. So, phocomelia is absence of the intermediate part of a limb with the presence of some fingers. There are individuals in the medical literature said to have phocomelia where they really don't match that description, so it's important to get this right. (Fig. 17)

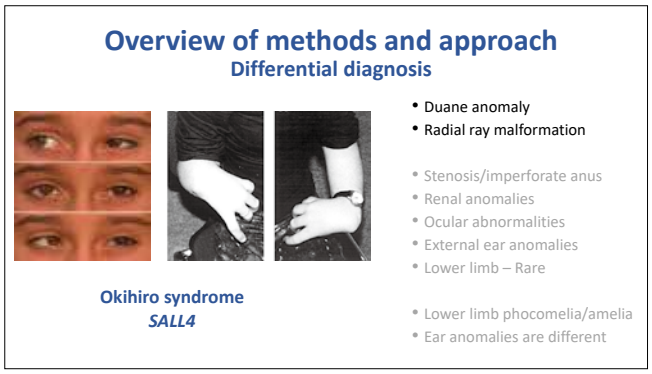


Fig. 13

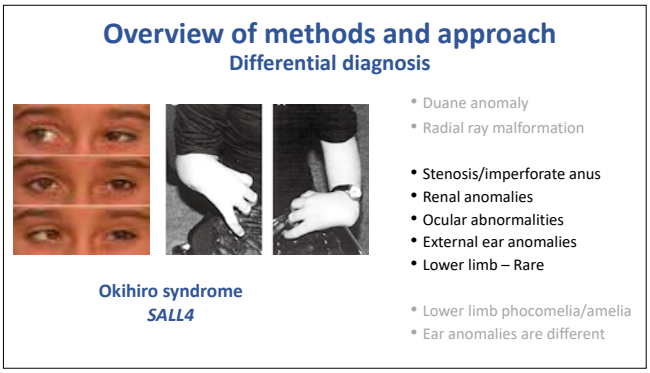


Fig. 14

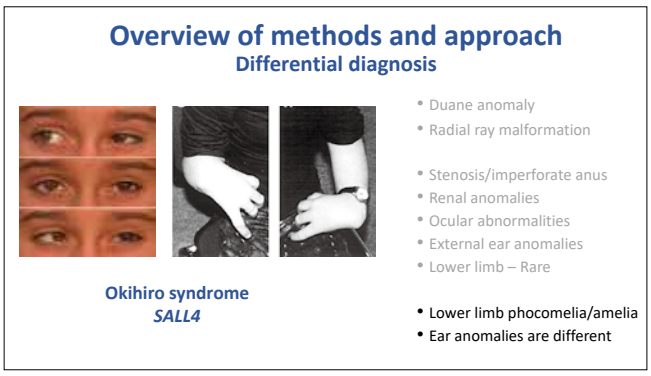


Fig. 15

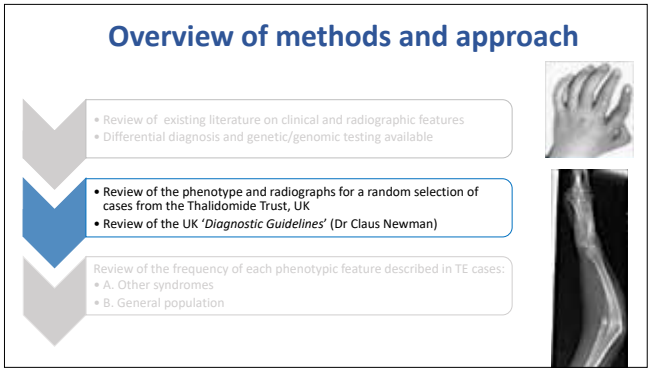


Fig. 16

And actually, before I go any further, I guess that's the one lesson I've learned from this what's written in the literature and what you actually see when you examine or really look at radiology can be very different, and it's important when you are trying to recognize the features of something that you are absolutely accurate.

So, this is a little boy with TE who is now grown up. He gave me this picture of him on the beach when he was little. And what this picture happens to show is a very characteristic feature of TE. This is pointed shoulder. This pointed shoulder is really unusual. We don't really see this in any other disorder. It is characteristic of TE and is due to this abnormality, which you can see on the X-rays here. (Fig. 18)

So, you get this very long clavicle and acromion process – which is indicated by these arrows. And this is what gives you this pointing of the shoulder shown here. You also see this hypoplastic or absent glenoid fossa, which is indicated by these arrows on the X-rays, and it's that combination that's creating this pointed shoulder. (Fig. 19)

So, we think again about the other disorders that overlap with TE. Children affected by these disorders may have been diagnosed with TE because they would have still been born with this during the time thalidomide was around. If you look at pictures of these children's shoulders, you will see that they look different. For example, in Holt-Oram syndrome, the shoulders never have that point. In fact, they are actually very characteristic in appearance. They slope downwards. And if we look at Roberts syndrome, which can be an almost exact phenocopy of TE, you don't see those pointed shoulders, so that's really important. (Fig. 20)

There are other abnormalities that you see in TE affecting the upper limbs that are also unusual. This is proximal hypoplasia of the humerus. You see this unusual appearance at the top of the humerus and often very bizarre shapes to the bones, which you don't typically see in other forms of skeletal dysplasia. You can see a very short humerus and a subluxed shoulder joint. (Fig. 21)

These fusions around the elbow joint are also unusual, particularly the longitudinal fusion that's seen here, this humero-ulnar fusion that's seen here. This is very unusual, but is sometimes seen in TE. You can see fusion around the elbow in TE: humero-radial, humero-ulnar, or radio-ulnar fusion. So here you've got this very nice illustration of humero-ulnar fusion, and then there is oligodactyly.

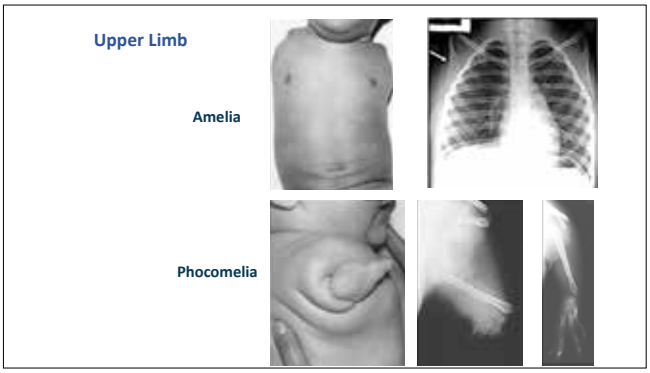


Fig. 17

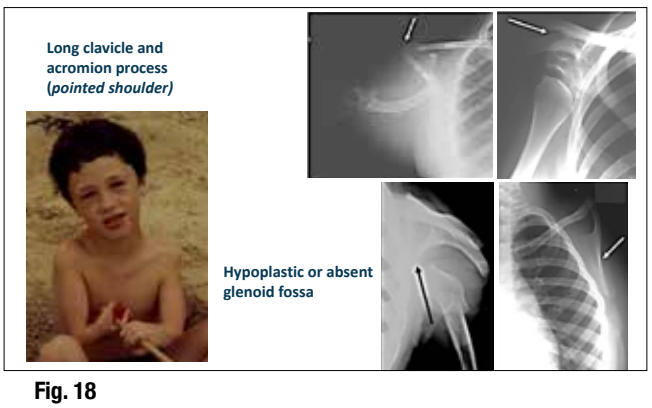


Fig. 18

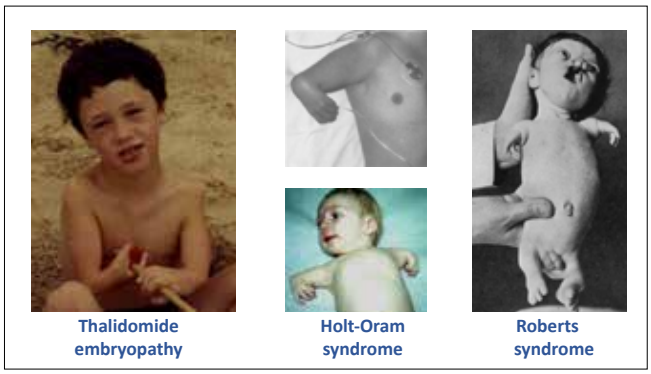


Fig. 19

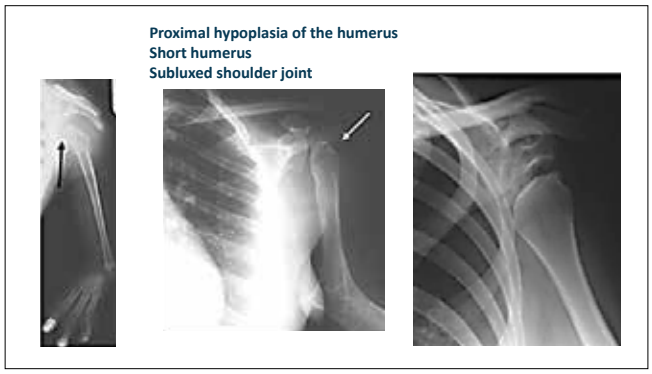


Fig. 20

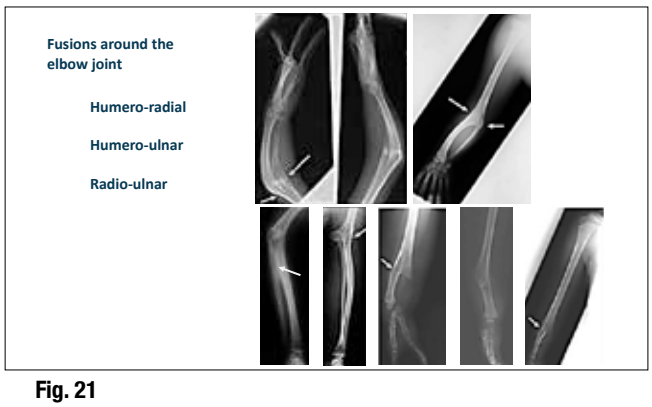


Fig. 21

So, other abnormalities that we see moving down the upper limbs are hypoplastic and absent radii. So, you'll notice as I'm going down, these pre-axial defects that I am highlighting. Here we can see that you've got an absent radius or hypoplastic radius, and the thumb coming off of it is unusual or absent. (Fig. 22)

The ulnar, and I want to emphasize this, is abnormal in these radiographs. It doesn't look normal, but the ulnar abnormalities that you are seeing are occurring as a secondary consequence of the radial abnormality. So, there's a lot in the literature about TE around the possibility of ulnar abnormalities being part of the condition. Yes, this is true, but only in association with radial abnormalities, not on their own. So, here, essentially, the ulnar is being pulled around by the absent or hypoplastic radius and is thickened you can see the stress lines in the ulnar. So these are secondary abnormalities. (Fig. 23)

Carpal bone abnormalities. Again, carpal bone abnormalities are frequently described in TE. We know that they occur. What's important though is the type of carpal abnormality that is seen. So, you can see these transverse fusions, these fusions across the rows of the carpals. You can see them here and here, both proximal or distal. You often see absence of or abnormally shaped bones on the radial side, the pre-axial side again, for example, the scaphoid is missing here. The scaphoid and trapezium are missing here.

This is what I want to draw your attention to though.

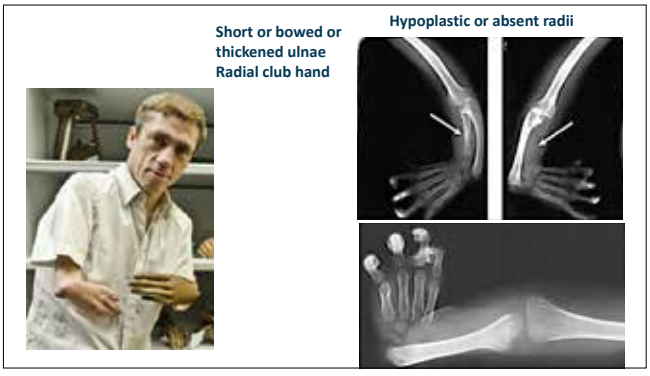


Fig. 22

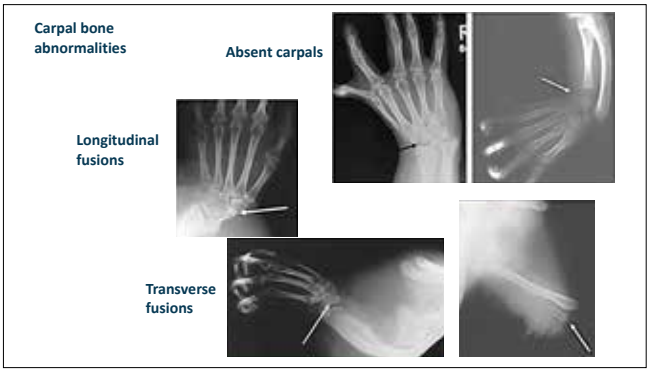


Fig. 23

This longitudinal fusion, this fusion between the scaphoid and the trapezium, this is basically not seen outside of TE. It's really unusual. So, if you see that, that is a characteristic feature seen in TE.

Thumb abnormalities. So, thumb abnormalities can include a triphalangeal thumb, a hypoplastic or absent thumbs, and pre-axial polydactyly. (Fig. 24)

Lower limb abnormalities are analogous to upper limb abnormalities with the exception of the foot. So, you can see the absence of the limb or phocomelia. (Fig. 25)

Moving down the limb, you often see proximal femoral deficiencies. So again, similar to what we've seen with the humerus, you see these unusual looking femora, and the bone itself can often look very unusual, and you can see the proximal deficiency here. You get very shallow acetabula of the hip, and the femora can be short. (Fig. 26)

Again, emphasizing the preaxial abnormalities that are

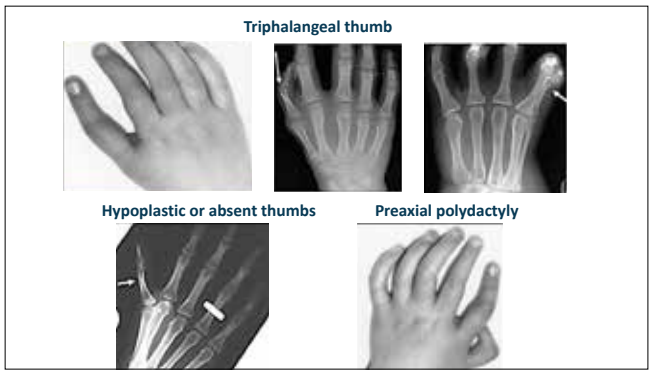


Fig. 24

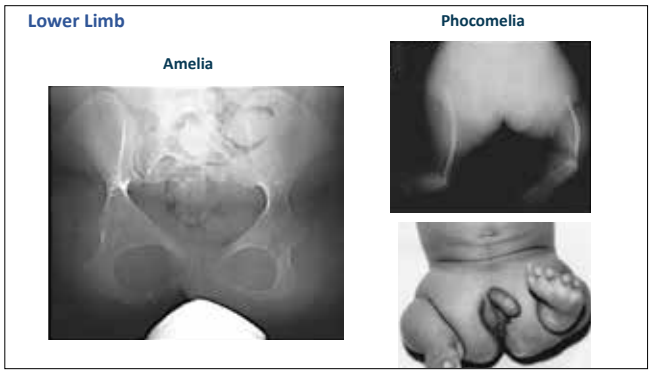


Fig. 25

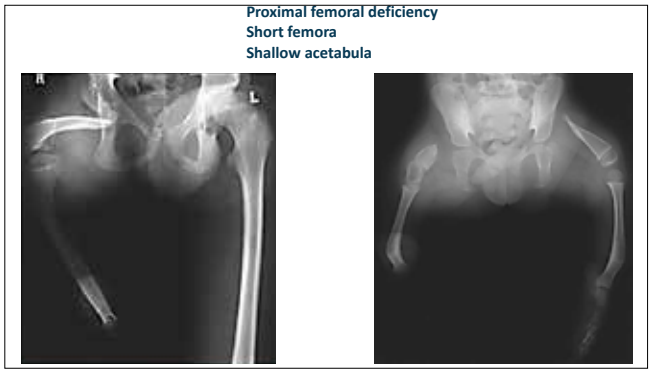


Fig. 26

seen in TE. You see absent or hypoplastic tibiae. The fibula is relatively unscathed in this abnormality. It's relatively preserved. It can be abnormal, but its abnormality again we believe is secondary to that of the tibia. So, it can be dislocated, it can be a bit shorter. In the feet, we tend to see pre-axial polydactyly, so a little different from what you are seeing in the hands with extra digits. (Fig. 27)

You can see fusions in the knee joints. I couldn't find any X-rays that clearly demonstrated that. But fusions in the knee joints are seen, they are just less common. (Fig. 28)

So, what did we do after that? Well, we next reviewed the frequency of each phenotypic feature described in the TE cases, in other syndromes, and then in the general population because we wanted to define what was really characteristic of TE, what were the cardinal features of TE, and what do we not see as part of TE? (Fig. 29)

This is the London Dysmorphology Database, a tool that clinical geneticists have used for many, many years. (Fig. 30)

If you look up TE, you find that there are huge numbers of defects listed. Its fifth in the database for the number of defects associated with it, and there are a lot of genetic syndromes and teratogens in that database.

So, what were the limitations to our approach? We did a literature review and a review of the UK cases initially, but much of the detailed and original clinical information wasn't available. There were no full skeletal surveys. An accurate interpretation of the radiology is crucial, so although there was some great literature out there, we couldn't get ahold of the original old radiographs that the clinical descriptions had been based on. Many of them had been destroyed, so we are relying on what people said that they saw. And when we looked at the radiographs with contemporary eyes, what people had written and what we saw were sometimes quite different. So, accurate and contemporary interpretation is crucial. (Fig. 31)

For a small number of cases that were included, we could clearly recognize an alternate diagnosis, from either their radiology or their photographs. It's very rare to have evidence of thalidomide intake during pregnancy, so it is often presumed, and that's clearly an issue.

So, the conclusion we came to was that we needed an international consensus on the diagnostic criteria for TE. (Fig. 32,33)

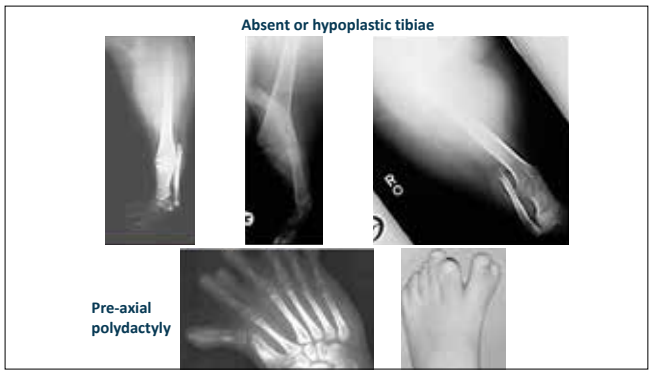


Fig. 27

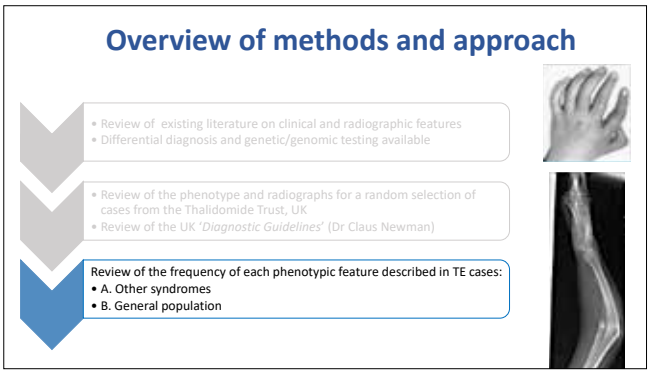


Fig. 28

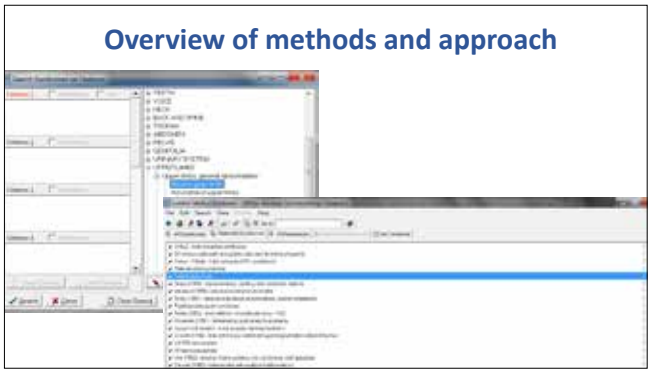


Fig. 29

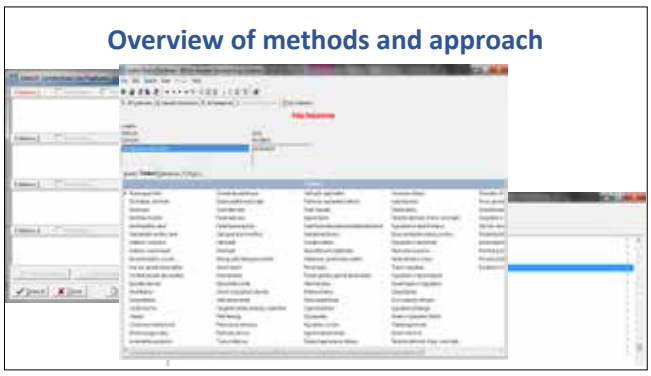


Fig. 30

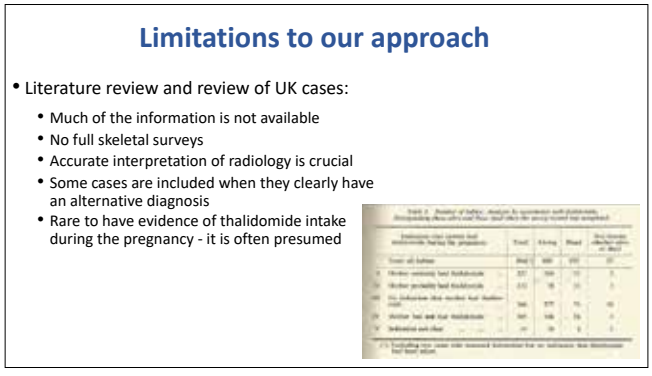


Fig. 31

And, to inform that, we were going to put together a diagnostic algorithm that would help, and that could be refined as part of that international criteria, and we were going to call that diagnostic algorithm DATE. (Fig. 34)

What we basically did was look to create a score that would indicate the likelihood that an individual's abnormalities were due to TE. Those scores were going to be weighted depending on whether the features were classical of TE, so, typical and highly suggestive of TE, otherwise rare, and occurring rarely outside of it. Those unusual fusions that I was talking about, amelia and phocomelia, we would include those, as well as clinical features that are often seen in TE, but rarely outside, rarely in other genetic syndromes.

Nonspecific features of TE that occur both in TE and in other conditions would include things like triphalangeal thumb. We know we see these outside of TE, so, they are not as specific.

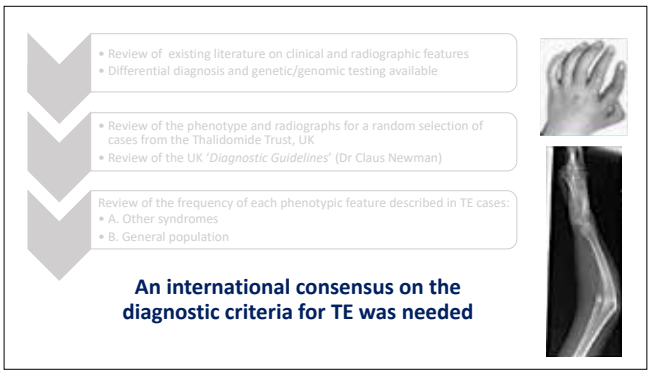


Fig. 32

Fig. 33

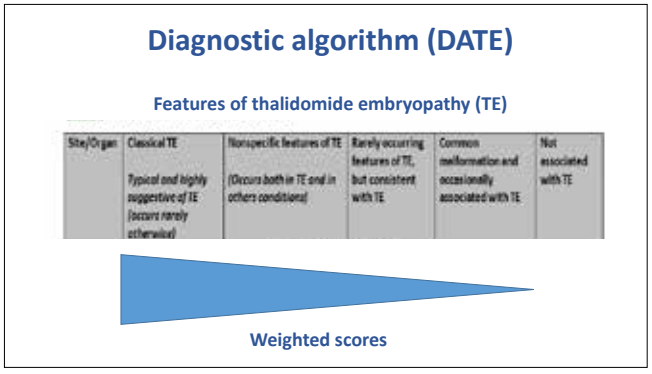


Fig. 34

Common malformations that are occasionally associated with TE would include dislocated hips, for example. Then, also importantly, some presentations are not associated with TE, where we would say we don't need to go any further with our investigations. These would include transverse limb defects, ectrodactyly, isolated unilateral limb defects, and isolated post-axial limb defects. So we gave each feature a weighted score. For some features, we know that one feature always occurs with another feature or more commonly with another feature. For example, facial palsy and Duane abnormality, these would get a combined score that was basically synergistic. In other words, the score was enhanced by that combination occurring together. (Fig. 35)

So, this is what the algorithm looked like. And in fact, it was my husband that originally designed the prototype software for this algorithm, so I'm going to thank him for it. So, this is what it looked like. It was effectively a piece of software, and the user would answer questions with bilateral, unilateral, none, or unclear. They would have a definition and would have radiographs as examples and pictures to help to inform their choice. And at the end, the user would get a score for the case. (Fig. 36)

We also wanted to give an indication of the differential diagnosis. So depending on what features the person put in, the software would pull out the features that were found in that individual, and also in the genetic syndrome, and give you a list of differential diagnoses. Then you could click on that diagnosis and it would give you information, telling

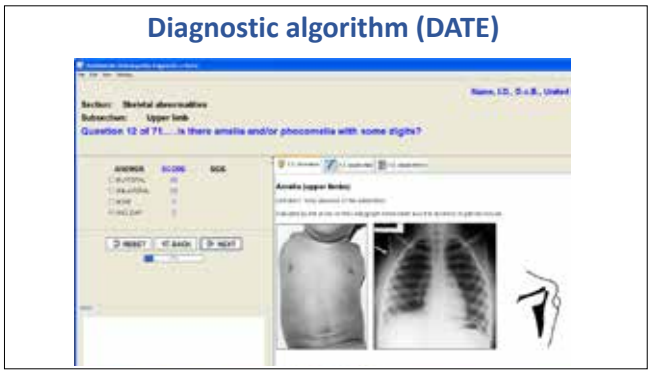


Fig. 35

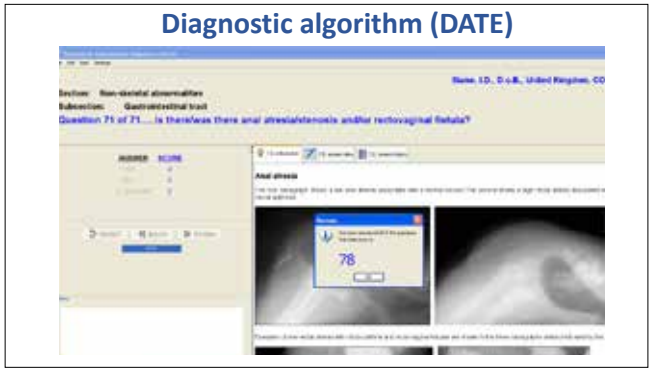


Fig. 36

you about the disorder, the genetic test that was available, and the features that were characteristic of that disorder not found in TE that you might want to look for. (Fig. 37, 38)

And so, we took DATE to a conference organized at the World Health Organization (WHO). We had approached the WHO and explained that TE was still a big problem worldwide and that there was a lack of consensus on the diagnostic criteria. The WHO wanted to invite international experts, many of whom are sitting in this room, to a meeting to use this piece of software and to help us refine this piece of software. The experts were asked to bring cases and to help us to define three score cutoffs: probable TE, possible TE, and unlikely to be TE. (Fig. 39)

So, that conference was over a long time ago now, in 2014, and it was described as an expert workshop to establish the diagnostic criteria for TE. Experts from the UK, Germany, Sweden, Australia, Brazil, America, and EUROCAT came to help us and to be involved in this work.

The goal set out by the WHO was to define the minimum diagnostic criteria required for a diagnosis of TE. The aim of this was to target help and support for victims of TE and to develop a better understanding of the underlying mechanisms.

So, this is a case that Lavinia Schuler-Faccini brought to the meeting: a little boy with TE. This little boy has features, including bilateral upper limb phocomelia, that you can see here. Importantly, you can see his very pointed shoulders. He had bilateral lower limb phocomelia, facial hemangioma, bilateral narrow auditory canals, bilateral hearing loss, and bilateral cryptorchidism, as you can see here. (Fig. 40)

His score was 73, and in terms of the score that we had as a cutoff as probable TE at that time, he very much exceeded that. (Fig. 41)

If you were to put his features into DATE, you would find that the differential diagnosis was Roberts syndrome. But I think you can differentiate his case from Roberts syndrome, genetic testing or not. (Fig. 42)

So, after that conference, we had some spirited debate and discussion about what were really characteristic features of TE, and probably most debate around what were not features of TE. We wanted to take that forward and develop DATE. (Fig. 43)

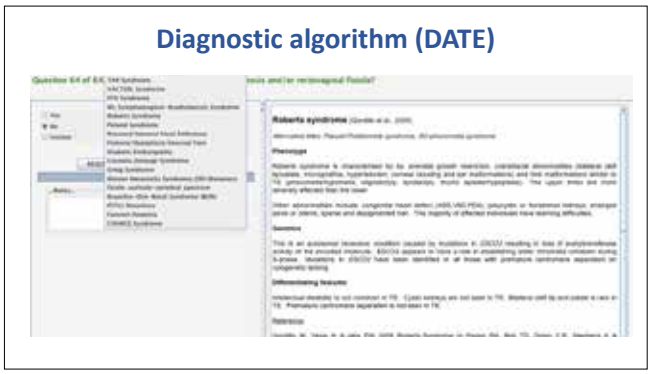


Fig. 37

Fig. 38

Fig. 39

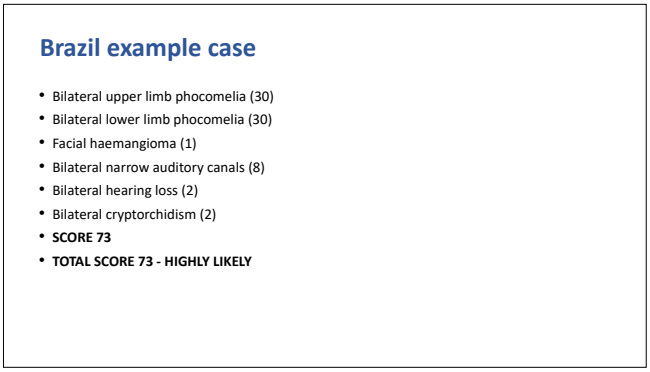


Fig. 40

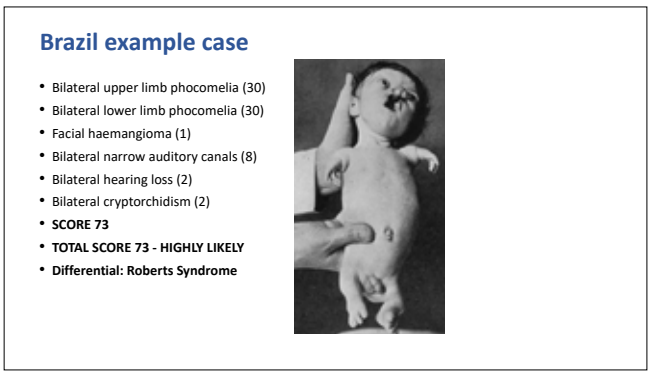


Fig. 41

So, we needed to do some more work, really. We'd had good input at the meeting, but we really needed to validate DATE. And how did we do that? Well, we took these three German papers that were translated and included very extensive information about TE cases. There were 142 cases across these three papers, and really, these three papers contained extremely good information on a case-by-case basis, and that's what we were looking for. We used DATE to assess those cases.

And what we found, which was interesting, was that 87% of cases had upper limb abnormalities, almost all bilateral, a very high proportion of which had amelia and phocomelia. Only two individuals who had lower limb abnormalities did not have upper limb abnormalities.

Anotia and microtia were found in one-fifth of the cases; 26% of individuals with facial hemangioma also had anotia and microtia. Anotia and microtia were found in all of the individuals with facial palsy.

However, although we had really good information in those papers, we couldn't go back and look at individual radiology. Contemporary cases like those from Brazil are therefore really important for us in terms of trying to fully establish the radiological features of TE. You could say we could go back and get repeat radiology for all of the individuals from The Thalidomide Trust. I would debate the ethics of doing that now, but more than that, it wouldn't be a huge amount of use to us because of the damage that would've been done to those joints over the years.

So, the cases that would be most useful going forward for really helping to refine this are cases from countries like Brazil, where we know that we have got contemporary radiology that we can look at. We put all of this work together, refined DATE, and published a clinical review, "An Introduction to the Algorithm", which came out earlier this year.

You've seen this already today. It is a bit of a busy slide, but this was the pathway for assessment of TE that was in our manuscript. I have changed the name to ValiDATE here, so there is one difference. What we had originally included in DATE, and people will possibly remember, that we brought to Geneva in 2014, was that we had questions about the mother's country of residence, date of birth, and negative family history. We've removed that from the software for reasons that you've heard about already today. This is helpful information for us to collect, but it shouldn't be a reason to not go forward with the algorithm. So, we've removed this now, and that was really through direct feedback from the meeting in Geneva. (Fig. 44)

We would suggest that ValiDATE be used only by individuals assessing patients and those being very careful about how you use that sort of information if you are going to use it to exclude TE.

So, the software starts after that point. If you get a low score, then TE is excluded. If your patient has some of those features that I talked about earlier, like a transverse limb defect, you won't go any further and will exclude TE you will get a zero score and it will not let you progress any further. Once you are in ValiDATE, it may be that you find you need further information about the patient. It might be that you cannot answer the questions that are asked because you don't have that information about the case.

If ValiDATE gives you a score that's probable or possible TE, and I'll come down to this in a minute, then further investigations that might be warranted could include a physical examination, further radiographs, and/or genetic testing.

Fig. 42

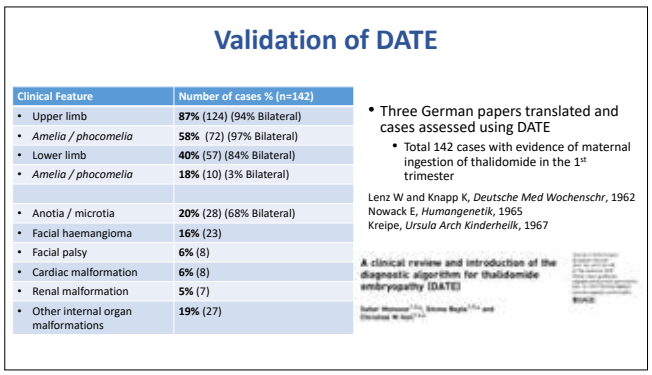


Fig. 43

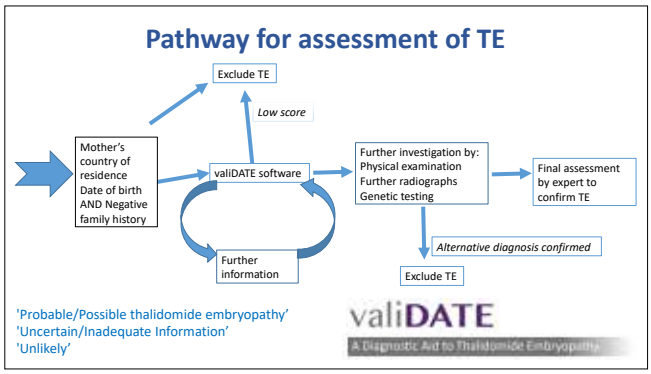


Fig. 44

So ValiDATE, instead of being called a diagnostic algorithm now, is termed a diagnostic aid to TE. It's not a standalone tool that you should use to say yes or no. This is important. It's an aid that's giving you a score of the likelihood an individual suffers from TE.

If after this, an alternative diagnosis is confirmed, then you've excluded TE; if not, then we suggest a final assessment by an expert in TE to confirm or refute the diagnosis.

So, we have also refined our categories I told you about earlier. When we went to the WHO, we had three: probable, possible, or unlikely. Probable and possible have now been merged.

I should touch "Uncertain", inadequate information and unlikely.

So, what have I told you about TE that you did not already know? Not a lot really. It still presents a diagnostic dilemma. The work that we've done has helped to characterize some of the clinical and radiological features. I talked a lot about radiology, but in DATE, we included all of the excellent work that was done by the Swedish teams and others looking at the non-radiological features of TE. Accurate phenotyping will lead us, we hope, to a better understanding of the underlying mechanism. But, most importantly, accurate phenotyping of contemporary cases will help us to really refine the features of TE. (Fig. 45)

So, what's the future? Well, ValiDATE is currently being refined. We have adjusted the scores and criteria in response to the Geneva Conference and some additional work we have done subsequently on cases and with others. We are refining and establishing the final scores within the algorithm, and the software is being beta-tested to assist us all in providing an accurate diagnosis, and to allow us to consider alternative genetic or teratogenic diagnoses for TE. (Fig. 46)

It will be available to everyone soon via an online interface. So any clinician only for clinicians I would point out, reviewing potential TE patients will be able to use this as an aid to the work that they are doing.

The Thalidomide Trust set up the ValiDATE Trust to make sure that this algorithm doesn't just stand still and does not evolve. It will be maintained and refined as new knowledge comes about. We want to continue to review and refine the algorithm, and we would welcome input from others who are experts in this area. (Fig. 47)

This is a picture of the St. George's team that went to Geneva back in 2014. I want to thank you all for listening to me today, and I would also like to say that The Thalidomide Trust would welcome any questions that you have about ValiDATE. This is the e-mail to use if you have any questions. (Fig. 48)

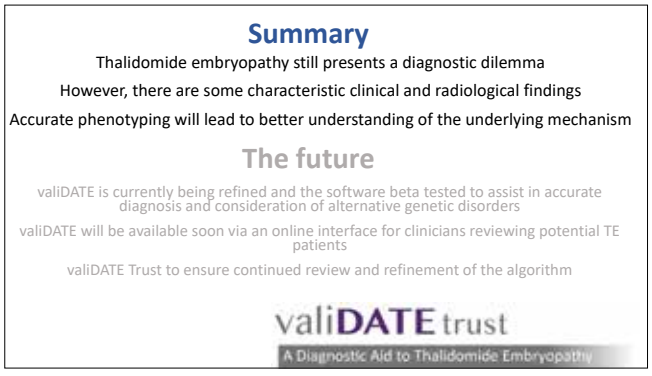


Fig. 45

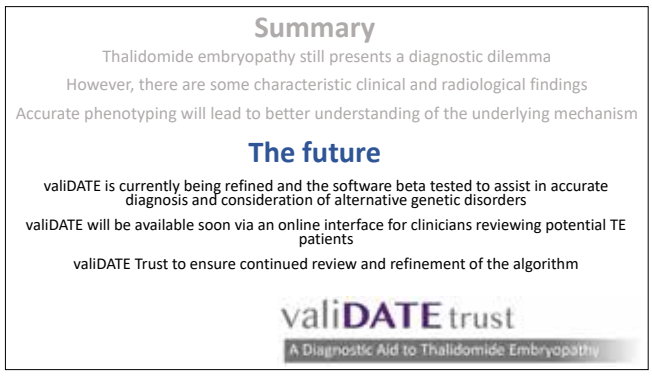


Fig. 46

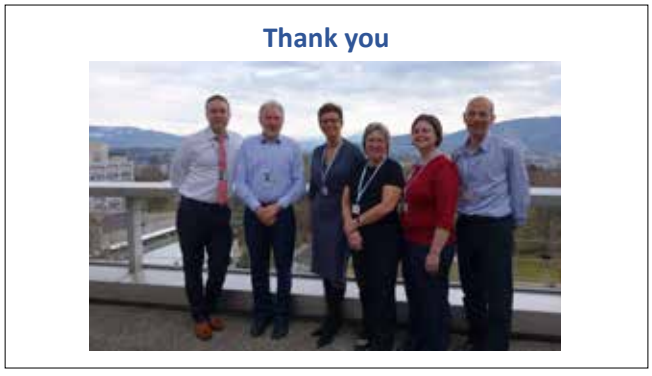


Fig. 47

Fig. 48

Q&A

Ryoji Kayamori: Thank you, Dr. Baple. We are now open to questions or comments.

Nobuhiko Haga: Thank you for your lecture. My name is Nobuhiko Haga from the University of Tokyo. I want to ask about pointed shoulder.

Emma Baple: Yes.

Nobuhiko Haga: You told me that the length of the clavicle is relatively long, so this leads to pointed shoulder. But I wonder if it comes from the true overgrowth of the clavicle or from the hyperplasia of the glenoid fossa or something like that.

Emma Baple: I think it's possibly a combination of both of those things. I think in the Brazilian case, you could really see that point that I am talking about.

Ryoji Kayamori: Any other questions?

Nobuhiko Haga: In the last slide, you told us that the ValiDATE system will be available for all clinicians. So does this mean that it is available also in Japan as long as we clinicians?

Emma Baple: Yes. It's not quite available yet. The software company we are working with is a company called Certus Technology. We need to make sure that the algorithm works the way it did in our software by putting in test cases again and again to make sure there are no glitches in the code. But it will be available online, and there will be a way that you can apply for a password to use it, put in the information, and get back a report for your patients that you are assessing. And that should be this year.

Nobuhiko Haga: Thank you very much.

Ryoji Kayamori: Any other questions or comments?

Klaus M. Peters: I think DATE is a very helpful tool to prove if a victim has a TE. But you say the next step is that one of the experts says it is TE or it isn't. That is still a problem we have to deal with in Germany at the moment. We have a lot of cases in Germany that could be TE. And one group of experts says "it is TE" and the other says "no, it's not", and then the problem is that the cases stay unclear.

Emma Baple: So, what, so, in terms of your question, how do you want to see that addressed? Because I believe that ValiDATE will help to address that.

Klaus M. Peters: Yes. To make the last step a bit easier because we have the Commission in Germany, and the Commission comes to a result and the result is not explained. It's said that it's unlikely and then it's finished.

We haven't used DATE up to now. But I think it will be helpful for us. But the last step will remain a problem because the German Commission normally says no to all new cases.

Emma Baple: Oh, I see. Okay. I can't help with that. But I hope by actually collecting these cases and using this algorithm, we will be able to show them that that position is not correct. So maybe it can help in that way.

Klaus M. Peters: Okay. Maybe I can help with cases.

Emma Baple: Absolutely, we would love that.

Ryoji Kayamori: Okay, next one.

Lavinia Schuler-Faccini: Thank you Emma for your brilliant conference, and this algorithm is going to be very helpful in Brazil. I think that most clinicians using the application are going to be from Brazil. However, my question is, do you have or are you planning to have a genetic panel, and do you use exome sequencing for the differential diagnosis?

Emma Baple: So, the answer to that is, I have together with Dr. Mansour and Professor Hall, put together a list of genetic tests that could be used. And we've done that for, other parts of the world have asked us to do that. I personally think that doing the different, looking at the differential diagnosis for the patient and testing them appropriately for those differential diagnoses is a better way forward. I say that because of the limitations of genetic technologies and the interpretation of the results that come out of genetic technologies.
We could do genome sequencing on all of these individuals, but we will, and I know from having done this for some patients with TE, find variants of uncertain significance in genes. And then you are stuck with, clinically, I do not feel the patient has this disorder, but they now have a variant of uncertain significance in a disorder that's said to have phenotypic overlap with TE, and you are in a worse position than you were to start with because you won't have relatives to test in order to help you to increase your certainty.

So I am in less in favor of that approach and more in favor of the approach we would typically take, which is clinical genetics, which is testing for the disorders that you think the patient may have. And that is really what I guess I feel we should be doing, and if we don't find that they have one of

those, then actually, we have to err on the side of this being TE, particularly in patients who have these characteristic abnormalities that are not found or very rarely found outside of TE.

Lavinia Schuler-Faccini: Thank you very much. I totally agree.

Emma Baple: That's good. That's really good.

Ryoji Kayamori: Next, please.

Christina Ding-Greiner: Thank you for your presentation. It was very interesting. What do you think about asymmetries? I saw in your pictures that the children you showed us were not typically symmetric. And in all the old papers, a certain amount of asymmetry is described. But our foundation states that if a person is asymmetric, there is no possibility of being thalidomide-affected. I can't believe that because if you look at non-thalidomide-affected people, we all are asymmetric.

Emma Baple: I am sorry, I didn't emphasize that in my talk. You do see some asymmetry in TE. What I do not believe you see is isolated unilateral abnormalities. I think that, having reviewed quite a lot of radiology now, what we think is that people misinterpreted the findings, and you do see abnormalities on the other side. They may be less extreme, but you do see some asymmetry.

Christina Ding-Greiner: Okay. Thank you.

Female Participant (Unknown Speaker): Thank you very much. It was really interesting to hear about what you have been doing. About asymmetry, is it anything—can you say if it's asymmetrical malformations on the upper limbs and lower limbs? Because you were saying that the most cases you found had upper limb malformations, which was, if I understood you correctly, a little bit, I mean when, I mean me and my supervisors looked at the all thalidomiders, and in 31, we actually found just five proximal femoral deficiencies, and some of the cases were unilateral.
I mean, we found some other malformations on the other side, but it wasn't PFFD (proximal femoral focal deficiency). However, for the upper extremity, it was more symmetrical, although it wasn't exactly the same. So what, I mean I am getting a little bit confused about what we've been looking at in those 31.

Emma Baple: So I think if you looked, if I've understood, I want to make sure I've understood your question correctly, but if I've understood your question correctly, you will see when I showed that table, I don't know if I can go back to it, can I? I don't know if I can. You will see when you look at the lower limb, I showed you the phocomelia and amelia, we were sure we saw that there was more asymmetry in the lower limbs, exactly as you've said. That was from the German papers.
Sorry, I can't – I haven't got the numbers at hand. What was very interesting about the review of all of the cases that we did was the temporal relationship between the abnormalities. So, I think that's what you are asking, isn't it?

Female Participant (Unknown Speaker): Yes.

Emma Baple: Yes, yes, good.

Ryoji Kayamori: Thank you, Emma. So, we have 1 minute to go. Symmetry or asymmetry, that has been a long-debated point. So, being symmetry with certain variations, that is suspected TE. In Germany, what is the most contentious is symmetric. So, one side, normal or healthy, the other side abnormal, that is not acceptable. That has been extensively debated in Germany. This is a question I would like to ask Dr. Baple. Scores. So 73 is a high score, that is why the diagnosis is TE. And that particular part we are not sure. Probable, possible, unlikely—unfortunately, we do not have enough time to understand the criteria. So diagnostic aid or algorithm, features about a diagnostic aid or algorithm, which is better? Your article title is "Diagnostic Algorithm for TE", but this time you mentioned this as being a diagnostic aid for thalidomide. Which is better?

Emma Baple: Well, I suppose what we were trying to get at with aid as opposed to algorithm was to say that it's an aid. It doesn't mean that you shouldn't use your brain or clinical acumen.

Ryoji Kayamori: Okay, thank you. Thank you very much.

Mechanisms of Thalidomide Teratogenicity

Hiroshi Handa

Department of Nanoparticle Translational Research, Tokyo Medical University, Tokyo, Japan

Nobuhiko Haga (Moderator)

Now, I would like to proceed to the last lecture of the first day of this symposium. The presenter is Professor Hiroshi Handa. He is now working in the Department of Nanoparticle Translational Research at the Tokyo Medical University. He graduated from Keio University, Faculty of Medicine, in 1972, and he obtained his PhD 4 years later. Then, he worked at The Tokyo University Institute of Medical Sciences, and then went to the States to study at the National Institute of Health and Massachusetts Institute of Technology. And then, he came back to Japan and worked at The University of Tokyo, Tokyo Institute of Technology, and the National Institute of Genetics.
So, the title of this paper is "Mechanisms of Thalidomide Teratogenicity". So, please start your lecture.

Thank you, Professor Haga, for your kind introduction. I am happy to have this opportunity to share our interdisciplinary research with you. I would like to talk to you about our work on the mechanisms of thalidomide embryopathy (TE). (Fig. 1)

Here is the content on my talk today. I'll talk about the five topics shown here. (Fig. 2)

So first, I will give you a little background of thalidomide, which is the same as Emma, the former presenter. Thalidomide, its structure shown here, was developed and commercialized as a sedative in the late 1950s. However, thalidomide was completely withdrawn from the market in the early 1960s, shortly after its negative effects on newborns became clear. About 10,000 affected children were born worldwide. On the other hand, thalidomide was later found to be an effective treatment for leprosy and multiple myeloma, and was returned to the market in less than a half century. Thalidomide is now approved for use in patients with multiple myeloma. However, little was still known about its mechanisms of action regarding both its beneficial effects and side effects. (Fig. 3)

Here, I show a timetable of the period in which embryos are sensitive to thalidomide. When pregnant mothers take thalidomide during the days after fertilization, it causes multiple developmental anomalies in their children, such as a shortening or complete lack of the limbs, as well as malformation of the ears and eyes. This indicated that TE develops in time- and site-specific manners, implying multiple actions. (Fig. 4)

This table shows the rate of site-specific anomalies caused by thalidomide. Thalidomide most frequently caused developmental defects of the limbs and ears among a wide range

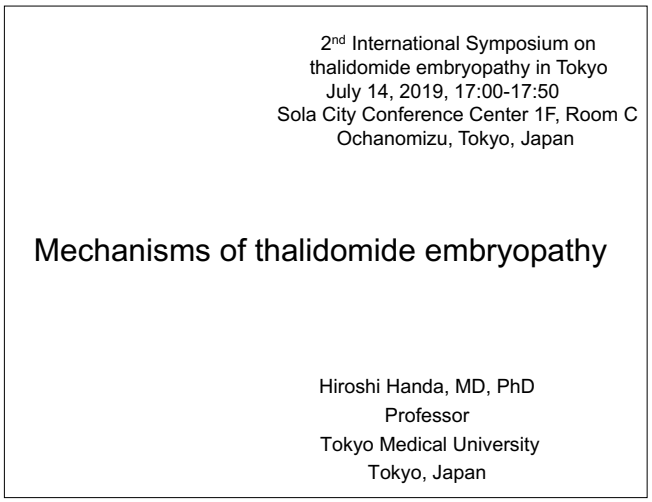


Fig. 1

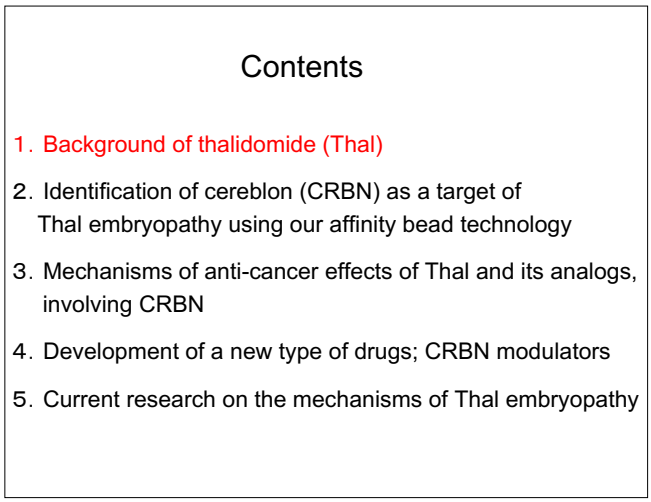


Fig. 2

of anomalies. (Fig. 5)

However, the pathogenic mechanism remained unknown, although various hypotheses, shown here, have been proposed. Disruption of angiogenesis was most commonly supported. But even this hypothesis was not firmly established because the target of thalidomide responsible for embryopathy remained unidentified. (Fig. 6)

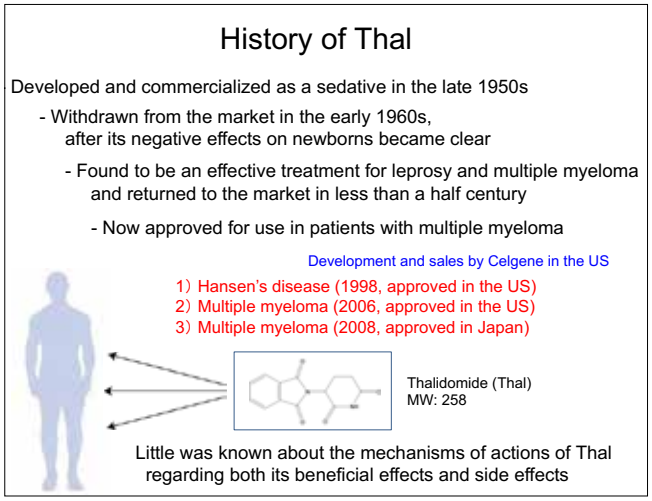


Fig. 3

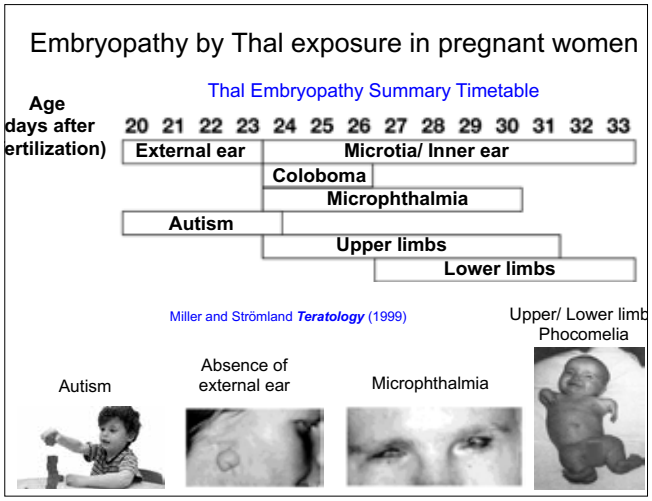


Fig. 4

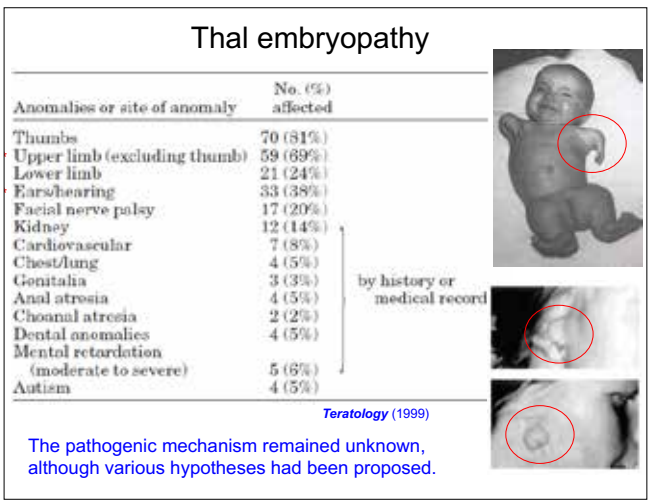


Fig. 5

The target in this case is expected to be a protein that directly and specifically binds to thalidomide with the highest level of binding affinity, resulting in TE.

And now, I'll talk about the identification of cereblon, or CRBN, as a target of TE using our affinity bead technology. (Fig. 7)

To isolate drug-binding proteins directly from protein libraries, we previously developed two types of nano-sized beads as novel matrices for affinity chromatography. (Fig. 8)

First, we developed double-layered latex beads called SG beads, which are composed of styrene-GMA copolymers at the core and poly-GMA at the surface. Then, to enable the automatic isolation of drug-binding proteins, we developed magnetic beads called FG beads, which have magnetite nanocrystals in the core of the SG beads. These beads, now often called Handa beads, have several advantages, including having large numbers of reactive groups, high dispersibility, extremely low nonspecific protein-binding, and resistance to organic solvents. These characteristics greatly increase the recovery rate and purity of the isolated drug-binding proteins.

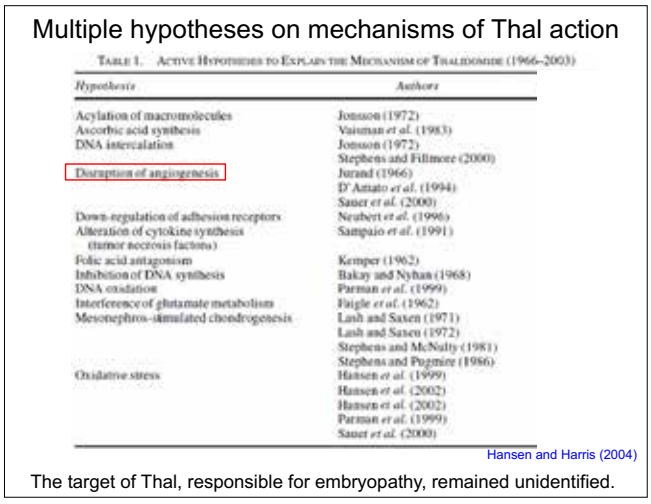


Fig. 6

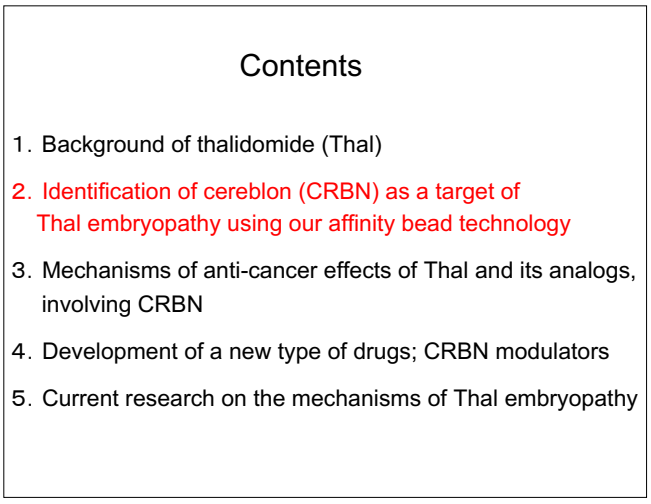


Fig. 7

As shown here, one-step affinity isolation is performed by mixing drug-fixed FG beads with cell lysates for more than 4 hours, and then washing the beads several times by magnetic separation. Then, drug-binding proteins, including targets, are eluted by adding excess drug or surfactant. A single 1.5-mL centrifuge tube is sufficient for the whole process. (Fig. 9)

This bead technology has further advantages. First, the binding specificity of the target to the drug can be assessed using a competitive inhibition assay or a competitive drug elution assay. I will introduce some practical examples of these assays later. Second, binding mode and binding affinity can be roughly estimated by altering the binding, washing, and eluting conditions. Therefore, a potential target that is involved in drug actions can be identified from the acquired information.

Here, I will show an example of the advantages of our bead technology. Alendronate, a drug for osteoporosis, was fixed to the beads through its amino group and mixed with cell lysates for 0.5, 1, 2, 3, and 4 hours, at which time, the proteins binding to the drug-fixed beads were eluted by detergent treatment and analyzed by SDS-PAGE and silver staining, as shown here. (Fig. 10)

The amounts of bound proteins varied with time, and were divided into three groups, namely those showing increased binding, decreased binding, and no change. Competitive inhibition assays showed that the group of proteins showing increased binding with time was selectively competed by the addition of excess alendronate, indicating that they are specific alendronate-binding proteins.

These results indicated that specific drug-binding proteins become concentrated with time, and that our simple bead technology with easy operation is useful for isolating specific drug-binding proteins directly from protein libraries. By the way, these isolated proteins were identified as dynamin 2, which binds directly to alendronate, and its associated protein, sorting nexin 9.

Here is a list of various ligands, including pharmaceuticals, biomolecules, and toxic chemicals, for which we have identified targets using our bead technology and published our findings, as shown here. As you can see, the list includes thalidomide. And now, I'll talk about our identification of

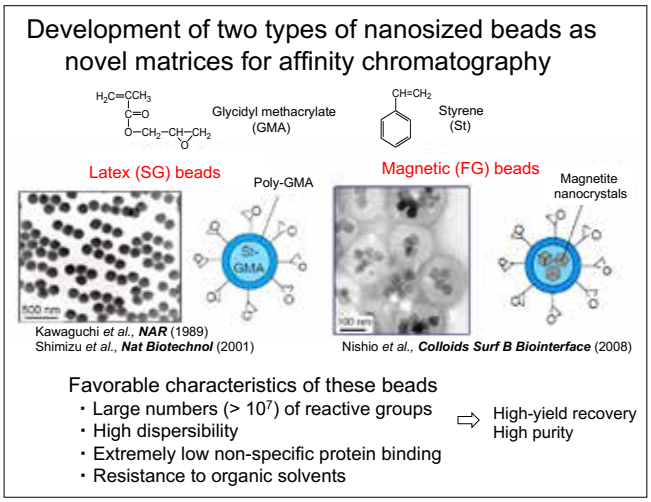


Fig. 8

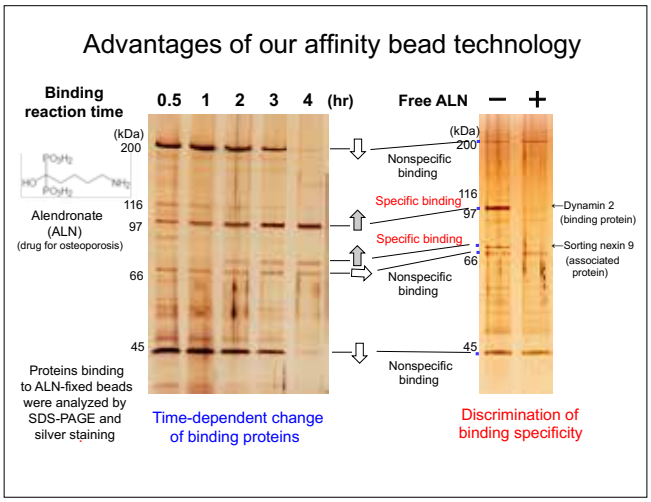


Fig. 10

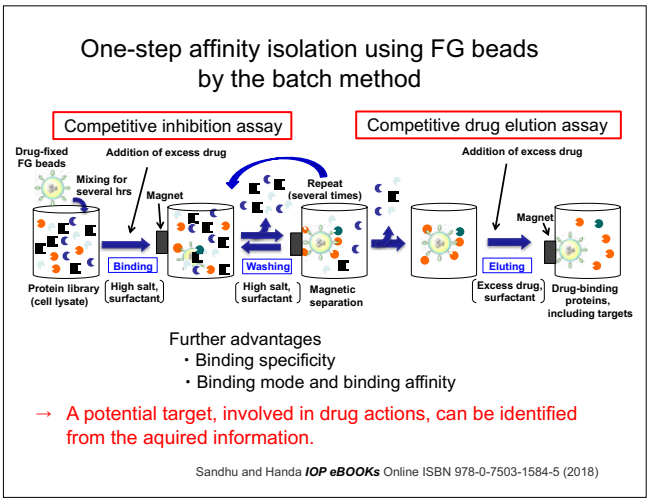


Fig. 9

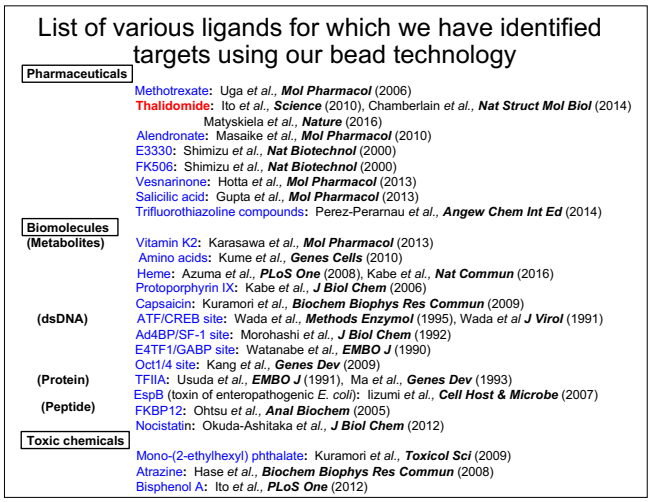


Fig. 11

the target of thalidomide.(Fig. 11)

To isolate and identify the molecular targets of thalidomide, we fixed a carboxylated derivative of thalidomide to our beads and then treated the beads with acetic anhydride to mask unreacted amino groups via acetylation and deduce nonspecific protein-binding caused by ionic interactions. (Fig. 12)

Then, the beads were mixed with cell lysates for several hours. After washing, the bound proteins were eluted by adding excess thalidomide, which is known as a competitive drug elution assay. (Fig. 13)

We isolated two proteins that selectively bind to thalidomide, which were competed by adding excess thalidomide to the binding reaction, which is known as a competitive inhibition assay. Then, we identified these proteins as damage-specific DNA-binding protein 1, called DDB1 for short, and cereblon by mass spec analysis. Both proteins were confirmed by immunoblotting using their specific antibodies.

Using the recombinant proteins and our affinity bead technology, we found that thalidomide directly binds to cereblon, but not to DDB1. (Fig. 14)

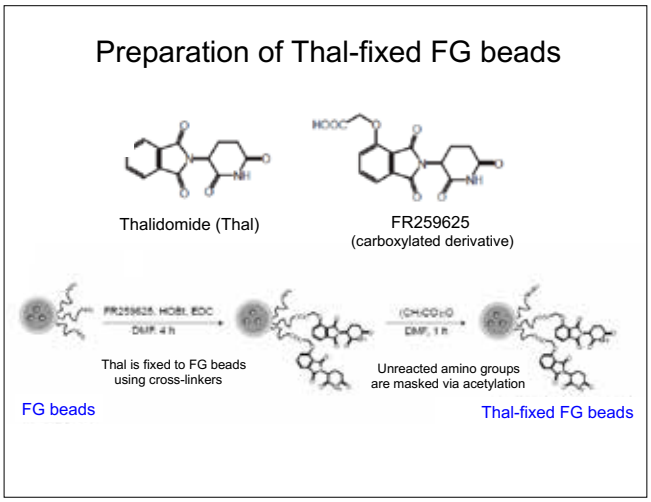


Fig. 12

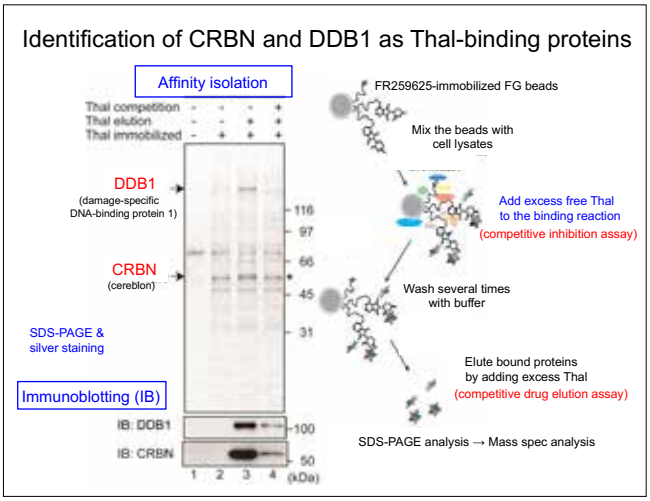


Fig. 13

We also found that cereblon is part of a ubiquitin ligase complex. Co-immunoprecipitation experiments showed that cereblon interacts with DDB1, CUL4, and ROC1. It is widely known that DDB1, CUL4, ROC1, and an established substrate receptor, such as DDB2, CSA, etc., form an E3 ubiquitin ligase complex, which is involved in the ubiquitination and degradation of substrate proteins. The question here was whether cereblon functions as a substrate receptor, and if so, whether it would compete with DDB2 for binding to DDB1. (Fig. 15)

As shown here, the amount of DDB1 co-precipitated with cereblon was gradually reduced as the amount of DDB2 was increased, indicating that DDB2 competes with cereblon for binding to DDB1. This suggested that cereblon works as a substrate receptor.

As the previously identified substrate receptors were known to undergo auto-ubiquitination, we analyzed cereblon ubiquitination in cells treated with the proteasome inhibitor MG132. As shown here, cereblon was found to be ubiquitinated, and its ubiquitination was sensitive to thalidomide. (Fig. 16)

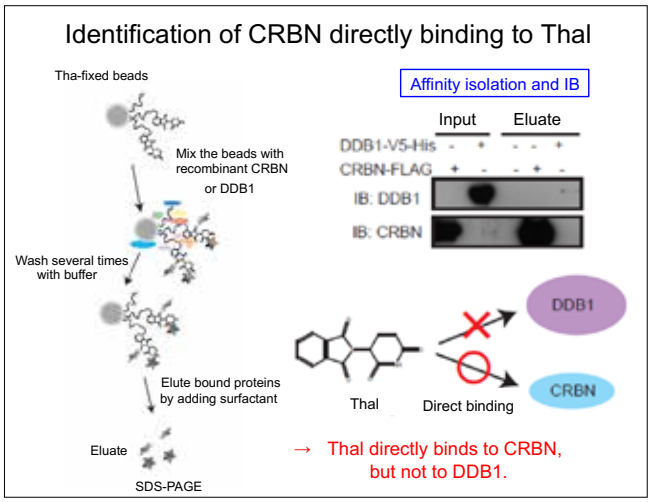


Fig. 14

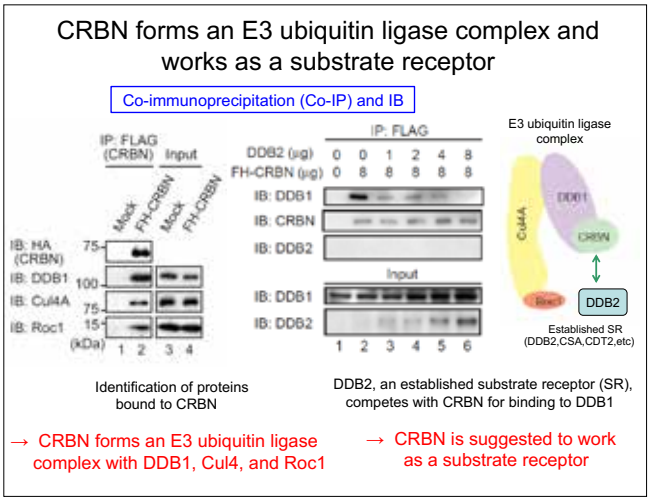


Fig. 15

We also examined the expression of thalidomide-binding cereblon and DDB1 in various cells using our affinity bead technology. We found that cereblon and DDB1 are ubiquitously expressed in all cells that were tested. Unexpectedly, mouse cereblon also binds to thalidomide, although rodents do not develop TE. (Fig. 17)

Next, we investigated the possible association between cereblon and TE in zebrafish, which has several advantages as an experimental animal, as shown here. Zebrafish cereblon shared 70% homology with human cereblon. The first thing we did was to make sure that zebrafish has a human cereblon homolog that can bind to thalidomide and interact with human DDB1. As the effect of thalidomide on zebrafish development was not yet known, fertilized zebrafish eggs were allowed to develop in media containing thalidomide. (Fig. 18)

When treated with thalidomide, there were no gross morphological changes except for in the pectoral fin, which was significantly smaller than that of control embryos. The fin defects were clearly detected by alcian blue staining of cartilage. We also found that the development of the otic vesicle, which is the zebrafish equivalent of the ear, was significantly affected. These results indicated that thalidomide causes similar developmental anomalies in zebrafish and in humans. (Fig. 19)

Our next question was how can we definitively prove that cereblon is the true target of thalidomide involved in embryopathy? If TE is suppressed by a cereblon mutant that does not bind to thalidomide, but is otherwise functional, we can confirm that cereblon is the true target of thalidomide, leading to embryopathy. Thus, we designed cereblon mutants that do not bind to thalidomide. (Fig. 20)

We first identified the thalidomide-binding site as the C-terminal region of cereblon. Then, we found that that the tyrosine 384 and tryptophan 386 of cereblon are important for binding to thalidomide, and the double-point mutant does not bind to thalidomide. (Fig. 21)

The double-point mutant formed the E3 ubiquitin ligase complex with DDB1, CUL4, and ROC1, and was auto-ubiquitinated. The mutant was co-localized with wild-type cereblon. As expected, the ubiquitination of the double-point mutant was not affected by thalidomide. So we successfully

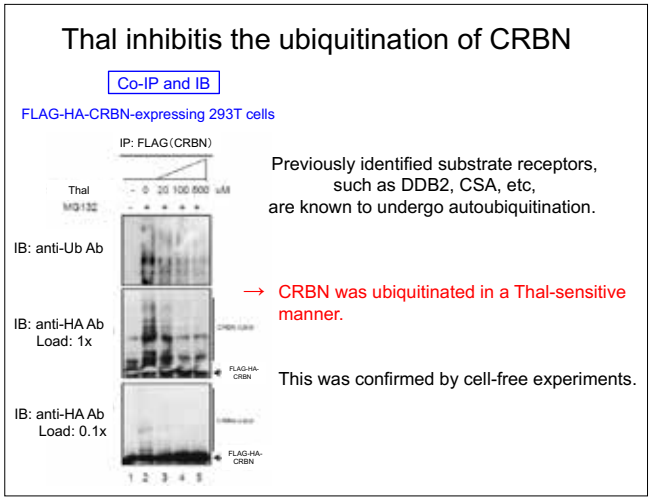


Fig. 16

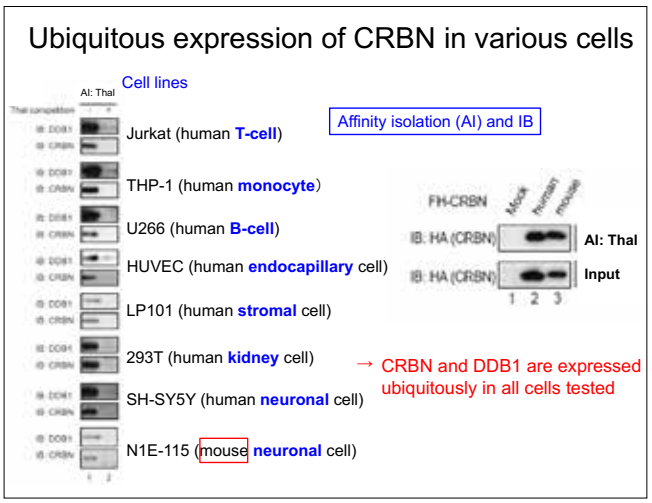


Fig. 17

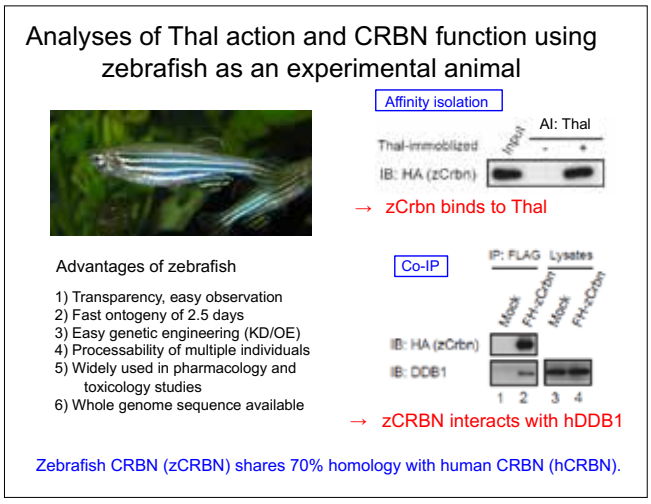


Fig. 18

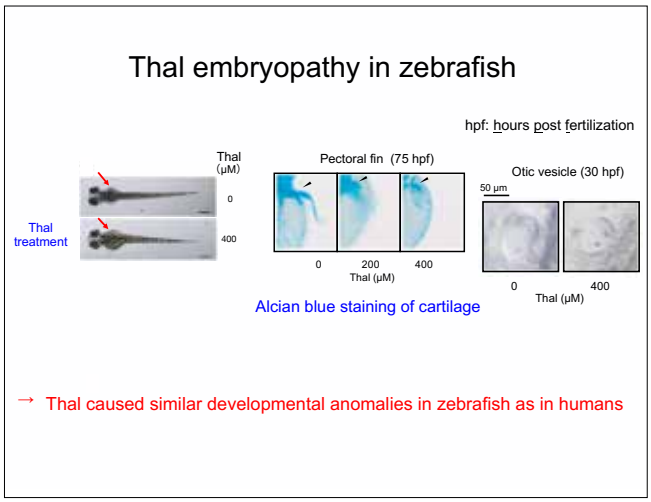


Fig. 19

identified a double-point mutant of cereblon that does not bind to thalidomide, but is otherwise functional.

I show here that the expression of our double-point mutant suppresses thalidomide-induced embryopathy in zebrafish. Embryos expressing wild-type cereblon were still sensitive to thalidomide as much as control embryos, but embryos expressing the double-point mutant were resistant to thalidomide. Essentially, the same results were obtained when analyzing the otic vesicles. We therefore confirmed that cereblon is a bona fide target of TE. (Fig. 22)

Next, we analyzed the potential involvement of the key signaling molecules such as FGF8 and Sonic hedgehog in TE. FGF8 is essential for pectoral fin formation along the proximal–distal axis, and is expressed in the apical ectodermal ridge, called AER for short. Sonic hedgehog is crucial for the pectoral fin development along the anterior–posterior axis, and is expressed in the zone of polarizing activity, called ZPA. (Fig. 23)

Thalidomide significantly reduced FGF8 expression, as shown here, but had little effect on Sonic hedgehog expression. In addition, the expression of the double-point mutant suppressed the thalidomide-induced downregulation of FGF8. These results hence indicated that FGF8 is a main downstream factor of cereblon and thalidomide.

We also investigated the possible connection between cereblon and TE in chicks, which had been routinely used as an animal model for TE. We first confirmed that chick cereblon can also bind to thalidomide and interact with human DDB1. Next, we administered thalidomide to this region of the egg, which strongly inhibits formation of the forelimbs only at the site of administration. This result indicated an important issue that thalidomide itself, rather than its active metabolites in the liver, is a causative agent of embryopathy, because the opposite forelimb is not affected at all. (Fig. 24)

Expression of the double-point mutant of cereblon significantly inhibited thalidomide-induced embryopathy and the downregulation of FGF8/FGF10 expression in chicks. Therefore, our findings in zebrafish were validated in chicks. (Fig. 25)

It had been considered that thalidomide-induced disruption of angiogenesis is a major cause of the developmental defects of pectoral fins. To address this issue, we analyzed TE using fli1:EGFP transgenic zebrafish that express a GFP

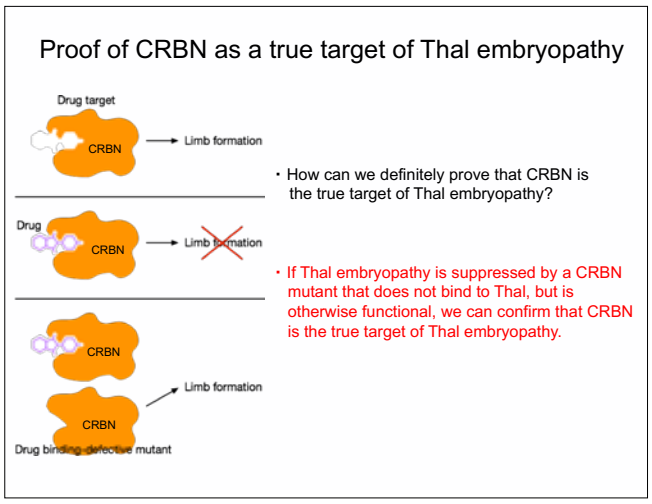


Fig. 20

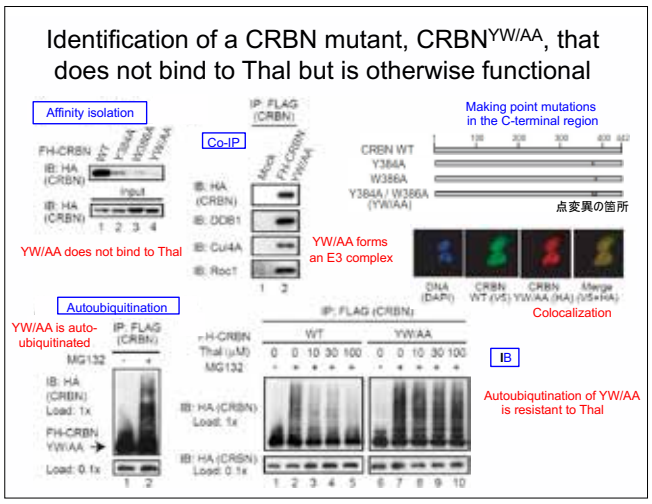


Fig. 21

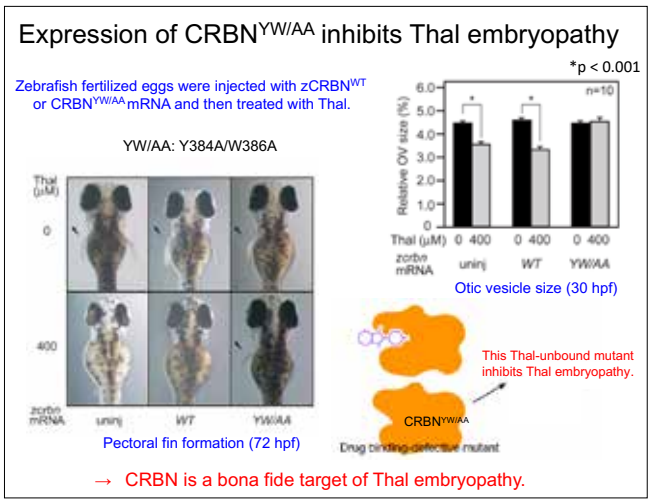


Fig. 22

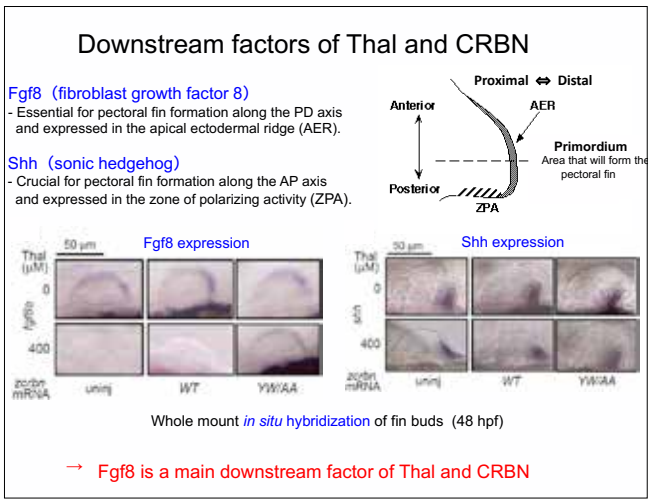


Fig. 23

fusion protein in the marginal blood vessels to visualize angiogenesis. (Fig. 26)

At 52 hours post-fertilization, both angiogenesis and pectoral fin formation were inhibited by thalidomide treatment. But at 48 hours post-fertilization, the marginal blood vessels were not yet formed, whereas pectoral fin development was clearly inhibited. These results showed that the thalidomide-induced deformity of pectoral fins occurs prior to angiogenesis.

Here is a summary of our major findings regarding cereblon up to this point, which were published in Science. We identified cereblon as a thalidomide-binding protein using our affinity bead technology. Cereblon forms an E3 ubiquitin ligase complex with DDB1, Cul4, and Roc1, works as its substrate receptor, and contributes to the normal development of the limbs and otic vesicles in zebrafish and chick models. Cereblon is a target of TE, and thalidomide exerts its teratogenic effects by binding to cereblon and altering cereblon E3 ubiquitin ligase activity. (Fig. 27)

Thus, our results indicated that thalidomide affects cereblon E3 ubiquitin ligase activity by binding to cereblon, suggesting two possible mechanisms of thalidomide action. One is that thalidomide blocks the binding of a natural substrate to cereblon. The other is that thalidomide alters the substrate specificity of cereblon. I will discuss a possible answer to this later in my talk. (Fig. 28)

Now, I will talk about the involvement of cereblon in anticancer effects of thalidomide and its analogs, and the mechanisms of their anticancer effects via cereblon. (Fig. 29)

In recent years, second-generation thalidomide analogs, including lenalidomide and pomalidomide, have been developed and commercialized. Lenalidomide and pomalidomide are much more effective than thalidomide against multiple myeloma. Lenalidomide is also approved as a treatment for MDS 5q minus syndrome and T-cell leukemia/lymphoma. (Fig. 30)

In addition to the activity of inhibition of multiple myeloma cell growth, these three drugs have immunomodulatory activity, that is, T-cell activation activity. Therefore, they are called immunomodulatory drugs, or IMiDs for short. We

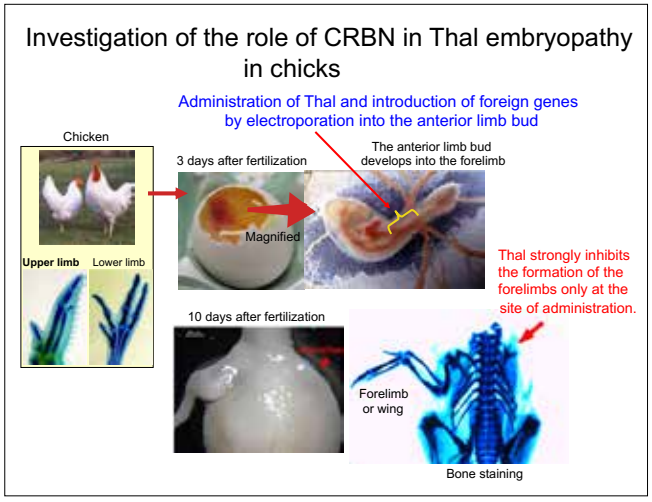


Fig. 24

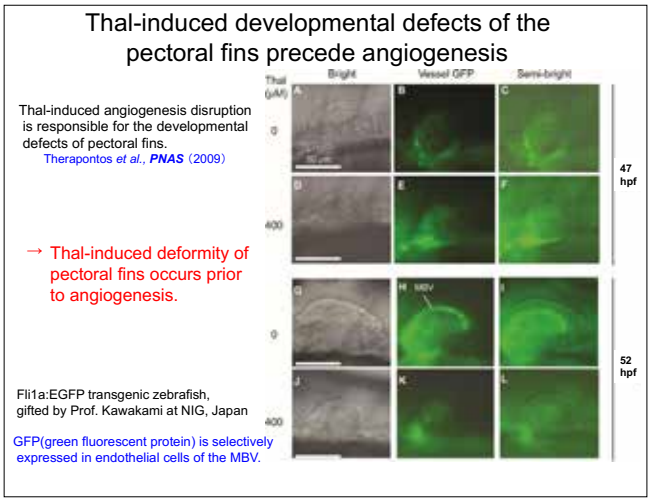


Fig. 26

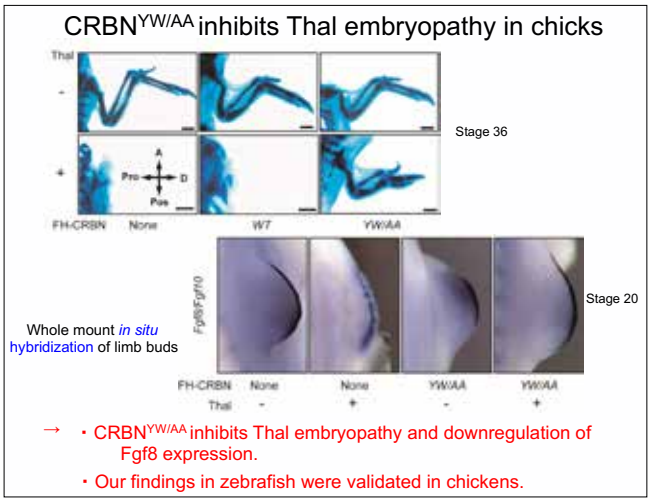


Fig. 25

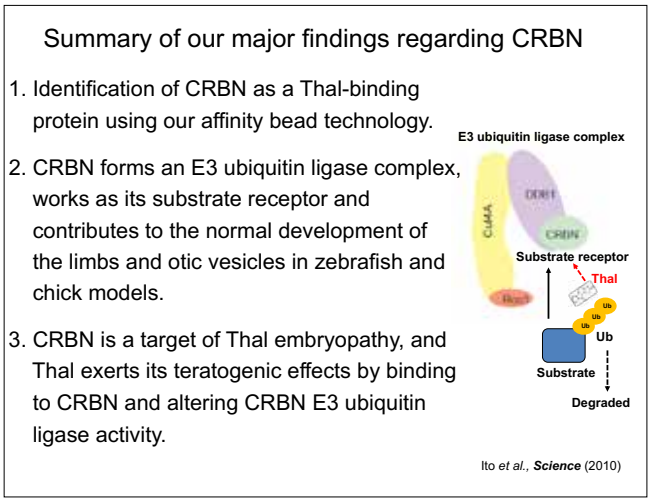


Fig. 27

hence tried to demonstrate whether cereblon is involved in the anticancer effects of IMiDs in collaboration with Celgene, which is the pharmaceutical company that returned thalidomide to the market and developed and commercialized second-generation thalidomide analogs.

To answer this question, we first investigated the association between cereblon and the anticancer activities of IMiDs. We used multiple myeloma-derived OPM2 cells, which are sensitive to IMiDs, as shown here. However, cereblon-knockdown resulted in the resistance of the cells to IMiDs. Then, we established lenalidomide-resistant cells by culturing multiple myeloma-derived DF15 cells in the presence of lenalidomide for a long time, which resulted in the cells becoming resistant to lenalidomide and pomalidomide. In the resistant cells, cereblon expression was clearly decreased. These results indicated that cereblon is involved in the anticancer activity of IMiDs. A research group at the Mayo Clinic also reported the same results. (Fig. 31)

Previous studies and our results showed that when OPM2 cells are treated with IMiDs, IRF-4, and c-myc, which reciprocally regulate each other and are essential for the growth and survival of multiple myeloma cells, they are usually downregulated, but p21, which inhibits cell cycle progression, is upregulated, though not in all cell lines. However, these IMiD-induced gene expression changes were not observed upon the silencing of cereblon, indicating that IMiDs downregulate the expression of IRF-4 and c-myc via cereblon, leading to the growth inhibition of multiple myeloma cells. (Fig. 32)

We then elucidated the 3D structure of the IMiD-human cereblon complex by X-ray crystallographic analysis. We found that the glutarimide ring common to IMiDs is inserted into a triple tryptophan hole in the C-terminal region of cereblon. (Fig. 33)

This slide shows the novel substrates identified that bind to the cereblon–IMiD complex. Novel substrates of cereblon, common to IMiDs, were identified as Aiolos and Ikaros, which are zinc finger transcription factors involved in lymphoid development and differentiation. The binding of IMiDs to cereblon recruits Aiolos and Ikaros as novel substrates

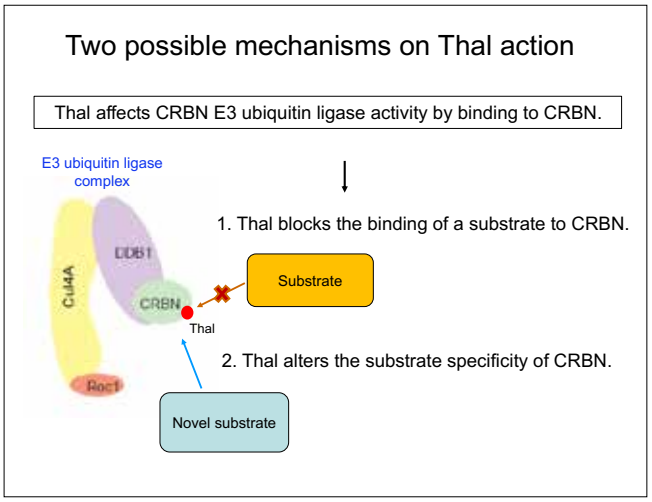


Fig. 28

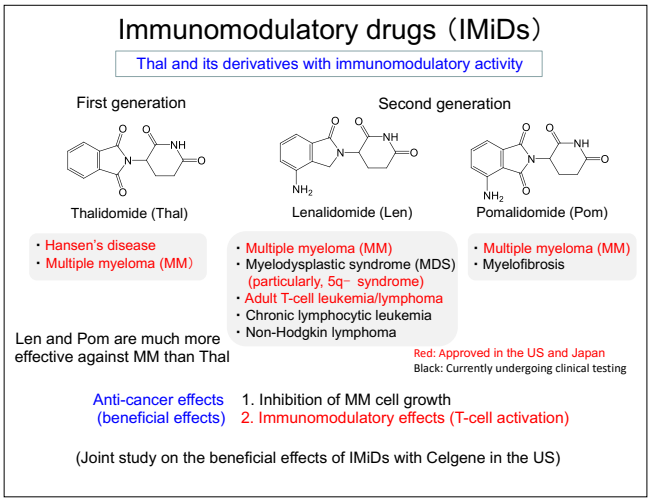


Fig. 30

Contents

Fig. 29

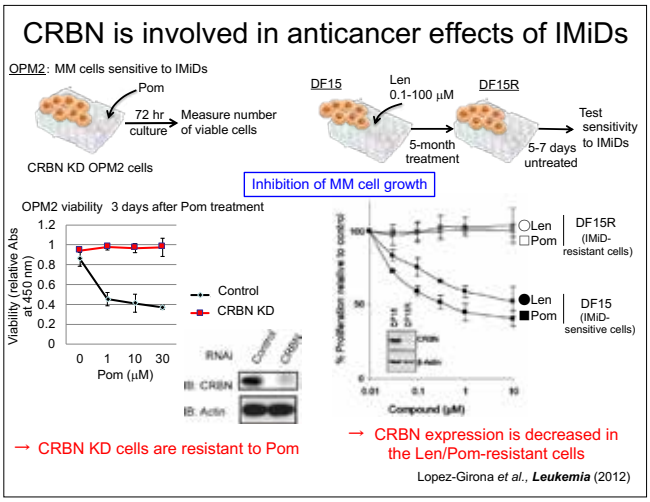


Fig. 31

and induces their ubiquitination and degradation, leading to a therapeutic effect against multiple myeloma. (Fig. 34)

In addition, a novel lenalidomide-specific substrate of cereblon was also identified as the enzyme casein kinase 1A1 or CK1a. The binding of lenalidomide to cereblon induces CK1a ubiquitination and degradation, leading to an effective treatment for 5q minus syndrome.

Now, I will talk about the optical isomers of thalidomide, which have an asymmetric carbon, named S-thalidomide and R-thalidomide. In 1979, Blaske proposed the hypothesis that S-thalidomide and R-thalidomide are involved in the side effects and main effects of thalidomide, respectively. As we identified cereblon as a target of both the main effects and side effects of thalidomide, we were in the best position to prove this hypothesis scientifically, although the main effects are not sedative effects, but anticancer effects. (Fig. 35)

Thus, we analyzed whether the optical isomers of thalidomide interact differently with cereblon and have different functions, in collaboration with Professor Hakoshima at the NARA Institute of Science and Technology and Professor Shibata at the Nagoya Institute of Technology.

I will not go into the details of our experimental data. I will simply talk about our conclusion. (Fig. 36)

Our biochemical and 3D structural analyses indicated that S-thalidomide has a much higher affinity for cereblon than does R-thalidomide, and that S-thalidomide is mainly involved in both the anticancer and teratogenic effects of thalidomide. Furthermore, thalidomide is easily racemized under physiological conditions. Therefore, S-thalidomide preferentially binds to cereblon, and then, the remaining R-thalidomide will be readily racemized, leading to a supply of S-thalidomide. So, we concluded that the optical isomers of thalidomide are not a crucial issue for its drug action.

Next, I will talk about the development of a new type of drug, cereblon modulators. (Fig. 37)

Here's a summary of the development of cereblon modulators. Second-generation thalidomide analogs have been developed and used for the treatment of multiple myeloma and 5q minus syndrome. More recently, third-generation thalidomide analogs have been developed. These analogs,

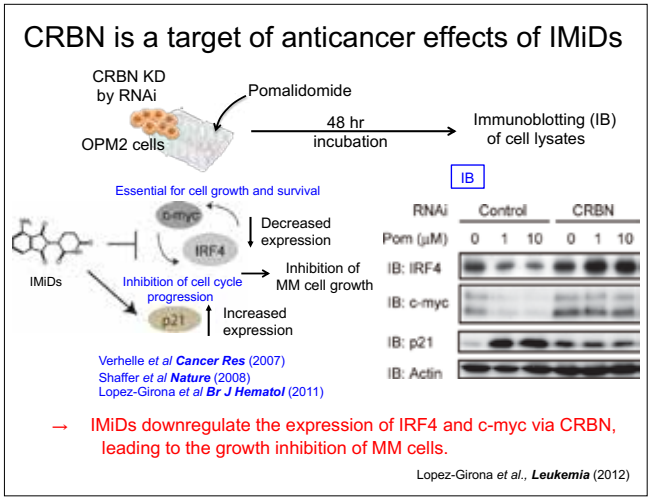


Fig. 32

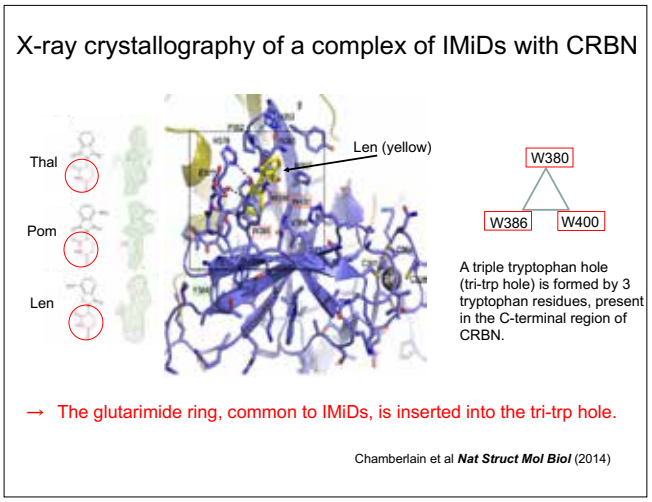


Fig. 33

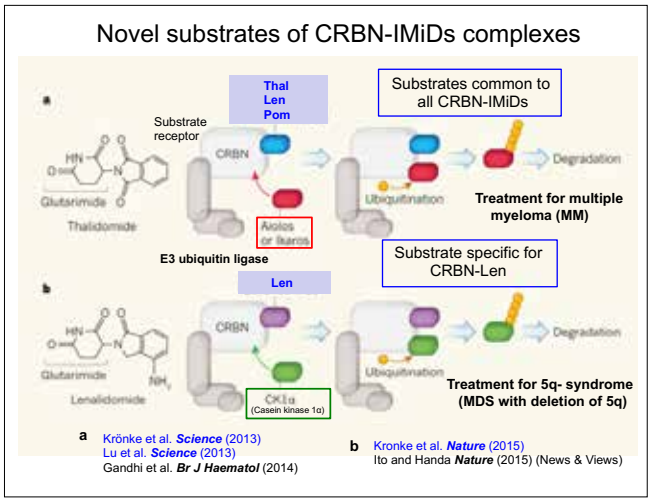


Fig. 34

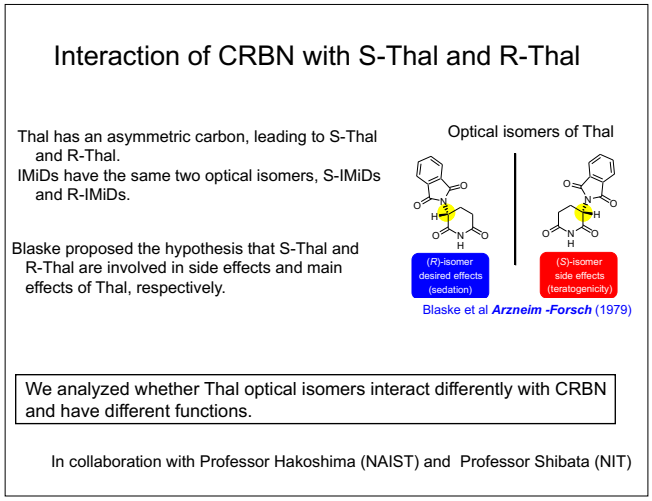


Fig. 35

CC-122 and CC-885, were found to exert favorable therapeutic effects against diffused large B-cell lymphoma and acute myeloid leukemia, called AML for short. (Fig. 38)

For CC-122, the neosubstrate, which is what these types of substrates are called instead of substrates, is not yet known, but the key neosubstrate of CC-885 was identified as GSPT1, a regulator of translational termination. As these analogs do not fit the category of IMiDs, thalidomide and its analogs are now collectively called "cereblon modulators".

We reported the 3D structure of the complex of cereblon, CC-885 and GSPT1, which was published in Nature.

I will just talk about our results on CC-885. CC-885, which has the structure shown here, exerts anticancer effects on various types of cancers, and is particularly effective against AML. Here, I show that the leukemic cells of AML patients are highly sensitive to CC-885 compared with normal lymphoid cells. I also show here that knockout of cereblon abolishes the anticancer activity of CC-885, indicating that CC-885 exerts anticancer effects via cereblon. (Fig. 39)

We identified GSPT1 as a novel neosubstrate of cereblon in the presence of CC-885 by co-immunoprecipitation experiments, as shown here. CC-885 induced the cereblon-dependent degradation of GSPT1. (Fig. 40)

We found that glycine 575 of human GSPT1, which is not present in yeast GSPT1, is essential for the CC-885-induced degradation of GSPT1, because the G575N mutant is resistant to CC-885. AML cell lines expressing this substitution mutant are resistant to CC-885, indicating that GSPT1 is a novel neosubstrate of cereblon and involved in the anticancer effects of CC-885.

Here, I show images of GSPT1 binding to the CC-885/cereblon/DDB1 complex, taken by cryo-electron microscopy. X-ray crystallographic analyses showed that CC-885 binds to cereblon and works as a molecular glue that attaches GSPT1 to cereblon. (Fig. 41)

We found various similarities between the actions of thalidomide and its analogs. Thalidomide and its subsequently developed analogs, which collectively are called cereblon modulators, bind to cereblon, recruit their unique neosubstrate, induce ubiquitination and degradation of the neosub-

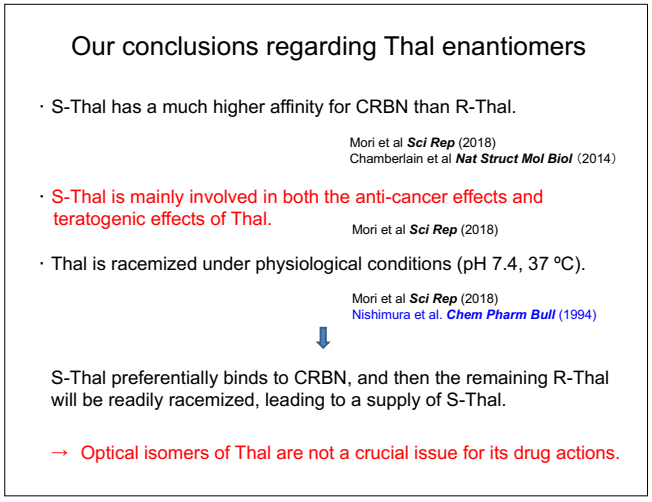


Fig. 36

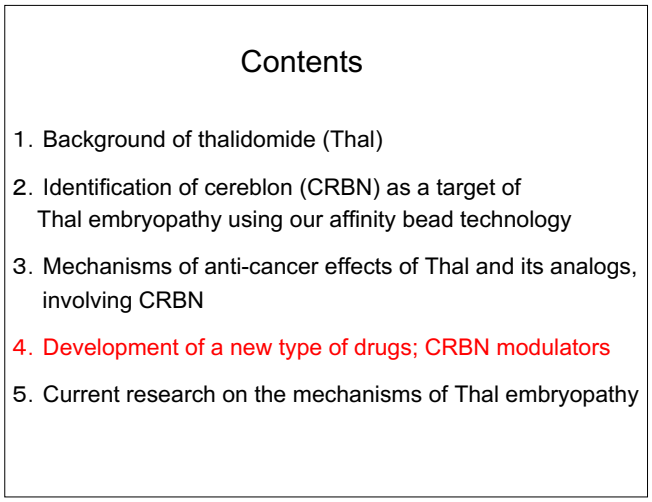


Fig. 37

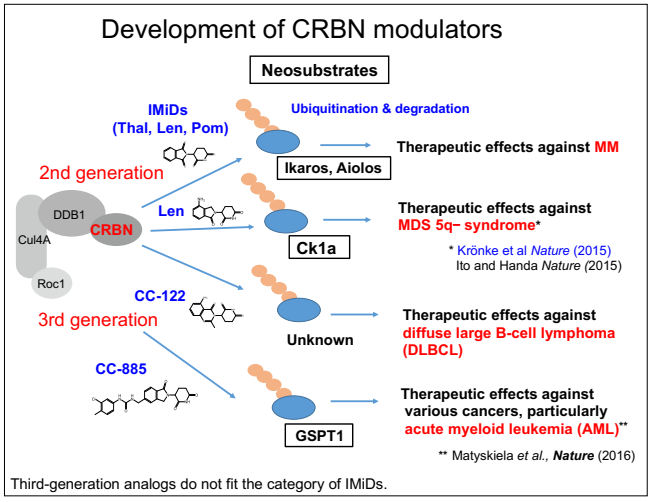


Fig. 38

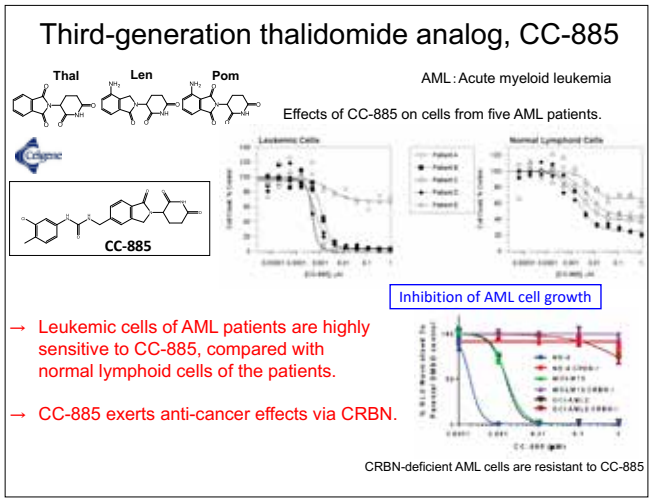


Fig. 39

strate, and exert anticancer effects. (Fig. 42)

I presented two possible mechanisms on the actions of thalidomide a while ago. And now, it is reasonable to predict that thalidomide alters the substrate specificity of cereblon.

In the last part of my talk, I will discuss the mechanisms of TE. (Fig. 43)

We have shown that when thalidomide forms a complex with cereblon, Aiolos and Ikaros are recruited as novel neosubstrates to the complex, and then ubiquitinated and degraded, leading to the anticancer effects of thalidomide. So, it is imaginable that thalidomide also exerts its teratogenic effects via cereblon in a similar way. (Fig. 44)

On that note, two research groups in the US reported that Sall4, which regulates the induction of differentiation, is a neosubstrate of thalidomide. They found that Sall4 degradation was most enhanced when iPS cells were treated with thalidomide. Thalidomide treatment in fact caused cereblon-dependent Sall4 degradation in iPS cells, and also decreased Sall4 expression in the forefoot of rabbit embryos. There was also a report that a genetic disease of humans involving malformation of the hands and eyes is caused by a mutation in Sall4. (Fig. 45)

These research groups also showed that, in the presence of thalidomide, Sall4 binds to cereblon in the case of humans, but not in the cases of zebrafish or mice.

These studies have two weak points. The first is that although TE develops in primates, rabbits, chicks, and zebrafish, Sall4 degradation does not occur in chicks and zebrafish.

The second is the absence of a rescue experiment for TE using wild-type Sall4 and its thalidomide-unbound mutant. Therefore, Sall4 might be partly involved in the multiple phenotypes of TE, and there may be neosubstrates other than Sall4.

We have actually found novel neosubstrates in collaboration with Luisa Guerrini at the University of Milan, Italy. I would like to talk about the details, but they are still unpublished results. So I ask you for your understanding and will call it LD1 here. There are reports of genetic diseases caused by LD1 mutations in humans and mice. Thalidomide induced the binding of LD1 to cereblon and the ubiquitination

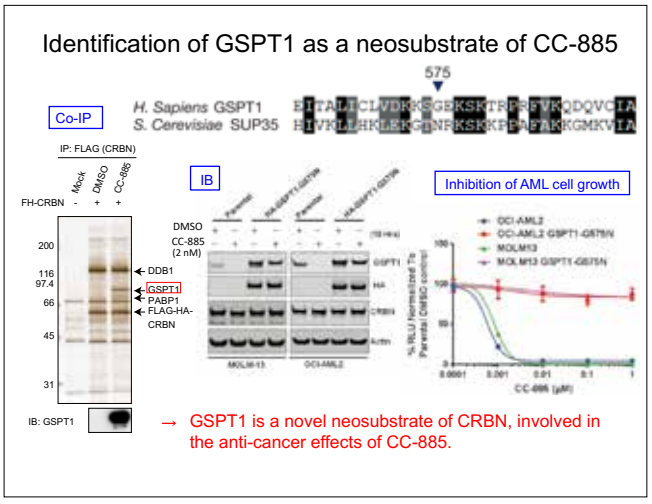


Fig. 40

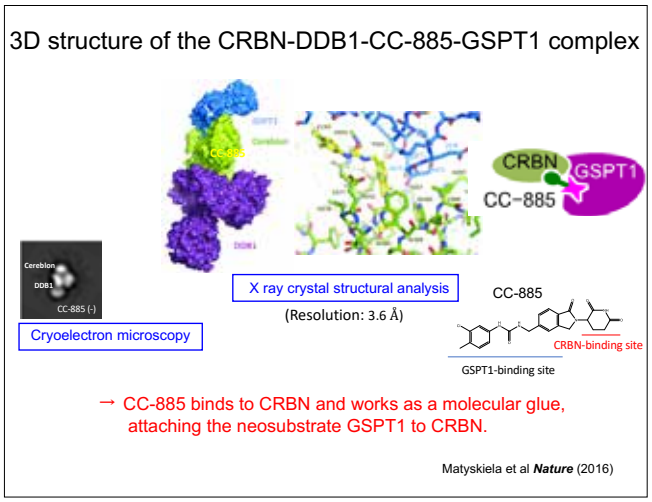


Fig. 41

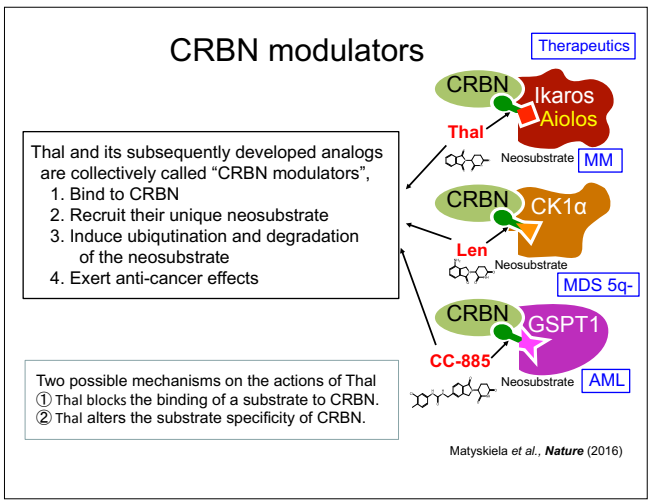


Fig. 42

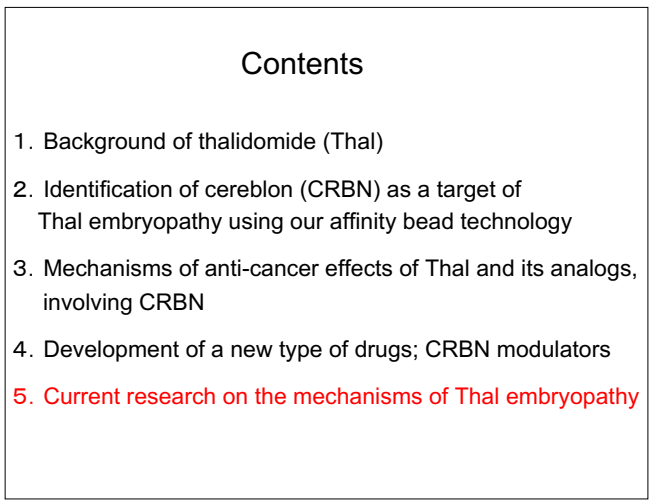


Fig. 43

and degradation of LD1 via cereblon.

We identified an LD1 mutant, named GA, which does not bind to thalidomide. Wild-type LD1 was degraded by thalidomide, but the GA mutant was not. We performed rescue experiments using this GA mutant. The results showed that the expression of the thalidomide-binding defective GA mutant blocked or rescued TE of pectoral fins in zebrafish more efficiently than that of wild-type LD1, indicating that LD1 is a true neosubstrate involved in thalidomide-induced embryopathy of the limbs. (Fig. 46)

At present, Sall4 and LD1, used here, have been identified as cereblon neosubstrates involved in TE. Other new neosubstrates are expected to be identified in the future. Furthermore, I believe that the mechanisms of thalidomide-induced embryopathy, which shows multiple phenotypes and develops in time- and site-specific manners, will be elucidated before too long.

Finally, I would like to thank the following colleagues and collaborators who participated in this research. (Fig. 47)

Thank you for your kind attention. (Fig. 48)

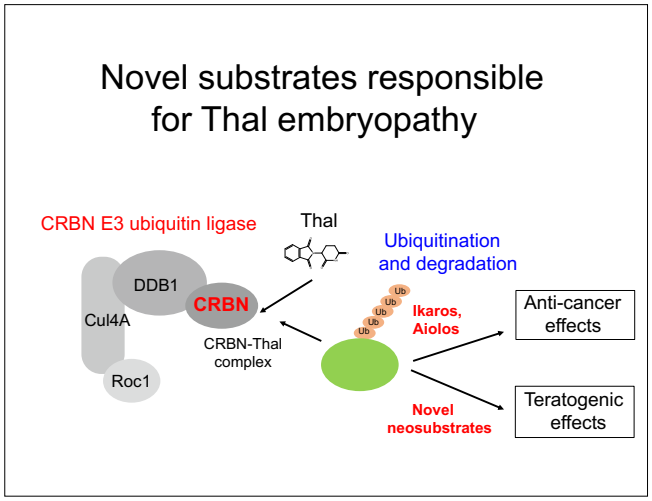


Fig. 44

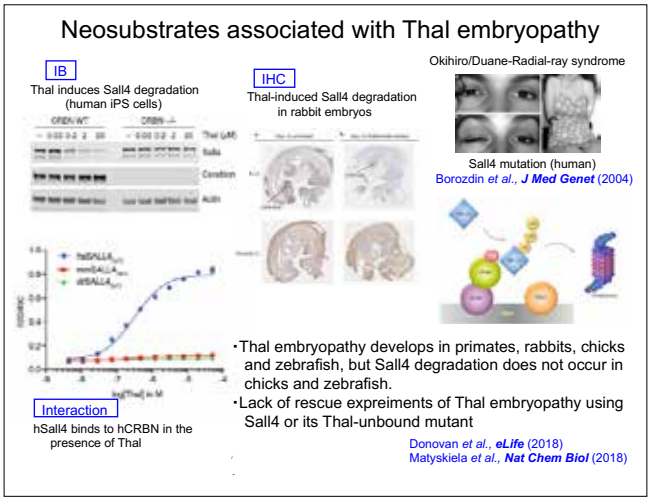


Fig. 45

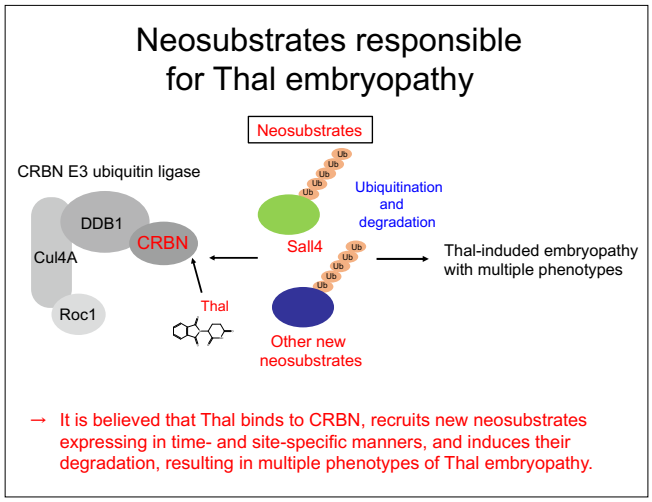


Fig. 46

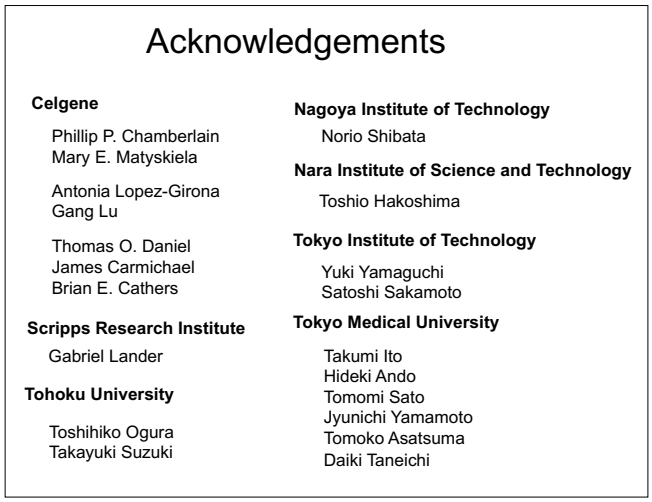


Fig. 47

Fig. 48

Q&A

Nobuhiko Haga: Thank you very much, Professor Handa. And now it's open for discussion. Are there any comments? Okay, yes.

Dee Morrison: Thank you Dr. Handa for a very detailed explanation. I first heard about cereblon when I attended the World Health Organization Conference in 2014, and it was a great surprise for me to learn about it then. It's been very interesting to follow the work since. I'm not sure whether you can answer my question, but I thought I'd ask it. Dr. Beyer in Germany who, unfortunately is not here, published a paper earlier this year showing altered vasculature around the body and the organs, particularly around the kidney and heart in those with TE.

He was reassuring us that those affected by thalidomide still had normal function of the heart and kidneys. The pattern of abnormal vasculature didn't seem to match the pattern of the external abnormalities. So, in looking at this and the cardiovascular risk, which is, I understand, slightly different in Japan, where we think there is a slight increased risk of cardiovascular disease, though we have no evidence, it is linked to thalidomide at present. But in talking to cardiologists, they were uncertain whether an area of the body could be more susceptible to the effects of abnormal vessels during fetal development, and then later to disease processes, depending on when thalidomide was given and the timing of the pregnancy. Now, for those affected by thalidomide, just to reassure you, we have no evidence and this is hypothetical, but in asking you and looking at your research, it would allow us to perhaps pick up a pattern of external damage that might be more susceptible to a certain area of the body and administer medication to try and prevent it.

So, for instance, whether a certain pattern of timing in the pregnancy might make those with TE more at risk of stroke, but not necessarily of heart attack. So, is your research at any point going to lead toward this, and what are your thoughts on it?

Hiroshi Handa: Thank you. I am not sure that thalidomide affects the altered or abnormal vascularization as you mentioned. We have checked the effects of thalidomide on the development of heart. The results showed that thalidomide definitely affects heart development in zebrafish. We have submitted our paper on the target of TE of pectoral fins and otic vesicles in zebrafish. I think that we have described just a little bit on heart in the paper.

Dee Morrison: Yes I know, I know it is a fact and I know obviously there were deaths. Those who are living at the moment…[Not recorded]

Hiroshi Handa: I think that multiple cereblon substrates, which are targeted for TE in a time-dependent manner, are present in different organs, and that thalidomide impairs the early development of various organs, such as the heart, blood vessels, limbs, and ears, via degradation of an organ-specific substrate.

Nobuhiko Haga: Okay, I can accept only one more question today. This is the last question.

Tetsuya Tagami: Then let me ask you this in Japanese. There are a couple of derivatives, and of course, their effects should be different. In the case of zebrafish or chicks, is there teratogenicity?

Hiroshi Handa: Thalidomide and its second-generation analogs, including lenalidomide and pomalidomide, cause developmental defects of the fins/limbs in different species, such as chicks and zebrafish.

Tetsuya Tagami: Yes, I understand that. But if we just limit this to zebrafish, are there three or four derivatives that might have…

Hiroshi Handa: Our data using zebrafish showed that thalidomide causes developmental defects of pectoral fins and otic vesicles more strongly than pomalidomide or lenalidomide.

Nobuhiko Haga: We will now finish this section. Thank you very much.

Activities of the Japanese Research Group on TE and Nation-wide Survey of Actual Life Situations in Subjects with TE in Japan, 2018

Fumihiko Hinoshita

Department of Nephrology, National Center for Global Health and Medicine, Tokyo, Japan

Tetsuya Tagami (Moderator)

I watched the Federer tennis match on television until 3 AM, so I am a little sleepy. Anyway, today's first speaker is Dr. Hinoshita. The title of his presentation is "Activities of the Japanese Research Group on TE and Nationwide Survey of Actual Life Situations in Subjects with TE in Japan, 2018". Dr. Hinoshita, please.

Thank you, Dr. Tagami. Anyway, looking around this venue, I feel that none of you are sleepy, or I hope so anyway. I am Dr. Hinoshita from National Center for Global Health and Medicine. So, let's go ahead to the first slide. (Fig. 1)

More than 300 thalidomide-impaired babies have been born in Japan. Thus, from 1959 through 1969, we had about 300 thalidomide victims. I will explain a little bit about the history of thalidomide or Contergan® in Japan. (Fig. 2)

Thalidomide victims and their relatives initiated legal proceedings against the Japanese government and pharmaceutical companies selling thalidomide-containing drugs in 1961. Both sides legally arrived at an amicable settlement in 1974. Based on the above settlement, a public interest incorporated foundation for thalidomide-impaired people, the Ishizue Foundation, was established in 1974. (Fig. 3)

Yesterday, the President of the Ishizue Foundation, Dr. Sato, gave opening remarks. Dr. Sato is also a pharmacology scientist.

Anyway, an official research group to study and support programs for the health and living situations in thalidomide-impaired people was newly organized for study and support by Ministry of Health, Labour and Welfare (MHLW) in 2011. The second official research group was organized by MHLW in April 2014, and I was appointed head at that time. The third group was renewed in 2017 under my direction, adding some new members. Basically, this official research

Fig. 1

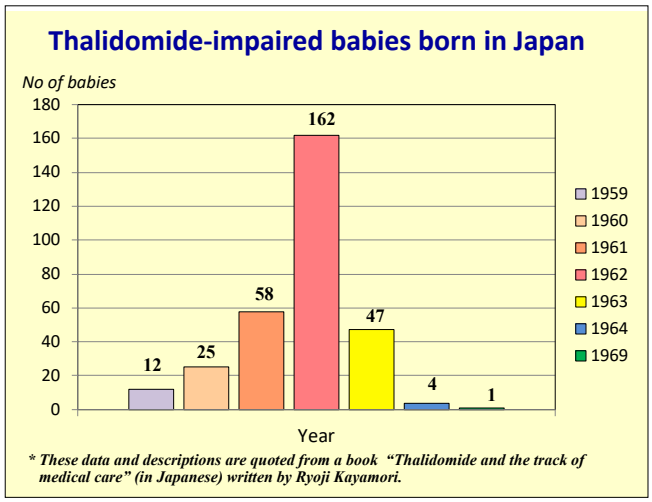


Fig. 2

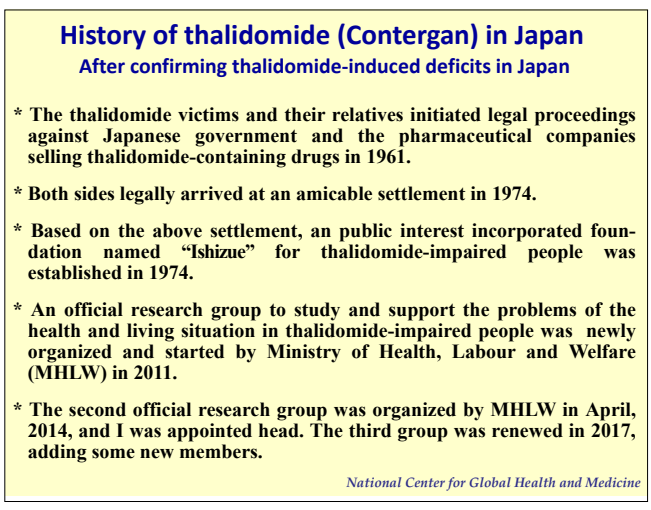


Fig. 3

group was renewed every 3 years.

Next, I will talk about the major activities of the Japanese research group. We have continuously conducted medical checkups every year. At its peak, this has involved 24 people with TE every year. In addition, we have also focused on visiting specialists of TE in Europe. For example, we visited Conterganstiftung in Cologne, Germany, The Thalidomide Trust in the UK, and the Ex-Center in Sweden, as well as some specialists on TE in Germany, the UK, and Switzerland. (Fig. 4)

As you know, the first international symposium on TE was held in Tokyo in 2015. We have established a working group on TE and its homepage in the Internet, and a workshop is held every 2 years in Japan. This workshop is held only for Japanese researchers and associates. We made a list of physicians, physiotherapists, researchers, pharmacists and so on, who can deal with TE in Japan. We also created a comprehensive guidebook on TE for clinical practice, as well as an English edition, called "Guide for the Management of Thalidomide Embryopathy 2017". Maybe we have already given this edition to the attendees who are participating in this symposium.

We also carried out a second nationwide survey on the health and living situations of thalidomide-impaired people in 2018. We have also been conducting new interviews with thalidomiders by rehabilitation specialists since 2017.

Now, I will show you some slides from when we previously visited Europe. This is a photograph taken when we visited Europe for the first time. This photo was taken at the Conterganstiftung in Cologne, Germany. In the same year, we visited an experienced specialist on TE, Dr. Jürgen Graf. He is now working in Nuremberg, Germany. (Fig. 5, 6)

Some of you may remember this photograph. This is the first international symposium on TE in Tokyo. (Fig. 7)

In 2016, we visited Europe for the second time. This photo shows when we visited the Ex-Center in Solna, Sweden. The other photo was also taken in the same year when we visited Dr. Jan Schulte-Hillen & Dr. Bettina Ehrt at St. Anna Clinic in Lucerne, Switzerland. (Fig. 8, 9)

Last year, we visited Europe for the third time. This photo was taken with Dr. Christina Ding-Greiner. The second photo was taken at the Dr. Becker Rhein-Sieg-Klinik, Nüm-

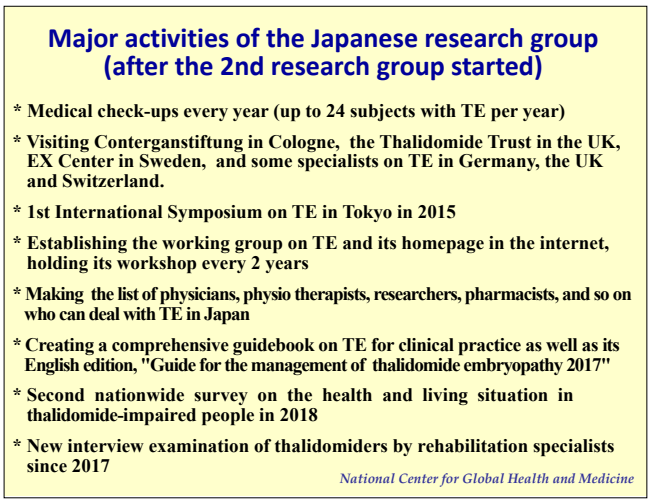


Fig. 4

Fig. 5

Fig. 6

Fig. 7

brecht, with thalidomide victims. In the center of this photo, Mr. Udo Herterich and Ms. Claudia Herterich, are both thalidomiders living in Germany. And next, the third photo is with the staff of The Thalidomide Trust. We can see Dr. Morrison and Ms. Newbronner here in the photograph. (Fig. 10, 11, 12)

And finally, we visited Dr. Beyer to share some discussions on TE. (Fig. 13)

Some visiting staff discovered this very precious thing in Heidelberg by chance. This photograph shows the original Contergan/thalidomide at Deutsche Apotheken-Museum in Heidelberg. (Fig. 14)

This is the guidebook for the management of thalidomide embryopathy (TE), which was created in 2017, and later

Fig. 8

Fig. 9

Fig. 10

Fig. 11

Fig. 12

Fig. 13

translated into English by the Japanese research group. (Fig. 15)

May I ask you who took a look at this homepage before? Oh, okay. If you haven't, please take a look at this homepage later, the homepage of the Japanese research group. You can find our website easily. (Fig. 16)

Then, from here, I would like to show you the results of the second nationwide survey of life situations of subjects with TE in Japan.

The aim of this survey was to clarify the actual medical health status of thalidomiders. A multicenter investigation was previously conducted in Japan from 2011 to 2014 to investigate the manifestation of TE in individuals aged around 50 years. That was the first survey. (Fig. 17)

The study above deals with socioeconomic programs and reveals the gaps in terms of health and social problems between thalidomiders and the general population of the same age in Japan. Therefore, we further carried out a nationwide survey mainly focusing on life situations in thalidomiders living in Japan in early 2018, and compared the results with those of the comprehensive survey of living conditions (CSLC) in the general population carried out by the government in 2016. A questionnaire was sent to 274 thalidomiders living in Japan whose mail addresses were recognized. The questionnaire included a great variety of questions, 38 items mainly, covering health, medical care, welfare, pension income, and some other basic items of living. Each form of the questionnaire was filled in based on the situation as of December 20, 2017. The questions were almost the same as those of the governmental survey, CSLC, in the general population. Responses were received from 173 thalidomiders, so the response rate was 63.1%. The results of the survey were compared with those of the governmental survey. (Fig. 18)

Okay, I'll show you a part of the questionnaire. For example, number 1, what do you think of your health condition? The answers were good, relatively good, average, relatively bad, and bad. And number 2, do you think your health problems influence your daily life, yes or no? And so on. (Fig. 19)

First, I should show you the basic characteristics of thalidomiders. The short-arm group, 126; hearing loss group, 27; the mixed group, 13. In total, there were 173 subjects. Regarding family structure, one-person household, 33; sharing

Fig. 14

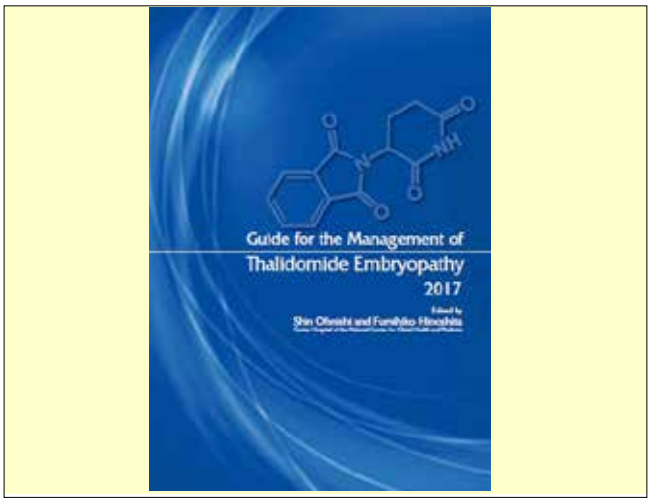


Fig. 15

Fig. 16

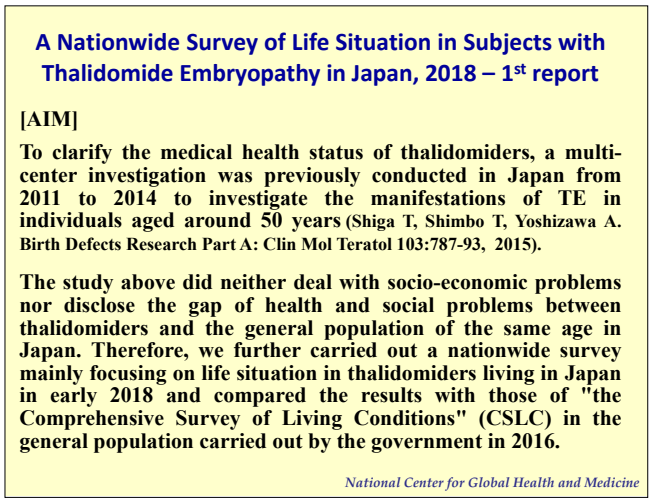


Fig. 17

household with parents only, 32; and other type of household, 102. (Fig. 20)

Family structure classified by type of disorder is shown here. Okay, so the hearing loss group tended to live with their parents, 28.1%. Sixty-nine percent or almost 70% of the subjects were living by themselves, especially those in the short-arm group. (Fig. 21, 22)

As for marriage, about half of the subjects with TE were married. Family structure classified by marital status showed that single unmarried persons were living by himself or herself, or only with his or her parents. Married thalidomiders were living with other family members. It's the bottom column. (Fig. 23, 24)

Okay, next, health condition. From here, I will show you

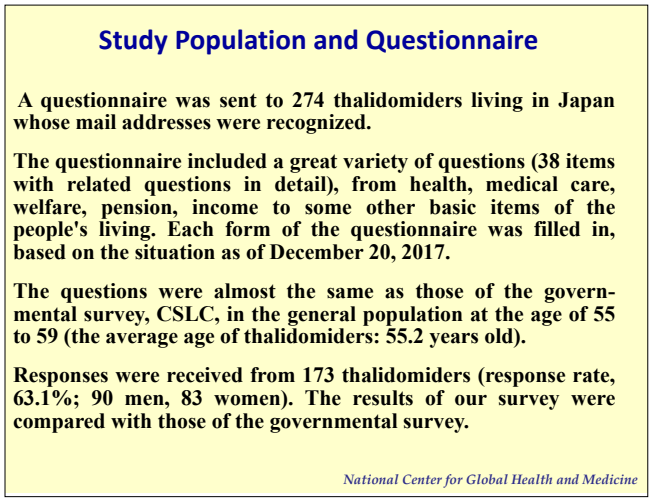


Fig. 18

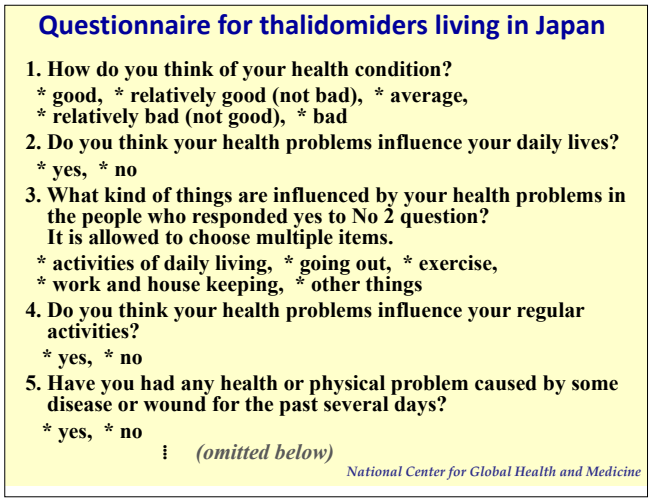


Fig. 19

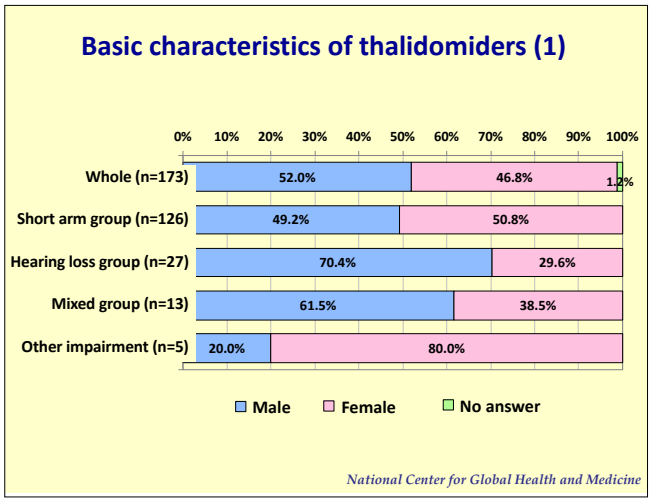


Fig. 20

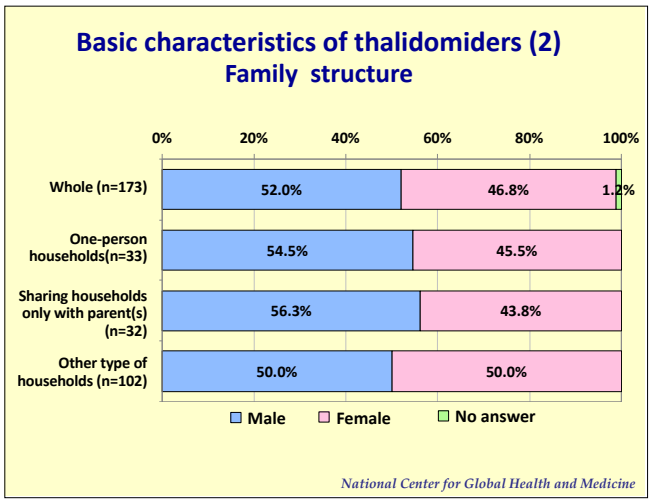


Fig. 21

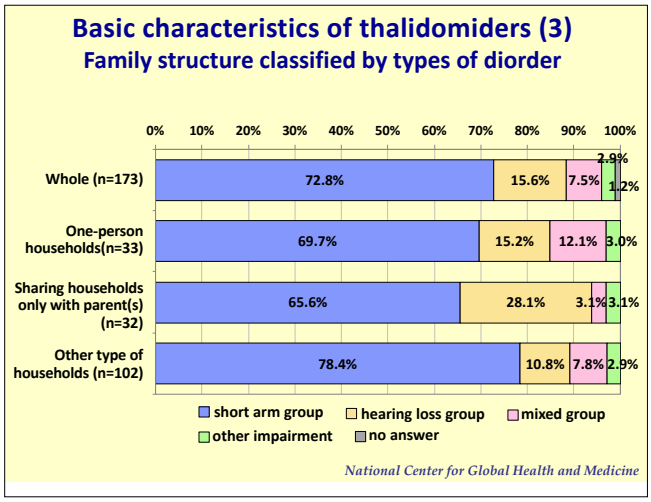


Fig. 22

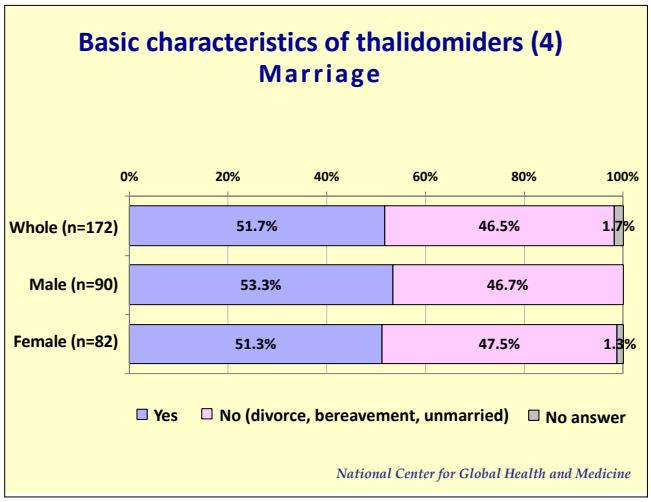


Fig. 23

the study items we focused on. As for health condition, most of the thalidomiders did not feel bad compared with the age-matched general population. (Fig. 25)

This slide shows the influence of health condition on daily living. More thalidomiders felt that their health condition greatly influenced daily living. In detail, for example, you know, work and housekeeping are greatly influenced by health condition. And also, for example, health condition might influence going out and exercising. (Fig. 26, 27)

This slide shows the influence of health condition on all of the regular activities in life; in total, the health condition influences thalidomiders greatly. (Fig. 28)

This slide shows the health and physical problems caused by disease or wounds at the time of the survey. Many more

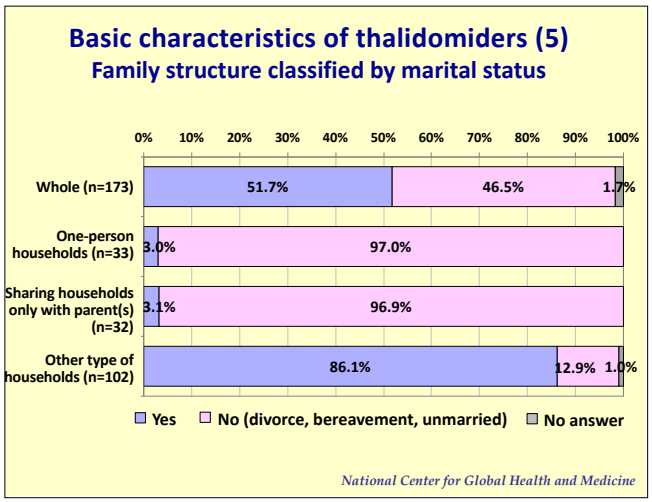


Fig. 24

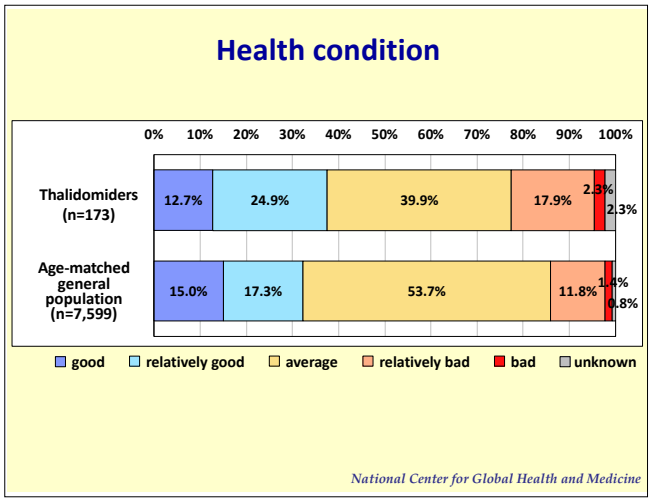


Fig. 25

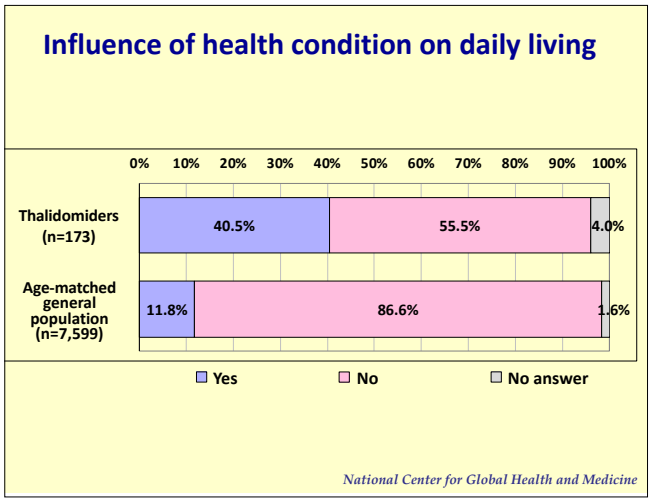


Fig. 26

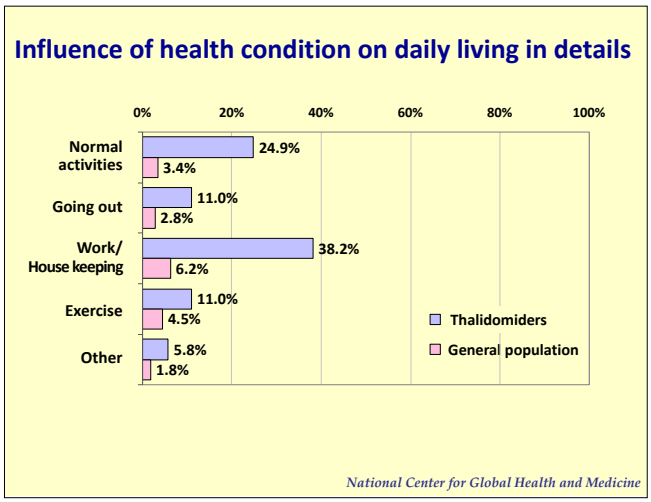


Fig. 27

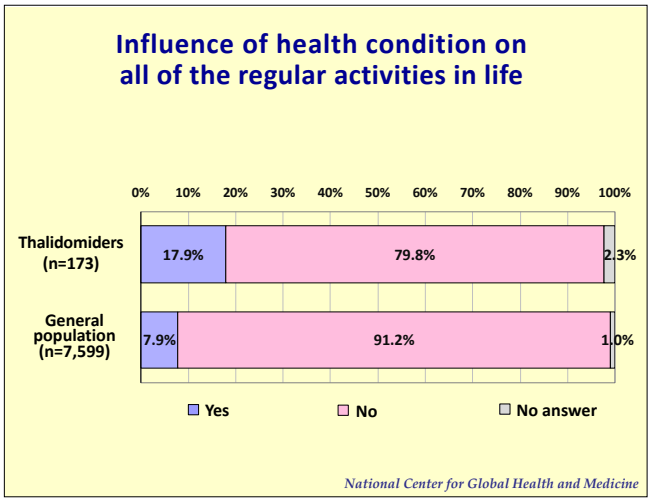


Fig. 28

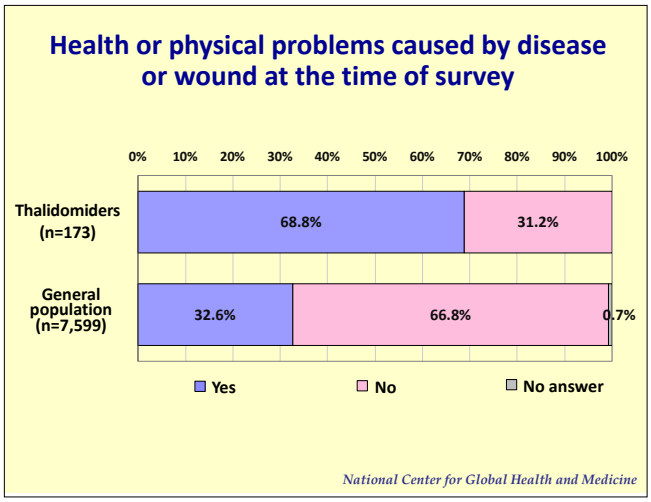


Fig. 29

people with TE thought disease or wounds were caused by health and physical problems. The next slides show the diseases and physical problems in detail. Thalidomiders had a higher prevalence of diabetes mellitus (12.7%), hyperlipidemia (13.9%), ocular diseases (19.1%), and dental diseases (17.9%) than the general population, as well as arthropathy, stiff shoulders, and lumbago or lower back pain. But interestingly, the percentage of subjects with hypertension was almost the same as that in the general population, at least in this national survey. (Fig. 29, 30, 31)

Next, this slide shows the visiting situation in subjects with symptoms and/or problems. As for this theme, there was no great difference between thalidomiders and the general population, but please pay attention to utilizing massage and acupuncture as well as chiropractic as shown in the slide. In this respect, more thalidomiders depend on these medical services. (Fig. 32)

This slide shows the distribution of annual income. Unexpectedly, no great difference was found between thalidomiders and the general population. (Fig. 33)

We also asked about general family circumstances. This means in short whether they feel good or bad, happy or unhappy, or uneasy, not only in regard to economic status, but also mental condition. (Fig. 34)

Anyway, interestingly, fewer thalidomiders felt that their general family circumstances were very difficult; more of those in the general population felt that their lives were difficult now.

Next, we also asked the current work situation. You know, we should focus on this important point. I mean, many thalidomiders, 9.2%, are unemployed, even if they want to work. But in the general population, no many persons are unemployed. (Fig. 35)

Next, this slide shows the results regarding worry and stress. More thalidomiders felt worry and stress, obviously. (Fig. 36)

From this slide, I will show you the results of the nation-wide survey, which were not previously revealed. I have shown the previous slides to part of the attendees here from the UK, Germany, or Japan. But from this slide, I newly show the other results on pain. Please keep in mind that these items were not compared with the results of the general population.

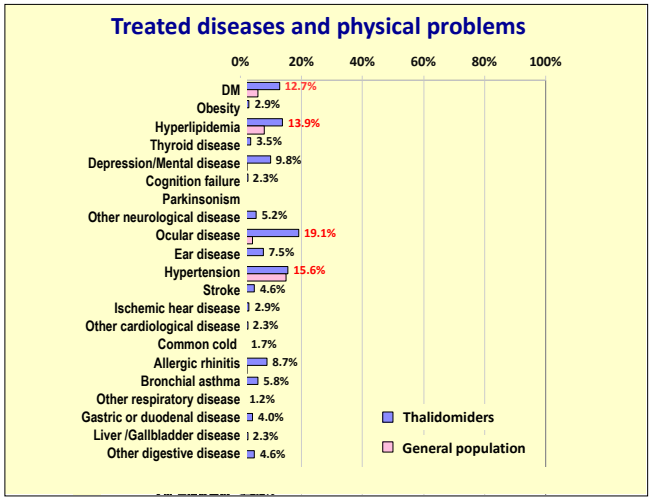


Fig. 30

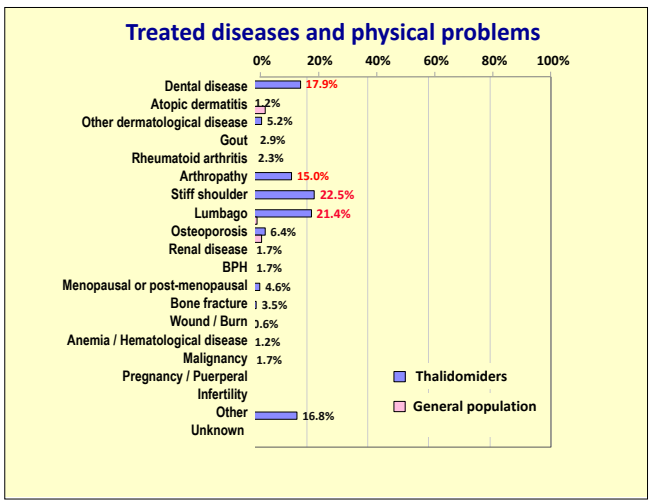


Fig. 31

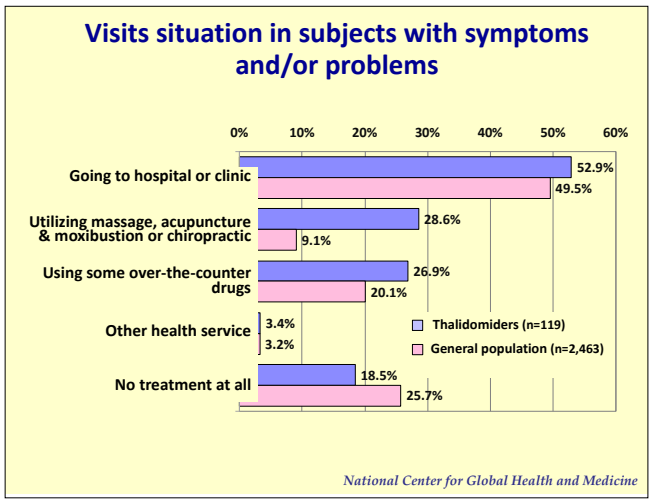


Fig. 32

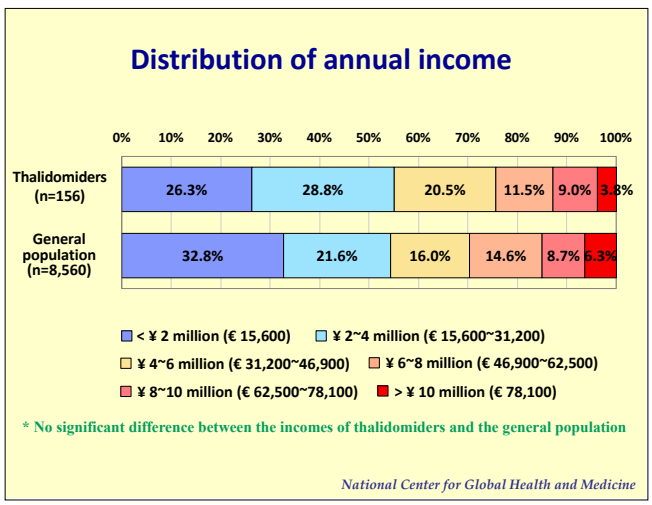


Fig. 33

As for persistent pain, more than half of the thalidomiders feel persistent pain every day. Especially in the mixed-type group, there are many people with TE who feel persistent pain. (Fig. 37)

We also asked about the body parts or locations with pain. We found, for example, pain was frequently reported in the shoulder and upper arm, neck and around the neck, and next hands and fingers. As for females, hip joint pain was remarkable. We also asked about changes in the pain grade for the past 5 years. Most of the thalidomiders responded that their pain had become stronger since 5 years ago. (Fig. 38, 39)

Now I will summarize the main results. More thalidomiders feel that their health condition is worse or relatively worse than that of the general population. More thalidomiders are influenced by their health condition in general than the general population. Especially, there are great gaps in conducting normal activities, going out, working, and housekeeping. Many more thalidomiders have health or physical problems caused by disease or wounds than the general population. Generally, thalidomiders have significantly more diseases, physical problems, and treatments than the general population, except for hypertension.

No significant difference was found between the annual income of thalidomiders and that of the general population. As for work, thalidomiders are at a disadvantage compared with the general population. There are more unemployed

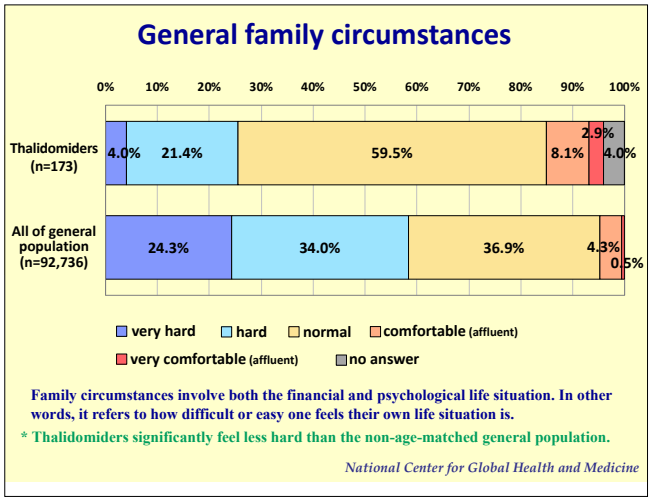


Fig. 34

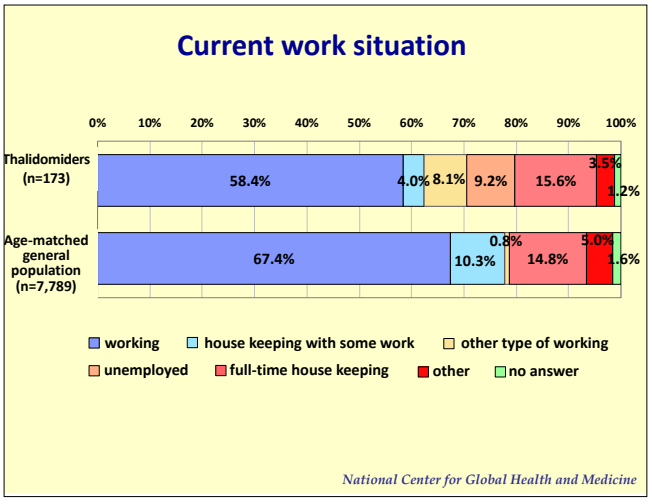


Fig. 35

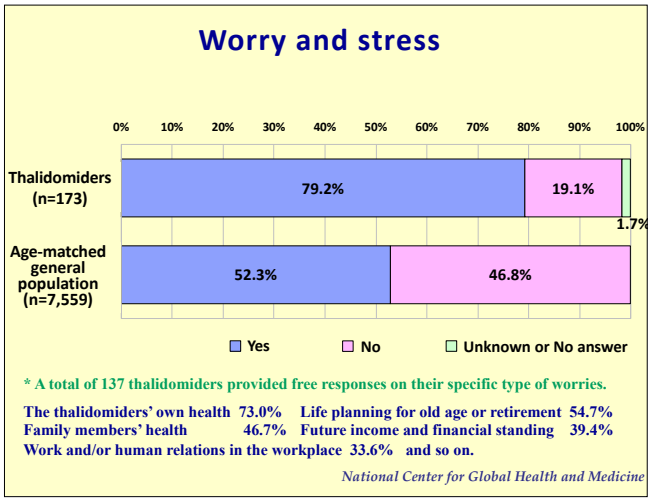


Fig. 36

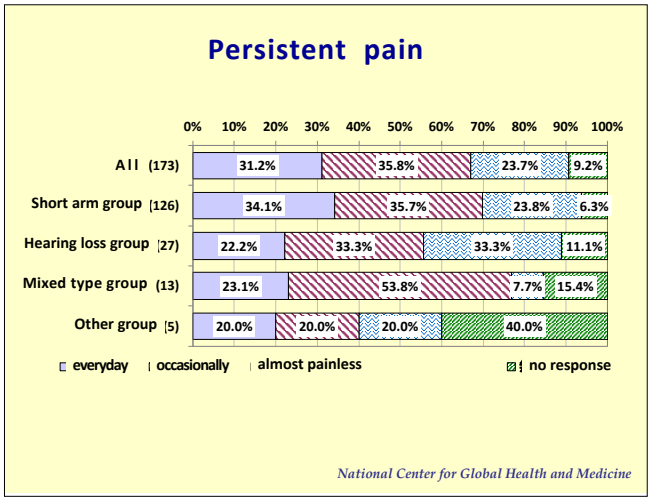


Fig. 37

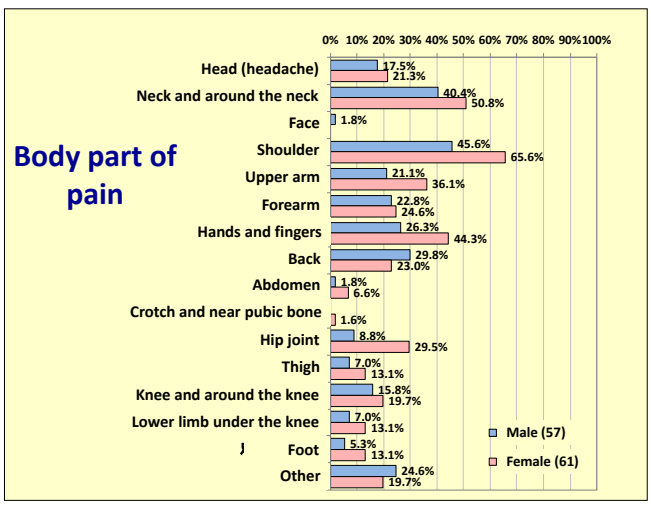


Fig. 38

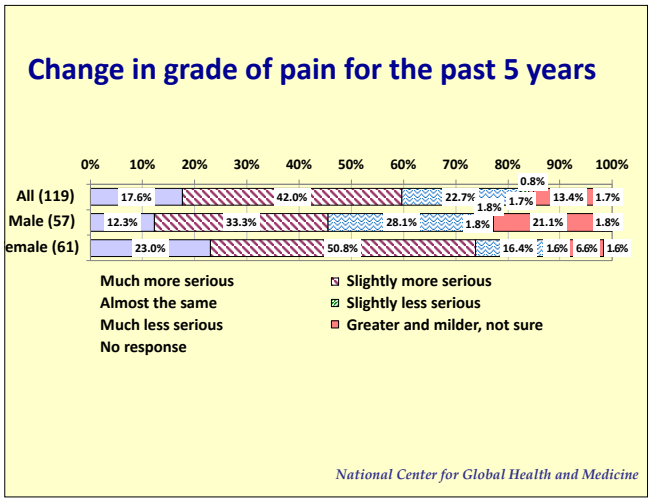


Fig. 39

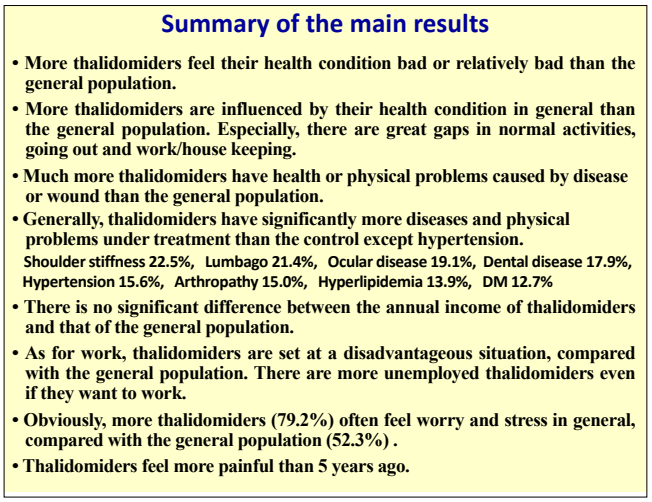


Fig. 40

Fig. 41

thalidomiders, even though they want to work. Obviously, more thalidomiders, 79.2%, feel worry and stress compared with the general population. Thalidomiders also feel more pain now than 5 years ago. (Fig. 40)

Therefore, I think all of us should continuously work towards the resolution of TE-associated problems. Hopefully, this global network on TE will successfully push forward and function well in the future, too. Thank you for your attention. That's all. (Fig. 41)

Q&A

Tetsuya Tagami: Thank you, Dr. Hinoshita. Are there any comments or questions?

Elizabeth Newbronner: Thank you very much, Dr. Hinoshita, for the very interesting presentation. It was nice to see some of your new data as well. Thank you. I was just interested in income, which you said was similar to that of the general population. Does that income level include people's compensation payments, so it's their whole income?

Fumihiko Hinoshita: We did not ask about that in detail, but I think the income shown here includes compensation, namely money from the fund or the government.

Elizabeth Newbronner: Yes. And I just wondered have you received any feedback from thalidomide survivors here about how adequate they think their income is in terms of covering the cost of living with their disabilities?

Fumihiko Hinoshita: Yes, as I showed, most of the thalidomiders think that their lives are not so bad, that they are doing well financially and in their activities, except for work, namely unemployment. But I believe they need to spend more, for example, on massages or chiropractic or other medical services or treatment, compared with the general population. So, we Japanese researchers think that in reality, they get less income than they need because of their greater expenses for medical services and so on.

However, I don't know about the thalidomiders in European countries, but at least in Japan, thalidomiders are patient and have become accustomed to a poorer situation. So they do not have great stress or worry, maybe because in a sense, they have been mentally strengthened in their physical activities from youth. That's it.

Elizabeth Newbronner: Thank you.

Klaus M. Peters: I think there are lot of parallels between the Japanese results and the German data. I think also that German thalidomiders need more medical treatment and have more pain than the others, and the retirement quote is much higher than the normal range of the German population up to now. A lot of them have retired in the last 5 years because of pain and poor health conditions.

Fumihiko Hinoshita: Yes, thank you. Thank you for your comment. We know there are more thalidomiders in Ger-

many who would retire from their job because of great pain or such other problems. And, according to your report, you said that German thalidomiders would not like to visit hospitals or clinics for their pain or so on. But based on our national survey in Japan, most Japanese thalidomiders can rely and depend on regular medical services, including massages and some medical examinations at hospitals or clinics.

Shadi-Afarin Ghassemi: Thank you very much. That was a very nice presentation. I have two questions. The first is from what I understand, you conducted your survey through e-mail and it didn't cover all thalidomiders or…?

Fumihiko Hinoshita: Just postal mail, not e-mail.

Shadi-Afarin Ghassemi: Okay, but anyway, I mean that you reached more than 200 of the over 300 you had. My question is why do you think you couldn't reach all of the thalidomiders in Japan? If you had answers from them, would it have changed the outcome of your studies? That's my first question. My second question is although it was very interesting, I wonder why you used your own survey according to your own questionnaires instead of validated questionnaires, such as the SF-36 or SF-12?
With respect to cultural differences, it would be nice to hear. I mean, the answers and outcomes were still quite similar, but why did not you use the outcomes, sorry, the validated questionnaires? That would be interesting to know. Thank you.

Fumihiko Hinoshita: Okay. As for your first question, we, the Japanese research group, did not know all of the addresses of the thalidomiders in Japan, partly because of privacy issues. The Ishizue Foundation, you know, the public incorporated foundation, knew almost all of the addresses of the thalidomiders in Japan. But I heard that they did not know all of the addresses because a small portion of the thalidomiders did not wish to disclose their address, situation or other private things. Then, as you pointed out, there might be the possibility that we cannot grasp or understand the actual situation of all of the thalidomiders living in Japan, especially in regard to the non-responders, who might be very sick or hospitalized with some serious mental diseases or such. Therefore, we could neither check nor know the situation of those specific patients.
To answer your second question, as you said, we did not use a global standard questionnaire, for example, the SF-36. But in parallel, the staff of the psychiatric subgroup in our TE research group are and have been carrying out a survey on thalidomide victims in Japan using the SF-36 or similar tool. Therefore, especially this time, I focused on the gaps and differences or similarities between Japanese thalidomiders and the age-matched general population.
Therefore, we adopted the standard questionnaires or question items of the survey regularly carried out by the government, the CSLC. That's it. Okay?

Junichi Horiuchi: I will speak in Japanese. My name is Horiuchi. I am the director of the Ishizue Foundation and I would like to thank all of the attendants here today at the symposium. This is just my personal view, but in terms of work, the staff members of the public organization entity made a contribution at the time to support and promote thalidomiders to be hired and employed by blue chip companies. In terms of work, this is often mentioned in dialogue and communication as a topic. In Japan, work–life balance is considered, and they have to work until 65 or 70 years of age, the retirement age.
But because of pain in the neck or shoulder area, thalidomiders and the disabled are wondering if they actually can work until age 65 or 70. When we pose them a question like that, they say, "No, I don't think I will be able to work until that age due to this persistent pain in my shoulder and neck and so forth," and 50% are single without a family, so what sort of support will be required for aging thalidomiders? This is something that we need to consider as a major issue.
Therefore, on this topic, support from MHLW as well as pharmaceutical companies will be necessary, with the cooperation and support of stakeholders. In terms of the use of massage, for the past some years, pharmaceutical companies have been providing support and some kind of subsidies or financial contributions. Amazingly, there are so many applications for subsidies for massage services. We receive many applications for the subsidization of massage services. I hope that the government will consider this as well.

Fumihiko Hinoshita: You know, massage, physical massage, is very popular in not only Japan, but also Germany, Sweden, and the UK. Most of the TE researchers and specialists think that massage is very advantageous and meaningful. However, I'm sorry to say that based on recent discussions, we think that massages would not be effective for a long period unless carried out on a consistent basis. That is a great problem. So, perhaps most Japanese thalidomiders would use massage often, I mean many times, which would have a steep cost.
Thus, not only the official research group, but also responsible pharmaceutical companies and the government should think about the great costs by thalidomiders. Yes, exactly, I think so.
Tetsuya Tagami: Anymore comments? Okay. Time is up. Thank you, Dr. Hinoshita.

Preserved Pulmonary Function in Thalidomide Embryopathy in Japan

Hiroyuki Nagase

Division of Respiratory Medicine and Allergology, Department of Medicine, Teikyo University, Tokyo, Japan

Tomoko Shiga (Moderator)

Good morning, everyone. I am Tomoko Shiga from Division of General Medicine, Tokyo Women's Medical University. I will be chairing this session. The next presentation will be given by Professor Hiroyuki Nagase from Department of Medicine, Division of Respiratory Medicine and Allergology, Teikyo University. The title of his presentation is "Preserved pulmonary function in Thalidomide Embryopathy in Japan". Please, go ahead.

Thank you very much, Dr. Shiga. My name is Nagase and I am a respiratory physician from Teikyo University. In my talk, I want to focus mainly on pulmonary function testing for thalidomiders. (Fig. 1)

I will discuss three topics in this session. First, I will present the pulmonary function data from a health check surveillance study of people with thalidomide embryopathy (TE). (Fig. 2)

We previously performed pulmonary function testing the patients at 50 years of age to assess the percent of vital capacity (vital capacity / predicted normal vital capacity). I will call this %VC. This value was 89.6%. The forced expiratory volume in 1 second / forced vital capacity (FEV1%), which reflects obstructive dysfunction, was 81.7%. (Fig. 3)

The normal %VC value is 80% and the normal FEV1% value is 70%. So, these data were within normal limits. At that time point, no specific pulmonary disease or dysfunction was identified in patients with TE aged 50 years. We are continuing health checkups for these patients, and I want to show here the results from recent health checkups in 2017–2018. At this point, the patient's age was 55 years. (Fig. 4)

These are the results regarding smoking status in Japanese thalidomiders who visited Teikyo University. The number of patients was 11. We excluded patients with asthma and cerebrovascular disease from this analysis. The average

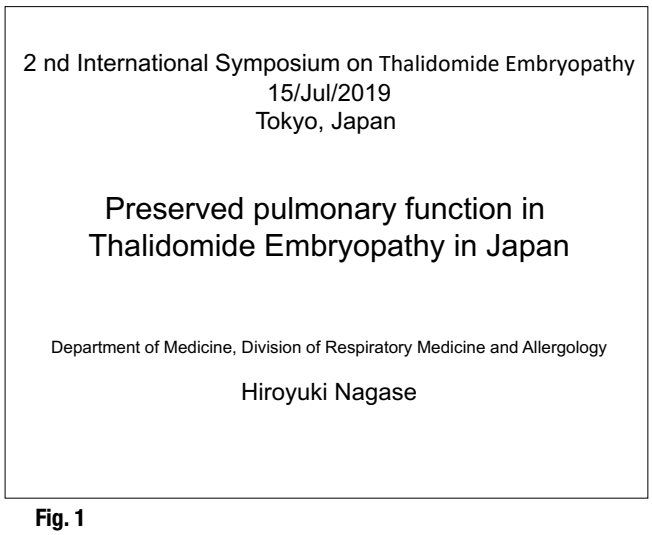


Fig. 1

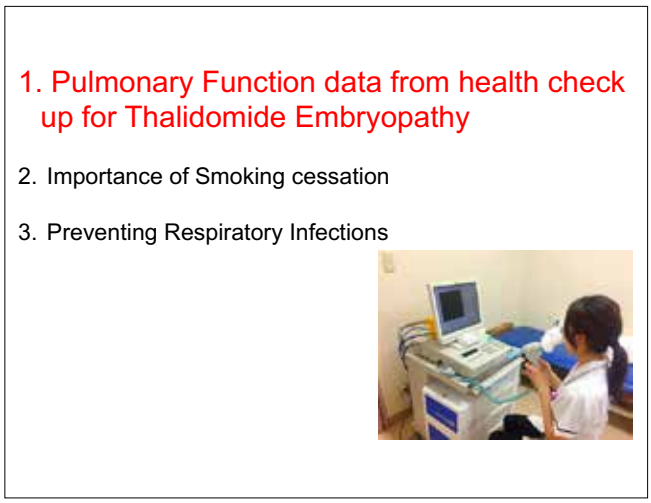


Fig. 2

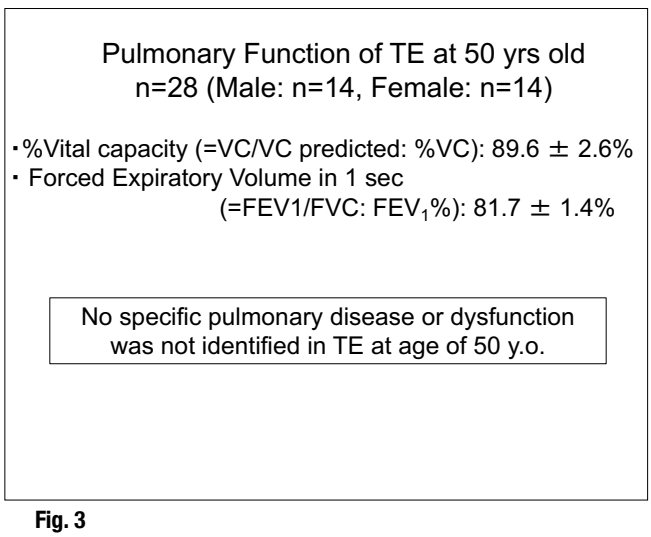


Fig. 3

age was 55.5 years old, and eight patients were male. And as you can see, the prevalence of current smokers was 23%, previous smokers was 39%, and never smokers was 38%. As shown here, a considerable proportion of thalidomiders were still smoking. (Fig. 5)

This slide shows the pattern of respiratory dysfunction and corresponding diseases. Restrictive dysfunction is defined as %VC below 80%, and the representative diseases are interstitial pneumonia or neuromuscular disease. Obstructive dysfunction is defined as FEV1% below 70%, and representative diseases include chronic obstructive pulmonary disease (COPD) and asthma. (Fig. 6)

This slide shows the flow volume curve, which is very useful for detecting peripheral airway dysfunction or obstruction. The y-axis shows expiratory flow velocity, and the x-axis shows lung volume. V.25 is defined as expiratory velocity at %FVC of 25%. This reflects peripheral airway obstruction. The V.50/V.25 ratio is also useful to detect peripheral airway obstruction because in patients with peripheral airway obstruction, the V.25 value decreases, so the ratio increases as peripheral obstruction progresses. Peripheral obstruction is suggested when this ratio is over 3. (Fig. 7)

From here, I will show the results of pulmonary function testing in recent health checkups. As you can see, %VC was not different between smokers and never smokers. The average value was 111, which is within the normal range. There was no problem. (Fig. 8)

Fig. 4

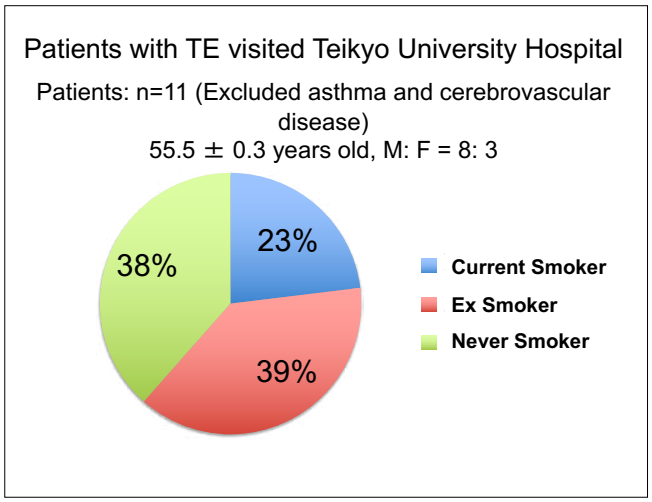


Fig. 5

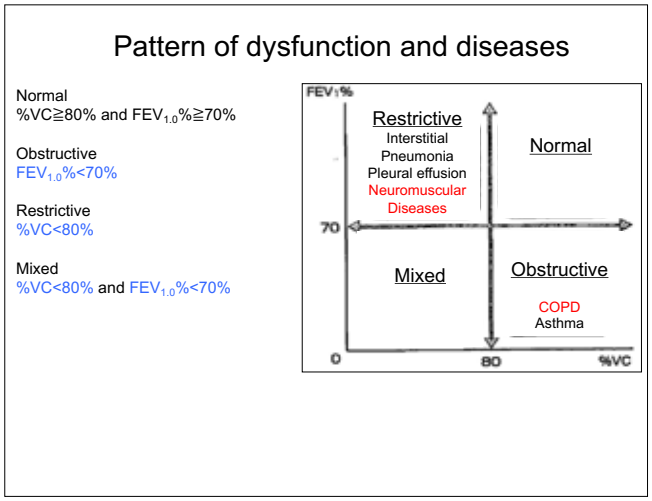


Fig. 6

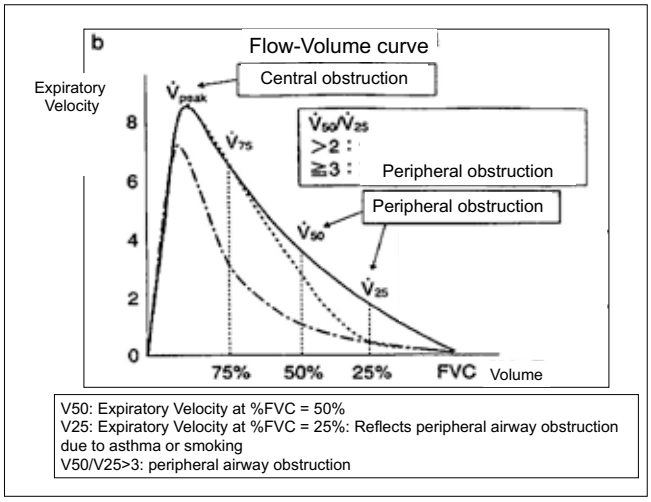


Fig. 7

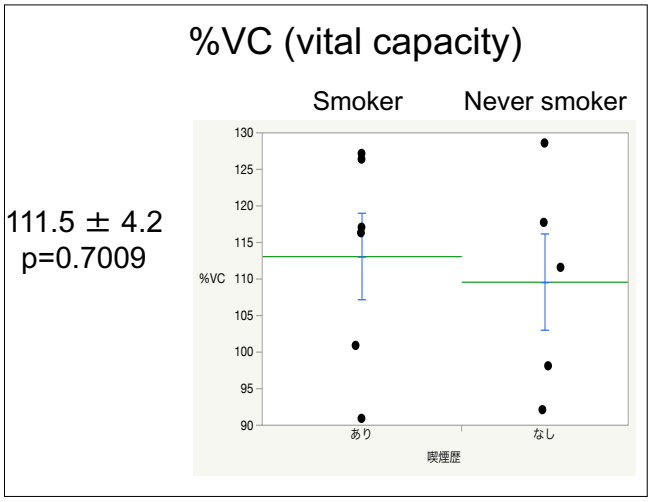


Fig. 8

Also, in case of FEV1%, there was no significant difference between smokers and never smokers. The average value was 79.1%, and this was also within the normal range. In general, FEV1% is considered to reflect central airway obstruction, not peripheral airway obstruction. Concerning the central airway, it was within normal limits. (Fig. 9)

By contrast, %MMF reflects peripheral airway obstruction. As you can see, there was a difference between smokers and never smokers. The value was numerically lower in smokers, but not statistically significant. (Fig. 10)

Here, I show the data for %V.75, %V.50, and %V.25. As you can see, %V.75 to %V.25 reflects the data for central to peripheral airway obstruction. For %V.75 and %V.50, there was no significant difference between smokers and never smokers. However, for %V.25, which reflects peripheral airway obstruction, the value was numerically lower in smokers. As you can see, central airway obstruction was within normal limits, even in smokers, but peripheral airway obstruction was observed in smokers. (Fig. 11)

This is the V.50/V.25 ratio. A value over 3 indicates peripheral airway obstruction. As you can see, the ratio was higher in smokers than in never smokers, which suggests peripheral airway obstruction. (Fig. 12)

This slide shows pulmonary function data from patients with or without block vertebrae. As you can see, there was no difference in %VC or FEV1% between patients with or without block vertebrae. The data were completely similar between groups. (Fig. 13)

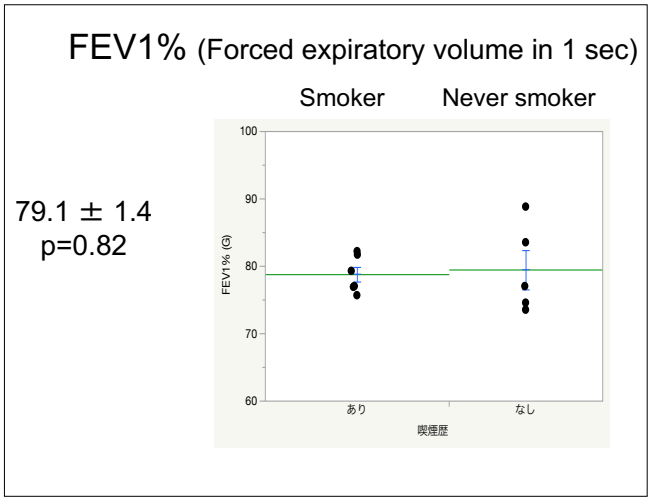


Fig. 9

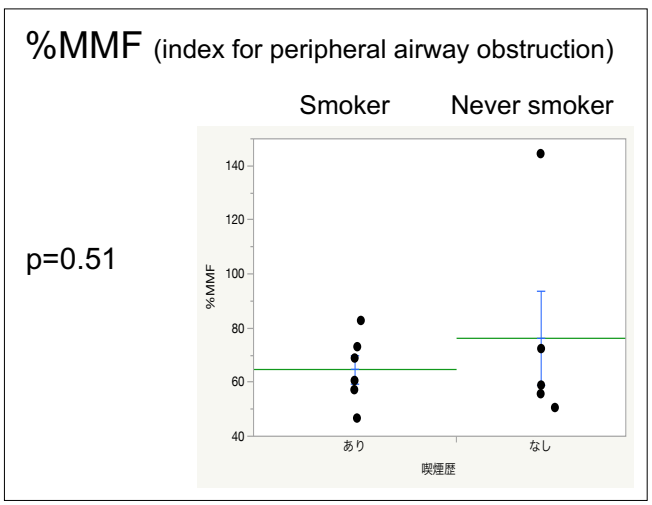


Fig. 10

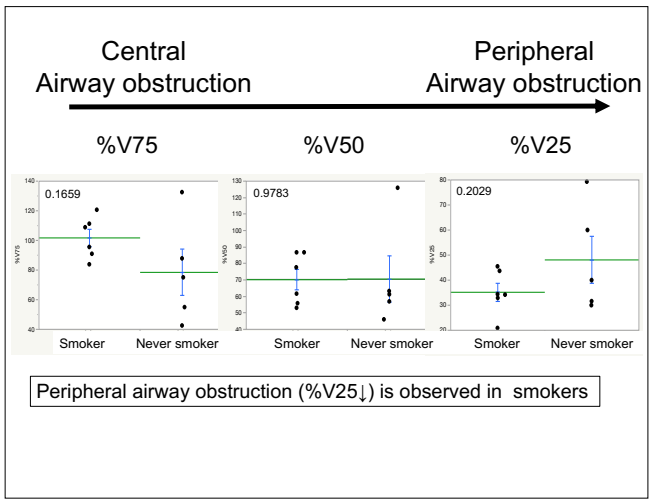


Fig. 11

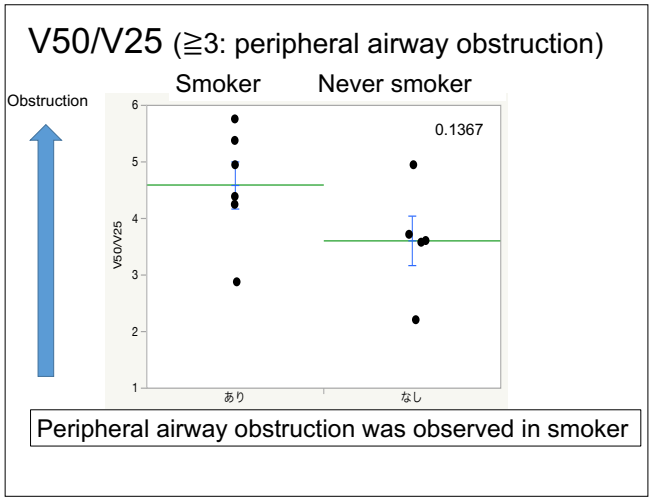


Fig. 12

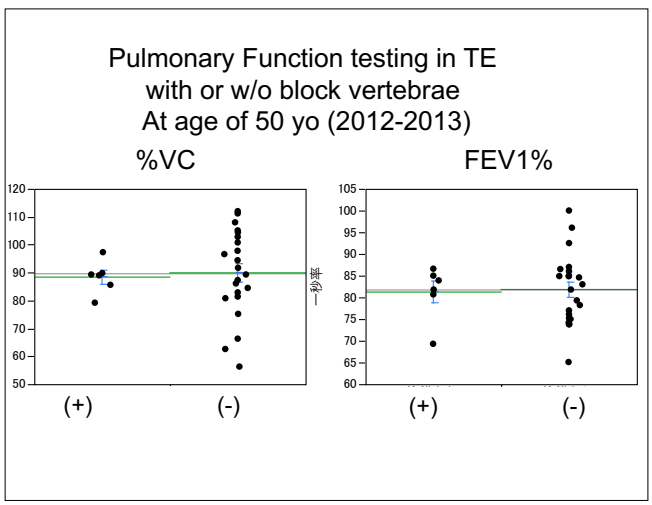


Fig. 13

This slide shows data concerning patients with upper limb defects. Concerning %VC, there was no difference. But the FEV1% value was slightly lower in patients with upper limb defects. The value was 80.2%, which was still within the normal limit, but the data were slightly lower in patients with upper limb defects. (Fig. 14)

This slide shows a summary of the results. The proportion of smokers in TE was 23%, which seems to be a little bit higher than the average value in Japan. The %VC and FEV1% values were preserved and within the normal range in all patients. I think this is good information. Especially in smokers, peripheral airway obstruction was observed, and FEV1% tended to be lower in patients with upper limb defects. Therefore, I think smoking cessation is very important for such patients. (Fig. 15)

This slide shows a photo of the alveolar space and enlargement in the elderly. These patients were never smokers, but alveolar space enlargement occurs spontaneously with aging. This alveolar space enlargement causes peripheral airway obstruction. Thus, aging is an important factor in peripheral airway obstruction. (Fig. 16)

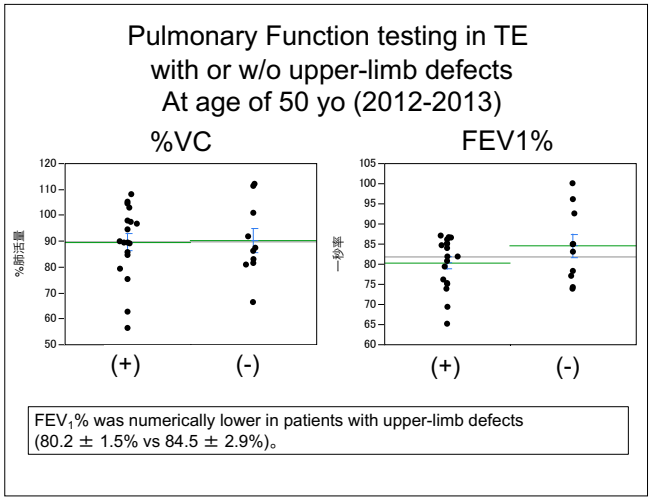


Fig. 14

Results

The proportion of smoker in TE was 23% (Average 17.9% in Japan).

The value of %VC and FEV1% was preserved and value in all patients was within normal range.

Peripheral airway obstruction was observed in smokers.

FEV1% tended to be lower in patients with upper limb defect.

Fig. 15

As you can see, these data depend on age. In the peripheral airway, aging greatly affects %V.25 as compared with the central index FEV1%. Thus, obstruction with aging is more dominant in the peripheral airway. Thalidomiders are now about 55 years old. The effects of aging are important for this generation, so we have to recommend smoking cessation, especially for current smokers. (Fig. 17)

In summary, pulmonary function in TE at age 55 years was within the normal range. But peripheral airway obstruction, especially in smokers, could be observed. As peripheral airway obstruction leads to COPD, smoking cessation is very important, especially for patients with upper limb defects. (Fig. 18)

Next, I want to mention the importance of smoking cessation. In Japan, smoking is generally prohibited in public spaces, but smoking is still permitted in designated areas around various public spaces. (Fig. 19)

These data show the prevalence of smokers in Japan, which has been continuously decreasing. In 2018, the average prevalence was 17.9%: 27.8% in males and 8.7% in females. (Fig. 20)

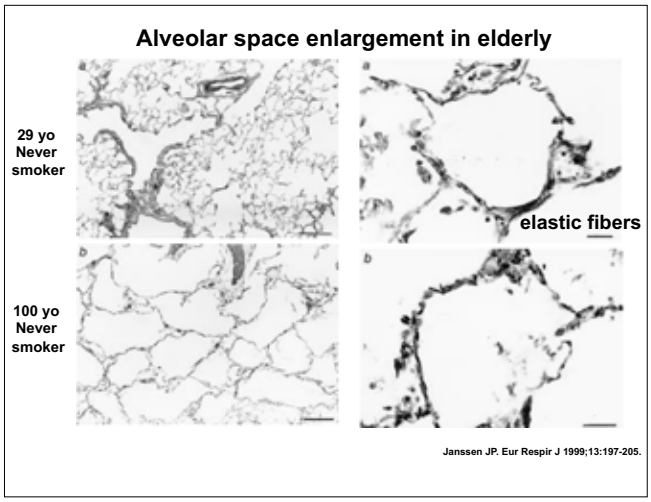


Fig. 16

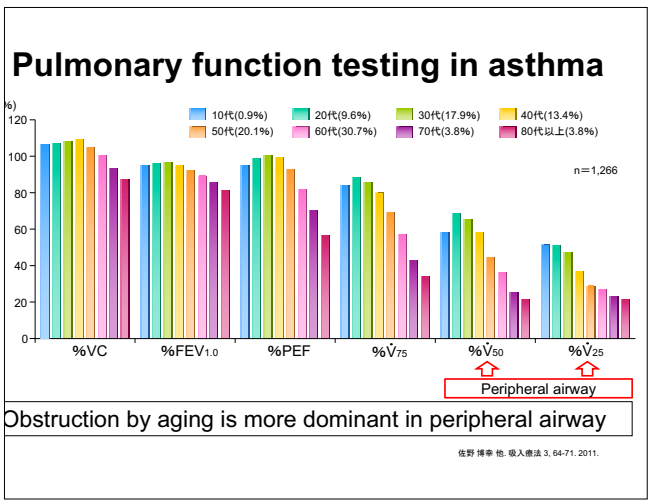


Fig. 17

As you know, smoking causes various diseases, including cancer, cardiac diseases, pulmonary diseases such as COPD, and various other diseases. (Fig. 21)

The problem concerning smoking in Japan is that tobacco vaping products, which contain nicotine, are becoming more prevalent. Three devices—iQOS, PloomTech, and glo—are currently available in Japan. Minors under the age of 20 cannot purchase these products, but they are becoming increasingly popular among the youth in Japan. The popularity of iQOS is rising, from 1.3% in 2015 to 4.9% one year later. And I think it's even more popular now. (Fig. 22)

The problem is that most prevalent use is the youth. This device is frequently used by males aged 20 to 49 years and by females in their 20s. In addition, 98% of all iQOS prod-

Summary

- Although pulmonary function in patients with TE at age 55 yo was within normal range, peripheral airway obstruction, which can lead to COPD was observed in smokers.
- As %FEV1 was numerically lower in patients with upper-limb defects, smoking cessation is highly recommended to such patients.

Fig. 18

1. Pulmonary Function data from health check up for Thalidomide Embryopathy

2. Importance of Smoking cessation

3. Preventing Respiratory Infections

Fig. 19

Prevalence of Smokers in Japan

2018年: 17.9% (Male 27.8%, Female 8.7%)

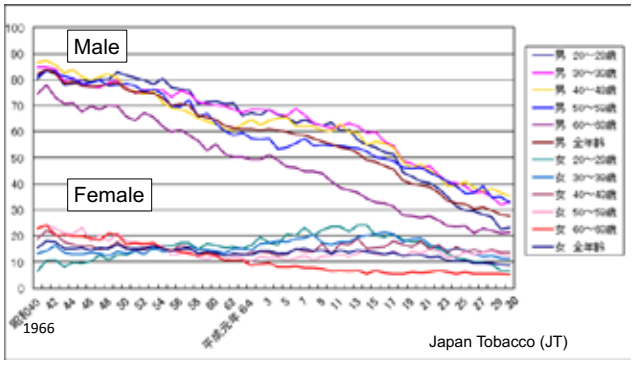
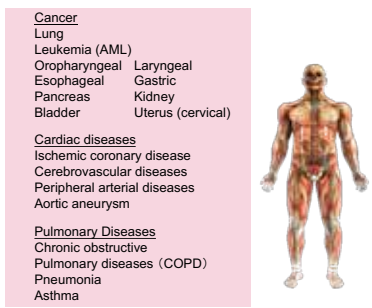


Fig. 20

Effect of Smoking on various diseases



Cancer
Lung
Leukemia (AML)
Oropharyngeal Laryngeal
Esophageal Gastric
Pancreas Kidney
Bladder Uterus (cervical)

Cardiac diseases
Ischemic coronary disease
Cerebrovascular diseases
Peripheral arterial diseases
Aortic aneurysm

Pulmonary Diseases
Chronic obstructive
Pulmonary diseases (COPD)
Pneumonia
Asthma

Reproduction
Low weight birth
妊娠合併症
不妊
Sudden infant death syndrome(SIDS)

Others
Osteoporosis
Cataract
Gastric Ulcer
Diabetes
Metabolic syndrome

Centers for Disease Control and Prevention: Surgeon General's Report—The Health Consequences of Smoking: 2004
1)Uchimoto, S. et al.: Diabet Med 16(11): 951, 1999
2)Ishizaka, N. et al.: Atherosclerosis 181(2): 381, 2005

Fig. 21

Prevailing Heated tobacco products in Japan

20 pieces ¥460 ($ 4)

- Contains nicotine
- iQOS (Philippe Molis) Oct/2014~
- PloomTech (Japan Tobacco) Sep/2015 ~
- glo (British American Tobacco) Oct/2017 ~
- Minor under age of 20 cannot purchase.

Fig. 22

Recent data concerning heated tobacco products

- Prevalence of iQOS is rising
  1.3% in 2015 → 4.9% in 2016
  The most prevalent age:
  Male: 20～49 yo、Female: twenties

- Ninety-eight percent of iQOS is sold in Japan.

- Used by previous smoker who wants to quit smoking: 19% > Never smoker: 1.3%
→suggesting the possibility of gateway for smoking.

Fig. 23

ucts are sold in Japan. iQOS is a product of Philip Morris. Another problem is the user: 1.3% of users are never smokers, which suggests that vaping can serve as a gateway for smoking. (Fig. 23)

This slide shows the mechanism for nicotine dependence. If a person smokes, nicotine binds to the alpha-4 beta-2 nicotinic receptor and causes dopamine release. Dopamine release induces satisfaction, and once dopamine levels decrease, the person feels the urge to smoke again. (Fig. 24)

In Japan, treatment for smoking cessation is covered by health insurance, and patients can be treated once a year for 3 months. Patients have to pay 30% of the total cost, which is about 200 USD for 3 months of treatment. In Japan, two drugs are covered by health insurance, one of which is varenicline. (Fig. 25)

Varenicline binds to the nicotinic receptor and blocks binding of nicotine, which decreases the satisfaction gained by smoking. The binding of varenicline also causes the release of a small amount of dopamine, which reduces the urge to smoke. Another drug used is the nicotine patch. (Fig. 26)

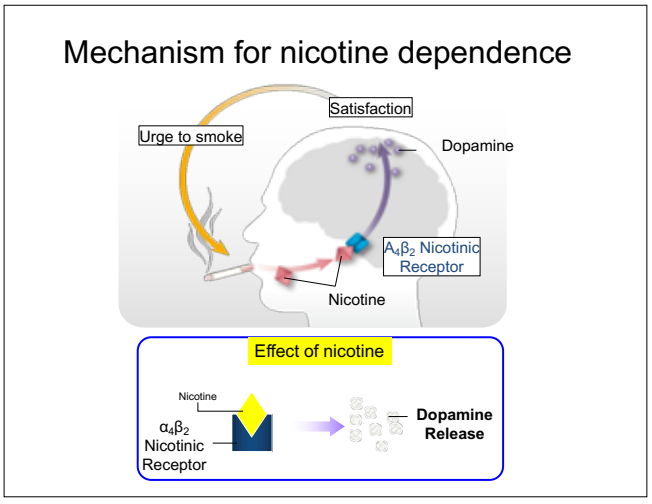


Fig. 24

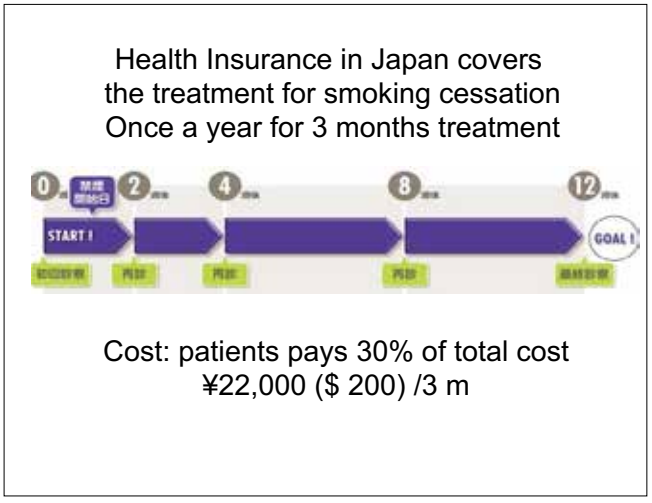


Fig. 25

This figure shows the time course of serum nicotine concentration. The nicotine patch achieves approximately half of the nicotine concentration as that from actual cigarette smoking; this level is continuously maintained, reducing the urge to smoke. (Fig. 27)

The success ratio was slightly but significantly higher in the varenicline group. Therefore, I recommend varenicline as the initial treatment for smoking cessation. (Fig. 28)

These data concern the ratio of successful smoking cessation depending on the month of starting treatment. The best months were March and April, and the worst month was November. I think this may be due to the drinking that occurs at many parties at the end of the year. So, the current season is not bad, and I can recommend current smokers to attempt smoking cessation now. (Fig. 29)

Here is a summary of this section. In Japan, treatment for smoking cessation is covered by national health insurance, and two drugs are available. As smoking rates in TE patients might be higher than the Japanese average, I think we have to inform such patients about the harmful effects of smoking

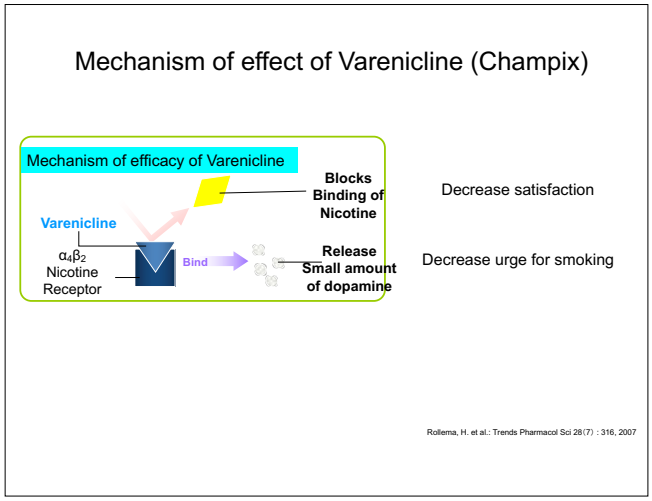


Fig. 26

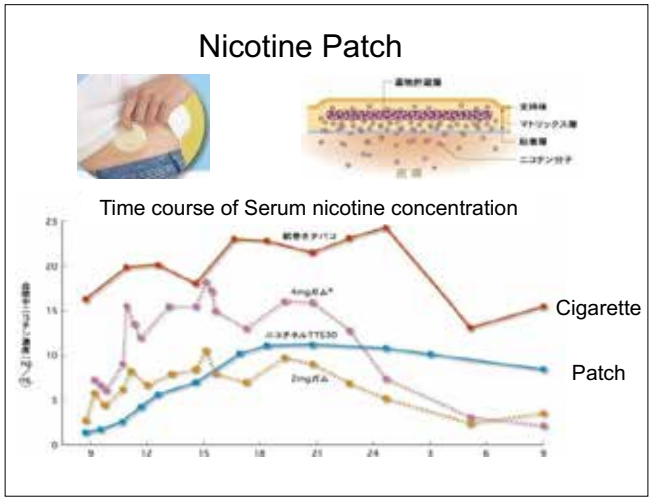


Fig. 27

to promote good health status. (Fig. 30)

I also want to mention the prevention of respiratory infections. This photo shows a crowded train in Tokyo. Very crowded trains are common in Tokyo, and viruses can easily be transmitted to other persons in such a situation. (Fig. 31)

As Dr. Hinoshita showed, I previously mentioned ways to prevent viral infections in a TE management guide published in 2017. I would now like to give some tips for preventing infections. Influenza virus infections generally peak around the winter season, in February of each year. (Fig. 32)

Viral transmission typically occurs through two main routes. One is droplet transmission, and the other is contact transmission. Droplet transmission occurs when one breathes virus from droplets expelled by patients. Contact transmission occurs when someone picks up virus from doorknobs or other surfaces touched by patients. (Fig. 33)

Wearing a mask and avoiding crowded locations are effective to prevent droplet transmission. There are such masks available in Japan. Masks for people with microears are available, and for example, there are masks with long straps, or strapless masks that can be adhered to the cheeks without any straps. In Japan, cedar pollinosis is very common, and these masks are also helpful for preventing such symptoms. (Fig. 34)

Alcohol disinfection is effective to prevent contact risk transmission of influenza virus. There are alcohol spray and gel products available in Japan. This photo shows automatic hand sanitizers that can be operated with one hand and can also be used for the feet. (Fig. 35)

In that guide, we stressed keeping appropriate humidity levels, adequate rest, nutrition, and vaccinations for the management of TE. (Fig. 36)

This brings me to my conclusion. Pulmonary function in TE at the age of 55 was within normal range. It was very good. But peripheral airway obstruction was observed, especially in smokers. And FEV1% values were lower in patients with upper limb defects. Therefore, smoking cessation is highly recommended for such patients.

In Japan, treatment for smoking cessation is covered by national health insurance, and two drugs are available. As

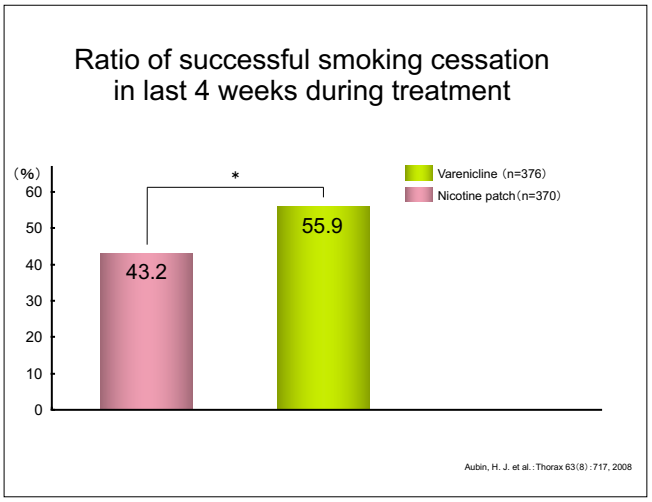


Fig. 28

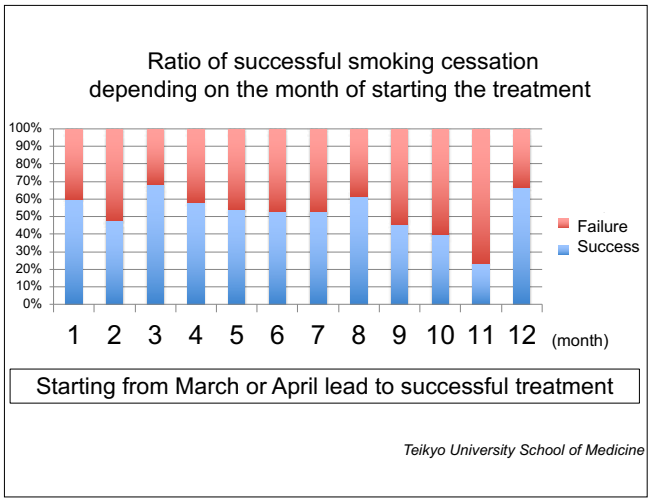


Fig. 29

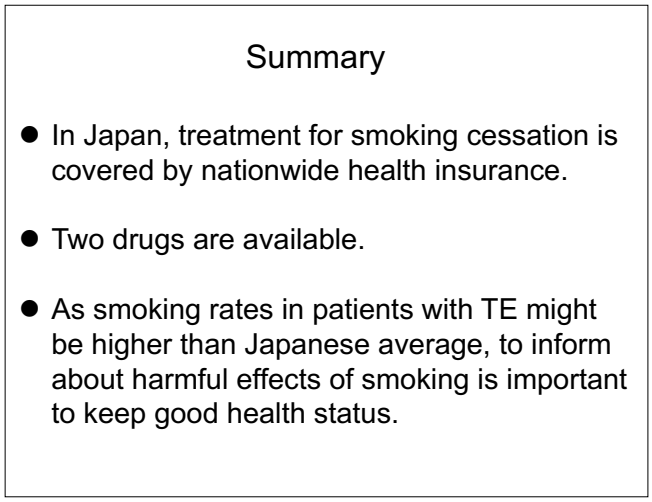


Fig. 30

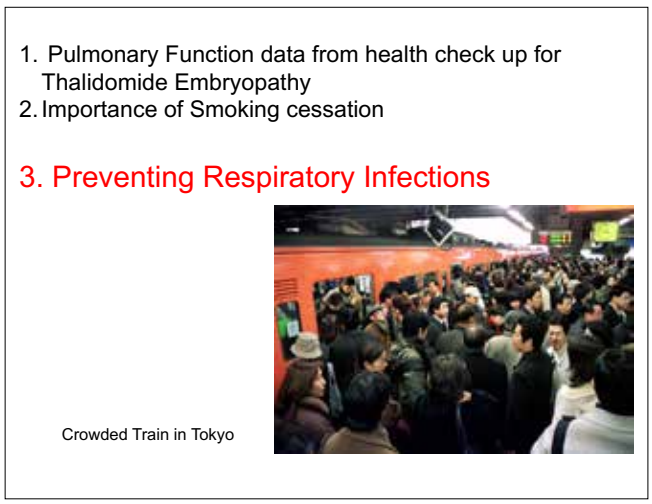


Fig. 31

smoking rates in TE might be a little bit higher than the average Japanese, it is important to inform such patients about the harmful effects of smoking. And because the physical activity of patients with TE potentially becomes lower because of muscle and skeletal pain, the development of COPD also leads to decreased physical activity. Thus, quitting smoking could help prevent the development of COPD. Various devices are also available in Japan to help patients avoid respiratory infections. (Fig. 37))

That is the end of my presentation. Thank you for your attention. (Fig. 38)

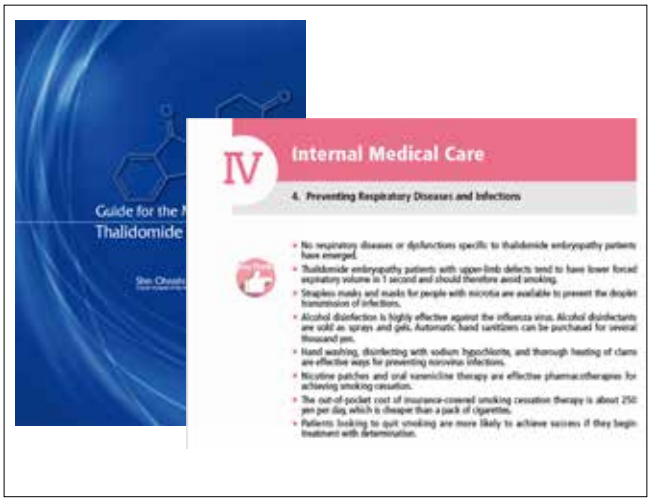


Fig. 32

Preventing Respiratory Infections

Focusing on prevention strategies aimed at the influenza virus

- Influenza virus infections generally peak around February of each year. Infections are generally transmitted via two routes.
- Droplet transmission occurs when someone inhales virus particles contained in droplets coming from the cough of an infected person.
- Contact transmission occurs when someone touches a doorknob or other surface touched by an infected person and then touches their nose or mouth.

Guide for the Management of Thalidomide Embryopathy 2017

Fig. 33

Strategies for preventing infection
Preventing droplet transmission

- Wear a mask and avoid going to crowded locations. Masks for people with microtia are commercially available. Examples are masks with long straps and strapless masks that are adhered to the cheeks with silicone tape.
- These masks also help prevent pollen allergies.

Mask with long straps

Strapless mask

Guide for the Management of Thalidomide Embryopathy 2017

Fig. 34

Preventing contact transmission

- Wash and disinfect hands after going out. Remember to wash your hands after returning home.
- Alcohol disinfection is highly effective against the influenza virus. Disinfecting the hands with an alcohol product is useful for people unable to rub their hands together.
- Alcohol sprays, such as Welpas, and gels, such as Softy Hand Clean, are available. Gel products can be dispensed and applied with one hand. Automatic hand sanitizers can be purchased for several thousand yen. They can be operated with one hand and can also be used for feet.

Guide for the Management of Thalidomide Embryopathy 2017

Fig. 35

- Maintaining optimal humidity levels: Breathing dry air reduces the defensive properties of the airway mucosa, which increases the chance of getting sick. A humidifier should be used to maintain proper humidity levels (50–60%).
- Getting enough rest and eating nutritious, well-balanced meals.
- Getting a flu vaccination: Influenza vaccination reduces the chance of getting the flu and prevents influenza infections from worsening. Flu shots require about 2 weeks to become effective and should therefore be given by mid-December. Only one shot is needed. A shot is needed every year because the effects wear off after about 5 months and prevalence strains change from year to year. Flu shots contain an inactivated vaccine free of pathogens and therefore cannot cause influenza. Adverse reactions, which include redness and swelling at the injection site, fever, headache, and fatigue, normally resolve within 2–3 days.

Guide for the Management of Thalidomide Embryopathy 2017

Fig. 36

Conclusion

- Although pulmonary function in patients with TE at age 55 yo was within normal range, peripheral airway obstruction, which can lead to COPD was observed in smokers.
- As %FEV1 was numerically lower in patients with upper-limb defects, smoking cessation is highly recommended to such patients.
- In Japan, treatment for smoking cessation is covered by nationwide health insurance. Two drugs are available.
- As smoking rates in patients with TE might be higher than Japanese average, to inform about harmful effects of smoking is important to keep good health status.
- As the physical activity of patients with TE potentially becomes lower due to muscle skeletal pain, development of COPD, which can lead to low physical activity, should be avoided.
- To avoid respiratory infections, masks with long straps and strapless masks are available.

Fig. 37

Teikyo University Hospital (Itabashi, Tokyo, Japan)

Fig. 38

Q&A

Tomoko Shiga: Thank you, Dr. Nagase. Are there any questions or comments?

Dee Morrison: Thank you for your presentation. About smokers in the UK, 25% with TE smoke compared with the national average of 17% to 19% according to gender. So this is an important topic for us, too, and we haven't yet tackled it. Obviously, it's quite a sensitive topic, and we are wondering about how to go about it as best we can. It's important that thalidomide survivors like the Trust, and we don't put them off because we are doing lots of other work as well. I am not sure how many really want to stop smoking at the moment. I wondered if you had any idea of how many of your smokers were receptive to stopping smoking and how they are going to go about it?

Hiroyuki Nagase: Yes, thank you very much. I think that some but not all patients with TE get a health checkup within this project. So there is a bias for accessing different types of patients. My impression is that TE patients who smoke do not like to visit the hospital frequently or have checkups regarding their health status. They don't want to see the real status of their health.

So I think it's very difficult to access such patients, especially current smokers. I want to ask the Ishizue Foundation to provide information on the importance of smoking cessation, and if possible, I want more access to patients with TE who smoke. Thank you for your question.

Junichi Horiuchi: Thank you very much. According to your statistics, there are many patients with TE who smoke. Well, I work in a hospital, and I don't have any statistics myself. But those born with birth defects tend to smoke more than others at around the age of 20, that's my feeling. And when they become adults, they would like to show others that they are adults, for example. Your statistics are of the general public. So, if you could present data for the young adults, that will be very helpful in showing that thalidomiders tend to smoke more than the general public. I would like to also emphasize to my fellow people to stop smoking. Thank you.

Hiroyuki Nagase: Thank you very much for your comment. The prevalence of smoking, especially in young females, is a big problem in Japan. The prevalence in males is continuously decreasing, but the ratio in young females is not. So, as you say, it's an important problem. Thank you.

Shadi-Afarin Ghassemi: Thank you very much. I feel like I have comments in every session. So, please excuse me. It's just a comment. I mean I think, a lot of work has to be done to prohibit smoking. And as you say, it's right for smoking thalidomiders to just seek free healthcare.

Actually, in Sweden, we have started to ask patients with prosthesis, endoprosthesis, and total hip or knee prosthesis not to smoke at all at least 6 weeks before their surgery, whether they are thalidomiders or non-thalidomiders. If they show that they have been smoking days or weeks before the surgery, the surgery is off. So, yes, we actually cancel that, yes.

And from this year, July 1, there is a new law that you cannot smoke even outside a restaurant. We usually have some places for smokers, like in a courtyard or outside the hospital, but not inside. It's been, I mean it's been forbidden for many years now. But from July 1, you cannot smoke even outside. So, if anybody is passing by the bus station or train station, it's free air, I mean, but you are not allowed to smoke.

So, I think these things don't make it personal when it comes from the governor. You know it's, you don't need to ask any person please stop smoking. You say, this is the law, and that's it. So it's much easier to handle that really. That was just a comment.

Hiroyuki Nagase: Thank you very much for your comment. I completely agree with you.

Fumihiko Hinoshita: An additional comment from me. You know, in Japan, there is also a tendency for the government to strengthen the regulation of smoking, year by year. And recently, some new acts were enacted by law, not to smoke in restaurants or public places, not only inside, but also outside of those buildings. Okay.

Hiroyuki Nagase: We are changing. For the 2020 Olympic Games in Tokyo, things are changing.

Klaus M. Peters: Thank you for your presentation.

Hiroyuki Nagase: Thank you.

Klaus M. Peters: I think the rate of smokers in Germany is also higher among thalidomiders than among the general population. But there are also other things being abused, especially alcohol. Alcoholism is higher in thalidomiders than in the general population in Germany, as is other types of drug abuse. I think that's a problem. This could be due to chronic pain.

Hiroyuki Nagase: Thank you for your comment.

Fumihiko Hinoshita: Thank you very much, Dr. Peters, for your nice comment. I should respond to that question. In Japan, I'm sorry to say, we did not examine how many thalidomiders abuse alcohol or drugs. So we cannot show you the exact percentage or ratio of thalidomiders who are alcoholics or drug abusers. Do you have any information about this, Mr. Sato?

Tsugumichi Sato: No, I don't have any information about drug abuse or alcoholism.

Fumihiko Hinoshita: Do you feel that there are many such thalidomiders?

Tsugumichi Sato: I've never heard it this among thalidomiders, Japanese thalidomiders. I don't know any Japanese thalidomiders affected by drug abuse.

Christina Ding-Greiner: We should think of the fact that thalidomiders have a higher percentage of psychic diseases, more bouts of depression, and more anxiety disorders. We know that people with mental diseases are the strongest smokers. I read a paper that said about 80% of people with psychic diseases smoke. So, I suppose it's comprehensible that there are more smokers among thalidomiders.

Hiroyuki Nagase: Thank you very much for your comment, and I completely agree with you. I work at a smoking cessation clinic, and in that clinic, the success rate of smoking cessation is significantly lower in patients with depression. The overall success rate is 67%, but in patients with depression, it is 33%. I think it's very difficult, but 30% of patients can quit smoking. So, we continuously have to say to patients, "let's try to quit smoking". Thank you very much for your comment.

Tomoko Shiga: So, the time is up. That's the end of this session. Thank you, Dr. Nagase.

Hiroyuki Nagase: Thank you very much.

Mortality in Thalidomiders in Germany: Is Underdiagnosed Hypertension the Cause?

Jan Schulte-Hillen

Notfallzentrun Klinik St. Anna, Luzern, Switzerland

Ryoji Kayamori (Moderator)

I am glad to be here with Dr. Jan Schulte-Hillen. He earned his medical degree at the University of Münster in 1988 and his PhD from the University of Münster in 1991. Currently, he is working as a GP in Lucerne, Switzerland. His clinical experience has been expanding, partially because he is multilingual. He has a good command of German, as it was his mother's tongue, in addition to English, French, Spanish, Italian, and Portuguese. His hobbies are also diverse, including sailing, skiing, motorcycle riding, skateboarding, vintage cars, and flying. This is unbelievable for Japanese people who grew up on a small island country.

One more thing, as you know, his father is Mr. Karl-Hermann Schulte-Hillen, the famous lawyer. Without him, there would be no thalidomide story. Jan was born on April 25, 1961 with short arms. In June, 1961, his father visited and asked Dr. Widukind Lenz in Hamburg why were lots of malformed babies born with so-called Wiedemann syndrome. What was going on in West Germany? Sadly, Mr. Karl-Hermann Schulte-Hillen passed away on January 14, 2017. Now, Jan's theme is mortality in thalidomiders in Germany and the prevalence of hypertension as a cause. Could you please begin your talk? Thank you.

Jan Schulte-Hillen

Thank you very much for the kind words, especially for my father. It is a big honor for me to speak to you today.

Yes, let me jump to the main slide of my discourse here. (Fig. 1)

What really concerns me and what really annoys me and puts a big question mark in my mind are the two graphs you are seeing here. This is the mortality, the age-related mortality of the German population data derived from the Federal Bureau of Statistics in Wiesbaden. And this is the same data for the thalidomiders. And here you see the first mistakes. I put the comma at the wrong place. It should read 1.24. That means that in the year 2017, a German person born in 1961 would have a 0.5% chance of dying that year. Whereas, a thalidomider born in 1961 would have a probability almost twice as high in 2017.

How did I get these data? I got these data by comparing the data from the statistics bureau or the federal bureau in Germany with the mortality rates issued and published by the Thalidomide Trust in Germany. (Fig. 2)

This is the same, only with the numbers in it. I think it's safe to say that at least in Germany, thalidomiders may be a population at risk with double the mortality of age-related groups.

The reason for this is not known, to my knowledge. I think we do not precisely know why this is so, and we do not know if the data from Germany are representative of the worldwide situation. (Fig. 3)

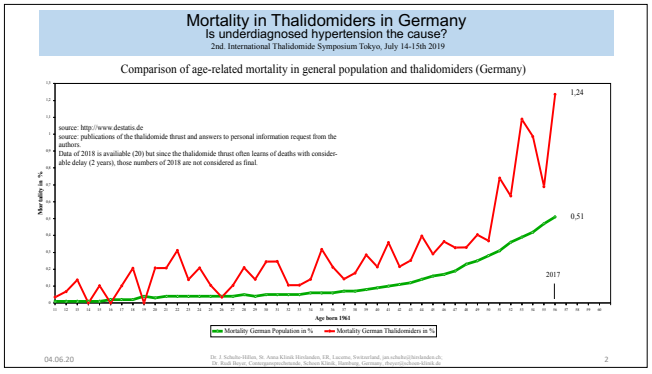


Fig. 1

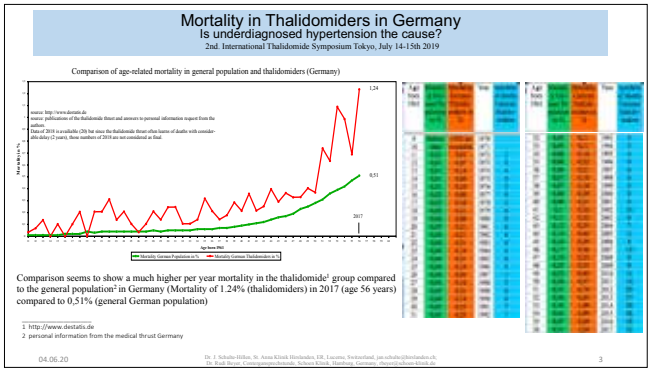


Fig. 2

What could be discussed may be a general accelerated aging due to unknown reasons or maybe social isolation, psychological problems, or a higher, let's say, "wear and tear," because of the limited range of motion and limb defects.

I mean, if you have to move your entire body to reach a glass of water every time in your life, this is not going to be without consequences on the tissue. And maybe there are higher stress levels, income issues, family life, and social aspects. We already heard from several sources that thalidomiders tend to have a much higher prevalence of metabolic syndrome, perhaps also due to the limited possibility of physical exercise.

And of course, a big issue is also limited access to public managed care programs due to limited mobility and iatrophobia. When I talk to peers and ask them why they don't go to see a doctor, many of them reply, "I don't want to stay in the waiting room and be stared at it." It can be as simple as that. There might be several reasons for the higher mortality, and I would like to focus on this one: possible arterial hypertension. (Fig. 4)

Is there any evidence for hypertension as a problem in thalidomiders? Yes, there is. We just heard from Dr. Hinoshita that he compared the rates of hypertension in thalidomiders with the normal Japanese population and did not find any significant difference. As I remember, Dr. Tomoko Shiga found a higher risk for cardiovascular diseases in her Japanese study group and a prevalence for hypertension of almost 50%, which would be an enormous number. We are comparing thalidomiders in Japan with normal people and non-thalidomiders in Germany. But the prevalence of hypertension in Germany in the normal population in an age-related group is 31%. So, this is much lower.

We have no idea why this is so, and there are no groups for comparison, so I really had to dig very, very deep, and what I found was a publication from Nallegowda, reported in 2012. He found a significantly higher prevalence of cardiovascular diseases in amputees, and he assumed the observed higher prevalence of hypertension in this group to be the reason for this.

In 2015, Kowalski found a higher prevalence of cardiovascular diseases in a Brazilian study group of thalidomiders. I have no idea how old this study group was, but I think the thalidomiders in Brazil should be about 10 years younger than us? No?

Lavinia Schuler-Faccini

The same age, no. I will show this later.

Jan Schulte-Hillen

This is very interesting, yes. I am looking forward to that. Okay. Just a couple of words about hypertension in general. (Fig. 5)

Like you all know, I don't have to put emphasis on this. Elevated blood pressure is considered the major risk factor for long-term multiorgan diseases involving the heart, brain, kidney, and eyes. Because most of the time, it becomes clinically relevant at the end point of a disease, it's called a silent killer because it does not show any preliminary symptoms. High blood pressure doesn't cause pain. The correct self-measurement of blood pressure is mandatory for prophylaxis of these diseases, and is part of every single modern health program. Every health program involves self-measurement of blood pressure. And this is the situation for thalidomiders. Due to anatomic reasons, thalidomiders with upper extremity defects show problems in measuring

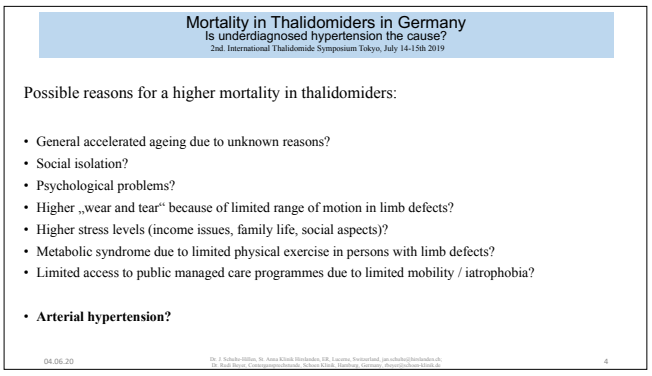


Fig. 3

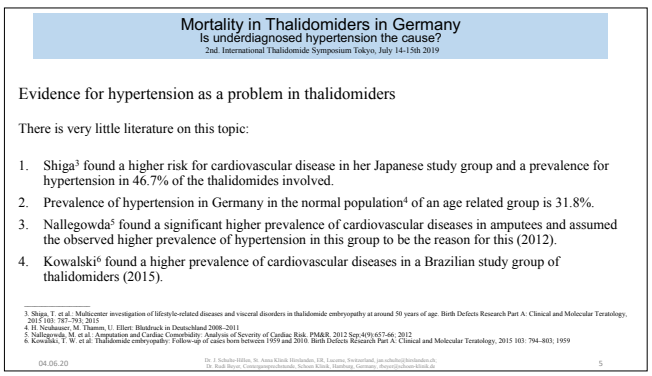


Fig. 4

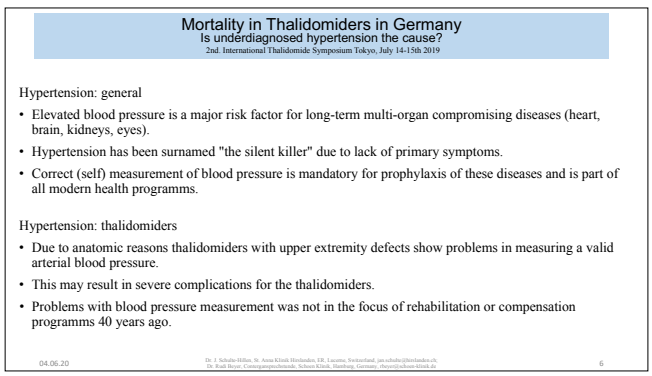


Fig. 5

valid arterial blood pressure. I will come to the reasons for that later. This may result in severe complications among thalidomiders.

I would like to put emphasis on the fact that problems with blood pressure measurement were not the focus of any rehabilitation or compensation program 40 years ago. Blood pressure, hypertension—no blood pressure as "blood pressure 'period'" was only an issue during surgical interventions when anesthetists just tried to figure out how to keep the systolic blood pressure above 120 mmHg or something like that, and then everything was safe. Nobody ever had any concern about diastolic blood pressure. And as you all know, this is more important in terms of the long-term defects of high blood pressure. (Fig. 6)

Indications for incorrect blood pressure measurements in thalidomiders. I do not have any doubt that you can take blood pressure in thalidomiders. But, as an educated guess, I would say most of them are wrong. What would be an indication for such an assumption? I told you I was working for the Thalidomide Trust in Germany, who have no idea that I am standing here now. My work is in no way endorsed by them. As one of the experts of the medical committee, I have come to read many, many medical reports of patients who, for example, apply for a higher compensation because they say "the hips don't work anymore," "I can't move my hands," or "I developed carpal tunnel syndrome."

Reading between the lines, I find strong evidence of a history of stroke and myocardial infarction from the age of 40 and upwards, which is mentioned only in as a side remark. This is one thing where I say that something must be going on. The other thing is that many, in many ophthalmologic investigations, fundus hypertonicus in random eye investigations for other indications has been found, in spite of the family physician having always stated blood pressure to be normal.

So, whatever the doctor measured was not the correct blood pressure. They also found elevated blood pressure with invasive measurements in surgical interventions without the patient having any history of documented hypertension. (Fig. 7)

So, these are what are regarded as mandatory conditions for correct blood pressure. A correct cuff diameter in relation to diameter of the arm and hand. However, in thalidomiders, this is not possible. The cuff must be fixed snugly and the arm must be at the height of the heart. In thalidomiders, this is often not possible. An upper arm with normal anatomy must be patent. It is not. The diameter of the arm artery must be in normal relation to the diameter of the upper arm, but there are no data available. The arterial brachialis should be in the normal anatomical location, but this is very questionable in thalidomiders. And in the case of, you know, wrist measurement devices, the arteria radialis on the radial side of the wrist must be patent for wrist blood pressure measurement devices. The arteria radialis is very often miss-

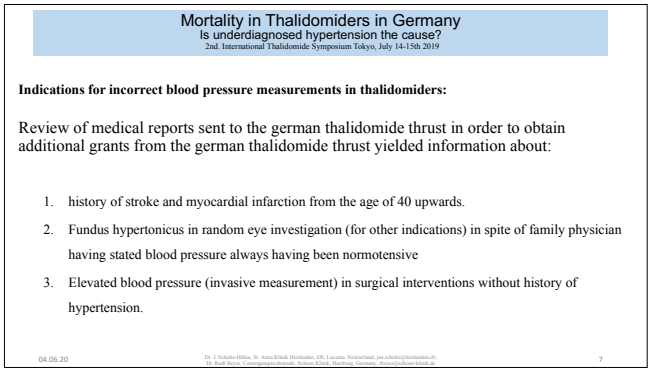


Fig. 6

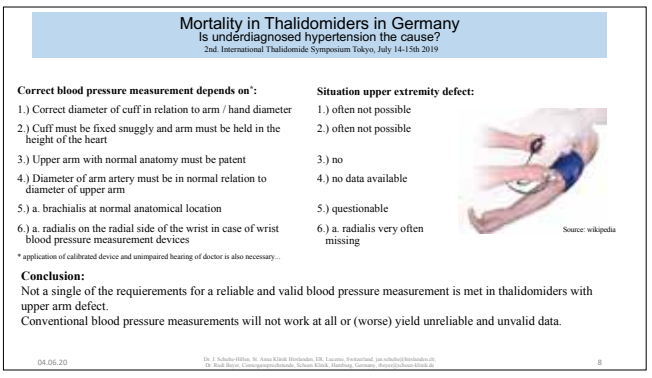


Fig. 7

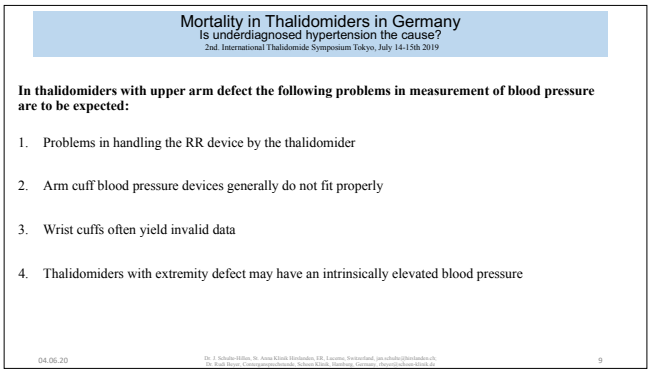


Fig. 8

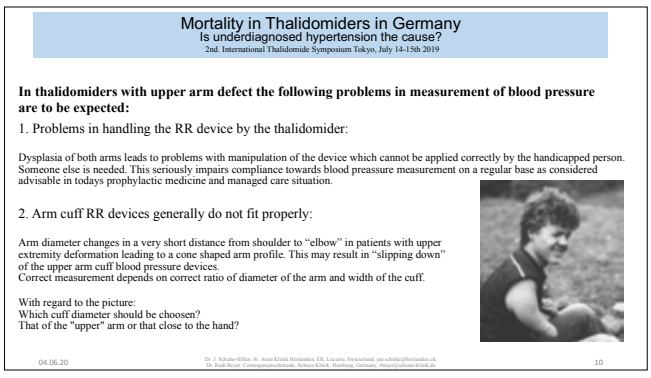


Fig. 9

ing in thalidomiders.

Concerning the radial artery, I understand that in Japan, there are many, many long-armed thalidomiders, and I would like to tell you that we have many long-armed thalidomiders in Germany with a missing arteria radialis. This goes to the extreme, where the hand is anatomically normal, and hypoplasia of the thenar is the only sign or indication of thalidomide damage you see.

Many of them are missing the radial artery, so wrist cuffs do not work properly, not even in long-armed thalidomiders. (Fig. 8)

Therefore, not a single requirement for reliable and valid blood pressure measurement is met in thalidomiders with an upper arm defect. Conventional blood pressure measurements will not work at all, or worse, will yield unreliable and invalid data. (Fig. 9)

In thalidomiders with upper arm defects, the following problems in terms of blood pressure measurement are to be expected. Handling the device itself is going to be problematic. I couldn't handle it with my arms. Arm cuff blood pressure devices generally do not fit properly. Wrist cuffs yield invalid data, and thalidomiders with upper extremity defects may have intrinsically elevated blood pressure, as I showed, compared with an amputee group. Handling the device is kind of self-explanatory, and the cuff generally does not fit properly. So, you see, this is a more conical shape, so the cuff is going to slip down. With regard to the correct diameter of the cuff, which arm diameter do you choose, up here or down here? This is very questionable. (Fig. 10)

This is a radiograph of an upper extremity. I would like to ask, where do you expect the arteria radialis to be? There is none at all. And, yes, I will skip this. I already told you that perhaps they have intrinsically elevated blood pressure due to the reduced overall diameter of the blood vessels. (Fig. 11)

So, thalidomiders in Germany seem to have higher age-related mortality than the general population. After all, the prevalence of arterial hypertension seems to be high in the thalidomide population, as mentioned by Dr. Shiga, but it still might be underdiagnosed because of the problems I described. (Fig. 12)

Thalidomiders are therefore excluded from one of the most basic and most important types of biometer monitoring. Higher mortality and underdiagnosed arterial hypertension could be related, and there is need for guidelines concerning blood pressure evaluation for thalidomiders. (Fig. 13)

We talked about this already. Suggestions for future mortality data and the prevalence of hypertension should be compared with those from other countries. (Fig. 14)

I did not find much on this topic in the literature. The development of the mortality rate should be subject to close follow-up, and family physicians and clinical doctors should be notified about problems when blood pressure measurements are not correct.

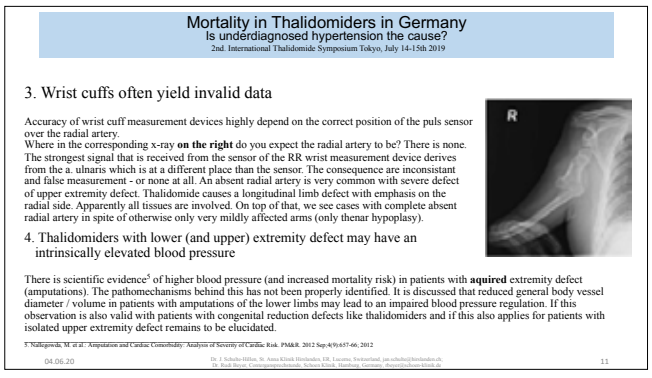
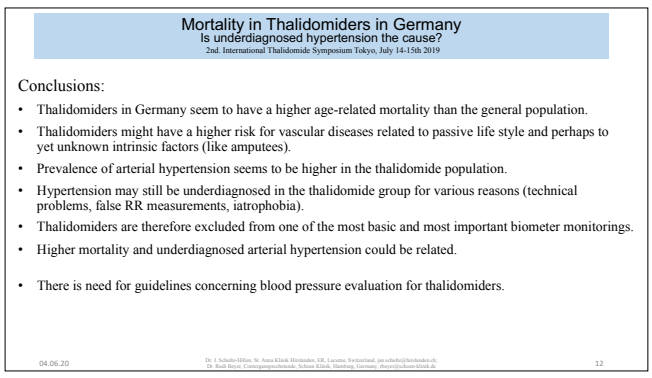


Fig. 10



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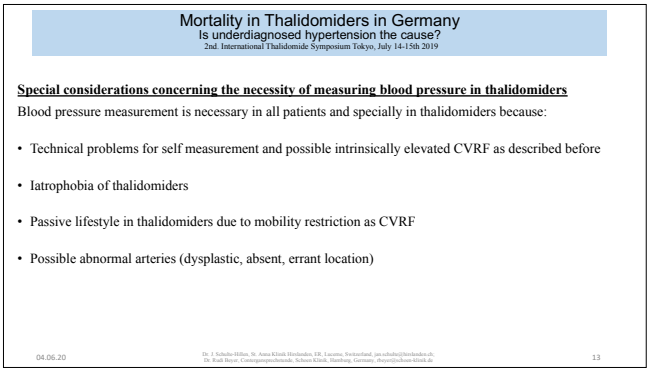

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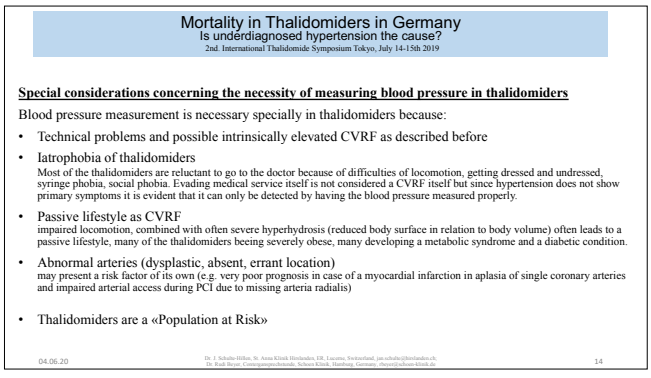


Fig. 13

I also think we are in dire need of clinical research on noninvasive blood pressure measurement devices that use something like pulse wave analysis instead of the traditional Riva-Rocci approach. All investigations in that direction should strongly be encouraged. There is also a need for guidelines, as I said.

I mean, the Riva-Rocci approach, if you come to think of it, is more than 100 years old. We are still working with it and it works well, except for three conditions that yield incorrect data. The first is thalidomiders, the second is diabetic angiopathy, and the third is arteriosclerosis. (Fig. 15)

My suggestions for thalidomiders and blood pressure measurement at this time is as follows. Patients with isolated leg defects and normal upper extremities should measure their blood pressure in the same way as every other patient with normal arms. Patients with upper arm defects should have their blood pressure measured once on both legs and both arms, and if the result yields a difference of more than 20 mmHg in the legs compared with in the arms, the legs should be used for future blood pressure measurements; that is, the arteria tibialis posterior correction factor, as mentioned above and shown by Yoshizawa.

The literature on this remains very limited. Yoshizawa found that he could get reasonable results if he took the systolic blood pressure of the arteria tibialis posterior, added 8 mmHg, and multiplied this by 0.88 mmHg. He considered this a valid correction factor.

Another possibility that I find quite appealing is measurement by proxy, that is, if possible, you find a healthy reference person not affected by extremity defects who matches the thalidomide patient in terms of age, sex, and leg circumference, and you take the blood pressure in the legs and arms with cuffs of adequate size. The ratio between arm and leg blood pressure in the normal person can be applied to evaluate the actual blood pressure in the legs of the thalidomider. You don't have to do this very often. I think it might be okay to get a correction factor once per year, maybe even less.

Then, I think patients with defects of the upper and lower extremities should have their intra-arterial blood pressure taken once as an equation for a personal ratio between the daily blood pressure taken at the determined localization, like, let's say a shortened limb, and the correct intra-arterial pressure. This can either be done with a planned surgical intervention, or especially for this purpose, after careful consideration of the risks and benefits, of course. I mean, it's an invasive procedure.

In general, as I said, for blood pressure measurement on the legs, the problems of false results in diabetic arteriopathy and atherosclerotic lesions must be taken into account because you get wrong results in those scenarios. (Fig. 16)

Talking about invasive blood pressure measurement, this is a plot that I had done during a surgical intervention, and I had the anesthesiologist take intra-arterial invasive blood

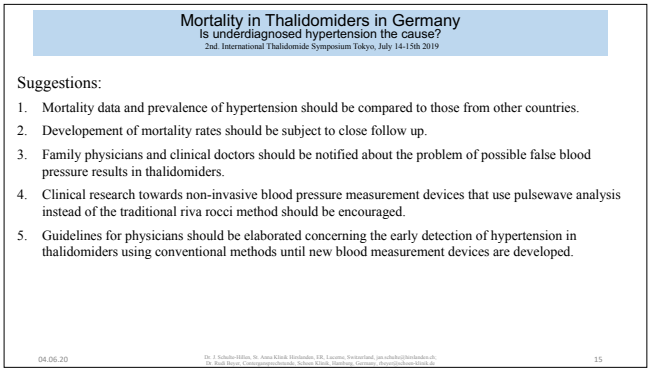


Fig. 14

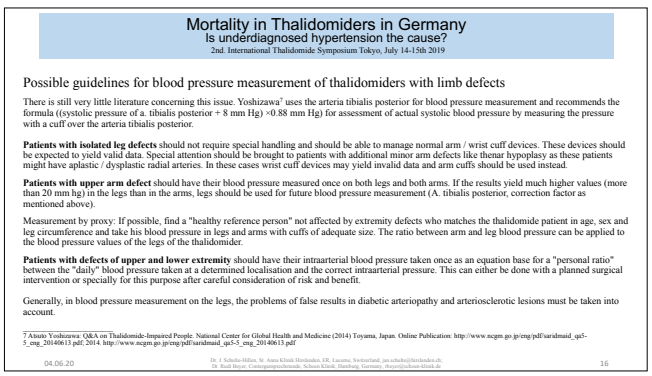


Fig. 15

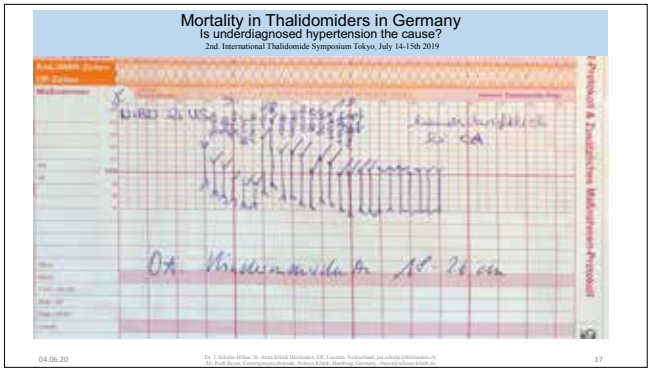


Fig. 16

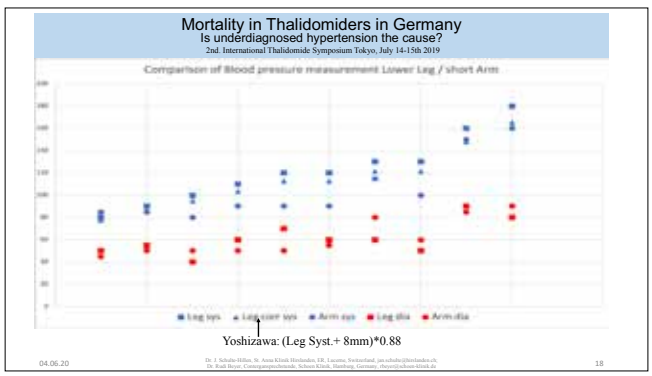


Fig. 17

pressure. Afterwards, he said, "I didn't want to. I didn't do the invasive measurement. What I did instead is noninvasive blood pressure on the left side, lower leg, and left side upper arm". I would like to show you what the problem is. (Fig. 17)

What you see here is not a graph. I just plotted several singular measurements. Blue is systolic. Red is diastolic. The square is a leg and circle is an arm. The triangle is this thing with a correction factor from Yoshizawa, which of course, shows an excellent correlation because it's a mathematical function.

If you take a look at this, systolic leg and systolic arm differ by up to 30 mmHg, which is completely unacceptable. And even in the diastolic, you have a difference up to, well, at least in my case, up to 20 mmHg; completely useless for any prophylactic program concerning or involving blood pressure. (Fig. 18)

Generally, and for all thalidomiders, we suggest the following procedures. As long as there is no other method available, we still suggest Yoshizawa's method, as described above, and a correction factor. And please, in all planned surgical interventions where invasive intra-arterial blood pressure is taken anyway, you should try to talk your patients and the anesthesiologist into making comparisons between invasive and noninvasive blood pressure measurements. And please note the diameter of the cuff that was involved, and the place where the blood pressure was taken. This is absolutely mandatory.

With this, you could establish your personal ratio for this patient between intra-arterial blood pressure and cuff measurement results. As an additional measure, I would suggest that regular laboratory investigations should include lipids, cholesterol, and uric acid, but not creatinine, because many thalidomiders have very reduced muscle mass. So, creatinine wouldn't work; however, a rise in creatinine would show you something, whereas isolated creatinine would not.

I was told that the more sensible thing would be to do the cystatin C, and of course, glucose and electrolytes and renal analysis should include microalbumin, and then, of course, further examinations like ECG, echocardiography, duplex sonography of extracranial brain vessels and 2D-echo vessels, 24-hour blood pressure measurements if possible, and then perhaps pulse wave assessment. In addition, I would send thalidomiders to a doctor once per year to see if they could find any sign of fundus hypertonicus because this is not a sign; this is proof of hypertension that is not well corrected.

This is a bit of a look into the future. There are possible technical approaches for blood pressure measurement. One is called ClearSight and another is called SOMNOtouch. But they do not work with our patients because they need a cuff measurement as a reference point. So, this does not work. (Fig. 19)

I think the most promising approach, which is still in the development stage, is Dr. Aflex's device. He measures in the buccal cavity. He measures blood flow in the arteria facialis. And I think this is very interesting. The approach is, I don't know if I get the word correct, photoplethysmography, that's low intensity infrared signal combined with an inflatable pad. So, he inflates the pad to the very point where the arteria facialis does not pass any blood anymore, and then he opens it and looks at how fast it recovers or something like that. I have not entirely understood the procedure, but I think this is a very interesting thing because I don't think the buccal or facial artery was affected in a single thalidomider, and you could use it for everybody else as well.

The gentleman in the picture is Gernot Stracke, one of the big players in thalidomide in Germany, from Hamburg, who works together with Dr. Beyer. If you could post this, if you could fix it to a wall or to a socket or something like that, the thalidomiders, even those without any arms, wouldn't even have to touch it to use it. All they have to do is to let their mouth use the system.

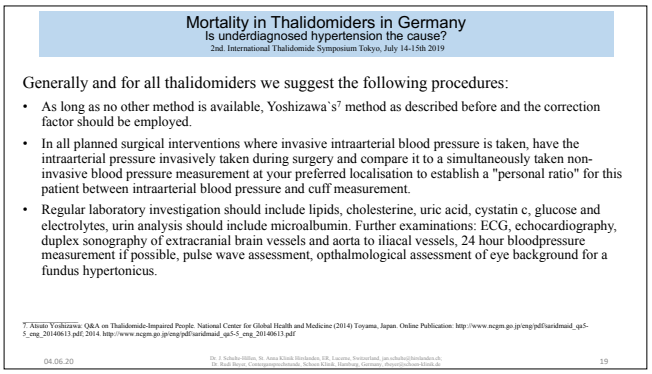


Fig. 18

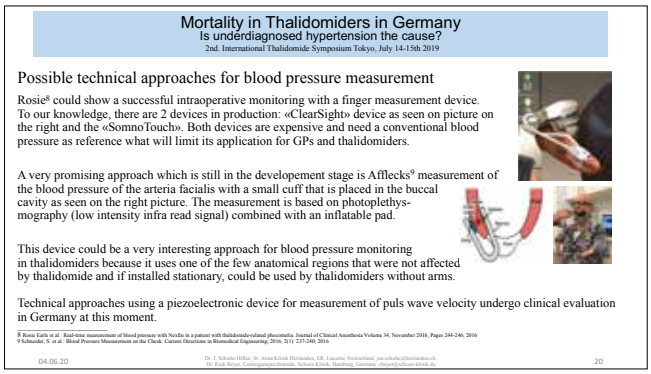


Fig. 19

And I think this looks like the shape of things to come, something like this. Okay, that's it. Thank you very much.

Ryoji Kayamori: Thank you, Jan. Lots of comments and questions would be expected, but time-wise, I have to move to another presentation. Thank you, Jan.

Jan Schulte-Hillen: Okay.

Lessons from Thalidomide Embryopathy and Sharing Information with the Next Generation: From the Physiatrist's Point of View

Nobuhiko Haga

Department of Rehabilitation Medicine, The University of Tokyo, Tokyo, Japan

Ryoji Kayamori (Moderator)

The next presentation is Professor Nobuhiko Haga from the University of Tokyo. The title of his presentation is "Lessons from Thalidomide Embryopathy and Sharing Information with the Next Generation: From the Physiatrist's Point of View". Could you start please?

Good morning, everyone. My name is Haga from the University of Tokyo. I work in the Department of Rehabilitation. I joined the research group 2 years ago. (Fig. 1)

So, what we as physiatrists have done since 2017 is participate in a mobility symposium in Hamburg in 2017, hold health meetings in five Japanese sites from 2017 to 2018, visit Germany and UK to meet experts, including some of you, last year, and examine thalidomiders in clinics. On every occasion, we had the chance to hold discussions with thalidomiders. (Fig. 2)

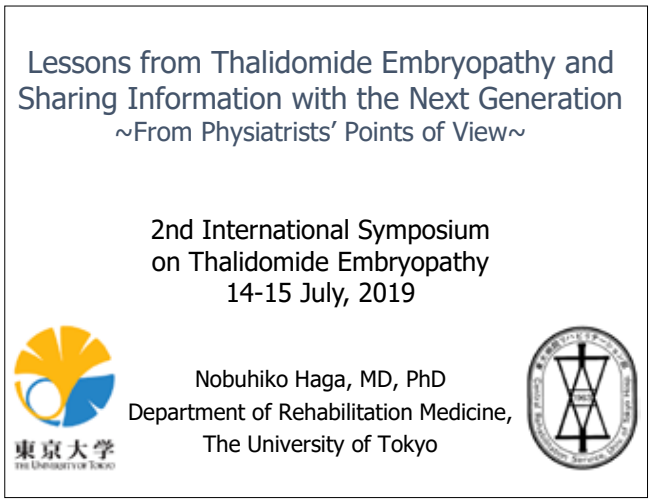


Fig. 1

Fig. 2

So, this is the mobility maintenance of people with thalidomide embryopathy (TE): prevention, pain therapy, and alternative therapeutic procedures. This symposium was held in September in 2017 in Hamburg by Dr. Rudolf Beyer. I have heard that around 200 thalidomiders participated from all over Europe. (Fig. 3)

This is the schedule for the first day. We had many topics related to rehabilitation medicine. (Fig. 4)

This is the schedule for the second day. On the second day, we had several topics on complementary and alternative medicines. From that symposium, I learned the importance of mobility maintenance, the use of assistive devices, a personalized rehabilitation approach, especially for pain, and the application of complementary and alternative medicines. (Fig. 5)

We then had health meetings at five Japanese sites. During these meetings, held at local thalidomiders' meetings, we discussed problems with health and daily living with thalidomiders. (Fig. 6)

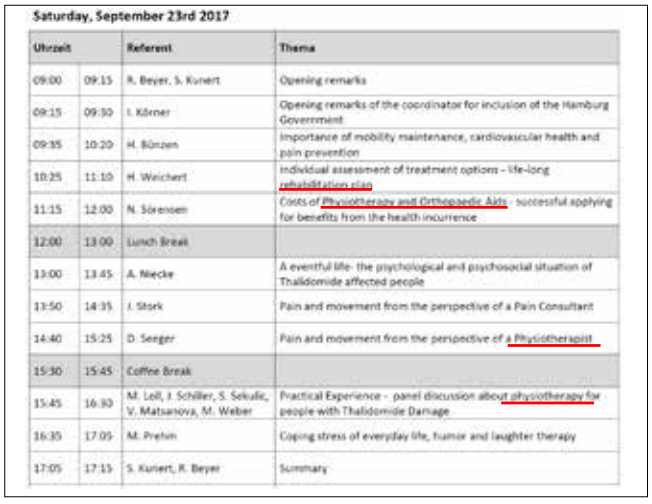
Fig. 3

All participants discussed their health problems. This was moderated by our rehabilitation specialist, Dr. Fujitani. The participants, after self-introductions, took turns presenting their recent problems with health and daily living. The moderator promoted a discussion on the participants' problems and their experiences of solving problems by referring to other participants' opinions. We then held individual interviews. Rehabilitation specialists had interviews with the participants who applied, and according to the complaints of the thalidomiders, we examined them and gave some advice. The total number of thalidomiders who applied for individual interviews was 36 in these five meetings. (Fig. 7)

The following shows health problems related to rehabilitation medicine. As for consulting a doctor, after the retirement of a doctor who had treated the thalidomider since childhood and had sufficient knowledge of TE, it was difficult to find another doctor. The thalidomiders cannot consult their family physicians about their pain or numbness. Thalidomiders feel stressed when the medical staff say that they have no knowledge of TE. (Fig. 8)

So, regarding pain and numbness, the thalidomiders cannot judge whether their symptoms are related to TE. Many thalidomiders complain of pain and stiffness in the shoulder and neck. Drug treatment and massage are common. Personalized exercise therapy was effective in some patients. There were opinions that the effects of chiropractic treatment and massage were temporary and not constant. Cervical spondylosis was detected in many of those who complained of numbness. Some of them were assumed to be affected by carpal or cubital tunnel syndrome. Some thalidomiders complained of chills in their forearms and hands.

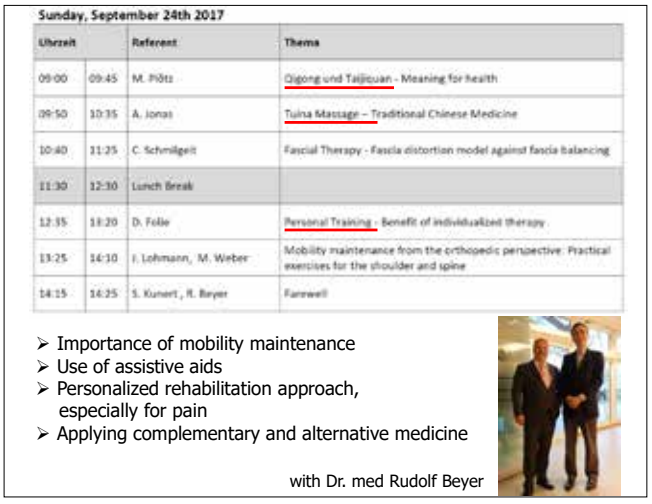
As for progressive physical dysfunction, some thalidomiders tended to drop objects when pinching with the fingers. Side pinching with fingers is common because of thumb hypoplasia. Some complained that their wrists often subluxated. Some who used their feet for many activities commented that they could not raise their legs as high as before, and that their balance decreased when standing on one leg and using another leg as a hand. Walking was common for the prevention of metabolic syndrome.



Saturday, September 23rd 2017

Uhrzeit		Referent	Thema
09:00	09:15	R. Beyer, S. Kunert	Opening remarks
09:15	09:30	I. Körner	Opening remarks of the coordinator for inclusion of the Hamburg Government
09:35	10:20	H. Bönzen	Importance of mobility maintenance, cardiovascular health and pain prevention
10:25	11:10	H. Weichert	Individual assessment of treatment options – life-long rehabilitation plan
11:15	12:00	N. Sörensen	Costs of Physiotherapy and Orthopaedic Aids - successful applying for benefits from the health incurrence
12:00	13:00	Lunch Break	
13:00	13:45	A. Niecke	A eventful life- the psychological and psychosocial situation of Thalidomide affected people
13:50	14:35	I. Stork	Pain and movement from the perspective of a Pain Consultant
14:40	15:25	D. Seeger	Pain and movement from the perspective of a Physiotherapist
15:30	15:45	Coffee Break	
15:45	16:30	M. Loll, I. Schiller, S. Sekulic, V. Matsanova, M. Weber	Practical Experience - panel discussion about physiotherapy for people with Thalidomide Damage
16:35	17:05	M. Prehn	Coping stress of everyday life, humor and laughter therapy
17:05	17:15	S. Kunert, R. Beyer	Summary

Fig. 4



Sunday, September 24th 2017

Uhrzeit		Referent	Thema
09:00	09:45	M. Plötz	Qigong und Taijiquan - Meaning for health
09:50	10:35	A. Jonas	Tuina Massage – Traditional Chinese Medicine
10:40	11:25	C. Schmilgeit	Fascial Therapy - Fascia distortion model against fascia balancing
11:30	12:30	Lunch Break	
12:35	13:20	D. Folle	Personal Training - Benefit of individualized therapy
13:25	14:10	I. Lohmann, M. Weber	Mobility maintenance from the orthopedic perspective: Practical exercises for the shoulder and spine
14:15	14:25	S. Kunert, R. Beyer	Farewell

- Importance of mobility maintenance
- Use of assistive aids
- Personalized rehabilitation approach, especially for pain
- Applying complementary and alternative medicine

with Dr. med Rudolf Beyer

Fig. 5

Fig. 6

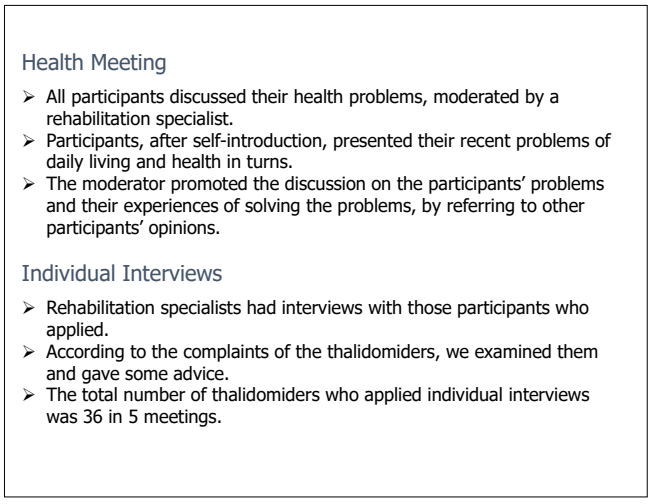


Fig. 7

As for inconveniences in work and life, though many workers complained of fatigue and shoulder stiffness, most hoped to continue their job. As for clothes, shoes, and bags, thalidomiders searched for products that were easy for them to use or modified them. They had difficulty in handling large objects, e.g., refrigerator doors, and in using small tools. Some used self-help tools. As for inconveniences in daily living, some thalidomiders positively sought support from others, some never bought products that were difficult to open, like vacuum-packed ham, and some abandoned what they could not do without support, like going outdoors with an umbrella on rainy days. (Fig. 9)

Last year, we visited Germany and the UK to meet experts like this. (Fig. 10)

In Heidelberg with Dr. Ding-Greiner, I learned that many thalidomiders were beginning to find difficulty in independent living because of pain and arthritis. To maintain independent living, they must change the height of various things in the kitchen, as well as the toilet, shower, and tables, and remodel their cars. No treatment methods for secondary impairments in thalidomiders have been established.

In Cologne, a German–Japanese symposium was held by Professor Peters. The outpatient center for thalidomiders is open 4 days a week, and provides examinations by medical doctors, physical and occupational therapists, and acupuncturists. They put a lot of effort into pain evaluation, partly because pain is influenced by psychological factors. (Fig. 11)

In London at The Thalidomide Trust, 93% of thalidomiders in the UK have musculoskeletal problems.

The Thalidomide Trust provides information advice on TE for general practitioners to foster good relationships between GPs and thalidomiders. In Hamburg, I again met Dr. Rudolf Beyer. The Thalidomide Clinic Hamburg provides initial medical examinations and admission for 4 or 5 days. Orthopedic surgeons, pain consultants, physical therapists, and psychologists join and conduct re-examinations in the outpatient clinic to control treatment. Though no new treatment exists for pain in TE, techniques focusing on fasciae, like physical manual therapy and osteopathy, are fundamental, he said.

Health Problems related to Rehabilitation Medicine

Consulting a Doctor
- After retirement of the doctor who has treated the thalidomider since childhood and has enough knowledge of TE, difficulty exists in finding another doctor.
- The thalidomiders cannot consult their family physicians about their pain or numbness.
- Thalidomiders feel stress when the medical staffs say that they have no knowledge of thalidomide embryopathy.

Pain and Numbness
- The thalidomider cannot judge whether the symptom is related with TE.
- Many thalidomiders complain of pain and stiffness in their shoulder and neck. Drug treatment and massage are common. Personalized exercise therapy was effective in 3. There were opinions that effects of chiropractics and massage were temporary or inconstant.
- Cervical spondylosis was detected in many of those who complain of numbness. Some of them were supposed to be affected by carpal or cubital tunnel syndrome.
- Some thalidomiders complained of chilliness in their forearms and hands.

Fig. 8

Progressive Physical Dysfunction
- Some thalidomiders tended to drop objects in pinching with fingers. (Side pinching with fingers is common due to thumb hypoplasia.)
- Some complained that their wrists often subluxate.
- Some who use their feet in many activities commented that they can not raise their legs so high as before, and the standing balance decreased when standing on one leg and using another leg as a hand.
- Walking was common for prevention of metabolic syndrome.

Inconvenience in Occupation and Life
- Though many workers complained of fatigue and shoulder stiffness, most of them hoped to continue their job.
- As for clothes, shoes, and bags, thalidomiders searched for products that are easy to use for them or modified them.
- They have difficulty in handling large objects (e.g. refrigerator doors), in addition to using small tools. Some used self-help tools.
- As for inconvenience in daily living, some thalidomiders positively sought for others' support, some never buy products difficult to use (e.g. vacuum packed ham), and some abandoned what they can not do without support (e.g. going outdoors with umbrellas on rainy days).

Fig. 9

Visiting Germany and UK to Meet Experts in 2018

Heidelberg:	Dr. Christina Ding-Greiner
Cologne:	German-Japanese Symposium with Prof. Dr. med. Peters (Dr. Becker Rhein-Sieg-Klinik)
London:	Dr. Dee Morrison (The Thalidomide Trust)
Hamburg:	Dr. med. Rudolf Beyer (Schön Klinik Hamburg Eilbek)

German Pharmacy Museum in Heidelberg

Fig. 10

Heidelberg: Dr. Christina Ding-Greiner

- Many thalidomiders are beginning to find difficulty in independent living due to pain and arthritis.
- For keeping independent living, they must change the height of kitchen, toilet, shower, and tables and remodel their cars.
- Treatment methods of secondary impairments in thalidomiders are not established.

Cologne: German-Japanese Symposium with Prof. Dr. med. Peters (Dr. Becker Rhein-Sieg-Klinik)

- The Outpatient Center for Thalidomiders provide 4-days clinic including examinations by MDs, physical and occupational therapists, and acupuncturists.
- They put a lot of effort into pain evaluation, because pain is influenced by psychological factors.

Fig. 11

As disabilities and secondary impairments in TE are complicated and varied, the standardization of managing secondary impairments is impossible. (Fig. 12)

How can we properly manage musculoskeletal impairments in TE? These X-rays are from the same patient with TE. (Fig. 13)

These are photos from Professor Kayamori's literature. The characteristics of Japanese thalidomiders show that lower limb malformations are rare. So, I will focus on only upper limb malformations and secondary impairments in TE. (Fig. 14)

When patients with TE use mainly the upper limbs for ADL, aging and overuse or misuse leads to joint dysfunction, tendinitis, or peripheral neuropathy in the upper limbs. And in those who use the trunk and lower limbs for ADL, aging and overuse may lead to spinal dysfunction or dysfunction in the lower limbs. Congenital musculoskeletal abnormalities associated with TE may have a partial effect on these. (Fig. 15)

In those who use the upper limbs for ADL, there is a paper from Dr. Merkle that shoulder osteoarthritis due to glenohumeral dysmelia in thalidomiders can be successfully treated with joint replacement. So, in thalidomiders, shoulder dysplasia is one of the problems.

From this paper on radial deficiencies, active motion of the wrists and digits is reduced, and grip and key pinch strength are lower than normal. The reduced active motion of the elbow and digits relates to the decrease in hand function. This is also true for thalidomiders. (Fig. 16)

As for peripheral neuropathy in the upper limbs, I will introduce two papers from Japan. In this paper on radial deficiency including TE, the anterior–posterior diameter and cross-sectional area of the carpal tunnel are small, as measured by computed tomography. Endoscopic carpal tunnel release is effective to treat carpal tunnel syndrome in TE. (Fig. 17)

For those who use their trunk and lower limbs for ADL, there are two papers related to this topic.

This is about children. Disc and endplate abnormalities existed in 14 of 28 children thalidomiders and appeared to be progressive in some, leading to intervertebral fusion. This

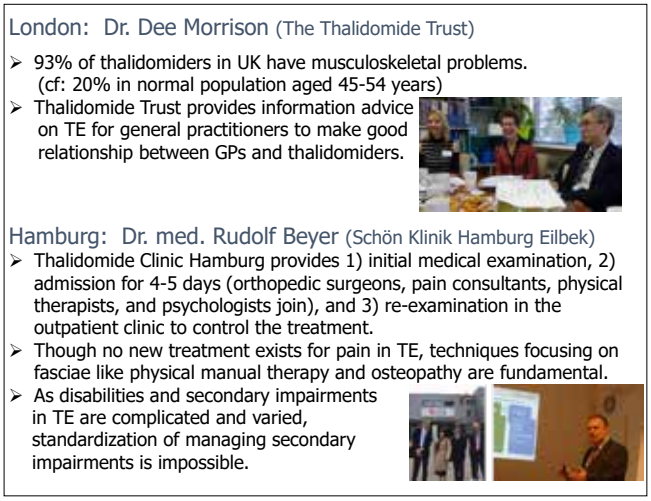


Fig. 12

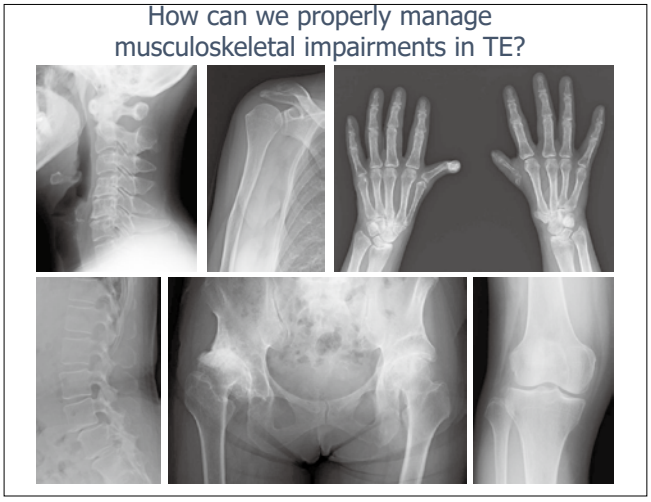


Fig. 13

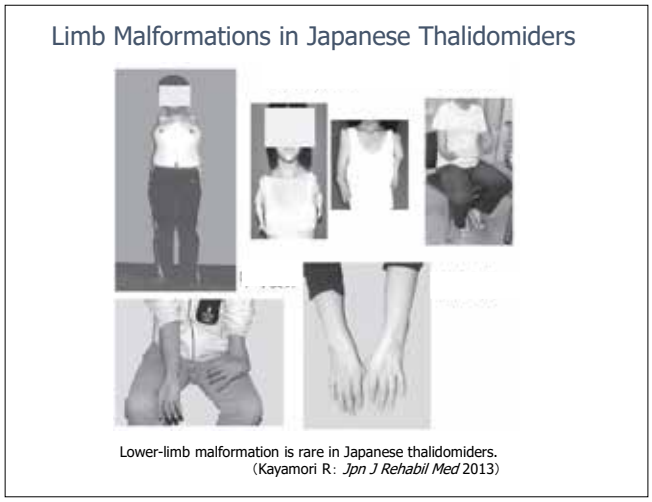


Fig. 14

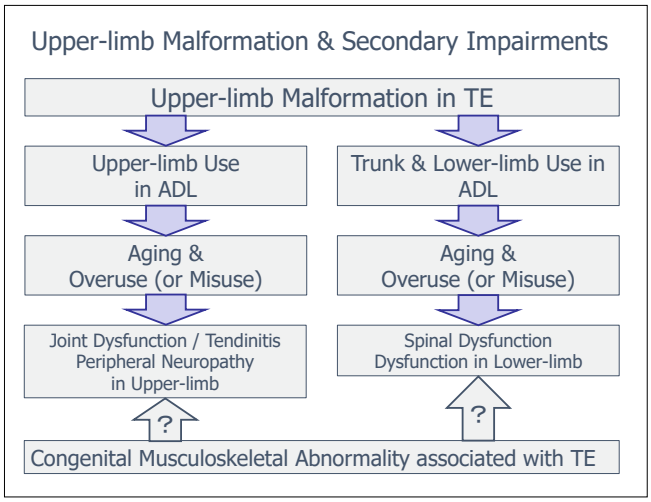


Fig. 15

is about the adults. Disc degeneration was detected on cervical spine MRIs in 24 of 27 middle-age thalidomiders. The degree of disc degeneration and foraminal narrowing was greater in thalidomiders than in controls. So, cervical disc degeneration is somewhat congenital, but affects age-related problems.

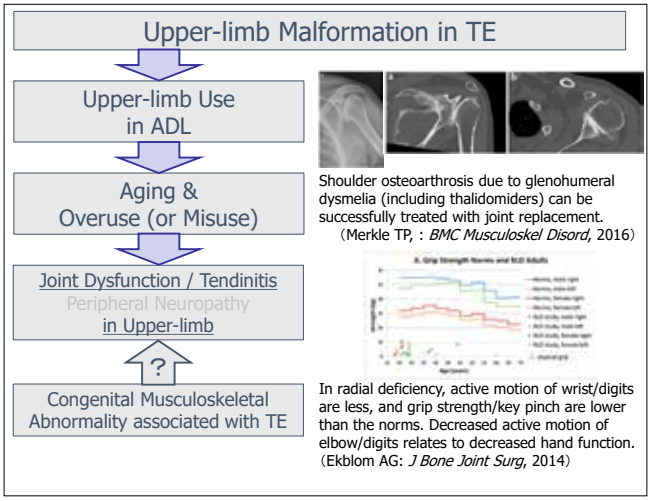
For those who use their trunk and lower limbs for ADL, there are two papers related to this topic.

This is about children. Disc and endplate abnormalities existed in 14 of 28 children thalidomiders and appeared to be progressive in some, leading to intervertebral fusion. This is about the adults. Disc degeneration was detected on cervical spine MRIs in 24 of 27 middle-age thalidomiders. The degree of disc degeneration and foraminal narrowing was greater in thalidomiders than in controls. So, cervical disc degeneration is somewhat congenital, but affects age-related problems. (Fig. 18)

This is a very old paper by a Japanese orthopedic surgeon about PFFD. This paper says that the degree of femoral hypoplasia is variable in TE, and accompanied by other lower limb abnormalities, including absent or defective tibia, absent patella, and inverted feet. So, these congenital abnormalities may affect the dysfunction in the lower limbs. (Fig. 19)

So, proper management of musculoskeletal impairments in TE needs, in my opinion, precise evaluation over the full body, including physical findings and imaging studies, to review congenital musculoskeletal abnormalities and the effects of overuse and/or misuse, investigation, and presentation of possible treatments, including surgical and conservative measures, repeated evaluations at regular intervals, advice on physical exercise habits, advice on accessibility to medical institutions, and support teams. Fostering TE specialists and providing education to medical professionals on TE is also necessary, I think. (Fig. 20)

Now, I will proceed to the next topic, sharing information on TE with the next generation. In 2013, to provide a multidisciplinary approach for patients with various limb malformations, we established a limb malformation clinic in a hospital. This is the University of Tokyo Hospital. Physiatrists, PTs, OTs, and prosthetists/orthotists joined together in



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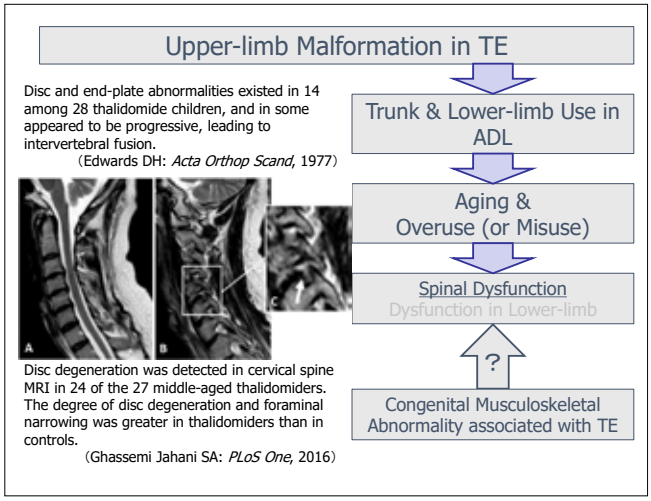

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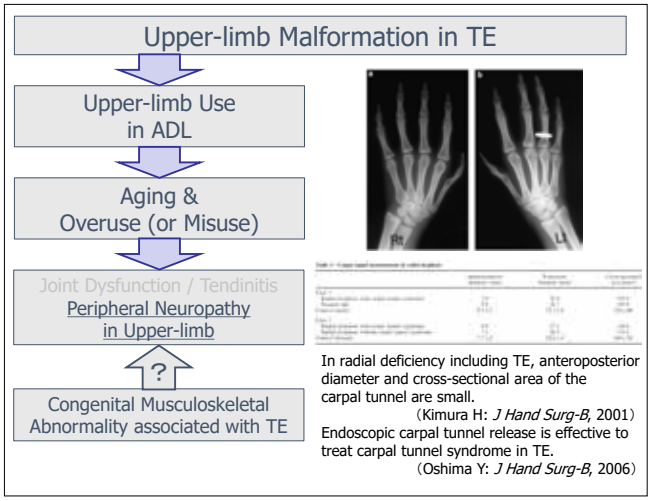

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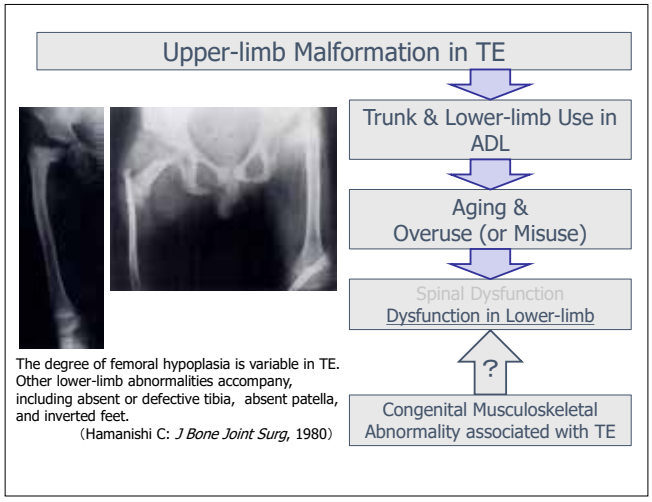


Fig. 19

this clinic.

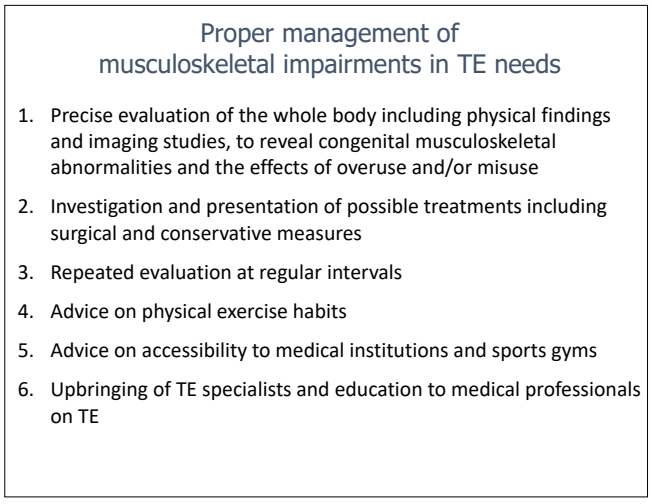
We are also related to another department in the hospital, and for orthopedic surgery and long-term inpatient rehabilitation, we connect to another national rehabilitation center for children. As for genetic counselling and genetic tests, we work together with another university hospital. (Fig. 21)

We also recently performed an epidemiological study of congenital malformations in Japan. According to these data, the estimated prevalence of congenital limb deficiencies in Japan was 4.15 per 10,000 live births. Overall, 67% affected only the upper limbs, 20% only the lower limbs, and 15% both the upper and lower limbs. From these figures, there were 3.39 affected upper limbs per 10,000 live births. This means that last year, about 300 babies were born with upper limb malformations. (Fig. 22)

Now I will introduce two very old Japanese papers. This is a paper on ADL in mainly acquired upper limb amputations. So, most ADL are independent in persons with unilateral upper limb malformations or amputation, though their motion may be slow and they may need self-help support or changes in their motion patterns. But for bilateral upper limb amputations, only 23% can perform ADL by herself or himself.

This is about the school lives of children. There are many activities, and these are the situations regarding limb malformation. Among school activities, even children with unilateral forearm deficiencies have difficulty in art, home economics, and music. Those with higher level deficiencies have difficulty in arithmetic and physical education, like this. And those with bilateral upper arm deficiencies have severely limited school activities. (Fig. 23)

This patient is not a thalidomider. He had a bilateral radial deficiency with severe forearm shortening. There is only a small portion of forearm and bilateral fibular deficiencies with deformed feet. We only performed the correction of his deformed feet. This is a photo from when he was in elementary school. He is now 21 years old, a university student, and nearly all of his ADLs are independent. One reason why he grew up like this is partly because I think his father was also affected. His father had a similar but milder phenotype



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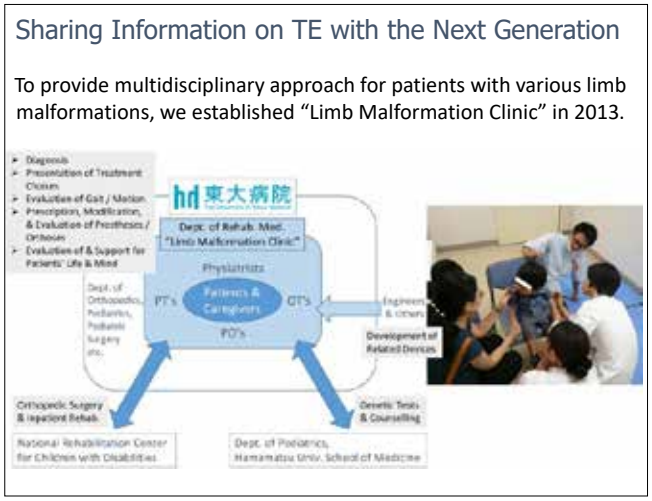

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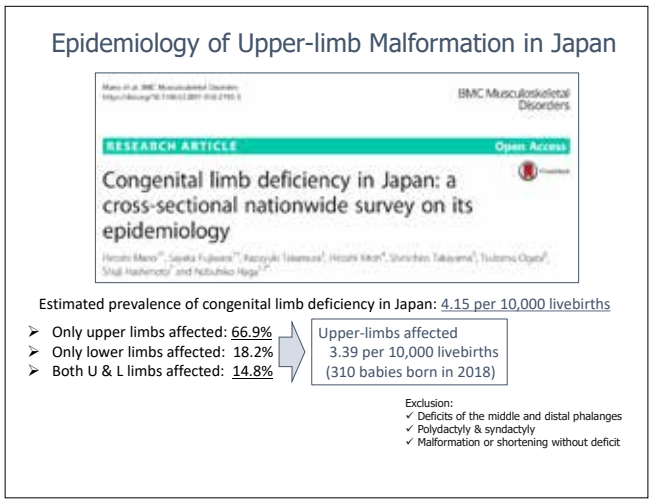

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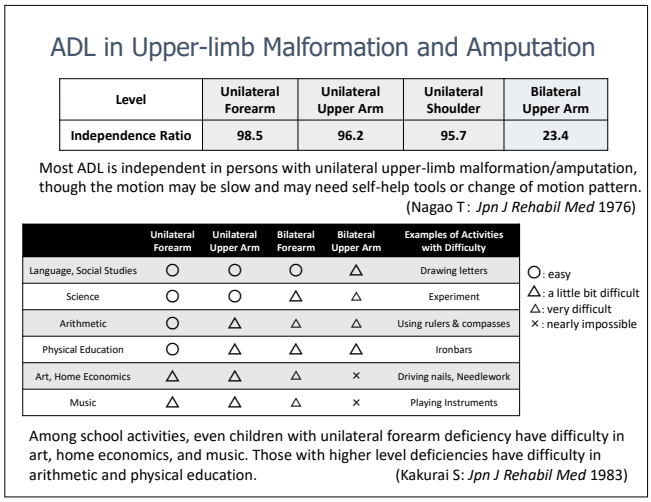


Fig. 23

with mild shortening of the forearm and mild shortening of the lower leg with fibular deficiency. (Fig. 24)

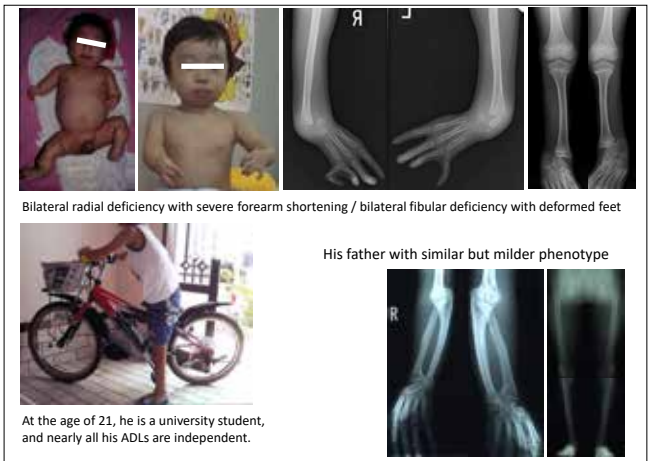
This is another patient. This is a 5-year-old boy with bilateral upper limb complete deficiency with scoliotic deformity. Although he received occupational therapy in another clinic to perform his ADL with his legs, his parents were eager to know how he would live his life in the future. (Fig. 25)

Thus, we conducted a small seminar on living with bilateral upper limb deficiencies to share knowledge and experience in March of last year.

Two Japanese thalidomiders from the Ishizue Foundation and two para-tae kwon do athletes participated in discussions with these children with bilateral upper limb deficiencies. (Fig. 26)

After that, my colleague joined a bilateral upper limb loss workshop held in October in Houston. There were many multiple amputees, including those with purpura fulminans. Because it was a very good seminar, a very good workshop, we held a similar seminar in Japan, Skills for Life Japan, in June of this year. Some upper limb deficiency patients participated, including very old persons. They showed how they lived their lives for a long time. (Fig. 27)

We are now in a research group of thalidomiders, but I think the lessons from TE can be shared with the next generation. Thank you for your attention. (Fig. 28)



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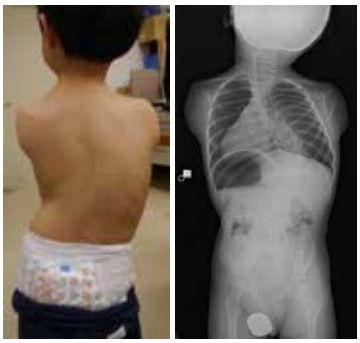

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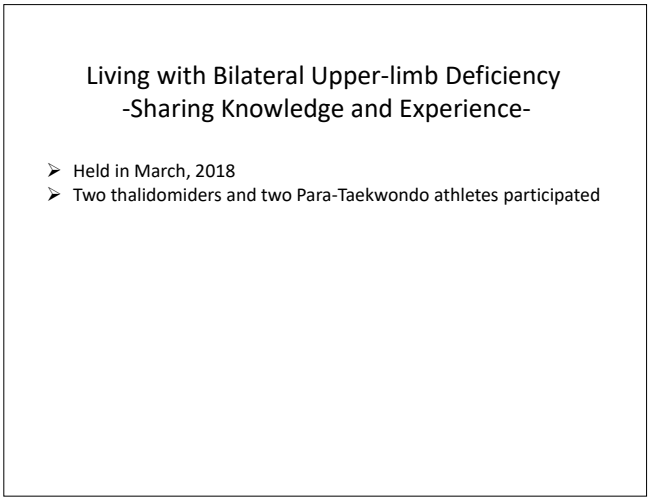


Fig. 26

Fig. 27

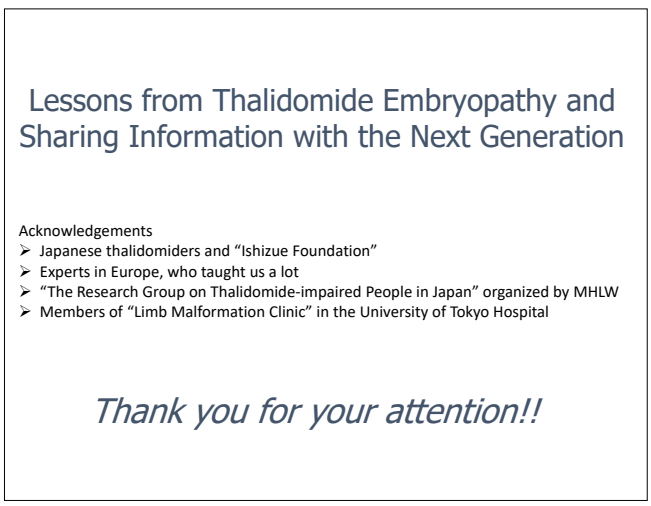


Fig. 28

Q&A

Ryoji Kayamori: So, are there any questions or comments? Okay. Yes, please.

Male Participant (Unknown Speaker with TE): Once again, thank you very much. Thalidomiders, age-wise, were born over a 5-year period beginning around 1961 or 1962. Recently, we have been talking about the reason for our existence. For example, sometimes, the upper arms can be donated to hospitals for the purpose of research, some patients have said. The Ishizue Foundation, which is an existing public corporation, is mainly for thalidomiders. But as you mentioned, we also have to think about the significance of our being. We are very creative about living our lives, playing sports, and other things that we can do based on our creativity. That's something we can communicate or hand down to those who have upper limb deficiencies. Also, together with people around the world, we would like to share our experiences, and having such an opportunity would be good for us. Sorry, this is only a comment. Thank you very much.

Nobuhiko Haga: Thank you so much for such a wonderful comment. I really appreciate it. Especially when it comes to deformities of the upper limbs, I mentioned that there are about 300 such children in Japan. For example, some of the finger defects are unilateral, that is, they are also included when we say upper limb deficiencies. So the children that I showed in pictures toward the end, we probably find just one or no such patients or children every year. They really want to have information. But even though we can give them medical information, we cannot give them sufficient lifestyle-related information.

Therefore, as I showed toward the end regarding the opportunities and meetings, it would be great if you get cooperation from thalidomiders. Thank you very much for your comment.

Ryoji Kayamori: The time is just now over. So, thank you.

Thalidomide Embryopathy: Orthopedic Aspects, Degenerative Changes and Quality of Life at Age 45

Shadi-Afarin Ghassemi

Unversity of Gothenburg, Gothenburg, Sweden

Nobuhiko Haga (Moderator)

The next speaker is Dr. Shadi-Afarin Ghassemi. She is now a medical doctor and PhD, and a senior consultant in orthopedic surgery. She graduated from the medical faculty of Gothenburg University, Sweden, and in 2006, she was licensed as an orthopedic surgeon.

In 2016, she obtained her PhD in orthopedic surgery. Since last year, she has been a senior consultant for the Osteointegration Unit, Orthopedics Department, at Sahlgrenska University Hospital.

Please start your lecture.

Thank you very much. Thank you for having me here today. I am going to talk about two studies involving my thesis. I will actually start with the third one, and once I tell you why, you will understand that more. None of the authors have any financial relationship to disclose. I need to say that. (Fig. 1)

The name of the, let's see, the name of my thesis is "Thalidomide Embryopathy (TE): Orthopedic Aspects, Degenerative Changes, and Quality of Life at Age 45." It seems like, well, it's quite old, but it's the time when we started gathering all the data. This was at the Department of Orthopedics, Institute of Clinical Sciences, at Sahlgrenska Academy, University of Gothenburg. (Fig. 2)

There are four papers. In 2015, I talked about my first paper, where we found a much higher risk of osteoarthritis in both the knees and the hips compared with the national population in Sweden. I am going to talk about papers 2 and 3. Paper 4 was, I mean, it's about orthopedic needs, both the surgeries and orthotic needs and so on. (Fig. 3)

I don't need to tell you more about thalidomide. You already know. We know that it's a potent substance, a very, very highly potent substance that was used in pregnant women in Sweden, especially between 1959 and 1962. When we started our study, we had, there were 108 individuals

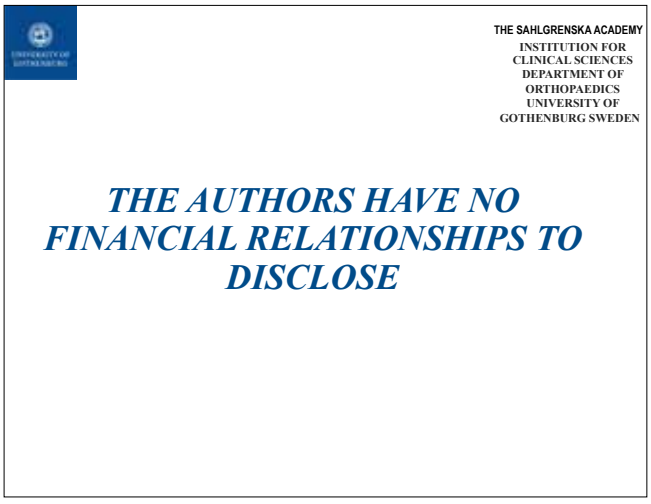
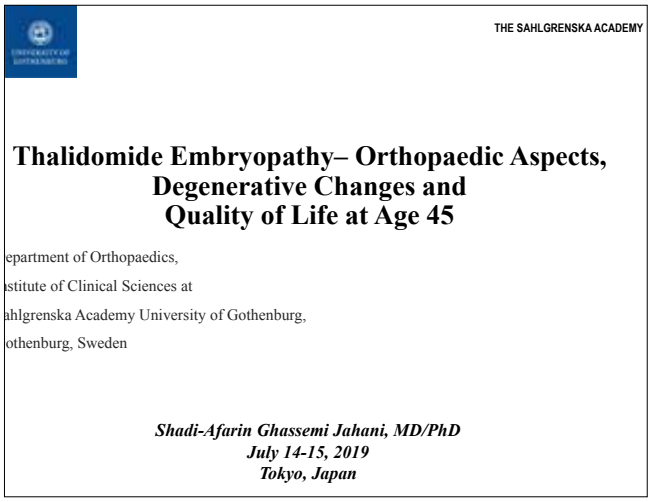


Fig. 1



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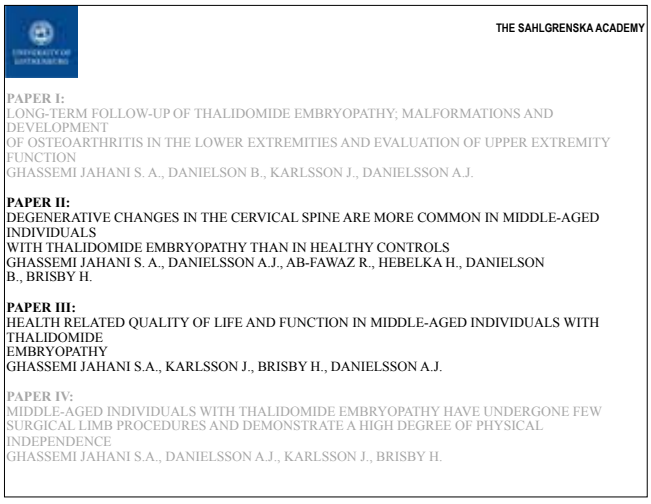


Fig. 3

registered in the Swedish Association of Individuals with TE. (Fig. 4)

And this is, I think this slide tells us a lot. My question to you, Dr. Hinoshita, is how come you didn't reach out to everybody? This was our main concern because out of 108 members, we were not allowed to send invitations to 24 because I mean, the association of TE in Sweden is very, very enclosed. So, if they say they don't want any invitation for any investigation, then you are not allowed to send anything. That's it. You don't even get their addresses.

So, 84 were invited and 33 didn't even answer. And also, a new law, I mean, it's the new, I mean, not new, but it's also another case of the rules that you are not allowed to send a new reminder.

Overall, 33 were accepted, and of those, one had recently suffered a stroke and one had a severe mental problem and was institutionalized. (Fig. 5)

So we had 31 participants: 18 males and 13 females. At that time, the mean age was almost 46 years. They came from different parts of Sweden. One was living in the US, and at the time, was actually visiting Sweden. One was living in Norway, and she came. The study was multidisciplinary, and conducted together with Professor Kerstin Strömland and Professor Christopher Gillberg.

Another problem was that many of the attendants who didn't want to come to this multidisciplinary study actually agreed to come to just the orthopedic part. But we couldn't do that. (Fig. 6)

As an orthopedic surgeon, I examined everybody, all 31 persons. We found that 25 individuals had malformation of the hand and 27 had poor grip function. We also found five individuals with a proximal femoral focal deficiency with a short limb, and they needed a wheelchair or orthosis. Regarding other conditions, we found diseases such as asthma, hypertension, sleep apnea, and migraines. These are the general diseases, but some others necessitated operations for carpal tunnel syndrome, total hip joint replacement, and so on. (Fig. 7)

This is a view of a proximal femoral focal deficiency, which is a deficiency of the femur and sometimes the hip joint. Depending on the extent of the malformation, it results in shortening of the leg, and in most cases, there is neither a

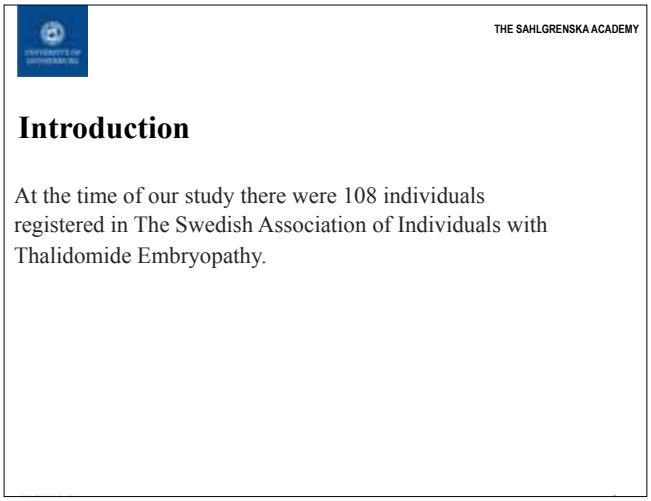
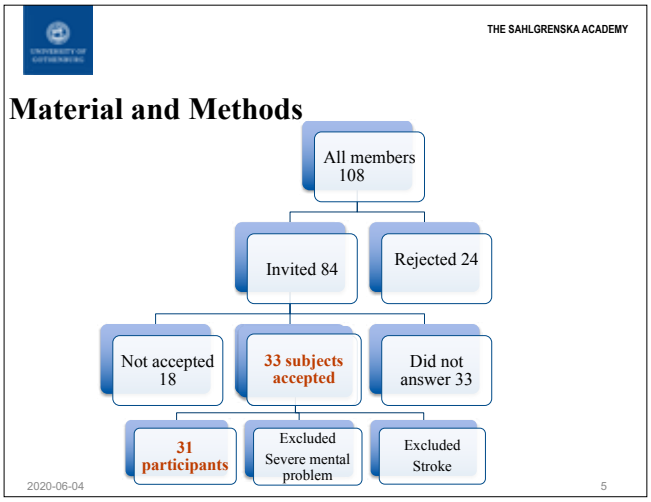


Fig. 4



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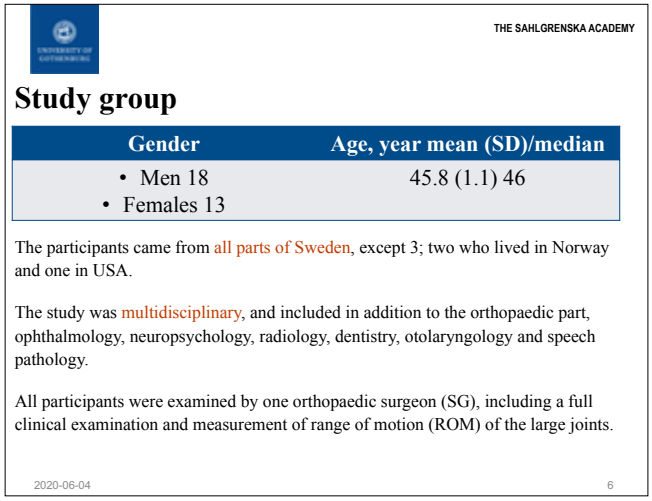

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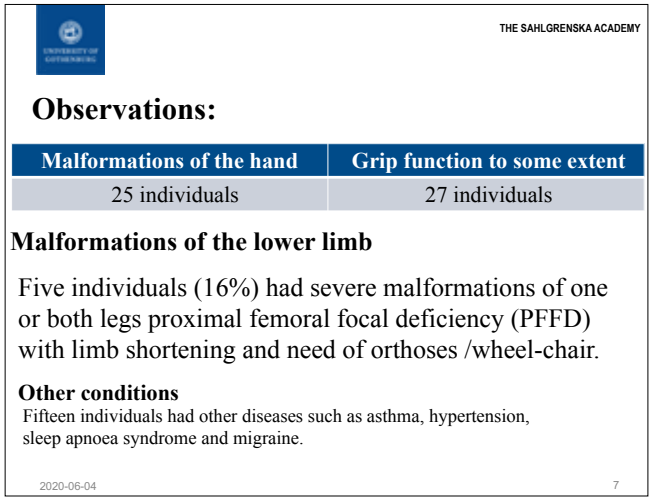


Fig. 7

thigh nor a hip joint. It causes the leg to grow from the groin, and foot to be at the level of the knee. (Fig. 8)

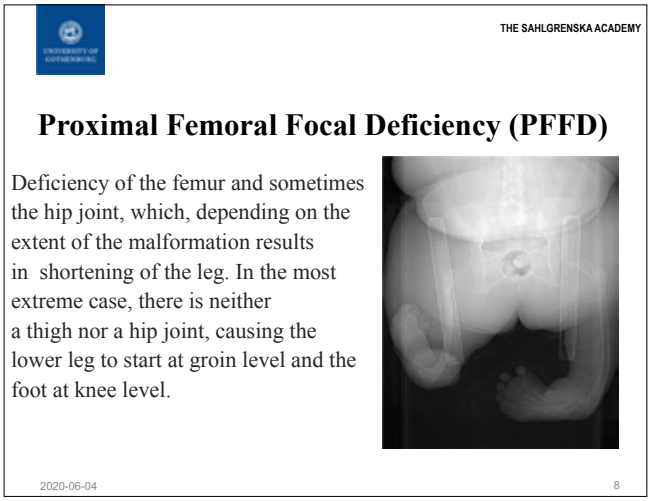
Other two patients of these five. The study is on health-related quality of life and sociodemographic characteristics of middle-age individuals with TE. (Fig. 9,10)

Knowledge about the function and health-related quality of life for the TE group is sparse. With aging, parts that were working quite well experience problems, and we need to address that as well. (Fig. 11)

The aims of the study were to assess whether the health-related control of quality of life is equal to that of the general population, to what extent limb malformation affects health-related quality of life, and whether the function of the upper and lower limbs, as measured by a validated questionnaire, is correlated with more general health-related quality of life. (Fig. 12)

We mainly used computer tomography (CT) for our previous study, but we also used the results for this one. We evaluated all musculoskeletal manifestations. We used validated questionnaires to assess disability in the arms, shoulders, and hands. We also used the Short Form-36 and EuroQuol-5 Dimension to evaluate upper extremity function. (Fig. 13)

The participants were totally divided in two different groups according to malformations, those with PF50 and those without PF50, according to how many limbs were affected. Thus, we had 15 individuals with more than one



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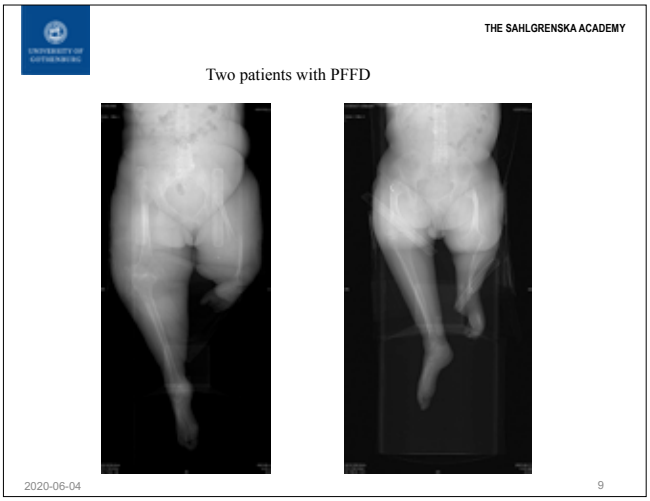

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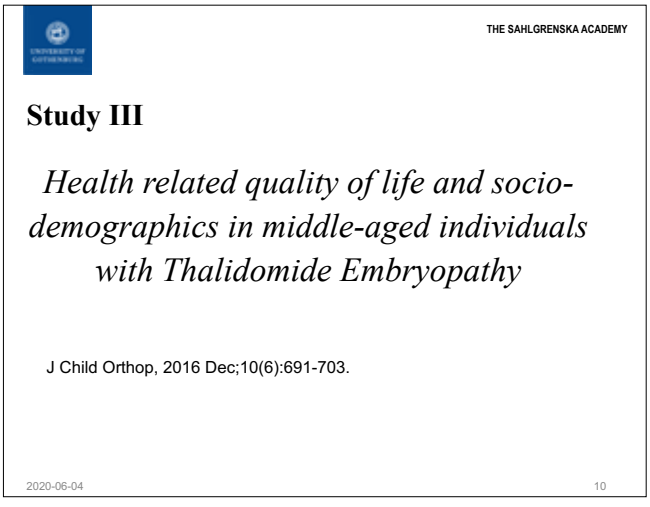

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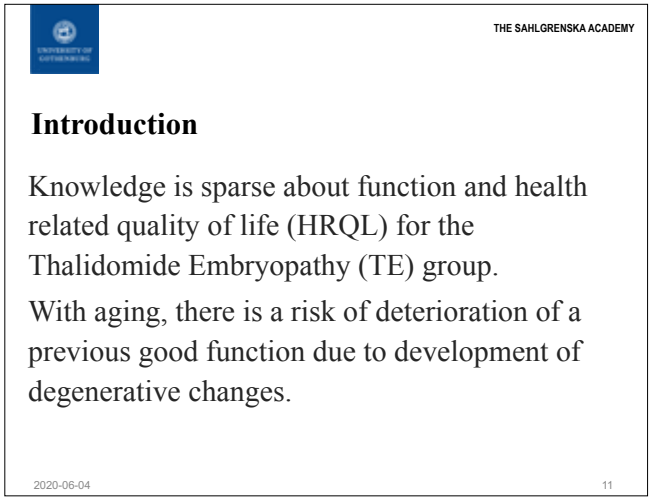

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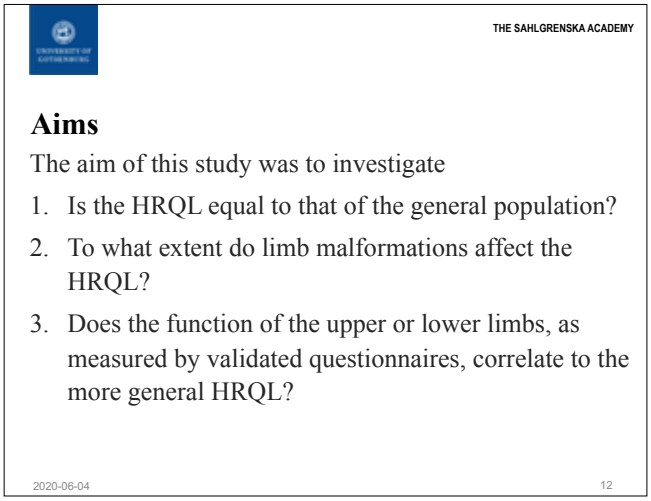


Fig. 12

limb with a major malformation and 16 with no limbs with a major malformation. We don't mean only thumb affection. We are talking about major malformations, shortening and so on. (Fig. 14)

Regarding sociodemographic status, 80% were married or cohabitating, and 77% were working. We also used the WHO questionnaire on stress during the day. The majority had some minor stress and only one had heavy stress. (Fig. 15)

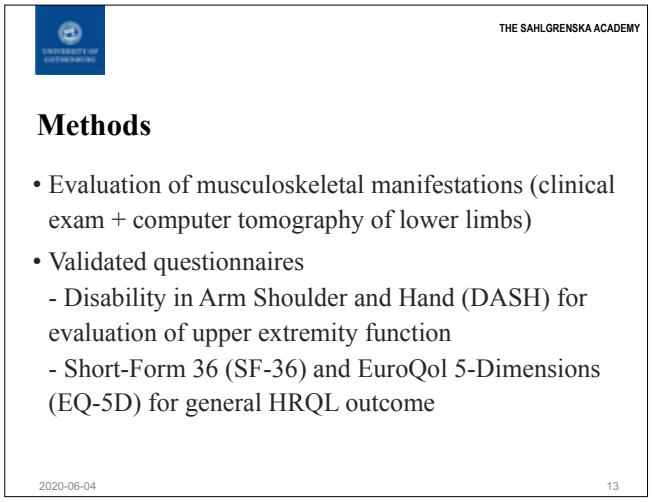
I would like you to see here the results regarding upper extremity function. The lower the score, the better the function. Scores range from 0 to 100. (Fig. 16)

All individuals had very good function. Those with no major malformations in the limbs were even better. Those with major malformations in more than one limb had worse outcomes for the upper extremities, and this difference was statistically significant. The results don't say if it was the upper or lower extremity. It's just the amount. (Fig. 17)

Those with PF50 actually had diverse outcomes for DASH. (Fig. 18)

Regarding the SF-36, these are the normal mental and physical composite summary scores for the general population. The ones in color indicate those with no extremity with a major malformation, and next more than one major malformation in the extremities for PF50, and the total group. (Fig. 19)

You can see that physical quality of life is lower than that for the normal general population for all groups, including



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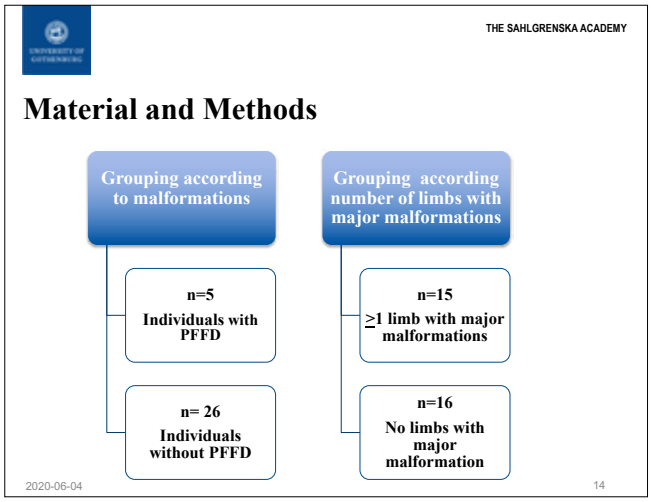

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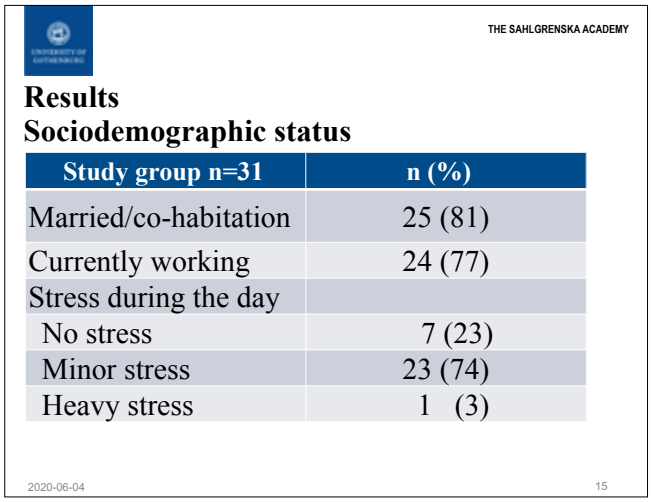

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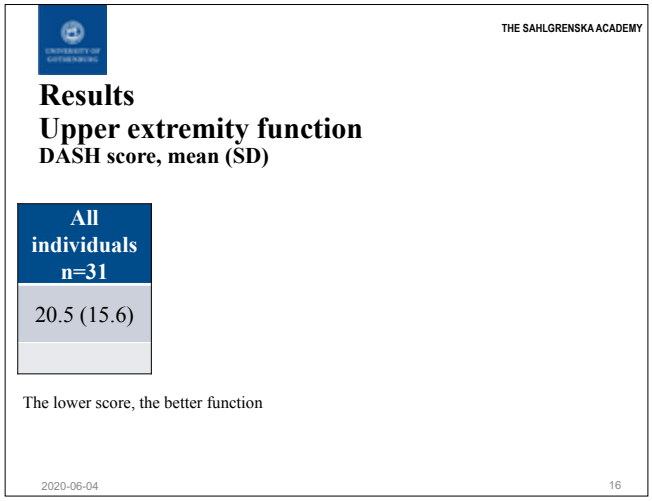

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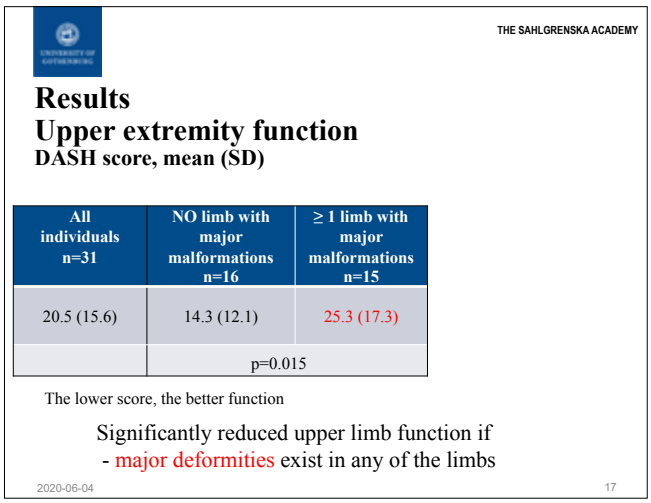


Fig. 17

the whole and subgroups. (Fig. 20)

Mental quality of life is actually the same, a little higher than the normal level which I think coordinates with most of the studies, both also showed the same. (Fig. 21)

If you look at the sub-scores, this is physical function bodily pain and general health, role physical vitality. This is the mental part and this is the sub-score for the physical part. The dotted line is the total study group, while the other one is the normal general population.

We also can see even here with those with more than one limb with malformation or a major malformation, it actually coordinates quite well. The most affected are the ones with PF50, of course, who have poor physical quality of life, even in the sub-scores, subgroups I mean, sorry. (Fig. 22)

We also looked at the EQ-5 Dimension and all from the whole group, the whole study group compared with the reference population. You can see that they have worse outcomes for mobility and self-care, and discomfort from pain is usual. But anxiety and depression is almost equal to that of the reference population of the same age. This can actually indirectly show the Western quality of life. (Fig. 23)

So, in conclusion, physical health-related quality of life is significantly reduced in many individuals and correlates well with existence of major limb deformities or with reduced function of the upper as well as the lower extremities, which I think is quite interesting. The mental aspects of quality of life are not affected, and the majority of the study

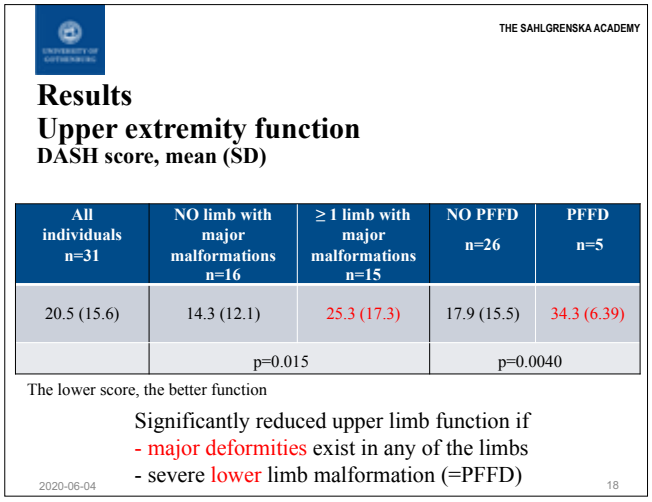


Fig. 18

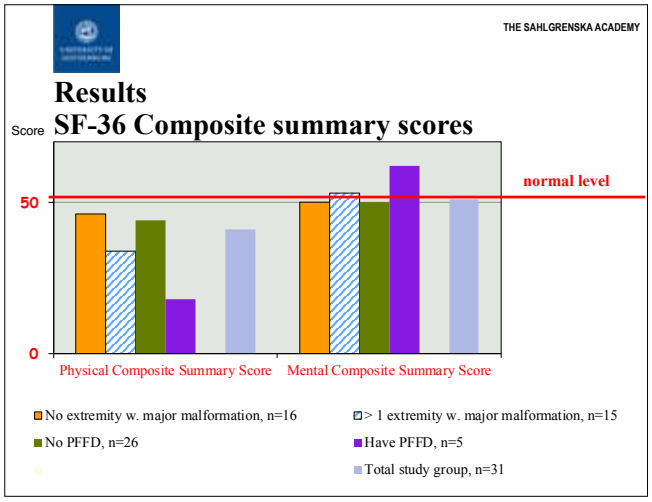
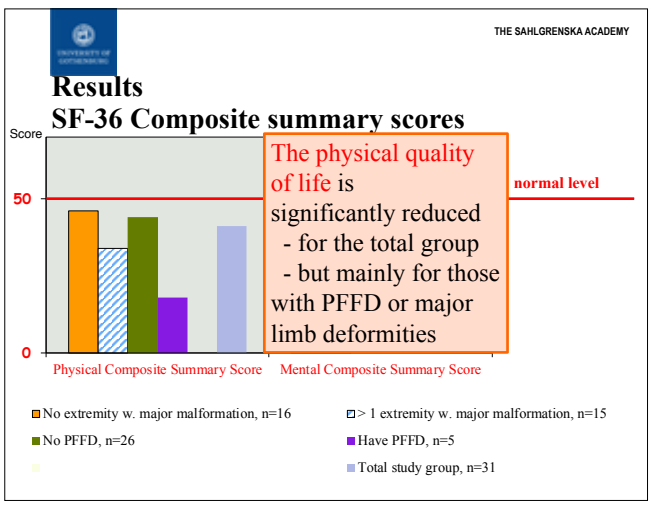


Fig. 19



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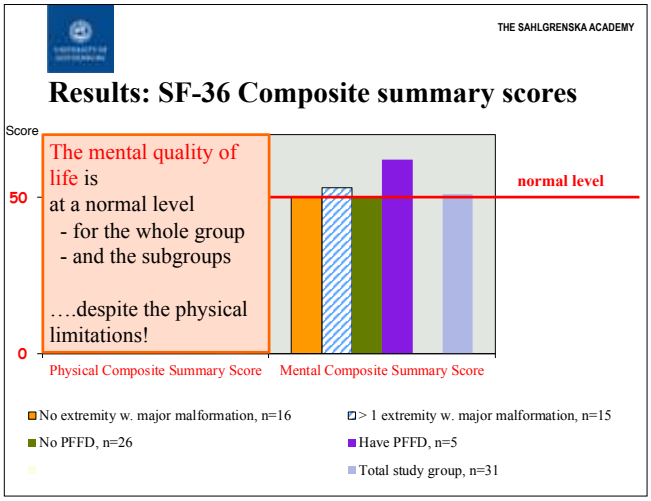


Fig. 21

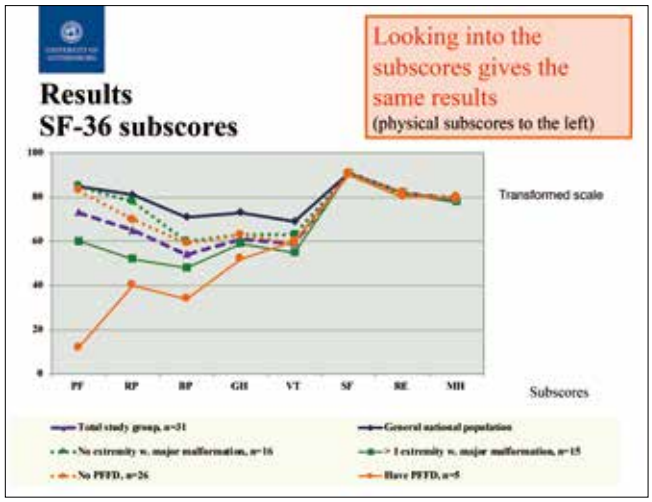
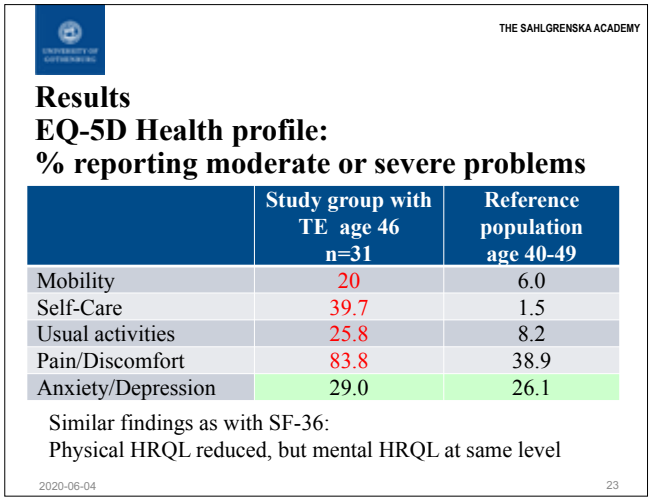


Fig. 22

group was working, had a family, and did not live under heavy stress. (Fig. 24)

I now turn to study 2 because we actually used the same 31 subjects, but not everybody underwent cervical spine MRI. Degenerative changes in the cervical spine are more common in middle-age patients with TE than in healthy individuals. (Fig. 25)



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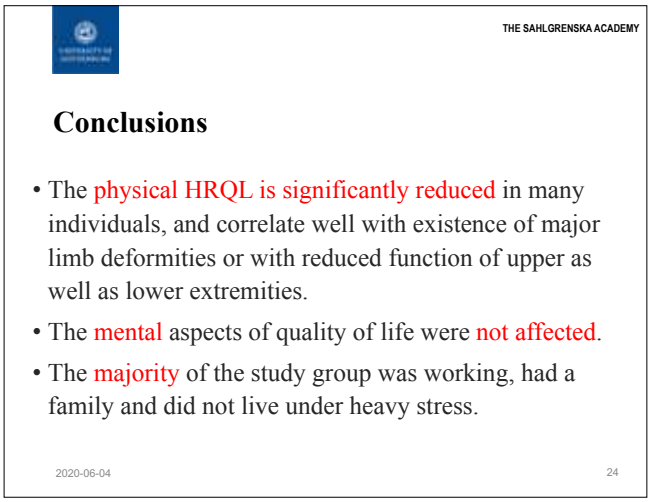

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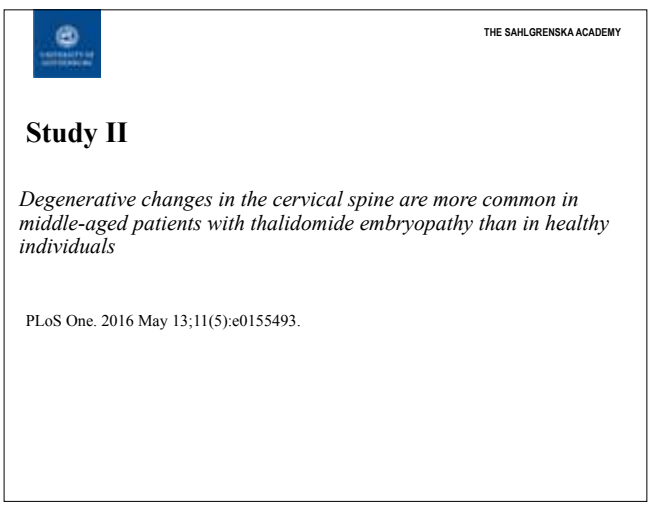


Fig. 25

Professor Haga just showed one figure that we had in that article. The aim of that study was to investigate persons with malformations and subsequent disc degeneration of the cervical spine in a group of middle-age individuals with TE and to compare these with a healthy group of controls. (Fig. 26)

We asked all 31 attendees if they could participate and invited them to undergo an MRI. One wanted to, but he was not allowed to because he had metal chips in his head, and two had claustrophobia. Actually, one of them went through with it, but they had to stop the examination, whereas the other one just refused.

Thus, the 27 remaining from the whole group underwent MRI. We compared them with 27 age- and sex-matched healthy controls. As earlier, we found that 85% had some degree of hand anomalies, so we evaluated disc signals according to the Pfirrmann grading system, which is grade 1 to 5 depending on how degenerate, which kind of degeneration they have in the discs. (Fig. 27)

Overall, 56% of patients had a deformity of one to four of the extremities, which we already knew. All had some function of the upper limbs, despite some individuals having

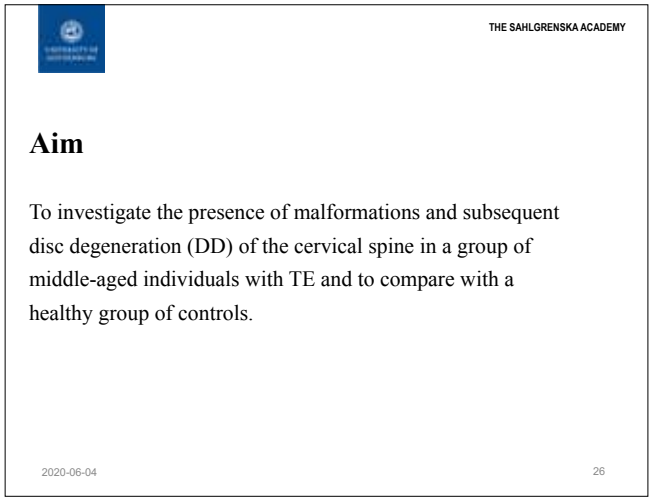


Fig. 26

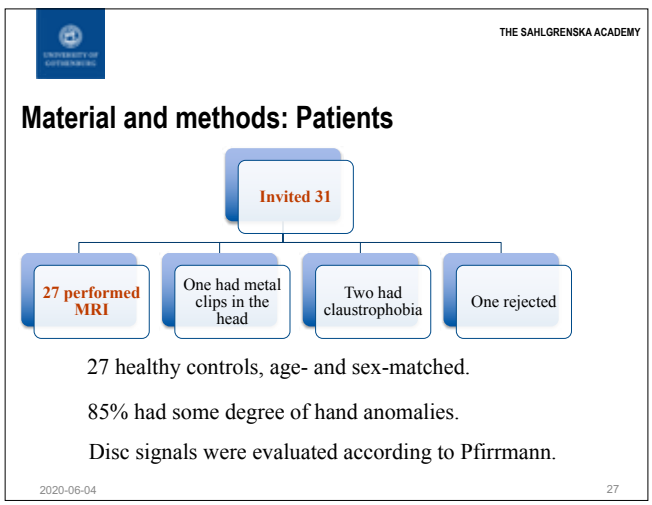


Fig. 27

short arms. Almost 80% had some degree of hand anomaly, and 30% patients had bilateral pincer grasp. (Fig. 28)

These are the Pfirrmann grades 1 to 5. This is the TE group compared with the control group. Every segment shows statistical significance in comparison. For TE, we already had grade 5 in the higher segments, which is quite unusual. We can find it only here in the C5–C6 segment and the C6–C7 segment in the control group, indicating a higher degree of disc degeneration in the cervical spine; thus, much earlier in the TE group and even in higher segments, which is quite unusual. (Fig. 29)

Therefore, 90% of the TE and 70% of the control group had disc degeneration of more than one level. Ten TE patients had more than four segments affected, which is also unusual. No one in the control group had more than three segments affected. And in both groups, the majority was still C5–C6, but the TE group had disc degeneration in upper segments C3–C4 and C4–C5. (Fig. 30)

Our findings support the earlier developmental course of disc degeneration in the TE group. This could be because we found more disc degeneration in the cervical spine in the TE group. We also found an increased number of affected segments in the TE group. But mostly they still come in the slower segments as it is in the control.

If the result is because of the drug itself, we don't know that yet. If it's because of the unusual loading on the neck, we also still don't know. Of course, we would like to have

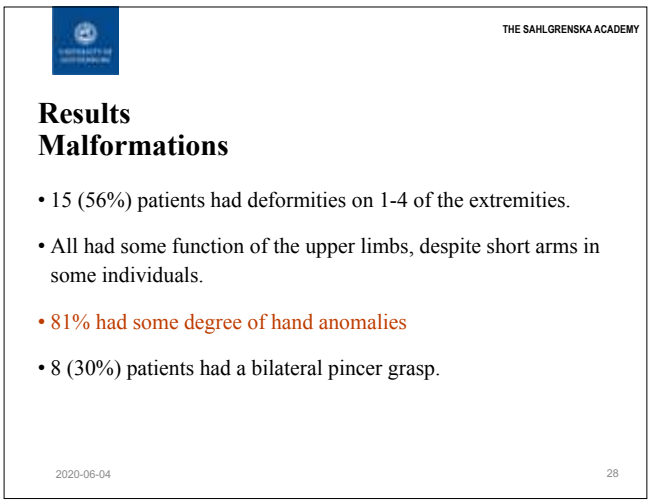


Fig. 28

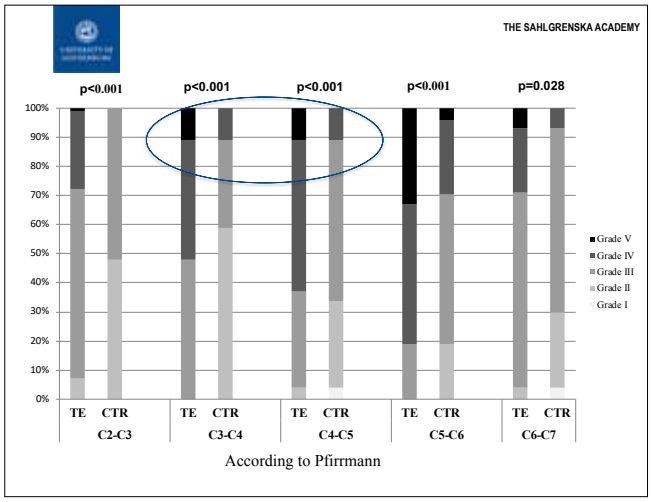


Fig. 29

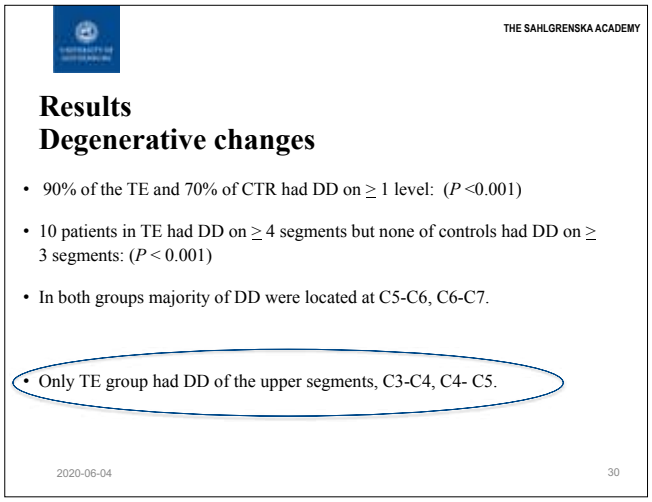


Fig. 30

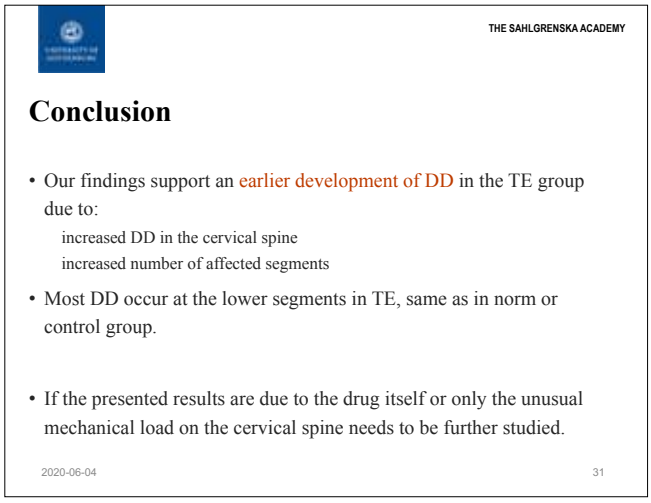


Fig. 31

Fig. 32

more studies on that, but I don't know if that's possible in Sweden. As I told you in the beginning, it's quite difficult. The group has been very enclosed, and we actually don't have, as I hear, any new claimers. It could also depend on, in Sweden, everybody has a personal number. I mean you cannot do anything if you don't have a personal number. So, it's very, very difficult to be somewhere in society and not be seen before. You cannot just come and say, "Okay, I have this and that problem, and it must be somewhat due to thalidomide." We will see if there is any possibility to do a new health-related quality of life survey, and then send it to these persons and compare the results with those regularly seen at 45 years of age. (Fig. 31)

I just wanted to show you this, so thank you very much, especially Dr. Hinoshita and the rest of the group who were in Sweden on August 3 years ago. I remember that it might have been cold, so I wanted to show you the very nice weather we have in April this year. Welcome back. Thank you. (Fig. 32)

Q&A

Nobuhiko Haga: Thank you. We are open for discussion. Okay.

Klaus M. Peters: Thanks a lot for the excellent data. I think that the high amount of disc degeneration in the cervical spine is due to the fact that they do more with the cervical spine. For example, some of them carry a water bucket with their mouth, their teeth. They carry weights with it, and therefore, I think it's a higher load for the cervical spine; therefore, I think degeneration is higher.

Shadi-Afarin Ghassemi: Of course, it could be that, but at the same time, we also noticed a lot of block segments, which makes it even more difficult to use the neck as a tool. But of course, we also believe it's more possible to believe that, yeah.

Nobuhiko Haga: Okay, please.

Elizabeth Newbronner: Thank you very much, Shadi. It was very interesting to hear your presentation. I was just interested because one of the things we have observed in the UK is that people have experienced a big change in their function, their pain levels, and their ability to work probably in the last 10 years. And knowing that your group, because of when you could collect your data, was sort of 45 at that time, do you have any sense of how things have changed in Sweden since then around things like pain, function, and capacity to work?

Shadi-Afarin Ghassemi: Thank you very much. It actually reminds me to say something I wanted to say, but forgot.
I definitively think that they have more problems with pain because they already had it, and that is why they were more keen to come and be part of the orthopedic part. They wanted, they didn't want to be part of the psychological part. They were not interested in that. But I actually called Ex-Center. I called Marie Wikström at Ex-Center before I came here because I just wanted to ask her what she wanted me to bring to that meeting and what she wanted me to say. She didn't mention the pain or the lack of money. She didn't even mention, but she did say that we have had some problems with the main, I mean, the vessel malformations. So we are interested to see if there are anymore.
Actually, I will talk to her about the Japanese study. We had also a patient with total hip replacement with iliac malformation. He actually, after the surgery, he was simply dying because they didn't know that he had that malformation. So, the only concern for her was that it would be nice to know to perform a body scan before we go through with any surgery. But it was completely normal. I mean, they knew that the hip might have been replaced. They might have a problem with the knees, and many others.
Since there is quite good economic management in Sweden, especially for the TE group, they are not much concerned about if they need to retire early. Actually, they don't need to work after some years because they have their retirement, yeah.

Elizabeth Newbronner: Thank you.

Shadi-Afarin Ghassemi: Thank you.

Nobuhiko Haga: Okay, do you have any other questions? I want to ask one question.

Shadi-Afarin Ghassemi: Sure.

Nobuhiko Haga: Do you know of any thalidomider who underwent surgery in their cervical spine in your country?

Shadi-Afarin Ghassemi: No.

Nobuhiko Haga: No, okay.

Shadi-Afarin Ghassemi: No, actually, they are very, very cautious. I mean the surgery should be very much needed. It's nothing that they just they have pain. It must be very much needed. And unfortunately, since the majority were not attending any of these studies, it's very difficult to know what problems they have, which is what I asked the Ex-Center about.

Nobuhiko Haga: Okay. No other questions? Thank you for your presentation.

Shadi-Afarin Ghassemi: Thank you very much. Thank you.

Outpatient Centre for Thalidomiders in Germany: Treatment Strategies and First Results

Klaus M. Peters

Dr. Becker Rhein-Sieg-Klinik, Nümbrecht,Germany

Nobuhiko Haga (Moderator)

So, the next speaker is Dr. Klaus Peters. He was born in Dusseldorf, Germany, and graduated from the University of Cologne and Basel. Since 1995, he has been a senior consultant in the Orthopedics and Osteologic Department at the Dr. Becker Rhein-Sieg-Klinik, Nümbrecht. Since 2011, he has been in the orthopedic and trauma surgery unit at Bergisch Gladbach. Since 2017, he has been the head of the medical center for thalidomide-damaged people in North Rhine-Westphalia. Okay, please start your lecture.

Thanks a lot for the introduction. I am pleased to introduce our results and data from our outpatient center for thalidomiders in Germany. (Fig. 1)

What's the background to establish such a center? The problem is increasing consequential damage in thalidomiders, and we have no real sufficient regular medical care to offer to thalidomiders in Germany. That's a problem. Therefore, the goal of the center is to improve the medical care situation for thalidomiders in Germany.

And what is the center? The structure of the center is as a medical institute for adults with multiple handicaps. The center is also part of a cooperation network with medical specialists and the Interessenverband Contergangeschädigter in North Rhine-Westphalia, an organization for thalidomiders like you have in Japan. We have very close cooperation with them. (Fig. 2)

As a medical expert center, the focus is on thalidomide-damaged people. They come from all over Germany, not only from North Rhine-Westphalia. It's important that thalidomide damage is accepted and recognized. Then, the cost of the statutory health insurance funds is guaranteed to be covered. Other people have a status of self-payer, especially those people for whom thalidomide damage has not been accepted up to now.

We have a so-called thalidomide competence team in the clinic consisting of physicians, physiotherapists, ergotherapists, and massage therapists. The competence team for thalidomiders currently has 16 members, all of whom can provide treatment. We have two coordinators for the center; these are very important persons who do the daily organizing. (Fig. 3)

The so-called MZEB is a special German organization construct. It's a medical center for adults with multiple handicaps. It can also be established for other diseases in Germany. It's an outpatient center that is important for thalidomiders because they don't want to stay in clinics. It is

Fig. 1

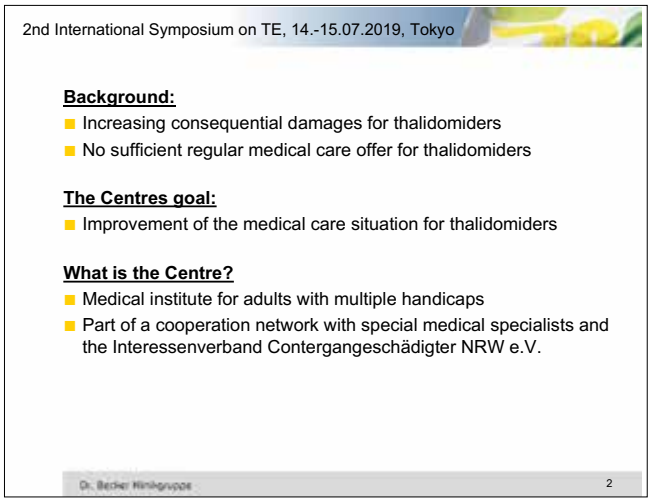


Fig. 2

licensed and contracted by health insurance companies in Germany. It's an expert center and contact point for thalidomiders. We offer medical and non-medical services. (Fig. 4)

What's the range of the services? Medical diagnostics, counseling, expertise, therapeutic assessments, training, and trial treatments. It also involves cooperating specialized doctors, mainly in Cologne, psychotherapeutic counseling, and explanations of treatment, often together with the University of Cologne. It also provides advice on aid, rehabilitation, retirement, care, assistance, individual living accommodations, applications, and much more.

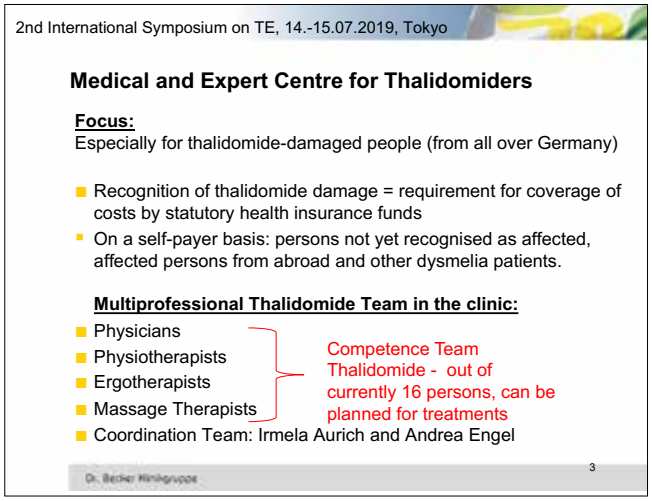
As a concept for elaboration, further treatment accompanying the prescription of necessary therapeutic re-treatments, remedies, and aid is provided, as is the initiation of close-to-home care. As a final service, follow-up visits are made at intervals of several months, mainly 3 to 6 months, to check and adapt to the causes for therapy. (Fig. 5)

What are the key points of thalidomider visits to the center? These are mainly 3-day visits to the outpatient center. If desired, the thalidomider can visit cooperating specialized doctors, resulting in a duration of 4 days. All treatments are covered by German statutory health insurance. Deaf thalidomiders are accompanied by a sign language interpreter the whole time.

An overnight stay in a pension hotel is at the expense of the patients. They organize visits on their own, but it is possible to arrange transportation from us. (Fig. 6)

How do they prepare for a visit? It starts when the thalidomider contacts the center and the coordinators. The coordinators send a questionnaire to the thalidomider who wants to come. The questionnaire is filled out and sent back to the center. With that questionnaire, we hold a treatment conference and make a treatment proposal for the thalidomider. This treatment proposal is then sent back to the thalidomider, and during that time, we contact the cooperating specialist doctors or consultants of the Interessenverband of the thalidomiders. If necessary, we use a sign language interpreter. There is a lot of work to do before the patient comes.

Then, we make a definite treatment plan. That treatment plan is sent in advance to the thalidomider. If it's okay, they get the date for the visit. We normally have a duration of 3 to 4 weeks until they can come. If it's urgent, they can come



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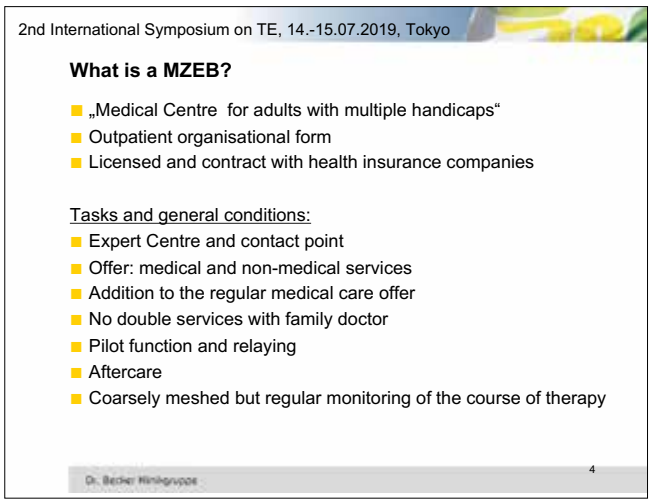


Fig. 4

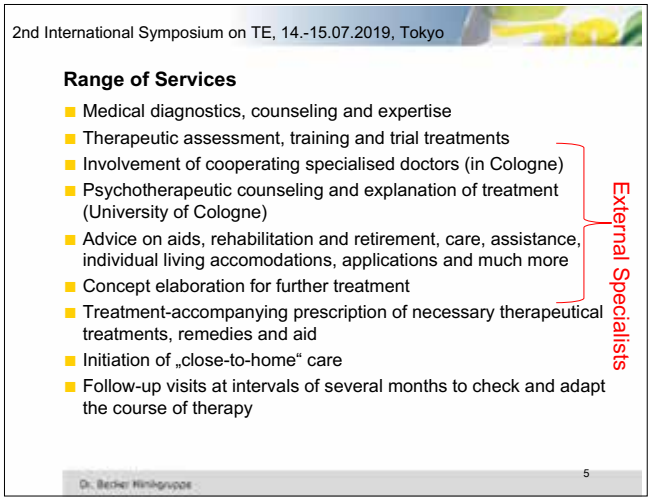


Fig. 5

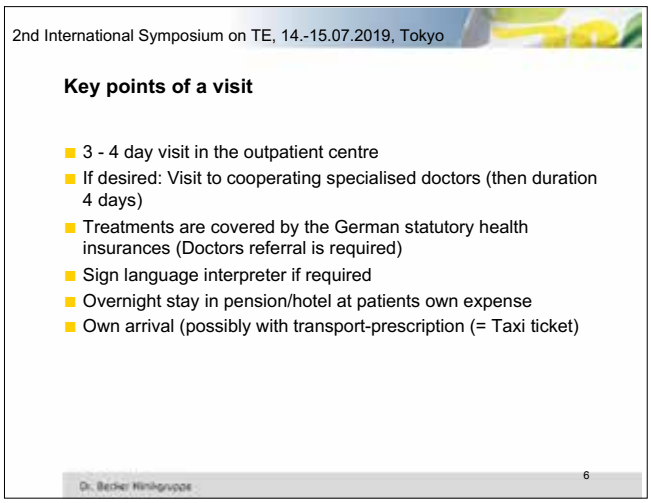


Fig. 6

earlier. We offer further support, including a doctor's referral, medical referral, transportation, prescriptions, accommodations, arrivals, taxi reservations, required aids for a visit, and incapacity certificates. You see, there is a lots of work that has to be done for thalidomiders. We have recognized that every applicant requires about 13 to 15 hours to prepare for a visit. That is a lot. (Fig. 7)

Where does the visit take place? The center is located at the Dr. Becker Rhein-Sieg-Klinik, Nümbrecht, which is about 50 km east of Cologne. (Fig. 8)

Here is an example of a treatment plan for a patient in our center for 4 days. The third day is the so-called specialist day. In this case, it was a psychotherapeutic consultation at the University of Cologne. (Fig. 9)

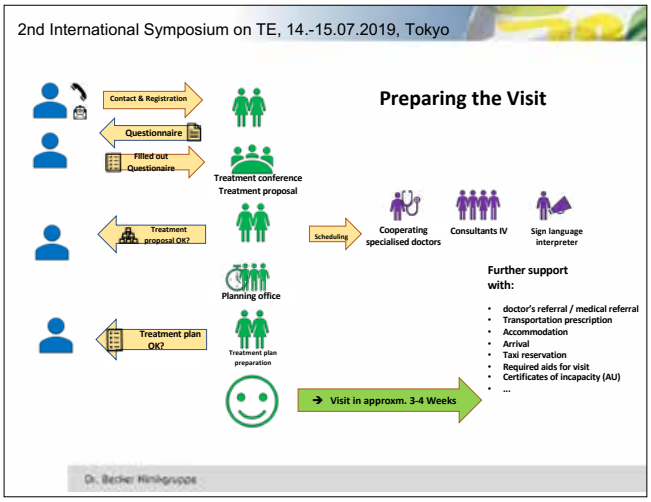
The visit in the center starts with a physical checkup. It includes examinations such as diagnostic findings, maybe X-rays, and bone density measurements, because many thalidomiders seem to have osteoporosis already. Blood pressure measurements are done for every patient. Acupuncture is provided for pain therapy if desired.

What are the therapeutic treatments? Physiotherapy with mobilization, a sling table, special exercises or physiological movements, physical therapy with craniosacral therapy, foot reflexology, connective tissue massage, ultrasound, ergotherapy with mobilization of hands, arms, and shoulders, and individual aid counseling. At the end of the stay, the physician speaks to the patient and suggests further therapies and prescriptions.

If they come again after 3 or 6 months, they come for 1 or 2 days and get another exercise pool. (Fig. 10)

What are our initial results? We started the center in September 2017, and have results up to June 2019. By that time, we had treated 59 thalidomiders: 35 females and 24 males. At that time, the number of visits was one to four, and the frequency of visits was 3 to 6 months. (Fig. 11)

What is involved in the visits? Cooperating doctors were appointed in 48 cases. Psychotherapeutic consultations were provided in 10 of these 48 cases. Consultation with the Interessenverband was provided in 29 cases, and a sign language interpreter in 11. (Fig. 12)



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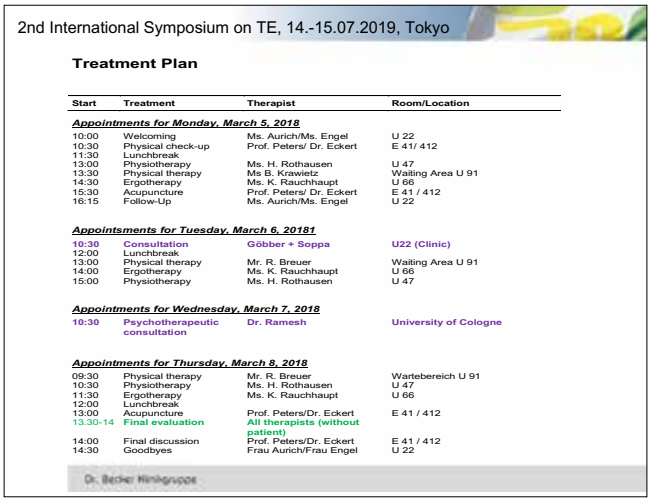
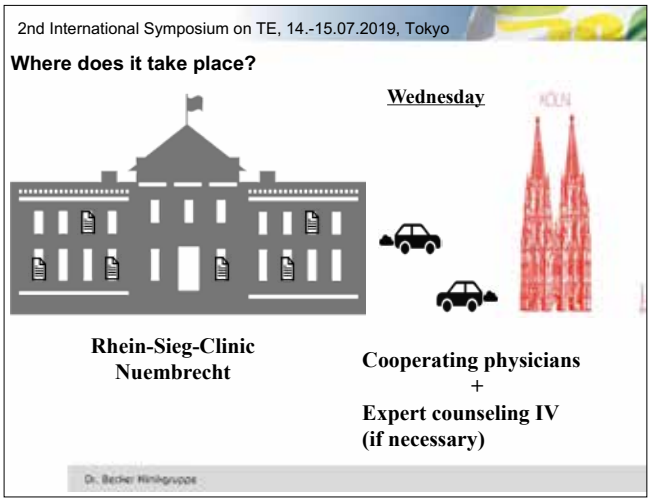


Fig. 9



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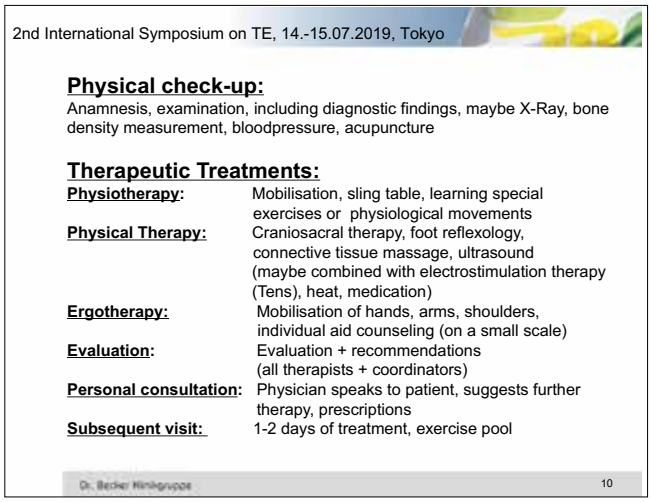


Fig. 10

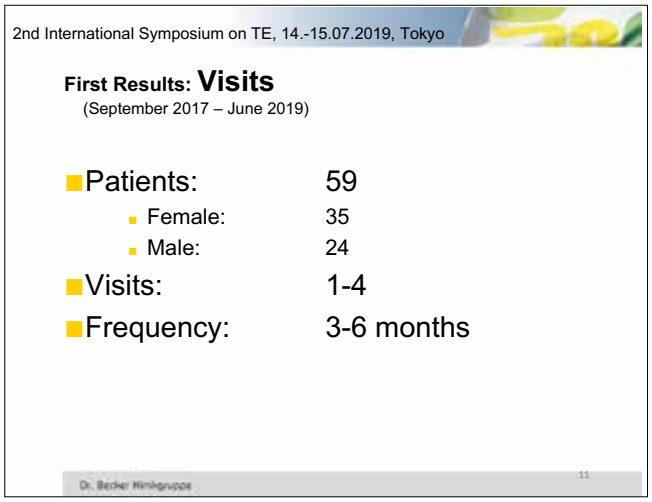
Why do patients want to visit our center? The main reason is pain, chronic pain. About one-third of the users have chronic unspecific back pain. Another portion (16 cases) has cervical spine problems, pain in the thoracic and lumbar spine. They can have several regions of pain at the same time. Shoulder and neck pain were seen in 44 cases. Problems and pain in the arms, hands, and fingers were seen in 30 cases, with the hips in 16, and with the knees in 17. In addition, problems with the legs and feet were seen in 15 cases, and with the ears, eyes, and jaws in 11. (Fig. 13)

Here are more data from another schedule. (Fig. 14)

What about treatments? What did we do within this time? Acupuncture was provided in 88 treatments. Physiotherapy and massages were given to nearly every thalidomider, and ergotherapy to a large percentage. Diagnostic X-rays were given in 25 cases. There must be special risks for this, otherwise we don't do it. (Fig. 15)

We did evaluated patient feedback because this is very important for us. We asked, "Are you content with your visit?" In total, 98% answered content or very content. We also asked, "Would you visit us again?", and 98% also answered yes. "Would you recommend the center?": 100%. I think it's very good feedback for us because it's very important to have high affinity with thalidomiders. (Fig. 16)

Finally, that's our address and that's our clinic. Thanks a lot for your interest. (Fig. 17, 18)



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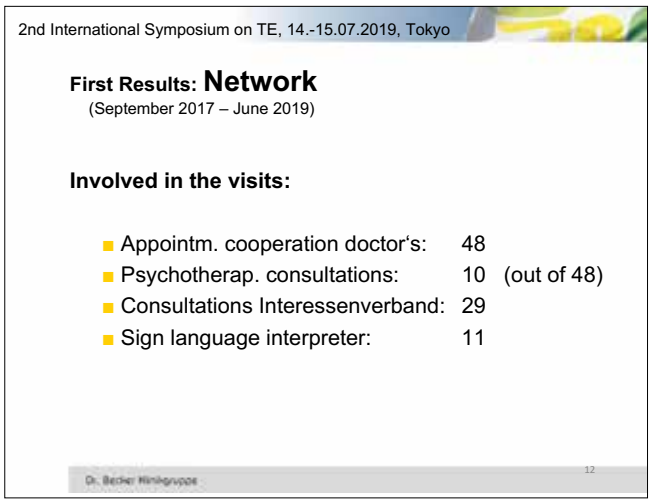


Fig. 12

Fig. 13

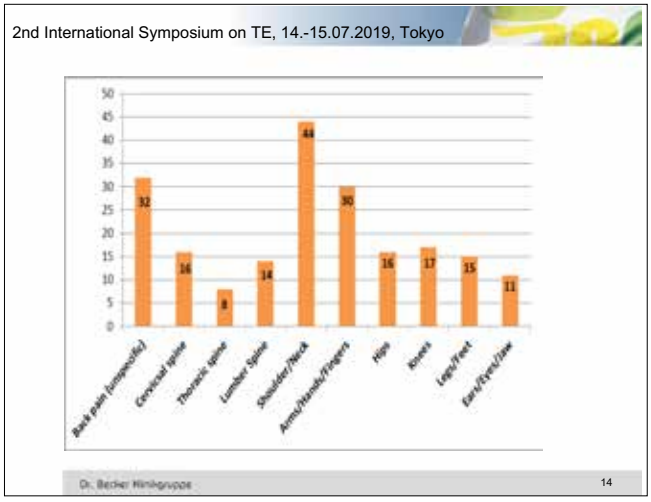


Fig. 14

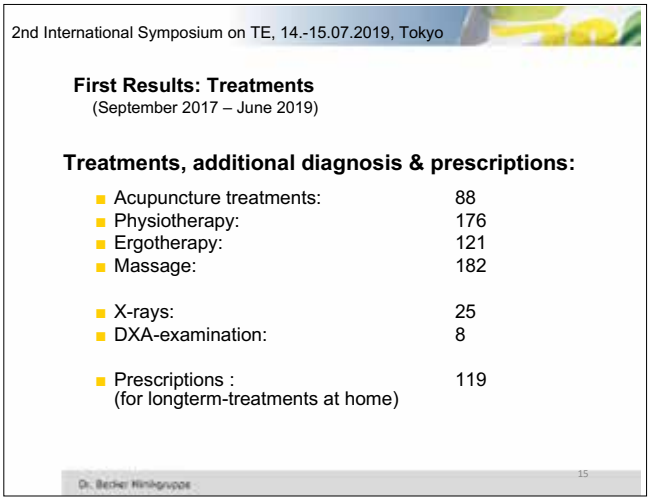


Fig. 15

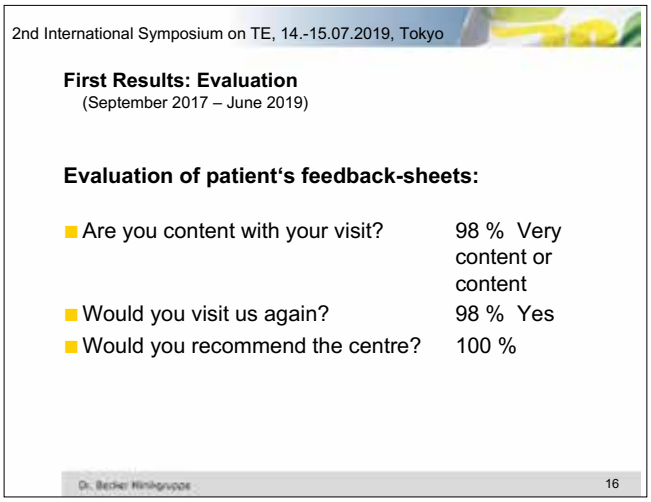


Fig. 16

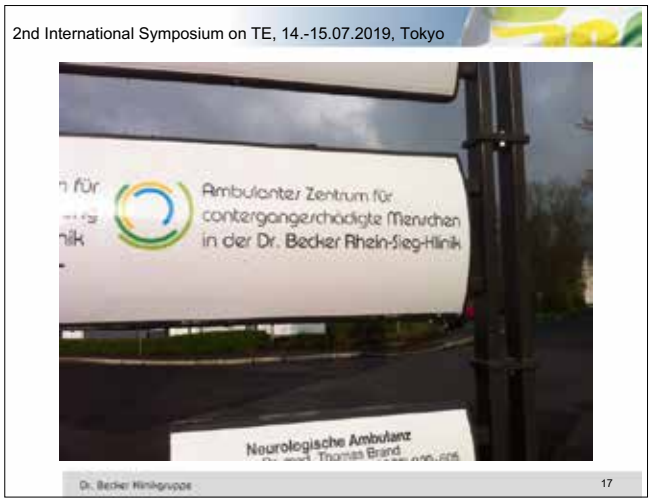


Fig. 17

Fig. 18

Q&A

Nobuhiko Haga: Thank you very much. Does anyone have any questions or comments? Okay, Dr. Peters, would you please explain the difference between physiotherapy and ergotherapy, because ergotherapy is not a standard concept in Japan.

Klaus M. Peters: In Germany, ergotherapists deal more with the upper extremities. It's divided. Physiotherapy is for the whole body, whereas ergotherapy is especially for the upper extremities, like the shoulders, elbows, and hands.

Nobuhiko Haga: So, is there a special category for ergotherapists in your country?

Klaus M. Peters: Yes, there is.

Nobuhiko Haga: Okay, thank you.

Junko Fujitani: Can your project provide pain relief for patients? Many patients have chronic pain, so what is the percentage of pain relief?

Klaus M. Peters: We measure it with an analog scale, and we have several possibilities to treat pain. One very common treatment is acupuncture because they are willing to do that. A lot of the thalidomiders don't want drugs for pain therapy. That's often a problem. They are undertreated with drugs because they don't want them. Therefore, we use acupuncture. We also use physiotherapy and massage for pain relief.

Junko Fujitani: In your project, patients stay in the clinic for several days, so do you expect to provide relatively focused, high-volume treatment during that time? After that, what treatments can patients receive?

Klaus M. Peters: Yes, they can. We give long-term prescriptions for people, mainly 3 to 4 units every week. And I think that will be a good thing for in between visits. After 3 to 6 months, they come back, and we check and control the results.

Junko Fujitani: Oh, so you recommend three or four sessions in a week?

Klaus M. Peters: Yes.

Junko Fujitani: Thank you very much.

Nobuhiko Haga: Okay.

Elizabeth Newbronner: Thank you very much, Dr. Peters. I found that really interesting. Can you also give people advice about adaptations to their homes and equipment that

they could use to reduce the strain on their bodies? Is that something that's available through the clinic?

Klaus M. Peters: Yes, we have expert employees from the Interessenverband who are looking to improve the circumstances at home, yes.

Female Participant (Unknown Speaker): Thank you very much. Very interesting. I just want to know if the cost of this investigation is covered by the government, or by the thalidomide foundation in Germany?

Klaus M. Peters: It's paid by only insurance, not the Conterganstiftung.

Female Participant (Unknown Speaker): It's from the government?

Klaus M. Peters: It's all from the government.

Female Participant (Unknown Speaker): Okay.

Nobuhiko Haga: Dr. Peters, do you have any experience that after a 3- or 4-day visit, you recommend some surgical intervention to the patients?

Klaus M. Peters: Yes, in some of the patients, surgical interventions are necessary. For example, hip or shoulder joint replacement. We also have another center in Bergisch Gladbach, Evangelisches Krankenhaus, where we can perform such operations. If they want to, they can also use other clinics.

Nobuhiko Haga: Okay. There are no other questions. Thank you, Dr. Peters. I will close the morning session at this time.

Growing Older with Thalidomide Embryopathy: Research and Support in the UK

Dee Morrison
The Thalidomide Trust, St Neots, UK

Elizabeth Newbronner
The University of York, York, UK

Christina Ding-Greiner (Moderator)

The doors are closing. I think everybody is back. I hope you had a good lunch and interesting conversations. Again, an interesting subject is waiting for us, "Growing Older with Thalidomide Embryopathy: Research and Support in the UK".

Dee Morrison is a general practitioner. For the last 7 years, she has worked for 3 days a week at The Thalidomide Trust. Her issues are varied. They include advising new claimers and research. But her main focus is assisting thalidomide survivors in health issues.

Liz Newbronner is a research fellow, PhD, and doctoral student at The University of York. She has cooperated with the Thalidomide Trust for 10 years. Her research involves the investigation of age-related issues and their impacts on prenatal and secondary damage. Now, we are very curious to see what you will tell us.

Dee Morrison:

Thank you, Dr. Ding-Greiner, and thank you, Dr. Hinoshita. It's very kind of you to invite us here. It's a fantastic learning opportunity for us, and I am sure it will greatly influence our work when we return home. For those of you who don't know the Trust, just a very quick recap. (Fig. 1)

The Thalidomide Trust was established in 1973. It was set up to provide support and assistance for those with TE. We have now 464 beneficiaries. (I think Professor Skinner said that we have 468, so I am not quite sure what has happened to the missing four). We basically have two aims at the Trust:

- To provide financial assistance. There are two grants we distribute annually. The first one is the main one from Diageo, from the original distributors of thalidomide in the UK, and the second one is a small one, more recent, from the UK Government.
- We also try and help with the thalidomide survivors' health and well-being. We are constantly improving our knowledge and resources, and we currently have a much improved website that we continue to try to improve upon.

We wanted to focus on the second area today. We undertake research with the University of York, so Liz Newbronner is going to present the research that we use to build the knowledge to develop our resources, and I will present the resources. Then, I will present three case studies to show how we use the resources, followed by a short video. The three areas we wish to focus on are mental health, lifestyle, and musculoskeletal issues. Now, I hand it over to Liz to present the research. (Fig. 2)

Fig. 1

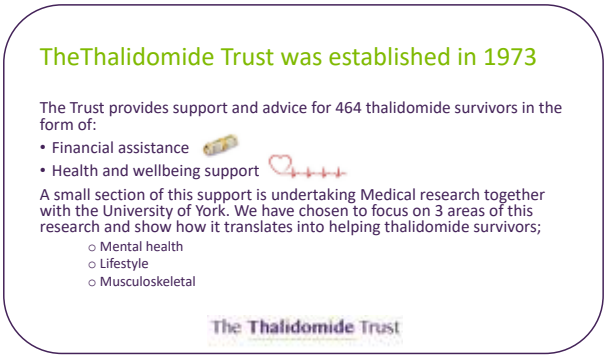


Fig. 2

Elizabeth Newbronner:

Thank you very much, Dee, and thank you to Dr. Hinoshita for inviting me to this important gathering. As Dee has said, what I'd like to do today is just give you a brief overview of some of the recent research in the UK around growing older with thalidomide embryopathy (TE). The research evidence comes from the studies that we've done jointly between the University of York and The Thalidomide Trust, and from my PhD research, which I am in the last few months of now. I've also included some data from The Thalidomide Trust routine processes from their needs assessments. So that's not really research evidence, but I think it adds to what we, you know, the picture that I'd like to present today.

So, just turning first to mental health. In the UK, mental health problems, common mental health problems, are the second-most common health issue experienced by thalidomide survivors. In 2015, we did a health and well-being survey of all UK thalidomide survivors, and almost half reported that they had recently or currently experienced depression and/or anxiety. And in the health needs assessment that The Thalidomide Trust conducts, it has also emerged as a common area of concern alongside broader issues such as loneliness and social isolation. (Fig. 3)

So last year, The Thalidomide Trust asked the University of York to conduct a mood survey. We called it a mood survey to make it seem a little bit friendlier to thalidomide survivors, but basically, it was a survey of common mental health problems. It went to all the thalidomide survivors in the UK via the Trust. We had 182 responses, which is about 40%, so it's a slightly disappointing response rate because in the previous health and well-being survey, we'd achieved a 75% response rate. But I think it perhaps reflects the sensitivity of the issue and concerns that people had about reporting on their mental health.

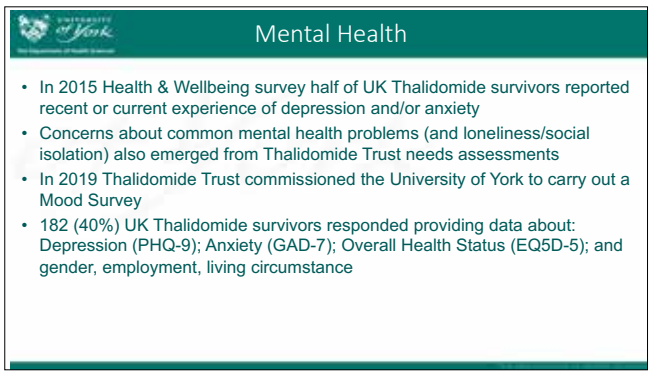


Fig. 3

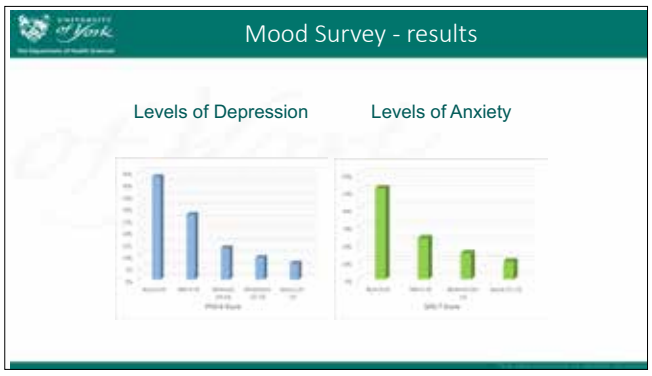


Fig. 4

And so, in that survey, we kept it quite short and simple, but in the survey, we explored symptoms of low mood and depression using the PHQ-9, a standard questionnaire. We also looked at anxiety, again using a standard measure, the General Anxiety Disorder 7 questionnaire. We also looked at overall health status using the EQ-5D-5. Alongside that, we collected some brief information about gender, employment status, and living circumstances. (Fig. 4)

I just want to sort of very, very briefly present some of the highlighted results and conclusions. Just looking at depression and anxiety, first, for depression, we found that over half of the survey respondents reported some symptoms of depression, ranging from very mild to severe depression. But around 30% were experiencing moderate to severe symptoms.

For anxiety, slightly under half of the respondents reported some symptoms. But again, a quarter were experiencing moderate to severe symptoms. I think those are very significant levels, really. (Fig. 5)

So, what conclusions have we been drawing from the mood survey? I think the first thing to say is that the prevalence of self-reported depression is much higher at all levels for thalidomide survivors than it is for the UK population of a similar age. And I think those findings echo the work in Germany and Brazil. So I think a picture is developing internationally.

However, the levels of depression and anxiety experienced by thalidomide survivors were not dissimilar to other people with early acquired disability, so, for example, peo-

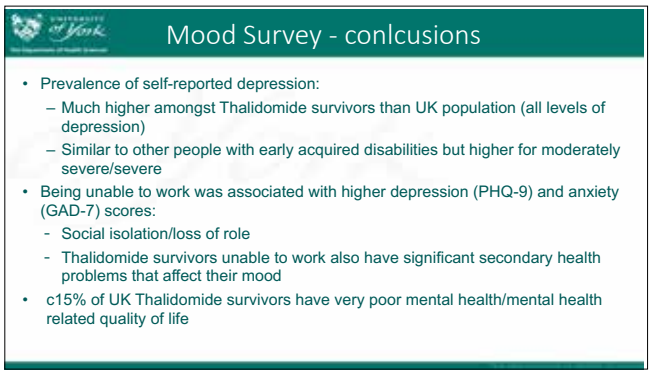


Fig. 5

ple with cerebral palsy or spina bifida, but the thalidomide survivors generally had higher levels of symptoms. So, although the overall picture was the same, thalidomide survivors were experiencing higher levels.

One of the things that we were interested in is that in the UK, almost two-thirds of the thalidomide survivors are no longer in paid work, and a very high proportion of them have given up work because they feel unable to work, not because they are choosing to, but because they simply feel unable to because of their physical problems or pain and so on. (Fig. 6)

Thus, we wanted to look at whether there was an association between being unable to work and having higher levels of depression and anxiety. We did indeed find that, and it was statistically significant. So, I suppose one thing that we've speculated on is why that might be the case. We think it might be partly due to do the fact that giving up work means that people perhaps lose their role, and that there is an increased level of social isolation, but also that thalidomide survivors who are unable to work are perhaps experiencing more significant secondary health problems, which is then also affecting their mood. So, it's sort of not a simple picture, really.

The other thing I wanted to just mention was that over the last few years, in the various smaller and larger studies that we've done, we seem to find that consistently, around 15% of thalidomide survivors have very poor mental health, whether we've looked at the measures that I've just described or mental health-related quality of life. I think, interestingly, in comparison with the quality of life study in Sweden, what we found was that people with lower levels of damage were more likely to have poor mental health-related quality of life, so it was the opposite of physical health, you see what I mean.

We think that might be because many thalidomide survivors have led very active lives, and now in later life, are experiencing new levels of disability, which is causing the problem. So, that's an interesting issue, I think. I've also sort of been thinking in my doctoral research about why thalidomide survivors' mental health might be so vulnerable.

I'd be interested in your thoughts, but my feeling is that there is a mixture of things going on. I think on one level, it's the accumulative effects of living with disability, particularly a rare disability, for many years, and the thalidomide survivors in the UK that I talked to described the effort of coping with daily life, year after year, and constantly having to sort of plan ahead and so on. But also, that sense of being different, and perhaps sometimes, sadly, unwanted attention, ranging from just people staring to actually having people being mugged or having discrimination at work and so on. So, I think that's a difficult issue. But more generally, I think there's an issue around the emotional impact of pain and loss of function. Particularly, that leads to difficulties with daily living, of activities of daily living, which are brought about by the secondary health problems.

However, I think what we found in the UK, and this is not surprising, I guess, is that there is a big influence in terms of people's individual circumstances, their family attitudes, and their life events, perhaps earlier in their lives, but also in sort of a wider social context; so, how much support and care they have, and whether they have a good social network and good financial resources. These things are all very important in determining how people respond to the pressures that they are coping with. And certainly in the UK, we found that the improved financial position of thalidomide survivors in the last 10 years has made a huge difference because people have much more choices and options in how they live their lives.

Dr. Morrison is going to talk a little bit more about how the Trust supports thalidomide survivors with common mental health problems, but one of the things that we are testing at the moment at the University of York is a short six-session behavioral activation program to help thalidomide survivors with low mood and depression. I have some

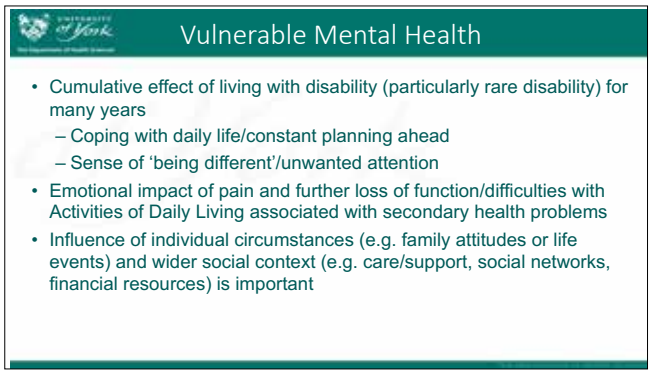


Fig. 6

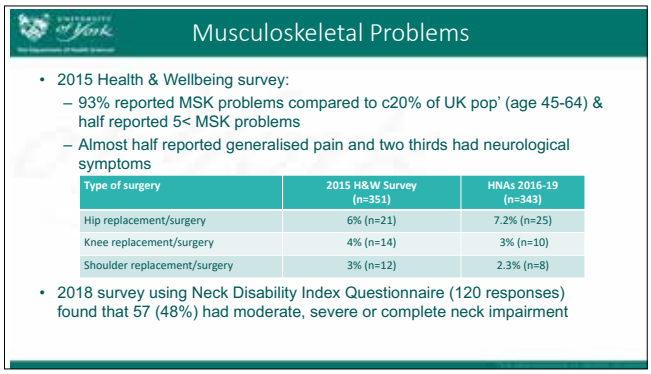


Fig. 7

copies of the booklet that we are using if anyone would like a copy toward the end of the session. (Fig. 7)

Now, turning to musculoskeletal problems, it seems to me that listening to all the speakers today and from looking at the literature that musculoskeletal problems are probably the most commonly reported health issue for thalidomide survivors. As I described when I came to the symposium 4 years ago, that certainly was the case in the UK. Around 93% of the thalidomide survivors who responded to our health and well-being survey said that they had some, one or more musculoskeletal problems. That compares with about 20% of the UK population of a broadly similar age, so a much, much higher proportion. (Fig. 8)

Interestingly, we found that many thalidomide survivors, over half, had five or more musculoskeletal problems, so they were dealing with a lot of different issues. More generally, people were reporting generalized pain and neurological symptoms. I have not gone into detail here because there's not really the time, but I just wanted to flag that.

I know from the panel questions that Dr. Hinoshita kindly sent us that there's some interest in joint replacement surgery. While our data aren't very solid, if you know what I mean, I thought it might be interesting to briefly present some of those figures. You see from the table that I've included the data that we have from the health and well-being survey, and from the holistic needs assessment, which the Trust staff carry out with individual beneficiaries. We estimate that around 6% to 7% of thalidomide survivors in the UK have had hip surgery or a hip replacement as an adult; this is not what happened to them as children, but as adults. That compares with I think around 1% of the general population of a similar age, although Professor Skinner might say more about that.

Similarly, for knee replacement surgery, it's around 3% to 4%, and again, this compares with about 1% of the general population. For shoulder replacement surgery, we think it's around 2% to 3%, but we don't have very good comparative data in the UK for that, so I am not quite sure how that compares with the general population, but we think it's higher. And just briefly, just to say, in terms of the other information that we have in the UK, last year, the Thalidomide Trust did a survey using the Neck Disability Index Questionnaire, and they had a good response, 120 responses. Of those 120 responses, 57 or nearly half had moderate, severe, or complete neck impairment.

I know Dr. Morrison is going to say a little bit more about how the Trust is helping thalidomide survivors with that specific problem, but more generally, with musculoskeletal problems.

I just wanted to sort of conclude talking about musculoskeletal problems by saying that it feels to me as though there is a real consensus internationally that consequential or secondary musculoskeletal damage is primarily caused by overuse and postural adaptations in very broad terms. But I think what I feel has emerged from my research is that often, injuries from falls and accidents, which are in some way linked to people's original damage, so for instance, mobility problems, balance problems, and sight problems, are a growing concern for a lot of thalidomide survivors.

Interestingly, I think a few thalidomide survivors in the UK have said to me that sometimes, surgical treatments are a mixed option for them, so that might reduce the pain they are experiencing, but they might then find some loss of movement or loss of flexibility, particularly in relation to shoulder treatments.

I think the other thing I just want briefly to say is that, it seems to me that musculoskeletal problems and the sort of issues that they cause, in terms of activities of daily living, pain, and a decreased ability to work, are completely intertwined with mental health issues, so it's really not possible to look at these things in isolation. (Fig. 9)

Turning briefly to lifestyle diseases, I would say that in the UK, our research information about lifestyle diseases is not very good and is a bit inconclusive, so I am cautious

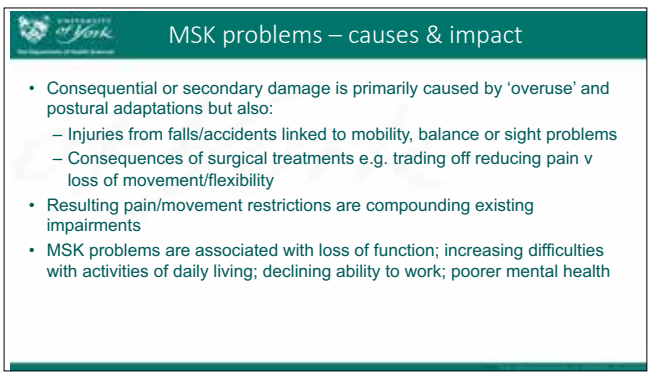


Fig. 8

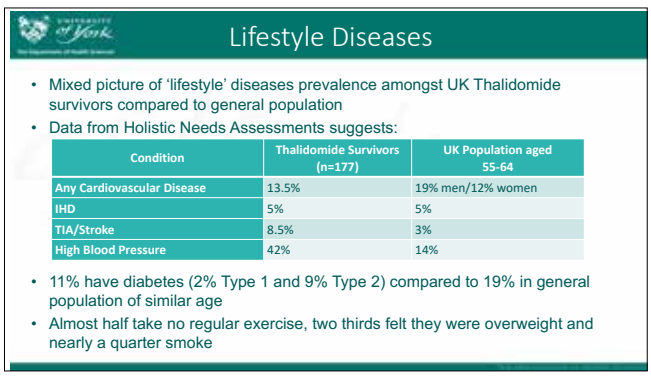


Fig. 9

about presenting some of the data here. But knowing that it is an area of interest, Dee and I just wanted to sort of show you some things. Most of the data actually come from the needs assessment that the Trust has done. So we can see by looking at the table here that for cardiovascular disease and ischemic heart disease, broadly speaking, the figures are very similar to the general population of a similar age. But for stroke and high blood pressure, the figures are much higher. The high blood pressure figure I think needs to be treated with some caution, because it's entirely self-reported, but it seems not dissimilar to all the data that have been reported, not so much in Japan, but in other European countries.

The data we have about diabetes, again, we are not too confident about it. But just to give you a broad picture, in the UK, it actually seems to be lower than that in the general population, so that's an interesting issue that perhaps needs to be explored further. But around the issues of risk factors for lifestyle diseases, certainly, almost half of the thalidomide survivors in the UK say that they take no regular exercise, two-thirds feel that they are overweight, and nearly one-quarter smoke. So again, as Dr. Morrison was saying this morning, I think that's higher than the national picture.

I think those things reinforce Dr. Shiga's work and the points that Dr. Schulte-Hillen was raising this morning about the need to be able to measure blood pressure and BMI accurately if people are going to be helped to live healthier lifestyles. (Fig. 10)

Before I close and hand things over to Dr. Morrison, I just wanted to say a little bit about multi-morbidity because I feel that it's something that perhaps isn't very explicitly discussed in the literature around aging with TE, but reading all of the work that has been produced here and listening to the presentations today and yesterday, it seems to me that it's a growing concern for thalidomide survivors as they grow older. I mean, it is a concern for populations at large, but certainly in the UK, the issue of multimorbidity is much more prevalent among thalidomide survivors than among the general population of a similar age. Almost half of the thalidomide survivors are reporting four or more separate health problems, which compares with about 10% of the UK population. So it's significantly higher.

I think the other point is that for thalidomide survivors, often, the morbidity burden is high. I think this presents difficulties for them in terms of the complexity of their needs and how the healthcare practitioners that are working with them provide support. But more generally, I think it presents issues for the thalidomiders themselves in terms of self-managing their health conditions, and that can be both practical and clinical, so people face a lot of practical difficulties, and also clinical issues.

To close, I'd like to just sort of draw some broader conclusions and perhaps try and set our research in the UK, in the context of the wider literature about aging with early acquired disabilities because I think there's much that we can learn from that broader field of research, and much that we can contribute, as Dr. Haga was saying earlier. (Fig. 11)

I think there's now clear evidence that the cumulative effects of living with a disability for many years contribute to a premature decline in health and social disadvantages, which of course, are interconnected. I think what we see is that the layering of secondary damage onto lifelong impairments creates new disabilities, but also a new sense of being disabled for some people, so the people who have previously led very active lives are now feeling disabled in a way that they perhaps didn't previously. Moreover, all of that is contributing to people's mental health problems.

Thus, I think for thalidomide survivors, like other people with early acquired disabilities, such as people with cerebral palsy, the sort of philosophy of "conserve it and preserve it" may be preferable to the old philosophy of "use it or lose it". I think in fact that thalidomide survivors themselves are making that choice; they are looking at ways to preserve their function while at the same time trying to keep as much

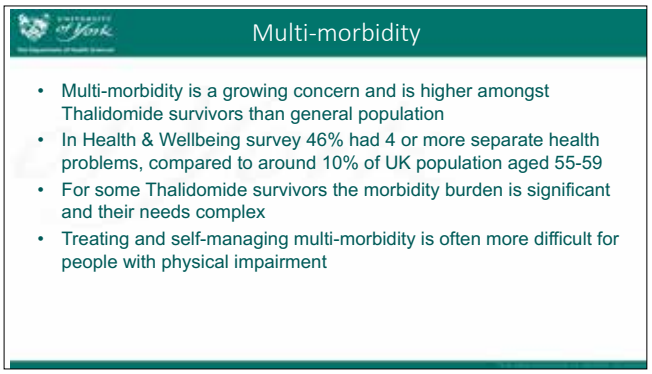


Fig. 10

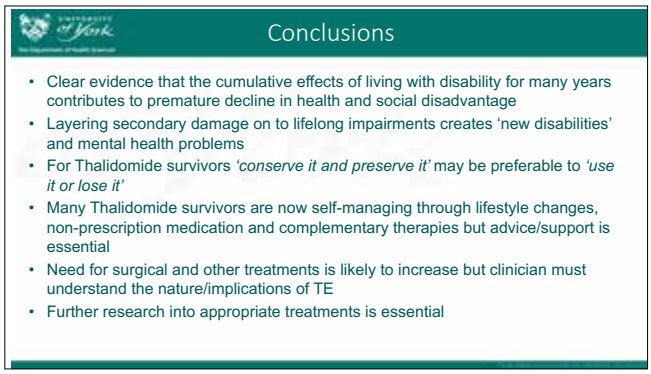


Fig. 11

independence as possible. So I am sure in all countries, they are making greater use of aids and adaptations, making lifestyle changes, and using complementary therapies as we were hearing about earlier.

But I think out of all of that, what sort of comes home to me is the importance of having really good access to advice and support, I think that's absolutely essential. But alongside those self-management options and choices about preserving function, it feels as though the need for surgical and other interventions or treatments is likely to increase in the coming years, and I think the work that's going on in Japan to educate doctors and other healthcare practitioners about TE is really wonderful because I think that's something that is so needed. If thalidomide survivors are going to be given good care and good treatment, they need doctors and other healthcare practitioners who really understand their condition and how it's affected them.

So with that, I'd like to pass things over to Dee, who's going to talk more about how The Thalidomide Trust supports beneficiaries.

Dee Morrison:

Thank you, Liz. So you've heard now some of the research we've been doing, and I am just going to try to explain how we use the research to help build our knowledge and put resources in place to try and help the individual. (Fig. 12)

I'll start with mental health support. I'll just briefly run through the resources we can pull in to help the individual. We can offer telephone support call from the Trust staff. This can be on a weekly basis or a bit more regularly. We can also offer an assessment from a medical advisor (I say medical advisor because I have a fellow GP, Dr. Susan Brennan, who joined the Trust last year, so now there are two of us). We look at the local services that are already being offered, what's happening with their GP, and what's happening with counselors, medication, etc., locally.

Then we can decide whether to pull in a bit more support to try and help further. We can call on volunteers, and we have two ways of doing this. So, the volunteer is actually a thalidomide survivor or a thalidomider, as some of you call them, and they can either visit them informally or call them. Or we have a more formal project called Talk Together. This is where the volunteers have actually received training in a project and have support. They usually call at a set time during the week.

We have a low mood improvement research project that Liz is involved in, which she mentioned briefly, for which, I held the booklet up earlier (Fig. 13)

I'll share a little bit more about the case study later. We recently involved a psychotherapist. This is quite an important resource for us. He is very experienced; he has provided care for doctors, for the army, for people who return from war very burnt, and for the fire service. He can use a wide range of therapies. He Skypes, which allows us to access all beneficiaries who are situated all over the UK. He can treat anxiety and depression, as well as addiction problems; we do have a higher incidence of alcohol use. The other area that we had no therapy for was social phobia, the psychological issues from a very visible physical deformity. He is trained in existing psychological therapies, but he also offers a new therapy called metacognitive therapy. This targets overthinking and allows them to control their attention to thoughts and behavior. So, basically, when people start to get anxious or depressed, they ruminate, they look at what's happened in the past, and their thoughts go over and over, or they worry about the future, and they can't shut the thoughts off, and then they can't sleep. He teaches them to control this and control their behavior so they don't turn to alcohol, which allows them to focus their thoughts elsewhere.

We also have Trust events where we remind them to look after their mental health and well-being. (Fig. 14)

If I quickly go on to the next topic of lifestyle, there's a lot of information in the public domain about lifestyle. What we try and do is tailor the information and make it more

Fig. 12

Fig. 13

specific to those with TE, explaining the why and how. We can do this with either websites or talks and seminars. For example, I recently wrote "How healthy is your heart?", a blog pulling in research from Germany and Japan, as well as from Dr. Beyer's recent paper saying that we thought there was a slightly increased risk of cardiovascular disease. But I was able to reassure them that currently, there's no specific evidence to say it's due to thalidomide per se, but that we were taking steps to learn more about it. I explained what they themselves could do about it.

So that was the "why and how" regarding lifestyle. Then again, for the "how," we try and offer test sessions, either for the individual or for the group. Sweden did a very good project some time ago where they pulled in nutritionists and personal trainers over the course of a year. We learned from this and devised our own project, called Fit for the Future, where we did it over a weekend, so we had personal trainers, physios, nutritionists, and a group of beneficiaries. It was very successful. We followed up with the group over Facebook and we repeated this a couple of years later, for different beneficiaries, again over a weekend. One very important way that we try and help with lifestyle is to inspire them with stories from other beneficiaries. We got Simone on our website, logging her food. She lost 4-1/2 stone (1st = kg * 0.15747) in 2-1/2 years and we have also got Kath trying to improve her balance and prevent falls through exercise.

We designated 2020 as the year of health and well-being. So we're going to do events across the whole of the year. Underpinning this is the "One Small Change" campaign, where we are going to ask them to make one small change in say, about 6 weeks, and we're hoping then that they will follow up with other changes. That change could be eating a piece of fruit or going for a walk for 10 minutes three times a week. (Fig. 15)

Lastly, the third area is musculoskeletal problems, a really important area. Again, tailored information is very important. The work with our specialists has allowed us to build up our knowledge so we can tell them a little bit about what's causing their hip, shoulder, and neck pain, why they are getting more of it, and also about balance and falls, which I think is going to be a big issue as they age, and what they can do about it.

Backing this up are our beneficiary stories, and again, peer-to-peer support; so, stories about the hip, the shoulder, the neck, how they had their surgery, what implications there were, how it was organized, what the rehab was like, what they needed to order in terms of extra carers, and also working with physiotherapists or massage therapists.

We've also developed a professional network. This has been quite informal over the last few years, but with the new website, we have a special page, and we are building up there specialists and therapists who are known to the Trust or who've actually helped thalidomide survivors.

Individual support with the helpline is obviously an area that I care very much about. We liaise with the GP regarding medication, advice about massage, physio, and exercise programs, put them in touch with local therapists, and follow them through. But again, a major part of this work is the help with specialists, where we have a small budget in the Trust. We can facilitate a private referral to a specialist who is familiar with thalidomide issues and who is a complex surgery specialist, such as Professor Skinner. This allows us to speed up greatly the referral, and enables a really good conversation for the individual with a specialist familiar with their issues to explain what the issue is and what can be done to help them.

Lastly, the Trust staff go to a lot of events and can also help with ergonomics, personal assistance, wheelchairs, gadgets, etc.

So, those are the resources we have put in place. I'll just quite quickly take you through several case studies to show how we pull in the resources in individual cases.

These cases are not for publication, and have been omit-

Fig. 14

Fig. 15

ted from the written summary of the seminar. However, one case study showed the use of psychological help with the LIFT study, another case study showed how another individual was helped with depression, pain, and alcohol, and the last case study showed how one individual with neck and referred pain was helped by successful cervical spine surgery.

The video I am going to show you now is on David. This followed inspiration from attending Dr. Beyer's seminar on physio and exercise in Germany. It also followed a weekend seminar, called "Fit for the Future," that I mentioned earlier, and an expert from Loughborough University talking about exercise and how to create an established pattern. He said it needs to be fun, it needs to be sociable, and it needs to be easy to do. So we took this learning and ensured that the physiotherapy was followed up by exercise and the development of an established exercise routine. And this is what happened.

[Video begins]

The conversation between David and Fraser is shown below.

David: For a long time and in my late 40s and early 50s, I started having trouble in my back, and I just thought it was arthritis. I struggled a lot with my balance and going up and down stairs, and I didn't feel very secure when getting on and off buses. I spoke to Dee from The Thalidomide Trust, who suggested I contact Fraser, who is a physiotherapist.

Fraser (physiotherapist): From David's initial assessment, one of the biggest things that we found was that David has got a slightly shorter leg than the other one, and because of that shortening over a long period of time, it's put an awful lot of stress on David's back. So, what we've done is initially refer David to an orthotist, who has taken a mold of David's foot and provided a custom-made insole. And what that has done is just support the shorter leg, making it a little bit longer and evening out his posture, which will actually help David walk better.

David: The reason I got in touch with The Thalidomide Trust is because I went to a weekend Trust event called "Fit for the Future," and it was just about keeping your body in good shape, dietary help, what can help pain, etc. But the thing I was the most interested in and have never done before was Pilates. They encouraged me because I had never seen Pilates before, and now myself and my wife are looking into joining a Pilates class. But we intend to get a little bit more fitter before taking this further.

I've never done exercises before, I never really knew about it until Fraser told me, and then it all kind of made sense.

Fraser (physiotherapist): The ultimate aim of physiotherapy is to give David his independence back and to really get David to take ownership of his own health. So we are going to look at David going along to a local Pilates class after probably about 4 or 5 months of treatment.

David: Fingers crossed.

David (months later): In general, my back is 100% better, even walking is all better. I am more confident when I am out and about. I am walking a lot more, and I am not putting as much strain on my back, so obviously, the pain is not going to be as severe. I can reach things, and I can bend over a bit to get things from the cupboards, which is a lot easier.

Fraser (physiotherapist): One of the big things that David was wanting to be able to do is to be a bit more active regularly, so The Thalidomide Trust has put him in touch with a local Pilates instructor, and Pilates itself is quite a nice exercise program because it keeps you strengthened and stretched in the right way.

David: Yeah, the first two (Pilates) classes went really well, and she's quite surprised how good my balance is. But I would not have been able to do it without physiotherapy. I would have never ever dreamed of going to physiotherapy. I was too embarrassed, but I find that once you get started and get more involved with physio or Pilates, your confidence grows. I just took things for granted because of the shortness of my leg. This was the way I walked, and that was it, and there was nothing could be done. I honestly should have done it years ago (referring to physiotherapy).

[Video ends]

Dee Morrison: I hope you can now see how we have taken the knowledge learnt from the research, not just from the UK, but from the work you have all been doing, the specific projects in the UK and abroad, and the work with specialists such as Professor Skinner and symposiums like this, to

build knowledge within the Trust and put in place resources to help thalidomide survivors, as shown in these individual case studies. Thank you.

Q&A

Christina Ding-Greiner: Thank you very much for this very beautiful presentation. Are there any comments or questions?

Fumihiko Hinoshita: I have a question for Liz. You showed us the incidence of cardiovascular diseases and IHD, ischemic heart diseases, and then TIA and stroke, between the general population and thalidomide beneficiaries. Interestingly, the incidence of cardiovascular problems or diseases was almost at the same level in thalidomiders and the general population. But as for TIA and stroke, there is a large gap between the thalidomiders and the general cohort. What do you think is the cause? I mean, from hypertension or other problems, for example, some anatomical problems of the cerebral vessels or so. What do you think?

Elizabeth Newbronner: Dee can probably answer this better.

Fumihiko Hinoshita: Yeah, Okay.

Dee Morrison: We don't know. I think I asked my question poorly yesterday, but what I was trying to say was that we know there are lots of abnormal vessels, but we don't know whether the disease processes as they grow older might be more detrimental in certain areas than in others. But there isn't any evidence at the moment to say that for those who are affected by thalidomide in the room, so we really just don't know. We can really just monitor what's happening and keep a close eye on everything.

Fumihiko Hinoshita: Okay. I would like to know the further results of your survey, and then consider the cause, please. Basically, in your country, you have more cardiovascular events than we do, so I was very much interested in the gap. Interestingly, more thalidomiders are suffering from TIA or stroke in your country. That's it.

Elizabeth Newbronner: Just to say as well that I think we hope that The Thalidomide Trust is intending to repeat the health and well-being survey in 2020. I think we've learned from the past survey, so we're hoping that we'll be able to get much more accurate data about both the lifestyles and diseases in older age and risk factors, so hopefully, if we ever meet again, we'd be able to present some more accurate data.

Christina Ding-Greiner: Are there any more questions or comments? Nobody? Then, thank you.

Ageing with Thalidomide Damage: Evaluation 2019–Special Needs

Christina Ding-Greiner

Institute of Gerontology, University of Heidelberg, Heidelberg, Germany

Klaus M. Peters (Moderator)

Today, I am happy to introduce my German colleague, Dr. Christina Ding-Greiner. She studied medicine at the University of Heidelberg and Vienna, specializing in internal medicine. Afterwards, she got another specialization in gerontology. Nowadays, she is still a member of the Institute of Gerontology at Heidelberg. I think she's been dealing with thalidomide-affected people for several years. Her topic today is "Aging with Thalidomide Damage: Evaluation 2019". The focus is on special needs.

Thank you very much for your introduction. Thank you, Dr. Hinoshita, for inviting me. (Fig. 1)

As a result of our studies, which I presented 4 years ago, in 2015, we had two amendments to the Law of the Contergan Foundation for Disabled People, in 2013 and 2017. In 2013, rents for thalidomide embryopathy (TE)-affected people were raised sevenfold, and in addition, they got a sum of 30 million euros per year for special needs. This amount was budgeted in 2017, and they get now, in addition to rent, a yearly budget of between 5000 to 15,000 euros, depending on the degree of their damage. (Fig. 2)

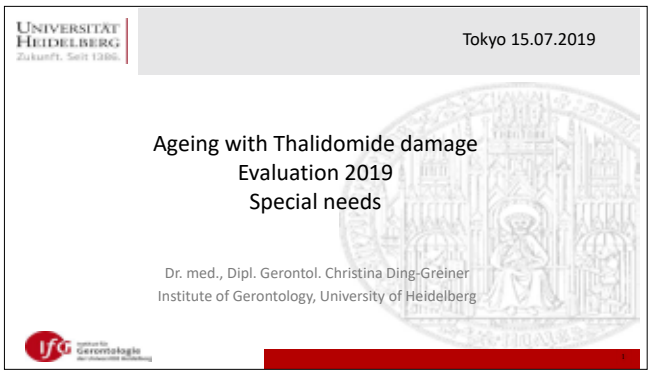


Fig. 1

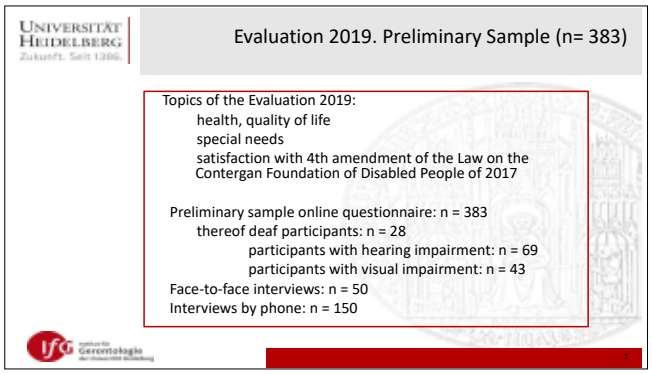


Fig. 2

The Institute of Gerontology was assigned to evaluate the outcome of the Fourth Amendment of the Law of the Contergan Foundation for Disabled People in 2017. We have not yet finished our survey; therefore, the data we present are only preliminary.

Our tools were: 1) an online questionnaire and video produced for deaf affected people with a sign language interpreter translating the online questionnaire; 2) face-to-face interviews with a mean duration of about 2 hours, which were analyzed with qualitative methods; and 3) interviews by phone calls lasting about 30 to 60 minutes, which were evaluated qualitatively and quantitatively with SPSS. (Fig. 3)

Overall, 40% of our sample were still employed; 54% had a full-time job and 46% part-time. Also, 40% of the TE-affected people in our sample who left employment since 1978 retired during the last 6 years. They benefitted from improved financial conditions and are now able to care better for themselves. (Fig. 4)

But why did they leave? It was not an easy decision for all. Almost 90% told us about a reduction in physical capacity. A second reason referred to was pain and reduced resil-

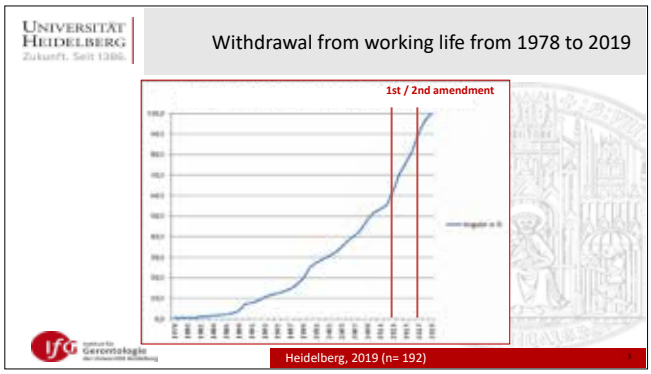


Fig. 3

ience; only 7% mentioned that they had no job offers.

The reduction in physical capacity is a problem in all TE-affected people. They describe it as a slow and constant process lasting more or less for 10 to 20 years. This process has accelerated during the last 3 to 5 years. There are acute episodes where affected people lose capacities in a short period of time. They often manage to restitute the prior condition to some extent, not entirely, but mostly. The trend leads step-wise downwards and implies a loss of strength, a loss of skills, and the stabilization of a lower level of physical capacity.

TE-affected people never know when it will happen or to what extent they may lose capacities or will be able to restore them. Especially those who are single are concerned and fear an acute event because they don't know whether they may be able to cope with it.

This is one reason why they rate the current situation concerning health as moderate to poor. Only one person told me in the interview she had a good healthy condition. (Fig. 5)

The prevalence of pain in our preliminary sample was high, with 82.5% declaring that they suffer from pain. We divided the sample into four groups depending on the damage points they had: up to 25, 25 to 50, 50 to 75, and 75 to 100 points.

As you can see, there were very small differences between the different groups concerning the prevalence of pain. Even those affected persons who have only a small amount of damage points, as they have few prenatal damages, show a high prevalence of pain, too.

Affected people with only slight damage lived a more or less normal life with stress and burden as if they had no damage. But obviously, there is a higher physical vulnerability in this group, too. Their physical health condition today shows an accelerated aging process, as we can see in all thalidomide-affected persons. Considering their condition, they are in a similar situation as other TE-affected persons with a higher amount of prenatal damage, and who therefore have higher benefits. The group with lower damage points and lower benefits are endangered, as their benefits don't meet their current needs.

Since 2010, an increasing number of participants in our surveys have told us about remarkable pain episodes, which can occur without any apparent reason in any part of the body at any time. There is a sudden, short, and very violent pain, like a bee sting. If they happen to carry something in their hands, they may drop it, or they may even fall if the pain occurs in the feet or legs. The origin of these symptoms is not known.

No doctor could tell them until now what the cause of the symptoms might be. It would be interesting for me to hear from you about whether your patients tell you about similar symptoms. (Fig. 6)

We asked the participants about the intensity of their perceived pain, considering a scale from 0 to 10, with 10 being the highest level of pain. For all four groups, we calculated the mean value for 2009, 2016, and 2019. The differences between the mean values of the years 2009, 2016, and 2019 were statistically significant, and this process goes on. The pain level was increasing over the years in spite of retirement or more physical therapy; some people have physiotherapy three times a week, they have massages, they go swimming, they have more rest, and they adapt their environment to their needs.

We had the impression in our interviews that some affect-

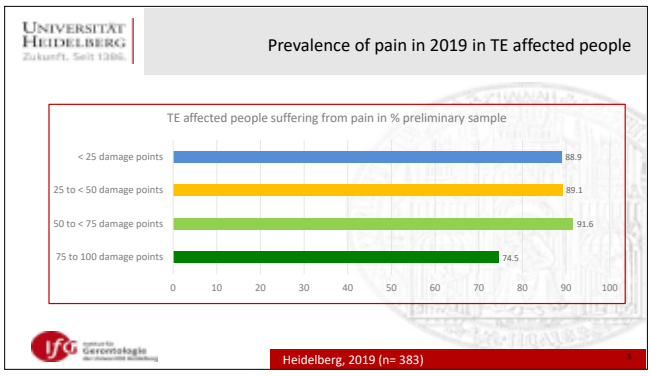


Fig. 5

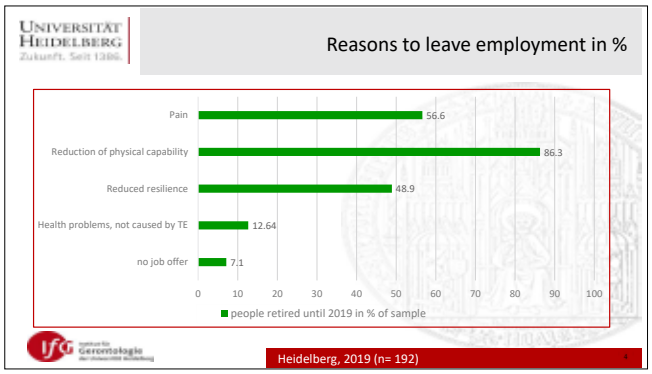


Fig. 4

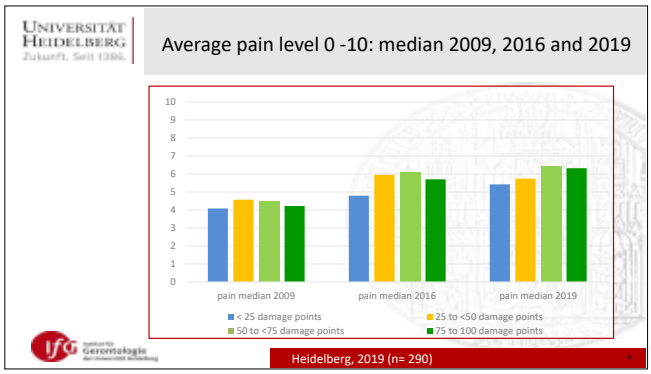


Fig. 6

ed persons showed no further increase of discomfort, as they had changed their way of life since they left employment. But all of them know that this will not last for a long time, that the aging process is in progression. (Fig. 7)

The pain disability index measures how much chronic pain prevents people from performing different aspects of everyday life. For different items such as family and home responsibilities, recreation, social activities, occupation, sexual behavior, self-care, and life support activities, we calculated the median index points for the sample. The higher the index, the greater the person's disability due to pain. We see as well that the differences between 2016 and 2019 in all items were statistically significant. There were severe and progressive restrictions due to pain in essential life activities.

TE-affected people try to palliate the situation with all kinds of physical therapies and sports, with good results. They get support from friends and family. But if the restrictions grow, the demand for assistance will grow, too. We learned in our interviews that first, they cut down activities that give support through participation in social life. Thus, they might become endangered in regard to mental health. (Fig. 8)

Overall, 43% of the participants in our survey had a regular need for assistance; the higher the degree of disability, the higher the need. Also, 30% and 35% of the participants with fewer than 25 or with 25 to 50 damage points showed a need for assistance, respectively. The collected data for hours per day of needed assistance, independent of who was assisting, showed a statistically significant increase from 2016 to 2019, and this trend continued. It was linked to higher expenses, which affected people will not be able to afford privately in the long run. In addition, more professional assistance includes lesser privacy, and quite a different individual orientation in everyday life; these problems are severe mainly for people living independently. (Fig. 9)

The participants were asked whether they had a regular need for assistance or care at present, or whether they thought they would need assistance or care in 2022. The actual needs were quite high, almost 50%. The estimated growth rate was 1.3 for future needs in 3years. TE-affected people in Germany live at the moment in quite a good condition. They are able to provide for almost everything they need, but as this trend proceeds, a distinct change in the general situation can be expected. There will be difficulties in funding and in finding adequate assistance to preserve personal autonomy. (Fig. 10)

The focus of required demands is on mobility, new cars with adapted equipment, and adaptations to the living environment, including the actual loss of strength and skills needed to remodel bathrooms and kitchens for more independence. Electronic devices provide better relief in everyday life activities. It is now possible for TE-affected people to cover their demands and care for the future. They adapt their homes for wheelchairs, even though they do not yet

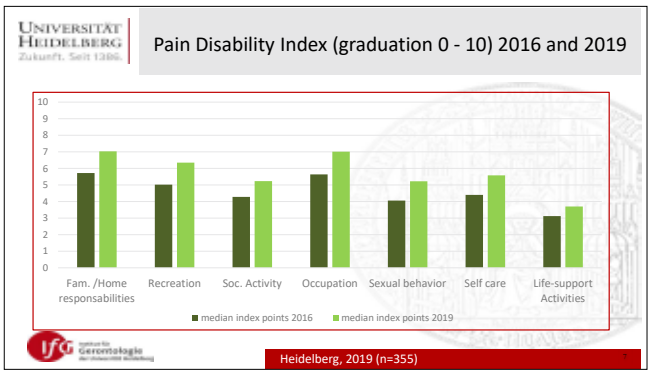


Fig. 7

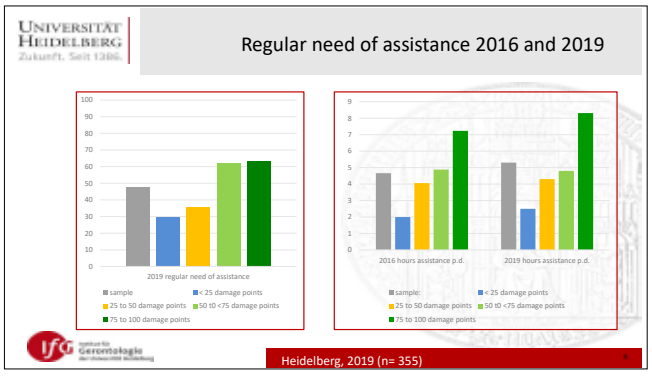


Fig. 8

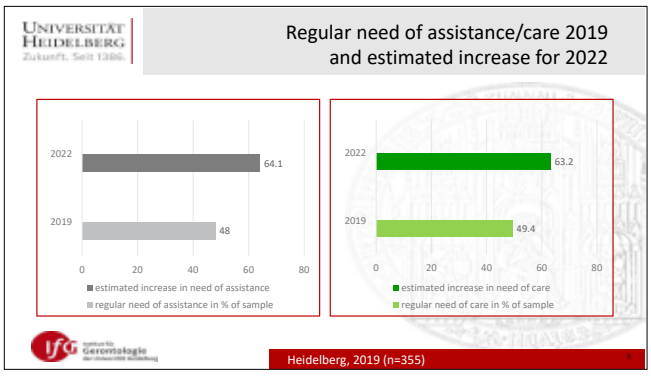
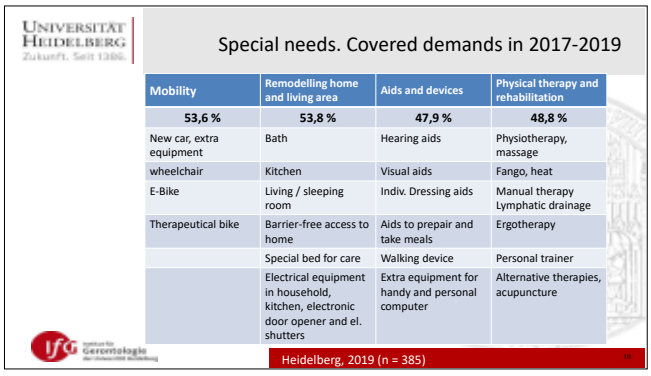


Fig. 9



Mobility	Remodelling home and living area	Aids and devices	Physical therapy and rehabilitation
53,6 %	53,8 %	47,9 %	48,8 %
New car, extra equipment	Bath	Hearing aids	Physiotherapy, massage
wheelchair	Kitchen	Visual aids	Fango, heat
E-Bike	Living / sleeping room	Indiv. Dressing aids	Manual therapy Lymphatic drainage
Therapeutical bike	Barrier-free access to home	Aids to prepair and take meals	Ergotherapy
	Special bed for care	Walking device	Personal trainer
	Electrical equipment in household, kitchen, electronic door opener and el. shutters	Extra equipment for handy and personal computer	Alternative therapies, acupuncture

Fig. 10

need one. They install an elevator in spite of not actually needing one. They try to anticipate future needs to be ready for old age with a high level of autonomy.

Concerning aids and devices, they have high demand for hearing and visual aids because they age as everybody else does. Physical therapy helps them palliate pain and physical decline.

These kinds of needs can be purchased, they can be paid for, but there are needs you can't pay for. We have been looking at thalidomiders from the outside, and I think it's important to let them speak for themselves. We only perceive their demands and problems from the outside since we are not affected. We have no idea what it feels like to be a TE-affected person and to live a whole life with congenital damages and impairments. Every thalidomider is unique, as their damage is never the same; thus, everybody has their own story. Last year, I had the opportunity to collect stories from thalidomiders and their parents, siblings, and children. I got about 80 stories.

I would like to read you the story of Antje Goebelsman, a thalidomider born in Germany who later lived in America. Antje wrote to me from America and wanted to have her story told because she wanted order in her life. She was first in quite a bad condition, and told me to publish her story anonymously.

A couple of weeks ago, I called her and I asked her whether I could read her story here in Tokyo. She told me, "You may read my story and you can say my name, I am much better now." I have shortened this story. The title she gave to her story is "Becoming Whole."

This is the original version.

Antje Goebelsman: Becoming Whole

Currently, I'm living in America with my son and husband, but Germany will always be my home. My friends and pets bring me much joy, and my son is the light of my life. I love designing and creating beautiful things. It is important to me to be a kind person, and to leave the world as a better place than it was when I entered it in 1960. I want everyone's life to have equal value, and I believe that we all deserve an equal chance at well-being and love.

Contergan determined much of my fate, but it is impossible for me to untangle the person that I might have become from the person I am. Now and then, I wonder which aspects of my personality are innate, and which are just adaptations to a life with deformities and disabilities. Would I have accomplished more if Contergan had been as safe as promised by the manufacturer? Sometimes I think about the many dreams, talents, and capabilities that were denied to the Contergan victims.

One thing I'm sure of is that there need not have been so much sadness in my life. My physical disabilities posed serious challenges and made many things impossible for me. I've endured much physical pain, and my body disappoints me every day by not being able to keep up with my ambitions. However, the rejection and hatred I encountered were much worse than any physical issues. I'm still shocked by how cruel people were to me. Perhaps children have a primal urge to eliminate the unfit. As an adult, I understand that the abuse had more to do with the abusers than it did with me, and I'm doing my best to let go of bitterness.

An Unpleasant Surprise

My mother never fully recovered from the trauma of bearing a child with deformities and serious disabilities. My mother loved me dearly, but wasn't ready to parent a child like me. She was still drugged from the anesthesia when the doctors told her that I had no ears and would never hear or talk. My mother insisted that she didn't want the baby if there was something wrong with it. My great-grandmother pointed out that Hitler would have had the authorities take me away. The midwife made it clear to everybody that I should be treated like any other baby, that I should be loved and talked to even if I couldn't hear. In 1960, the cause of my birth defects was unknown.

Surgeries

In my early twenties, I chose to undergo a series of five surgeries to construct facsimiles of outer ears using rib cartilage and skin grafts. The resulting ears were somewhat rough and lacking in detail, but I wasn't disappointed because I had known what to expect. My mother believed that I could now keep my most serious birth defect secret from a future husband. However, these new ears would in no way fool anybody who saw them clearly. However, this surgery improved my life tremendously. My embarrassing stumps were gone, and I no longer worried about strangers discovering my secret.

My blood-red left eye could not be hidden. Apparently, my ears were too awful to talk about, but everybody asked me what happened to my eye. I had my final day of being pretty when I was 8 years old. I had delicate features, shiny brown hair usually concealed my ears, and I was still skinny. My brown eyes were clear, albeit crossed and malfunctioning. I needed a "final" surgery for strabismus.

After several days of the usual post-surgery vomiting,

the bandage was peeled off my left eye. Later, when I was alone in my room, I checked the mirror to see if there were any noticeable improvements. The sclera, which is supposed to be white, was blood-red, and my eye was still immobile, but staring quite far to my left. I went into a sort of numb shock as I looked at myself. I wondered why the nurses hadn't removed the mirror to shield me from having to acknowledge my bloody eye. I was defined first and foremost by my red left eye, and few people looked beyond that.

Southern California

My father moved his family to the United States, to Southern California, to advance his career.

We were transplanted into a newly-built, pseudo-glamorous suburb in Southern California, where we had to adjust to new social rules. Here, it was important to be good-looking, fair-haired, tanned, and financially privileged. This move happened immediately after my life-disrupting eye surgery, and right before adolescence, when children are at their cruelest.

In the United States, nobody except for doctors knew about Contergan. My mother worked hard to help me hide my ears and my hearing aid. At that time, I had a bulky, body-worn hearing aid, which was concealed under my blouse. A wire snaked through my clothing to a bone-conductor. My mother sewed a blue hairband to cover the metal headband that kept the bone-conductor pressed to my skull. I walked with my shoulders hunched up to help hide my ears and the strange-looking hardware. I dreaded stormy days, when the wind would lift my hair up to expose my ear stumps. More than anything, I wanted to change myself so I could be exactly like everyone else.

Beauty, Shame, and Envy

My sister was a winner in the genetic lottery for beauty. Sylvia was born blond, with large, greenish eyes, high cheekbones, pleasing facial proportions, and a lovely smile. I resembled my father, but Contergan had interfered with my face. In addition to causing my face to be oddly asymmetrical, Contergan paralyzed much of it, leaving me with a grim, serious expression, which many people find off-putting.

My mother often accused me of being jealous of her and my sister's beauty, but she was wrong. I was jealous of the many unfair advantages that beauty provided for her—the main advantage being our mother's love. It seemed that everyone believed Sylvia deserved the best the world had to offer, and that I deserved nothing. I was furious that nobody would admit that this was an immoral system.

My being a kind, well-behaved good girl did not make people like me. My never making demands of anyone did not make people like me. My careful hiding of my ear stumps did not make people like me. My resentment of Sylvia made our relationship tense, and we argued and fought. This was very difficult for my mother, and I was often punished.

As if my life wasn't difficult enough already, I made it worse by pulling my hair out. I first pulled my eyelashes out after a difficult hospital stay in Germany, but I do not remember this. When I was 6 years old, I had the first episode of pulling out hair from my scalp. The day we arrived in Southern California, I created a large bald patch. Over the next year, my stress and anxiety levels became unmanageable, and I had to wear an ugly kerchief to hide the bald patches, hearing aid, and disgusting ear stumps. Despite my best juvenile efforts, I could not resist the urge to pull my hair out.

I'm dismayed by how much time we wasted with my family's pointless beauty drama. Of course, even I will admit that beauty can bestow many advantages, but I still maintain that the people who value it too much are shallow and not worth chasing after.

Boy Trouble

When my body became curvaceous, some boys became interested in me. It took a few years for me to realize that these boys would not give me the love and kindness I longed for. One young man told me that he could never love me because of my deformities. It seemed that I had become alluring enough to have sexual relations with, but wasn't beautiful enough to be loved and cherished. By the time I turned 20, I decided to avoid the boy–men and focus on my education. In my early 30s, when it seemed that I was the only unmarried woman I knew, I began to worry about running out of time, whereupon I made some more mistakes.

Feminism was good for me. After all, I couldn't achieve the vitally important task of being attractive to men. Not only was I disfigured, but I couldn't even camouflage myself with cosmetics. I was restricted to an unflattering hairstyle because my ears had to be concealed. My eyes were too dry for contact lenses, so I had to wear actual eyeglasses. My father laughed at the feminists, but the idea that my worth as a female human was not dependent upon my allure to men was liberating. This concept became a crucial factor in the construction of my self-esteem.

Design and Art Being Appreciated

It was in college that being good at art and design turned my life around. People in the art world were relatively tolerant of personal differences and idiosyncrasies. Being part of this world helped cure me of my intense desire to be just like everyone else. My peers admired me for my work and didn't publicly pass judgment on my looks. Also, the appearance of my left eye had been improved by surgery just in time for college. I was surprised to be invited to parties, and to make some very close friends at college. Somehow, my awful childhood was over.

Twisting the Hand of Fate

After my son was born, it took a long time for me to overcome the nagging feeling that I had grabbed onto something that was not intended for me. My life was suddenly much better than what I deserved, and I worried that fate would take my baby away from me. I was so happy to have a child, that I promised myself to never again be jealous of my sister.

It wasn't so easy for me to navigate relationships and marriage. My husband and I have the usual challenges, and my deafness frustrates him every day. But he has given me something other men wouldn't, which is that he was never bothered by my facial palsy, red eye, reconstructed ears, scars, and moth-eaten hair. When people ask me if my husband doesn't mind my deformities, I know that they have absolutely no idea of how hard I work, and how few demands I make of anyone.

However, my social network consists of nice people who don't need me to change myself. I am so grateful to have close friends whom I adore and love spending time with.

Mercifully, the Future is Concealed from Us

I don't want to elaborate on my physical issues because there are Contergan victims who have much more pain than I do. Bodies are fragile, and even minor issues can cause serious problems. We have had to use our bodies in ways they were not designed for. Death can sneak up on anybody, but it's disconcerting to worry about one's malformed internal organs failing prematurely. In addition to the typical health concerns of an older adult, I have constant musculoskeletal and nerve pain. My eyes seem to have everything wrong with them, and on some days, I just can't see clearly.

Hopefully I'll be able to recalibrate my desires as I age, so that I can find contentment even when my body prevents me from doing the things I want to do. I am grateful that I can still create artwork, and hope to have the chance to complete many projects. I would also love to do more to help and empower other people, to make the world a gentler place.

It would please me if my narrative could help convince people of the need for kindness and tolerance.

I thank you for your attention.

Klaus M. Peters: Yes, thank you, Christina, for the presentation of your data, and especially for the impressive story of a thalidomider. Any questions or remarks?

I think you've collected a lot of these stories. They are very interesting.

Christina Ding-Greiner: That's the inside story of a thalidomider. We can't know what is going on inside of them, but we may catch an idea about the meaning of life with such a terrible disability. I learned a lot from the conversations I had with the authors and their stories; therefore, I wanted to share this with you. Thank you.

Klaus M. Peters: Yes, and I think we as doctors can learn a lot from thalidomiders because of the management of their lives and their problems. I think it is also very helpful for other patients.

Total Hip Replacement in Thalidomide Embryopathy? What Are We Worried About?

John Skinner

Royal National Orthopaedic Hospital, Stanmore, UK

Dee Morrison (Moderator)

I'd like to introduce Professor John Skinner. He is a complex hip and knee orthopedic surgeon at The Royal National Orthopedic Hospital, the leading Hospital in the United Kingdom for orthopedics. He takes complex referrals from across the UK and occasionally internationally. He is a clinical leader for joint reconstruction and the Director of Research and Development. He told me he saw his first thalidomide survivor in 1999.

He's tremendously well thought of by thalidomide survivors, very helpful and supportive to The Thalidomide Trust, and some of the nurses have commented to our thalidomide survivors that they think he's the best.So, John.

Dee, thank you very much indeed, and thank you, Dr. Hinoshita, for the extremely kind invitation. I can't tell you what an honor it is to be here in this organized group to discuss such an important group of patients. I've called my talk "Total Hip Replacement in Thalidomide Embryopathy (TE): What Are We Worried About?" (Fig. 1)

Well, hip replacement, total hip replacement, is not yet 80 years old. This was the first total hip replacement performed in London by Sir Philip Wiles in a few patients. Until that time, the treatment was either to take the ball off the head and take the hip joint out, or to fuse the femur to the pelvis. (Fig. 2)

It matured through Charnley and various other people in the 60s to be described as the operation of the twentieth century. (Fig. 3)

And that was in no less a publication than the Lancet. So we know that with hip replacement, we've got happy patients, we can reproduce it, few complications, and people's function improves dramatically. It's cost effective, it sometimes seems expensive on day 1, but the cost of a hip replacement over the lifetime of its use is £7, or just under ¥1000 per week. That's incredibly good value healthcare when you consider what the drugs would cost to relieve the pain. (Fig. 4)

In the UK, we have the national joint register, which now has 2.5 million records. It's the largest registry in the world. Just over 100,000 patients a year have hip replacements. In the UK, two-thirds, or 60%, are in women, 90% for osteoar-

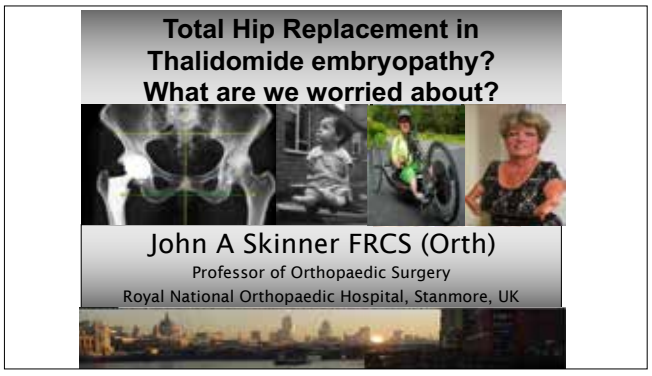


Fig. 1

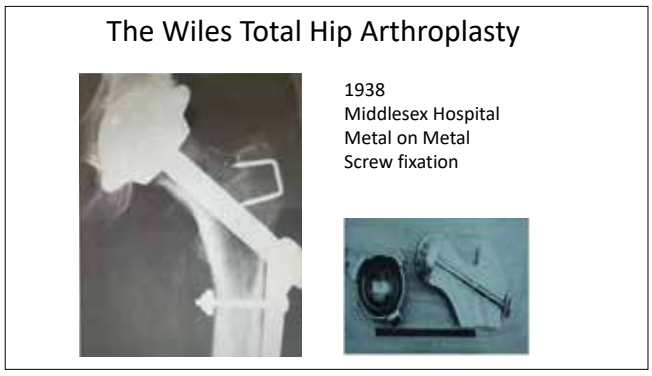


Fig. 2

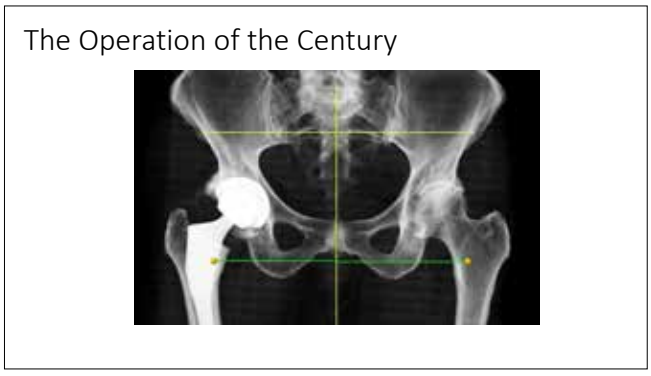


Fig. 3

thritis, and the BMI would be higher than that in the Japanese population, at 28. It's even higher for knee replacement patients, where it's over 30. (Fig. 5)

So, our challenge is to establish the role of hip replacement in TE. Is it worthwhile? Is it still effective in thalidomiders? Is it cost effective? Do we have any alternatives, or is this the best thing that we have, and can we adapt it to the wide spectrum of abilities and anatomies that we all see? (Fig. 6)

Hip replacement to an orthopedic surgeon is the best form of pain relief for arthritis of the hip. That's the prima facie reason to do a hip replacement. It does improve quality of life. It keeps people mobile. And I think keeping people moving is really important as they age, and that's for the whole population, not just thalidomiders.

And people do different things. The lady on the right is a farmer, and the lady on the left enjoys running, so we have to tailor what we do to patients' needs. (Fig. 7)

Arthritis, hip dysplasia, whatever it is, however you get there, the end game is arthritis, and it's painful and it's easy to dismiss; patients have a little bit of arthritis, and no one cares. If you say I've got cancer, everyone understands that and they care. You say you've got heart disease, you've had a stroke, people know what that means.

What we find is that patients feel a burden to their family, their friends, their GPs, their doctors; they feel that they are bothering them unnecessarily because it's just a bit of arthritis. (Fig. 8)

So we need to be aware of that. It's common. The UK has a population of 60 million people, 10 million of whom have arthritis of some form, so we lose 30 million working days a year. And almost one-third, certainly one-quarter to one-third, of all GP appointments have to do with musculoskeletal problems. (Fig. 9)

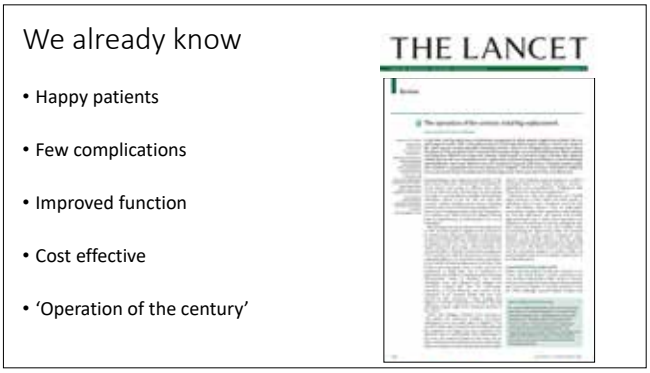


Fig. 4

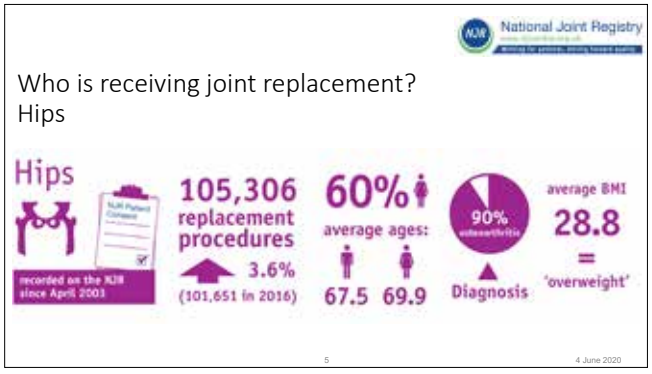


Fig. 5

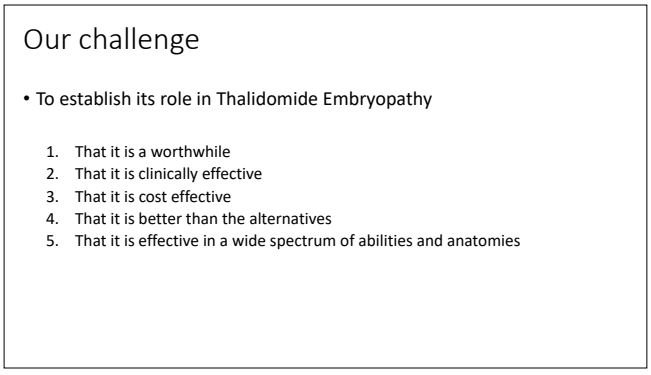


Fig. 6

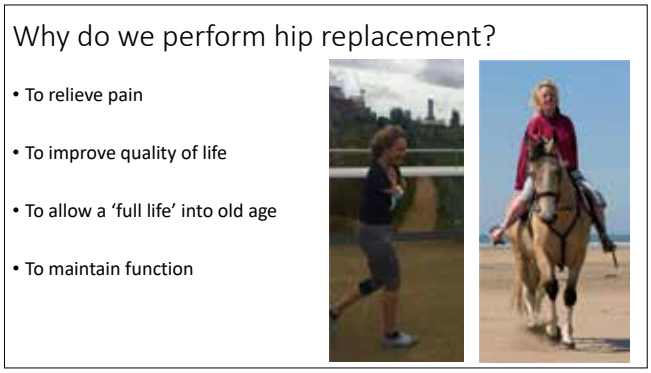


Fig. 7

Fig. 8

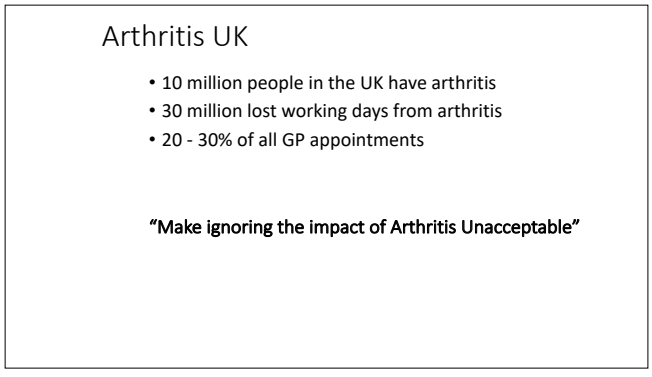


Fig. 9

What we've tried to do in the UK is to make ignoring the impact of arthritis unacceptable. I just wonder if we should look at the same in the thalidomide population because they are exactly the same. Is it acceptable to say that if you've got arthritis, you can't do things, you stop doing things? That's the bit we need to look at.

Patients waiting for hip replacement or patients in pain for whatever reason are miserable. It takes longer to do things. People adapt, humans adapt to whatever you put before them. If they are in pain, they stop doing things. Runners stop running, walkers stop walking, people stop going to shops, they avoid the stairs, they avoid driving in the end, and people just adapt. And we know that in the UK population, 32% of women and 25% of men in pain waiting for joint replacement have clinical depression. I think that's another principle that applies exactly to thalidomiders. (Fig. 10)

Does it matter? Well, it does. This is the Oxford Hip Score, which is validated, and goes from naught to 48. No matter where you are on the scale, if you have a hip replacement, your pain and quality of life gets dramatically better. But if we leave patients to get so disabled that they stop walking, they go off their feet, yes, they get better, but there's a ceiling effect, so we need to be cognizant of the fact that we don't want people to lose all muscle tone, become chair-shaped, become immobile, and lose cardiorespiratory fitness before we replace their joints. Because if we do it earlier, we can make them better. (Fig. 11)

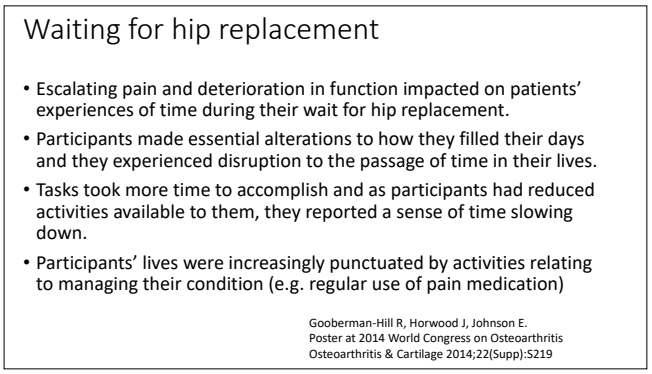


Fig. 10

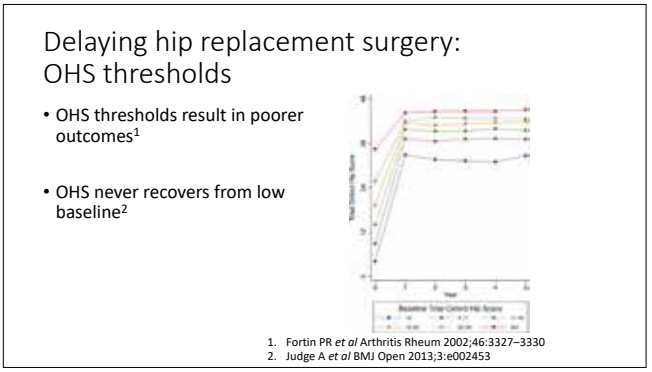


Fig. 11

But there's always a balance. We know that the quality of life improves, and it's maintained using any number of validated systems. (Fig. 12)

Most patients who are working will get back to work. Far fewer patients who've gone off work will get back to work. That's the same in anything, and is almost entirely understandable.

This graph shows leisure activities, the percentage of people finding it very difficult to engage in leisure activities, including sports, hobbies, social activities, and holidays. These are the fun things in life. After joint replacement, they get so much better.

We also know, Christina was the first person to mention it, that if you have a joint replacement, we hear from ISSA that 27% of patients have more sex, and 44% have better sex. It's difficult to have intercourse when you are in pain and disabled; therefore, it's an important part of the human existence to everybody. (Fig. 13)

Patients remain satisfied, 96% are still satisfied 13 years later. (Fig. 14)

This study involved half a million patients in the UK, which, for such a big operation, is a very low incidence of readmission to hospital within the first 60 days and reoperation. The people who have problems tend to be the extreme elderly, those with very low or very high BMI there's a bimodal distribution of BMI affecting outcomes and those living in poverty. We need to make sure that income does not

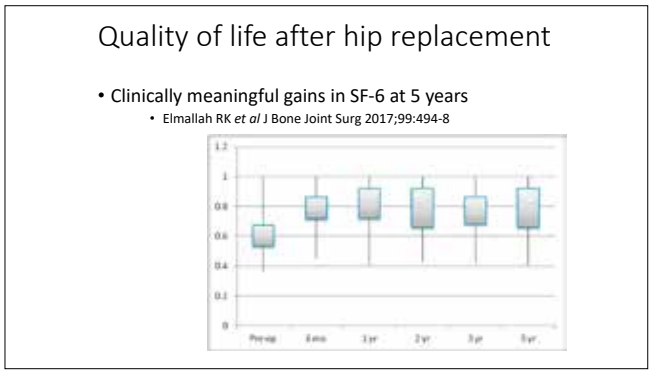


Fig. 12

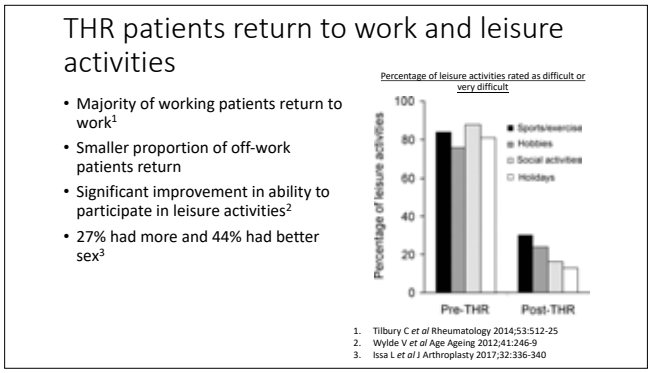


Fig. 13

predict and mandate outcomes.

Mental health issues, depression, as we have mentioned, dementia, and confusion, all of these things can lead to poor results. If you've been admitted to hospital, if you've got diabetes, let's control it. If you've got high blood pressure, let's control it. Uncontrolled, concomitant diseases affect outcomes, as do smoking and drug use. It's quite interesting that the patients who are now going on opioid medications worldwide have worse outcomes after joint replacement. When you get rid of the pain generator, they don't get off opioids; that's an important consideration as well. (Fig. 15)

Hip replacement is cost-effective. This is NICE (National Institute for Health and Care Excellence) data. It is £20,000 to £30,000, and this measures QALYs, or quality-adjusted life years. So, removing a brain tumor is £150,000 per quality adjusted life year. It's expensive, but if you've got a brain tumor, I'd put it that you'd want to have a go at it. Dialysis, it falls in this range, and no one will deny dialysis to a patient with renal failure. Coronary artery bypass when needed. Cataract surgery is very cost-effective to restore sight. But hip replacement is at the top of the list; per quality adjusted life year falls well within the NICE valuation. (Fig. 16)

Orthopedic surgeons know this, and we just need to make sure that other people realize how good hip replacement is as well. (Fig. 17)

Overall, 93% last 13 years, and 91% last 16 years. Even long-term, our patients we're talking about now are at that age, with 78% lasting 35 years, so it's got good durability already, and we believe it's getting better. (Fig. 18, 19)

One point I will just show in the NJR: survival. This is patients who are age 69–70. NICE expects 95% survival of the implant at 10 years. Among younger patients, thalidomiders are going to be about here, will have a higher revision rate. That's because if your joint is wearing out at a much young-

Fig. 14

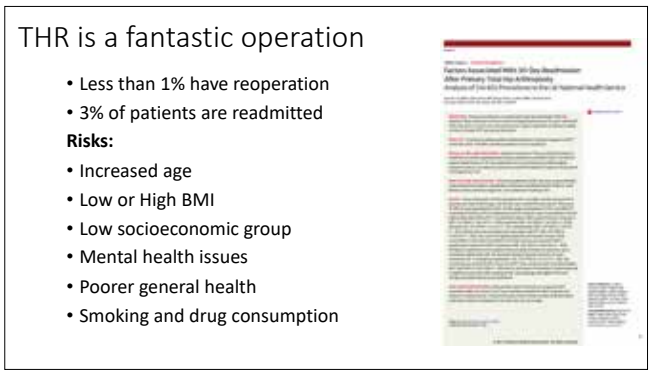


Fig. 15

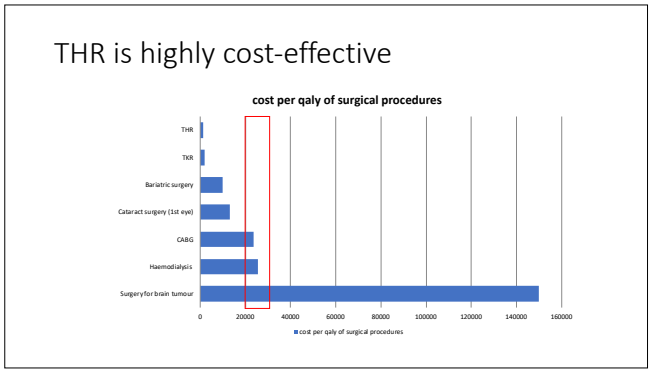
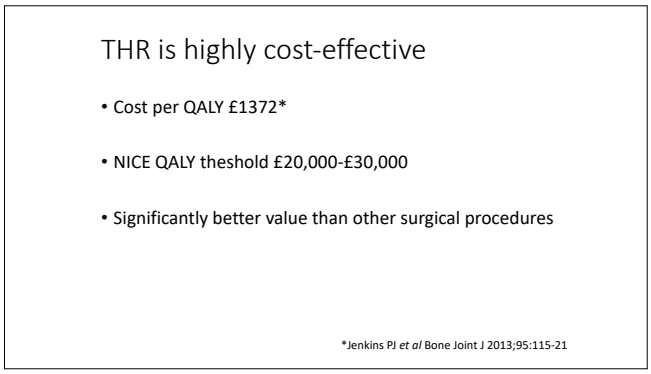


Fig. 16



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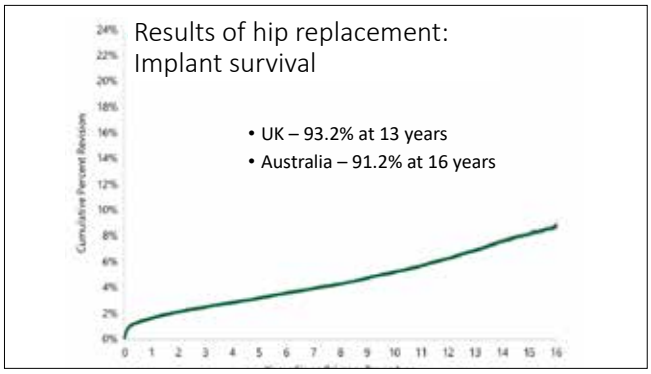

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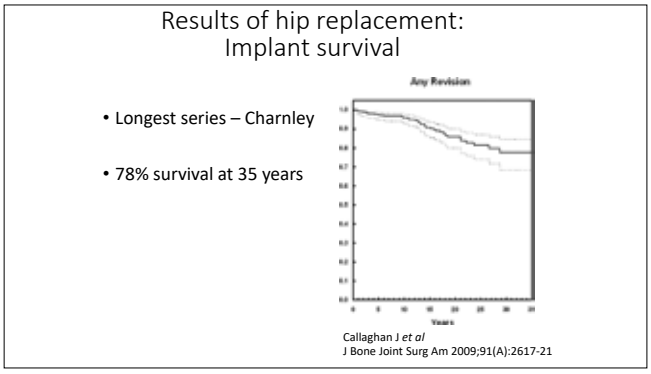


Fig. 19

er age, it's usually because the anatomy is not right. It's dysplastic or malformed, so the surgery is more complex and needs more thoughtfulness in planning to optimize fixation and the best possible result. (Fig. 20)

So, what affects function? We've got to fix to the skeleton, particularly with abnormal anatomy, we've got to make sure we can do that. We want the joint to stay in place. We've got to get a good range of movement; this is really important in thalidomiders, who use their lower limbs for much more functional things. (Fig. 21)

And that's important. Bearings we can work out, and we always need to consider pre-arthroplasty performance and what would we like to do after the hip replacement, so we can plan it. I said it's the best form of pain relief. It really can't be a good idea to resort to opiates and opioid drugs with addictive potential for a chronic condition with no obvious end. (Fig. 22)

So, in the UK, similar to everyone else, I think thalidomide was used from 1958 to 1961, and we think about 2000 babies were born from 1959 to 1962. We think half died in the first year, so there are 460, I am happy to take this figure of 464. Thus, our patients are now age 57 to 60. They are the new middle-age. (Fig. 23)

Regarding the patterns of deformity, everyone knows Henkel's work on the lower limbs, the full spectrum. But I would put it to you that for the patients I see and those I am operating on, this is the most common deformity: dysplasia. It's an almost normal joint that is weight-bearing, transmitting load, wears out, and presents a surgical opportunity to replace it and to relieve pain. (Fig. 24)

Thalidomide is still used in the UK; you know about myeloma. My dermatology colleagues tell me that it's still used for cutaneous lupus, and also recalcitrant itching or pruritus. But dermatologists are worried about it because of its potential to cause peripheral neuropathy. (Fig. 25, 26)

This is a video, I hope it'll play. I just want you to listen to this. Everyone is different, I think.

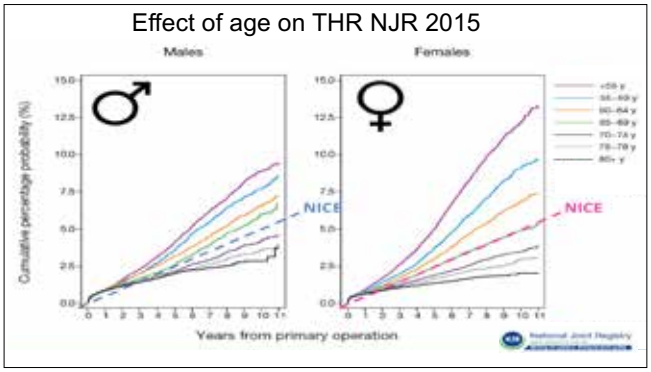


Fig. 20

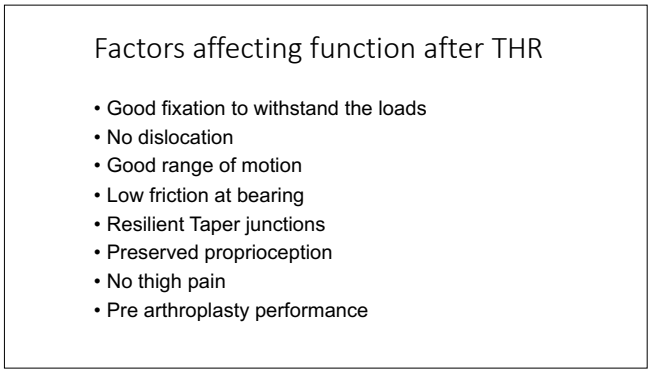


Fig. 21

Fig. 22

Fig. 23

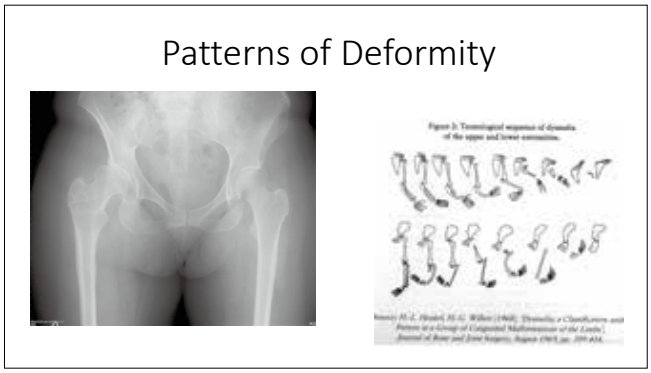


Fig. 24

[Video begins]

Some male thalidomider in this video

My life. I don't think thalidomide has affected my life in the sense that I was born like this. Therefore, I don't know anything else. I just get on and people think, oh, you can't do certain things, but you just adapt. You know, I've never seen it kind of getting in the way of anything I do, and that's been from an educational point of view or physical point of view, and I try and be active because I think it's extremely important, especially with my body as it is. I think the hardest thing about the challenge is that I've got to cycle 13 days consecutively in order to cover the 1000 miles, which on average work outs to about 80 miles a day.

People have asked me why am I doing this challenge. Well, I think one of the reasons personally is that if people tell you that you can't do it, then don't take that as your definitive answer because there's always a way around it. You might not be able to do it their way, but you can do it your way. I've got no right leg, I've got two short arms, and my hands look like this, but then again, limitations shouldn't stop you from doing anything in life.

[Video ends]

John Skinner: I think most of us would say he's a fairly elite athlete. I just feel sorry for the dog; I hope the dog is not going to do the whole 1000 miles. So dysplastic hips, again, it's a spectrum condition from mild, like I showed in the first X-ray, to this, which is a high dislocated hip, which is part of the same condition. (Fig. 27)

So, a little bit about how we classify these. What we're talking about is the percentage of subluxation of the femoral head from the acetabulum, so if it's within the acetabulum, it's type 1, type 3 is between 75% to 100% subluxated, and type 4 is completely dislocated. (Fig. 28, 29)

I think, from the surgical point of view, it is classified as dysplastic, it's still in the socket, low dislocation, and high dislocation. I think any classification certainly in surgery only needs three arms good, bad, and very bad and I think that works. (Fig. 30)

So dysplastic, low dislocation, and high dislocation with the sockets down here. (Fig. 31)

We have different ways to reconstruct them depending on where they are, and I think it's probably easier to show you that. So we can get, the natural acetabulum is here, we can

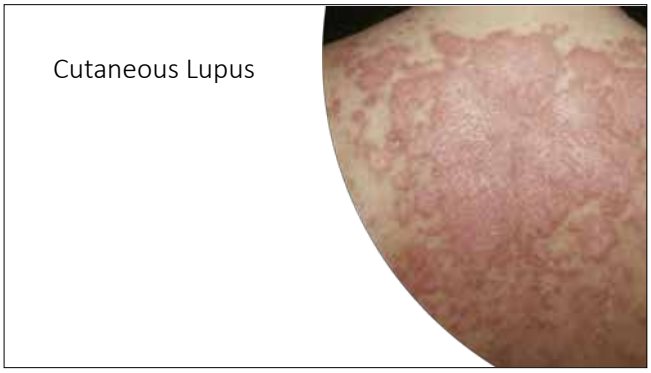
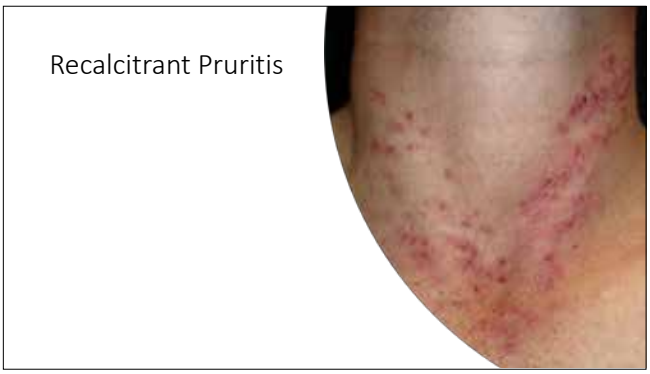


Fig. 25



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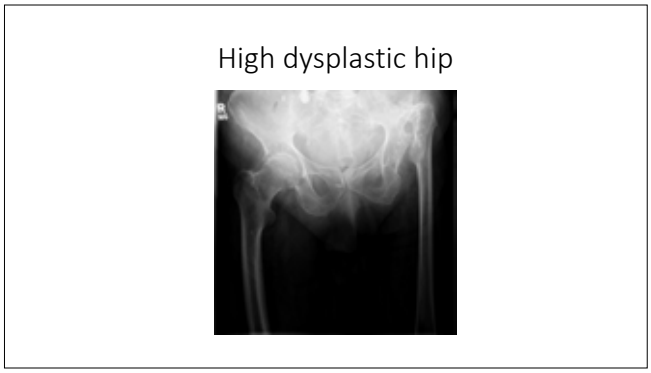


Fig. 27

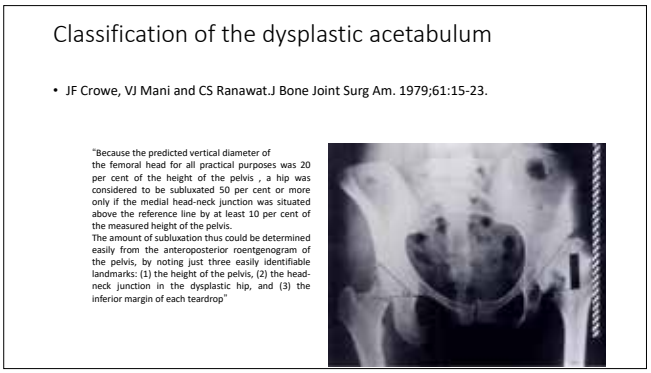


Fig. 28

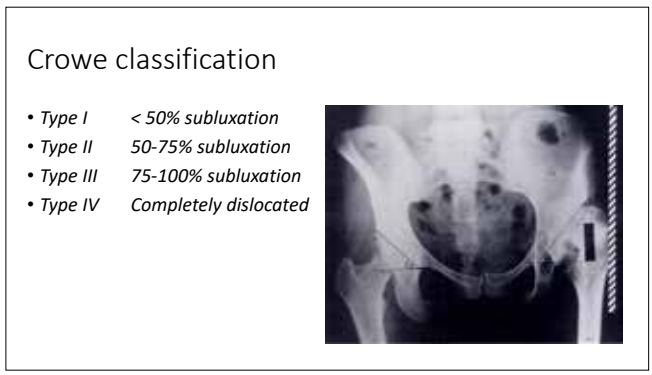


Fig. 29

go for a high hip center, put the femoral head, put the socket where the femoral head has always been. Technically, it's the easiest to do. Mechanically, it's disadvantaged because you don't get the muscles, the abductor muscle's moment arm. (Fig. 32)

If there's no roof, we're going to throw the femoral head away so we can use it as a bone graft and screw it back on, or we can build up the anterior wall and the floor with bone graft, so there are various things that we can do. (Fig. 33)

The femur, I think, the point is that the femoral neck, instead of pointing sideways, is anteverted and is pointing forward as part of the deformity, and the bones are small. Usually, it's a whole field defect in the limb, and the leg length also, the legs are maybe the same length, and dislocated or maybe short. I mean, usually, we can bring it down about 4 cm without getting too worried about the sciatic nerve. (Fig. 34)

Dysplasia and hip replacement are relatively straightforward because the socket is shallow, and there's a screw to increase fixation; that will work quite well. Low dislocation, the problem with this socket, it doesn't have a roof. [Unclear], it's got a roof where you could put a socket underneath, but this one doesn't. So this is the native femoral head here, and what we do is screw the femoral head back on, form a roof, put a socket in, and fix it. And this is a porous surface, which the bone on grows. (Fig. 35, 36)

We've got a high dislocation, so for both of these hips, the natural socket should be here and here. They are both up, and this femur is also angled and deformed, and this is what we see. This is where the femoral head has been articulating, and this is where it should have been. We can make that, shape it out with reamers to make it take a socket, and then put it down there. If you're an orthopedic surgeon, that is beautiful. (Fig. 37, 38)

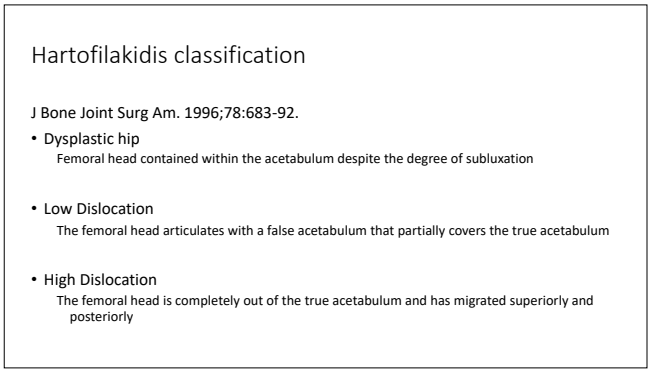


Fig. 30

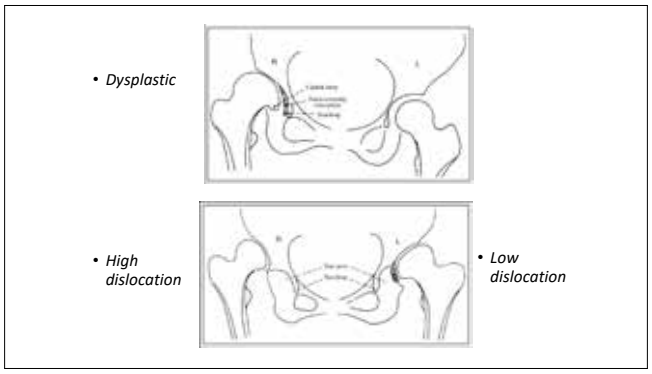


Fig. 31

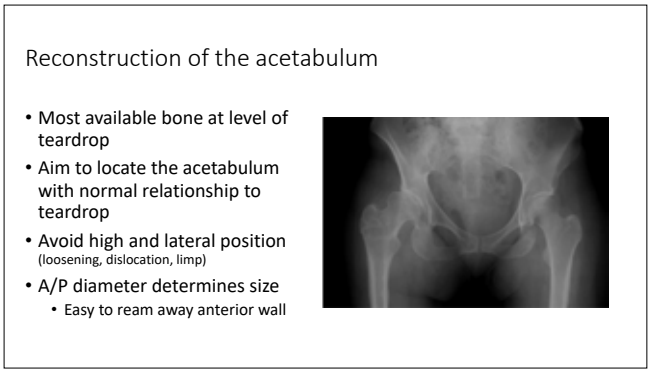


Fig. 32

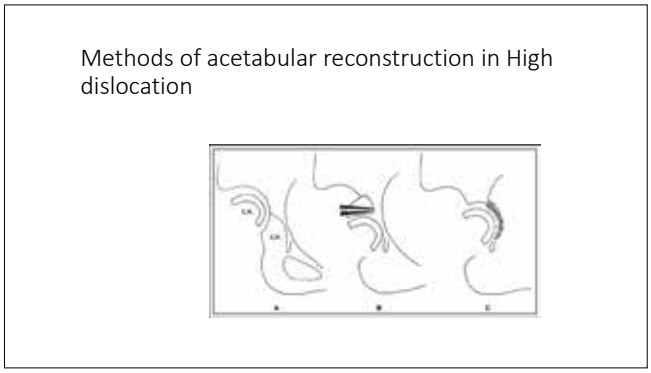


Fig. 33

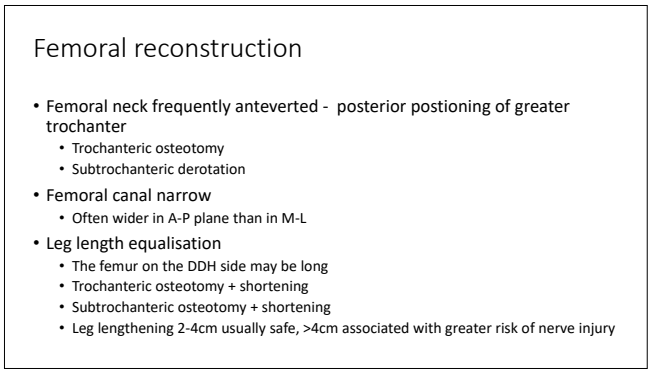


Fig. 34

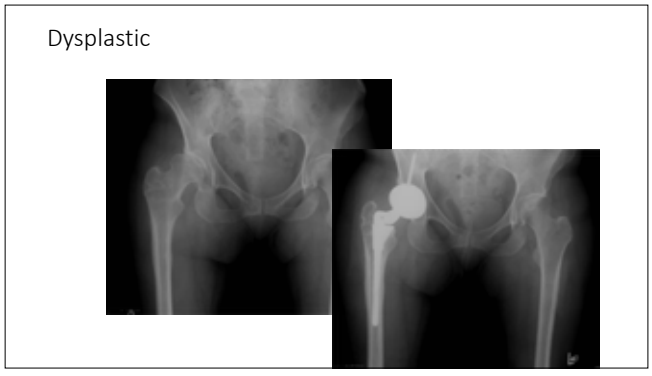


Fig. 35

As an orthopedic surgeon, an important part of the operation is to always admire the X-rays. So the hips have been brought down from there into here, that bend in the femur has been an osteotomy to straighten it as well, so we've restored good anatomy, it can be done. (Fig. 39)

This is a problem, so this socket is high dislocation and the leg lengths are equal. So, if I bring that down to here, I am going to lengthen the leg by 5 cm. Patients do notice if you do that to them, and they don't like it, and it hurts. (Fig. 40)

So, what we can do is, to plan it beforehand, to take out a disc of the femur of whatever we've measured, so the 5 cm, shorten it, and then use this as a bone graft around it. And you see, several years later, it's incorporated, and the patient is walking well. And because we've reconstructed the abductor arm, avoiding sciatic nerve palsy, the rehabilitation potential is great. It takes time, but it can be done. (Fig. 41)

The other one is when X-rays look like this. It's because the femoral necks are pointing towards you, they are very anteverted. This is a scan or an X-ray, very similar to one Dr. Kayamori showed yesterday, with really anteverted dysplastic hips. That's the epicondylar axis and the femur; that's almost 70 degrees of anteversion, whereas it should be 10 or 15. (Fig. 42, 43)

And with that, we can do a derotation osteotomy, twist it around, and reconstruct the anatomy again. So with planning, we can work out what we're doing. This is a patient who had some sort of operation in childhood with a metal plate, presumably some sort of osteotomy. Unfortunately, that's infected. (Fig. 44)

She has very little below here, and an extension prosthesis. She walks with a limp, and she manages. She has full employment, despite her upper limb defect. (Fig. 45)

This is the sinus, which is still there, so it's low volume. This is about a day's discharge. She manages it by changing

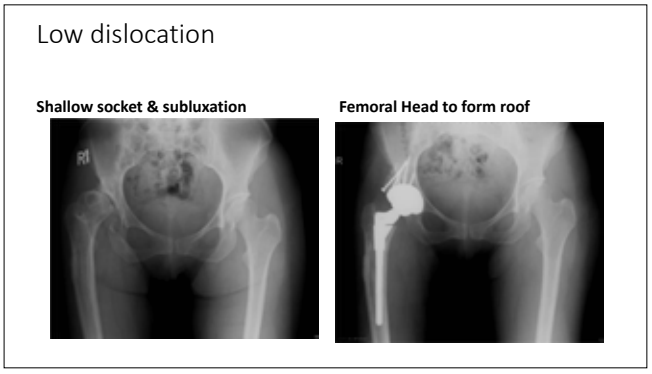


Fig. 36

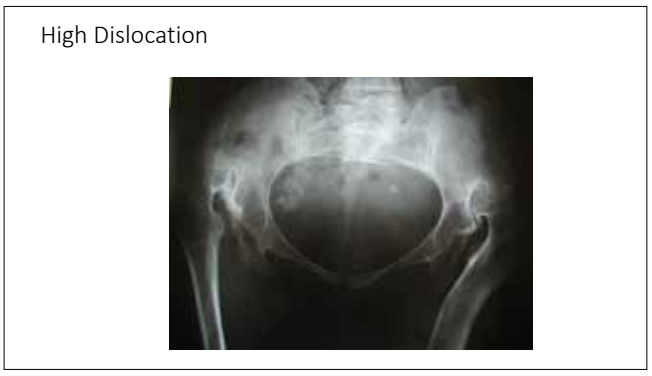


Fig. 37

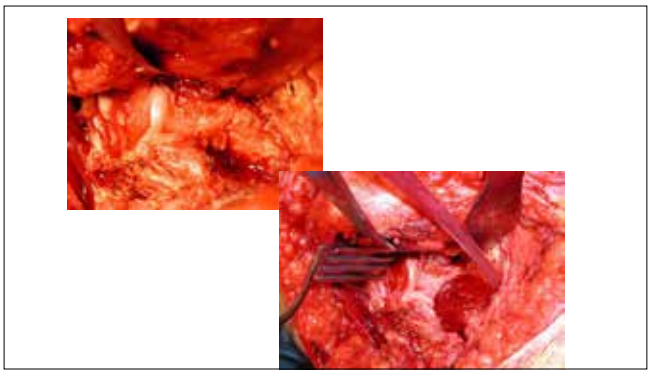


Fig. 38

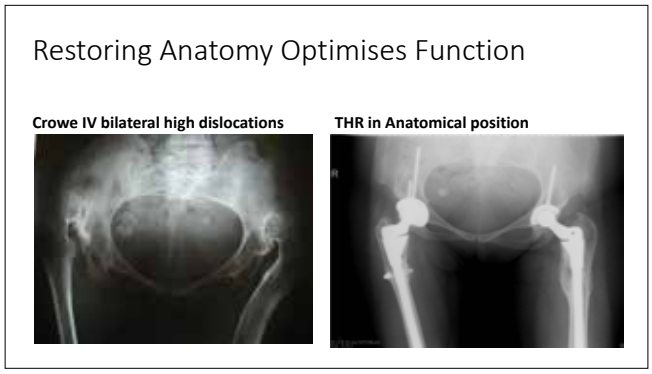


Fig. 39

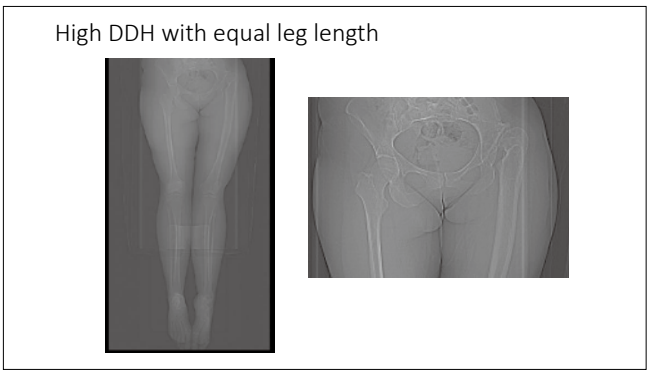


Fig. 40

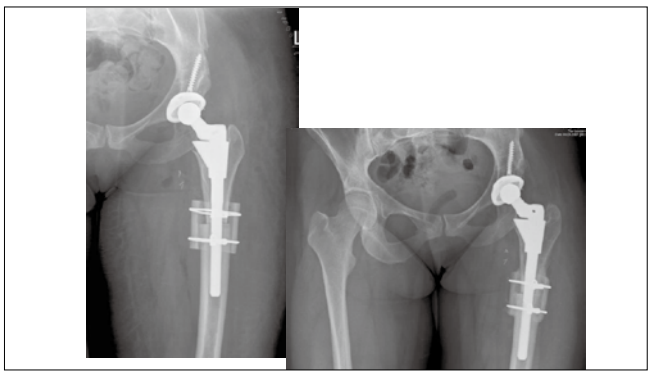


Fig. 41

it. It's not particularly painful, despite the hip looking like that.

So, I can't perform a hip replacement because it's infected. I would be wrong to do so anyway. (Fig. 46)

This is how she walks. It's not an elegant walk, but it's functional and with a cane, she can walk normally in full employment. (Fig. 47)

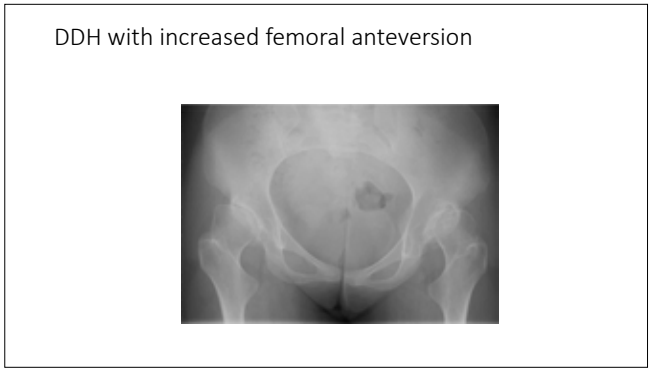


Fig. 42

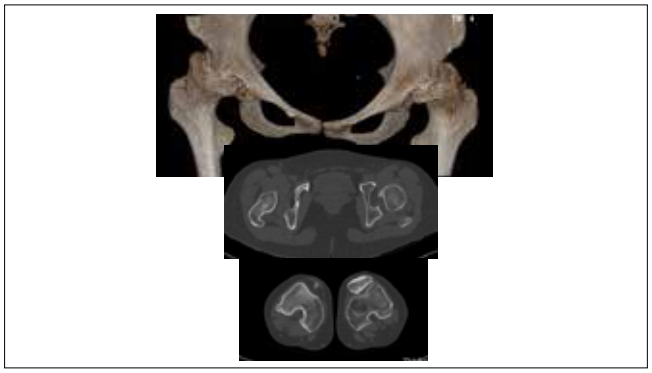


Fig. 43

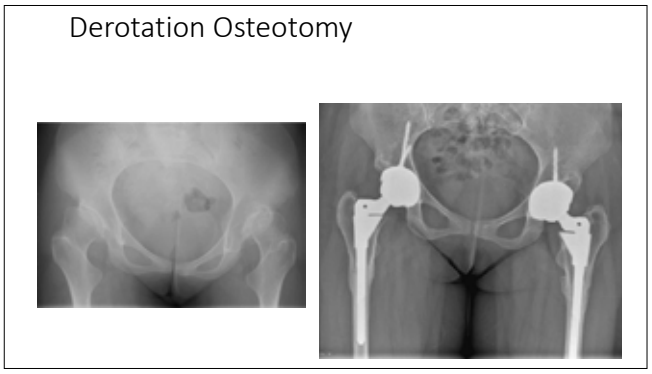


Fig. 44

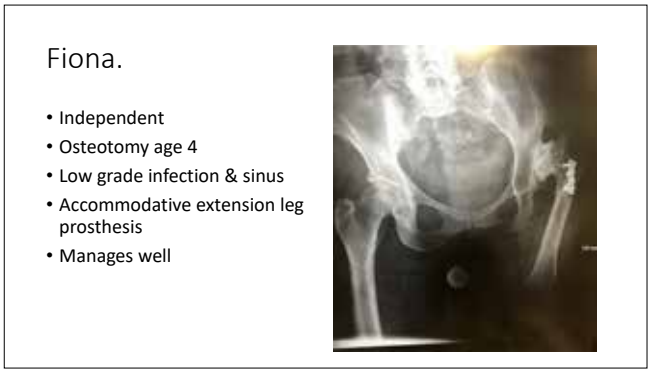


Fig. 45

This is a lady that you've seen before. This shows bilateral high dislocation, with poorly formed hips. But they seem to be working. This is her website. It's called "Flid-Fit", and this is what she puts on the website. She's amazing. This lady is small. She's 1.42 m tall, and she's lost 26 kg over time with exercise. She has a lifestyle website where she gives advice on diet and exercise. (Fig. 48, 49)

Fig. 46

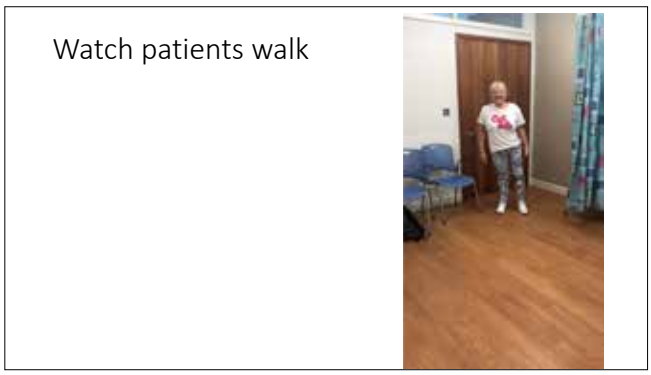


Fig. 47

Fig. 48

Fig. 49

These are those hips on an antigravity treadmill. We can't, we would never treat an X-ray. I think that's the most important thing we learned with these conditions in thalidomiders: you treat the patient. I am not going to make her much better than that, but I can make her a lot worse than that if I do a hip replacement, things don't go perfectly, and she gets stiff. So we've got to watch what we're doing. (Fig. 50)

Assess all patients individually. We have to know what the patient's goals are. There's no point in going for what my goals are or what Dee thinks they ought to be; it's what the patient wants to achieve. As well as how good their pain control is and what they want to do. A lot of thalidomiders are flexible; they've had to stretch and get increased movement and range to maximize their potential. We need to know these things because flexibility can be good or can be bad in joint replacement. We don't want them to have a dislocation. (Fig. 51)

What do human joints do? Well, very few of us do this, perhaps we are better in line, but the abduction, adduction and the rotation we don't do. A lot of thalidomiders can do this, and have learned to do this because they use lower limb function to use what's normally done with the upper limbs. So again, using detailed examinations, we need to know what they've done. (Fig. 52)

This child, I'd love to, we need to reproduce this, making it relevant to thalidomiders; this is what they can do. Put your foot on the floor to tie a shoelace, 124 degrees is the flexion you need. If you sit and bring your foot up to your lap and cross your leg, you need less flexion, but more rotation. Picking up objects, squatting, various things, you need 122 degrees. These are things we're looking at. You don't need so much flexion on stairs, but you do need some. So we need to work out what the goal should be. I'd love to do this now for thalidomiders and their function and what they do. (Fig. 53)

So we can do things. These are femoral heads, 28 to 36 mm. (Fig. 54)

The bigger we make the femoral head diameter, the greater the functional range of movement can be, and that's important. It's not just that, it's also the orientation of the cup. You set it to the maximize useful range of movement for any particular patient.

With 36 mm cups, it's always said that they wear. But materials have improved, so modern bearing surfaces are

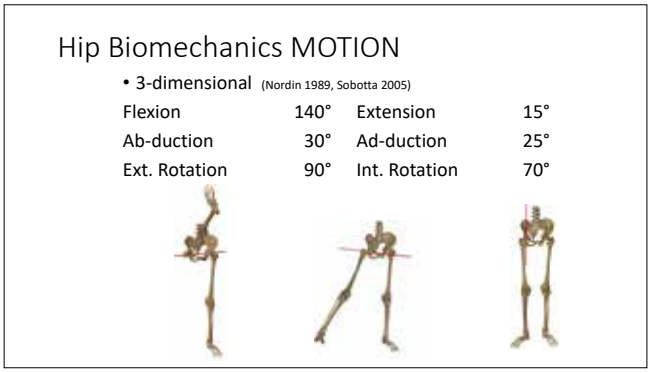


Fig. 52

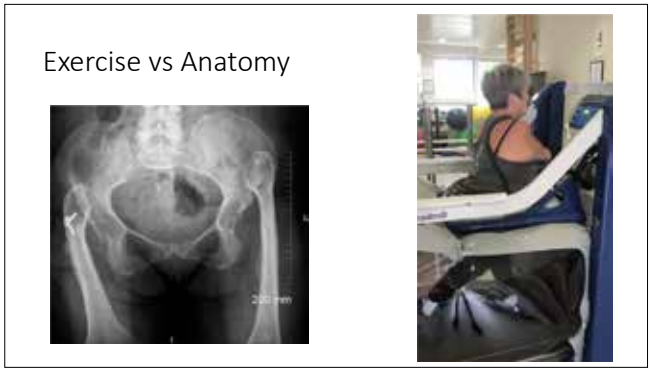


Fig. 50

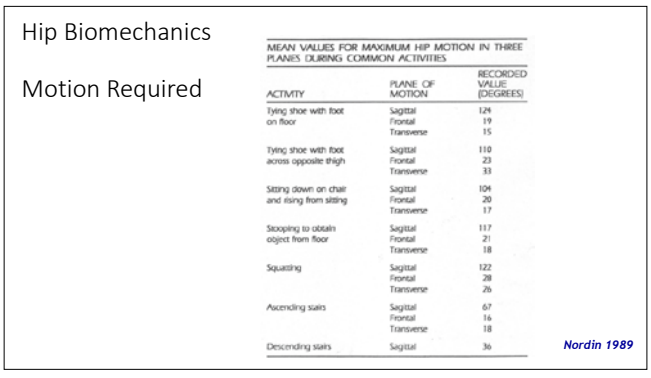


Fig. 53

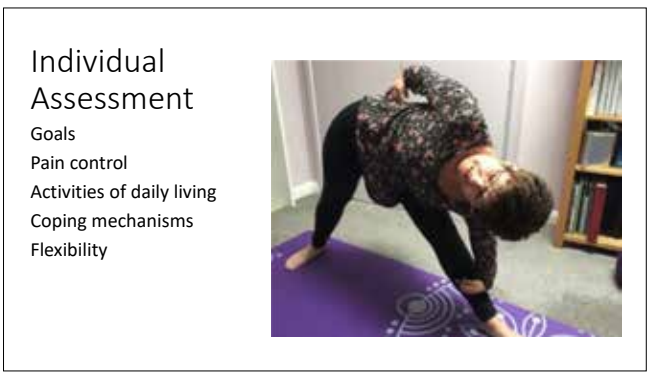


Fig. 51

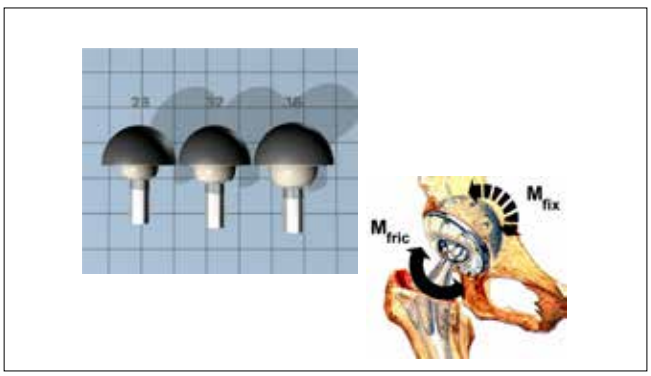


Fig. 54

wear-resistant. This is a tiny volume, you have ceramic on ceramic bearings. So implants have improved, and we just need to know what we are doing. (Fig. 55, 56)

So what are people doing? Working. Again, this lady works as a telephone volunteer with The Thalidomide Trust. (Fig. 57)

This guy is an actor and is amazing. He spent his first few years of employment as a rock drummer. He was a drummer in the opening ceremonies of the 2012 Olympics. He's an incredibly accomplished actor, and this is him playing Shakespeare's Richard III. (Fig. 58)

What else are people doing? Sue, this lady is a sports masseuse. Her arms aren't up to it, so she's learned to be incredibly skilled. She's in demand using her feet for massage, sports therapy, and relief. So people are doing amazing things. Everyone is different. (Fig. 59)

This is a patient with, from an orthopedic point of view, that's relatively straightforward. It is dysplastic. There are some considerations. We need to look at the femoral neck version. But this is end-stage arthritis in a dysplastic hip. (Fig. 60)

This is our assessment. This lady has short phocomelia with rudimentary fingers and no upper limb function. She has osteoarthritis from dysplasia, bilateral agenesis of upper limbs, and right-sided deafness due to TE.

So the first thing they say, it's anticipated that she is going to need 10 to 14 days. She's going to be in a hospital for a long time. They've noted that she's independent, has good trunk control, can go from sitting to standing comfortably, and can transfer. How does she shower? Well, she gets in the bath, where she has a stool, and she holds the shower head with her left foot. She independently toilets, despite having

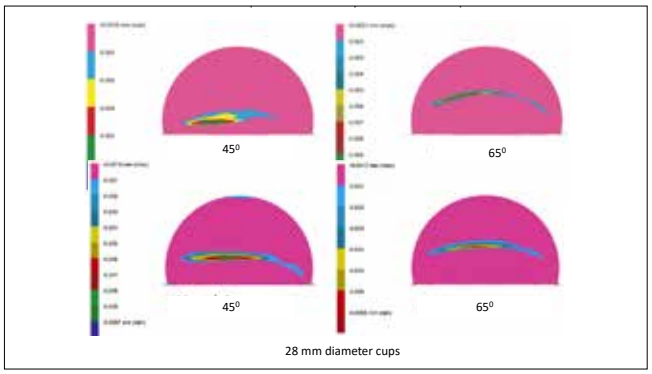


Fig. 55

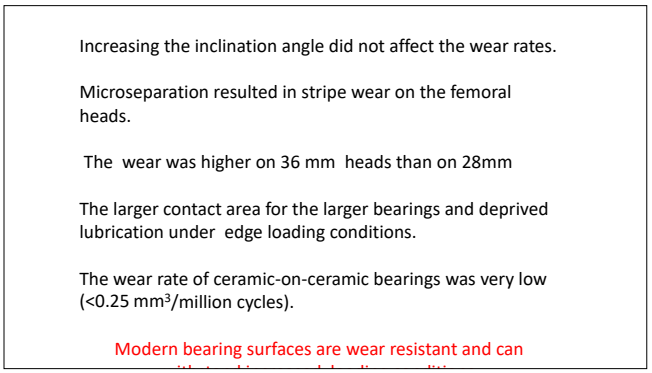


Fig. 56

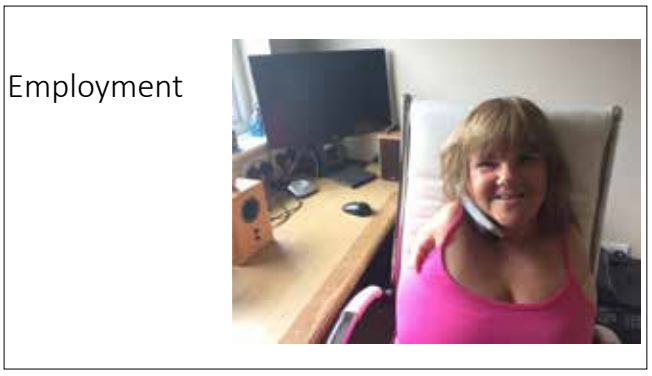


Fig. 57

Fig. 58

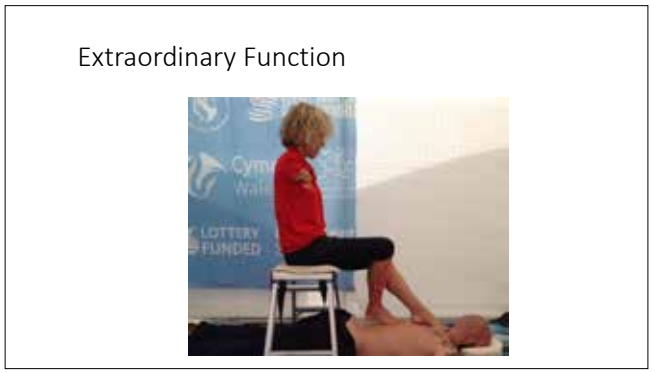


Fig. 59

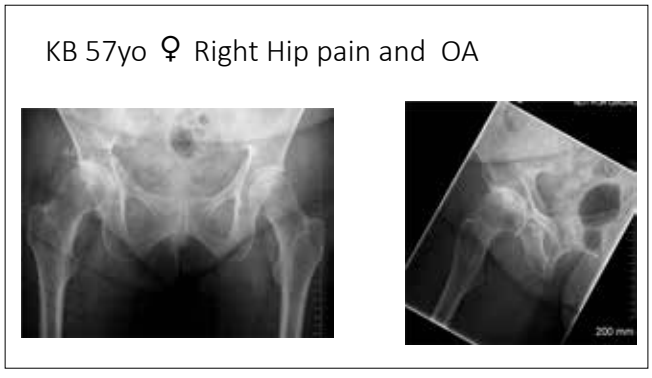


Fig. 60

no upper limbs.

For meal preparation, she still does some cooking tasks, and she can chop food with her feet while sitting on the worktop. My therapist said this may not be a good idea in the early stages after hip replacement surgery. (Fig. 61)

So, we need detailed plans what's going to happen and what could happen before surgery. What we've done, we've planned the position. If you make the cup slightly more vertical, you get more flexion, and if you antevert it slightly more, you can affect the range and position. She's got very good function and is still independent. (Fig. 62)

This is a different case. This is a quite significant problem on the right. Everyone thinks with hip replacements in thalidomiders, that this is where we are going to be doing joint replacements. I don't think I can do much for that, but this side, which has DDH (developmental dysplasia of the hip), there is a very poorly formed hip that has become painful. He's walked poorly all his life. He's got an extension prosthesis that he uses, but he's independent. He's had his L5-S1 segment fused, and this was painful. (Fig. 63)

So what we did again, we did a hip replacement slightly higher. I haven't brought it all the way down because I needed the bone to fix and to get onto here. You can see spinal fusion, good position, and good function. This was difficult early on. This was not a "fire and forget" operation. We had to bring him in for inpatient rehabilitation to optimize and maximize his function and to get his abductors working, because they never really worked in this sort of position. We have to do that. Sometimes with these patients, you have to plan and expect to do that to optimize function. (Fig. 64)

Another lady without upper limbs and really quite severe arthritis had come a long, long way before we did that. And again, because it's slightly tentative fixation, adding multiple screws, we've got to get primary stability for this


Royal National Orthopaedic Hospital NHS

THERAPY PRE-ASSESSMENT REPORT

Transfers:

Bed:

Chair:

Toilet:

Bath:

Management of ADLs:

Self-Care:

Toileting:

Meal Preparation:

Fig. 61

Fig. 62

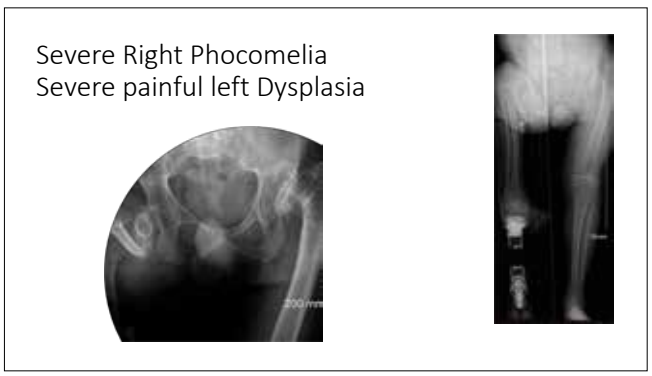


Fig. 63

Fig. 64

Fig. 65

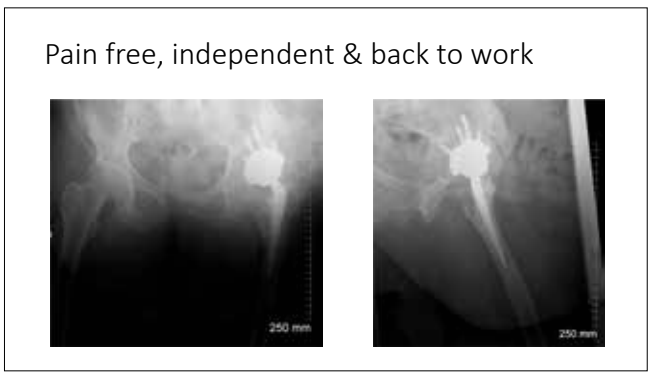


Fig. 66

implant. It's a small stem, but it has good function, and she was back to work 6 weeks after hip replacement surgery. (Fig. 65, 66)

What can go wrong? Joint replacements can be painful. This is a variation of a SPECT-CT image with some pain. That's probably loosening of the socket. We need to avoid that. (Fig. 67)

Dislocation is a disaster if it happens. We've got to make sure it doesn't happen. We haven't seen that in the ones we've done, thankfully. This is not a thalidomide patient, but just an example of dislocation. It can happen to anyone. The incidence is somewhere between 1% and 5%. (Fig. 68)

Again, regarding the increased femoral head size, we are making bigger heads to maximize the range and minimize this. (Fig. 69)

We're also using new technology and patient-specific instruments whereby we can use custom-made guides to show us where to make the femoral cut and how to position the acetabulum in the right place. (Fig. 70)

We can make 3-D models, 3-D printed models of the hip itself to check the anatomy and rehearse the operation. (Fig. 71)

We do CTs, we get cross-sectional images of the hip joint, and we can plan it. The important thing is segmentation with CT. This is the engineering part and the computer graphics part. You need to be able to separate the femur, the ball from the socket, and to plan it, to plan where you are going to put the femur. (Fig. 72, 73)

And so, again, this is the anteversion view. The top end of the femur transposed on the bottom. This is the epicondylar axis of the knee. The femoral head is usually 10 to 15 degrees anteverted from that axis. We can plan where we are going to make the neck cut and where we want to put the femoral component so we restore the center of rotation. (Fig. 74)

We get guides that fit. They match the surface and hold

Fig. 67

Fig. 68

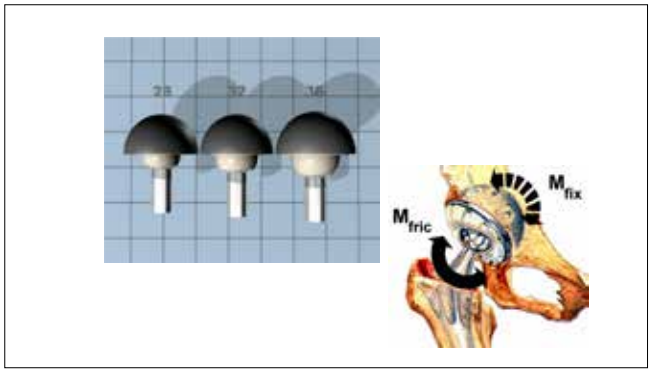


Fig. 69

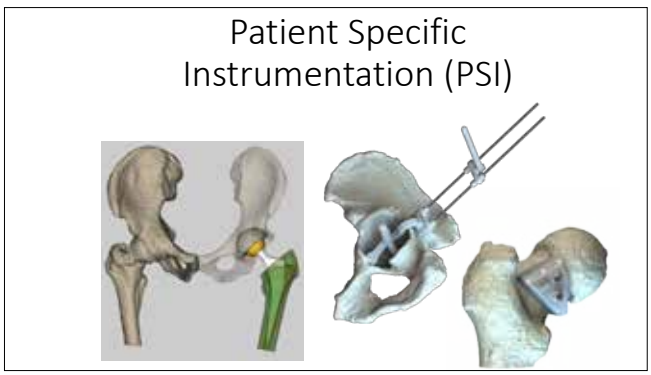


Fig. 70

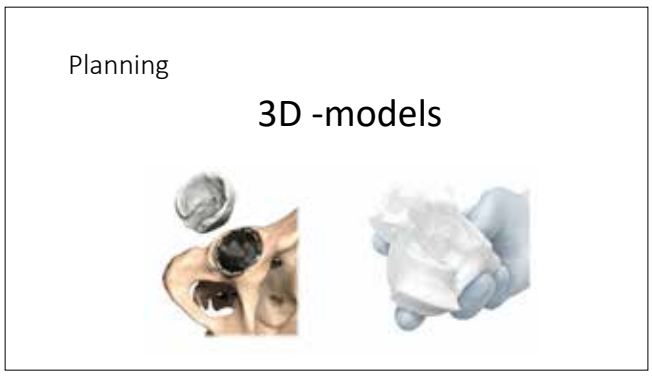


Fig. 71

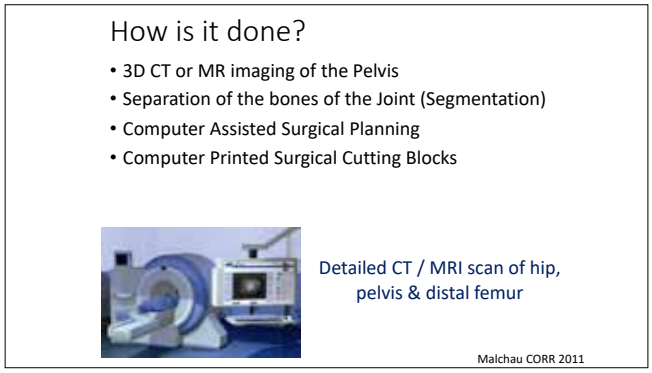


Fig. 72

them with screws, and then make the femoral cut for you and tell you exactly where you're going to be. (Fig. 75)

The ones in the socket are slightly more difficult to use, but by using this guide to put these pins in, we can put something over there that has exactly the right angle that we need to mimic putting the acetabular component in. (Fig. 76, 77)

This is something interesting we're working on with EOS scans that has real applications for planning surgery in thalidomide patients. This is a sitting and standing low-dose CT scan showing what happens to the angle of the hip going from sitting to standing. What we are planning is a series of thalidomide patients without upper limbs to see what position they put their legs in when they are brushing their hair or teeth with their feet, because that's a useful function to them. If we can work out the optimal position in which to place these components, then that's got to be a good thing to do using real-life information to plan function in the future. (Fig. 78, 79)

This again, is a thalidomide patient. This lady has no functional arms, phocomelia, with digits only, and really quite severe dysplasia and arthritis. She's independent, she drives herself, lives alone, and functions amazingly well, so she's got a lot to lose. But her pain is becoming unbearable. (Fig. 80)

We planned her anatomy, which is a problem. If you look at where the anteversion is, it's 66 degrees anteverted. Now that's incredible, it should be much lower than that. We've got to plan that out of the operation somehow, and where we are going to put the components. We planned 40 degrees of inclination and 20 degrees of anteversion. (Fig. 81)

Using technology mobilized at 2 days postoperatively,

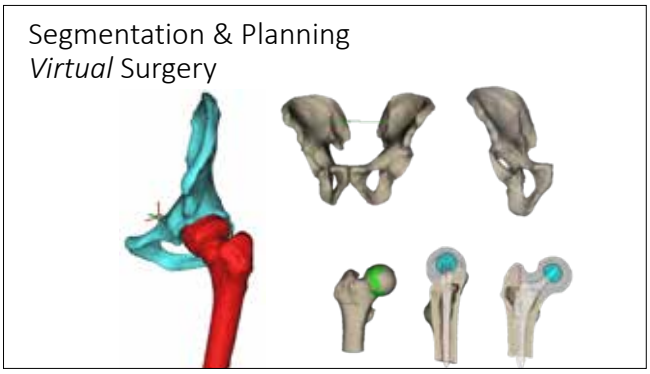


Fig. 73

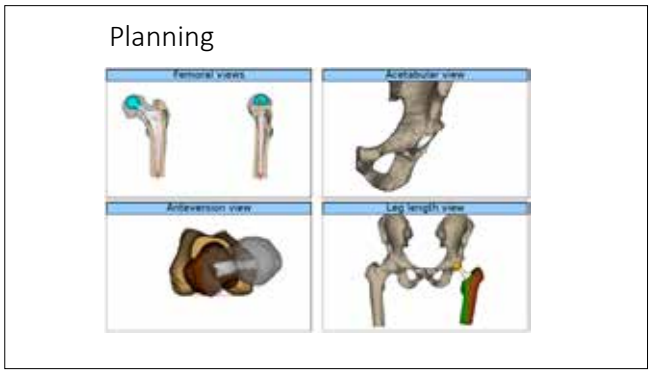


Fig. 74

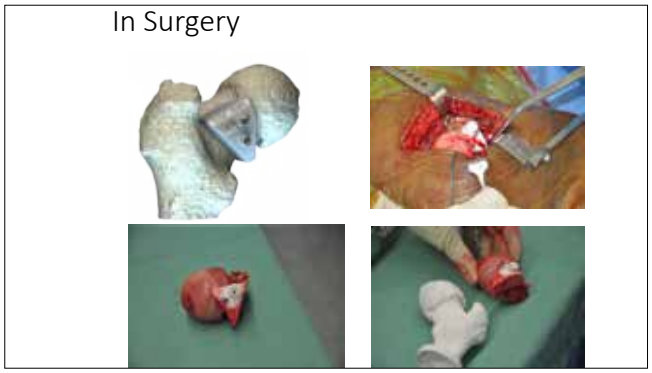


Fig. 75

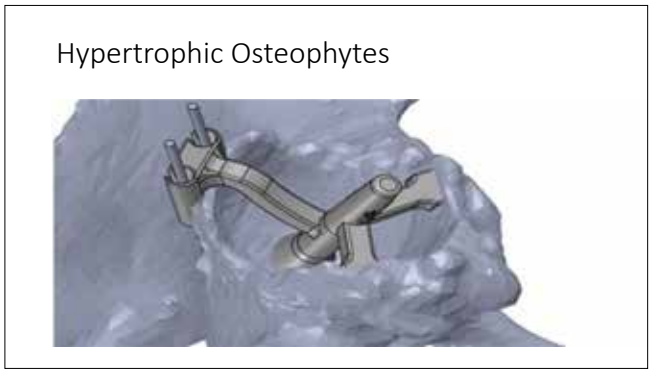


Fig. 76

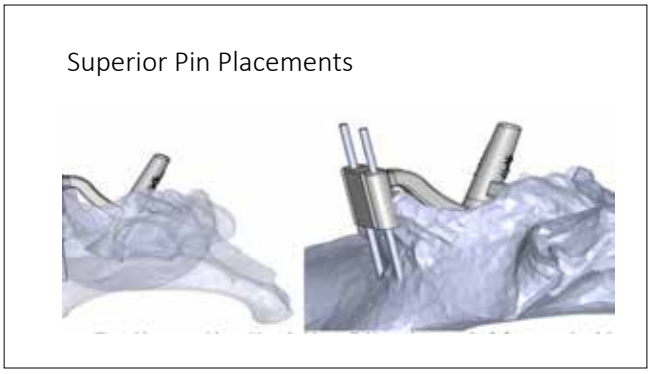


Fig. 77

Fig. 78

we got her walking pretty quickly. She was back driving her adapted car at 6 weeks. So if we get it right, patients get it right. I don't know if I mentioned it, but the last lady, for whom we predicted a 14-day stay, went home on the third day. So once it's right, the patients will go home. We'll plan the other side of this to get equal leg length. (Fig. 82)

Regarding results, dysplasia has been harder, but we've seen good 10-year survival for dysplastic hips. High hips have had problems in the past with fixation and what people were trying to do. We are looking at this. We haven't had any problems, but we're following our patients and we hope it's going to be much better than this. But yes, for difficult anatomy and difficult surgery, probably not everyone should be doing these operations. (Fig. 83)

So, for hip replacements in dysplasia and thalidomide patients, you really got to do careful preoperative planning. These are small components. You've got to make sure that you've got them, and if necessary, have them custom-made. That can be done, and they can be 3-D printed. (Fig. 84)

The stems are small, and the canals are narrow; it's a reduction of the whole limb. And you've got to watch nerve tension. Sciatic nerve palsy is very disabling and painful,

Fig. 82

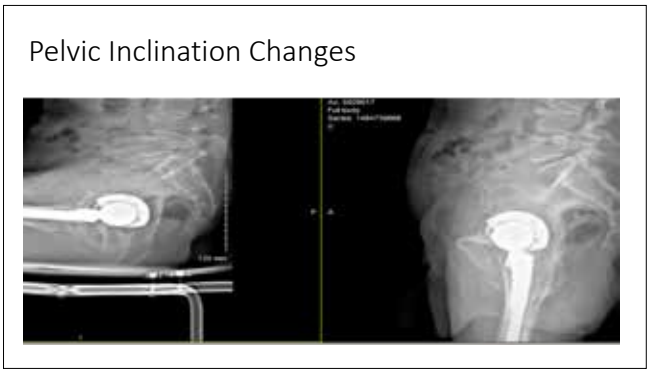


Fig. 79

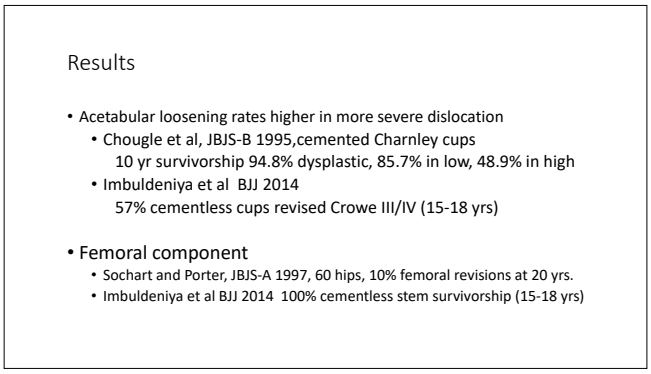


Fig. 83

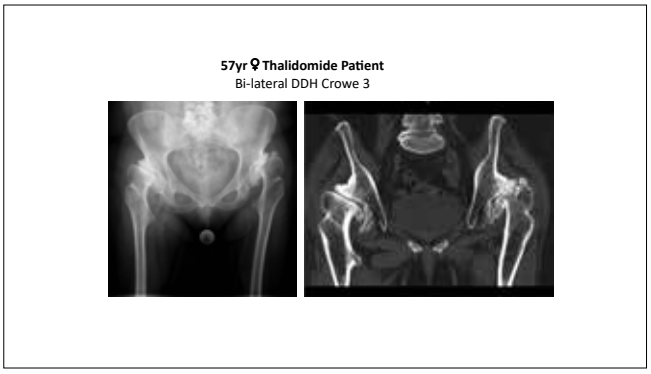


Fig. 80

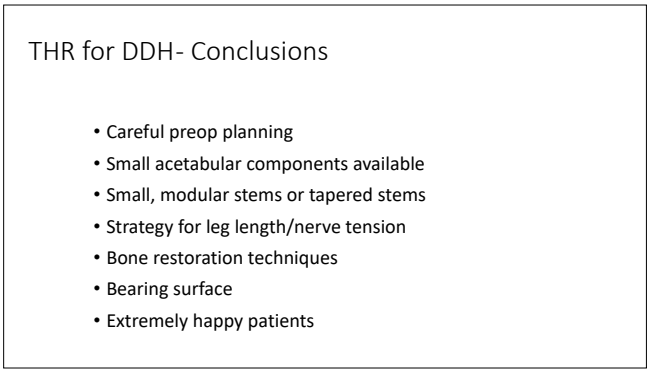


Fig. 84

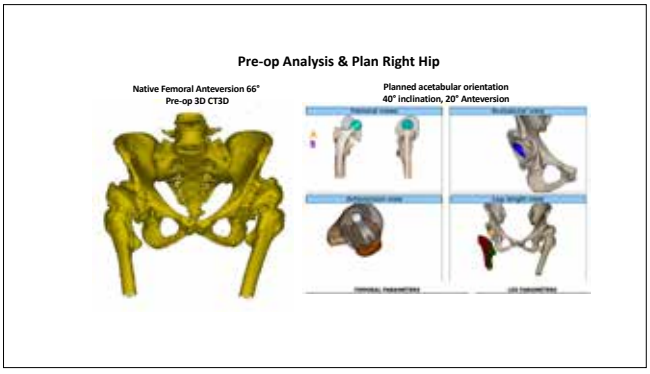


Fig. 81

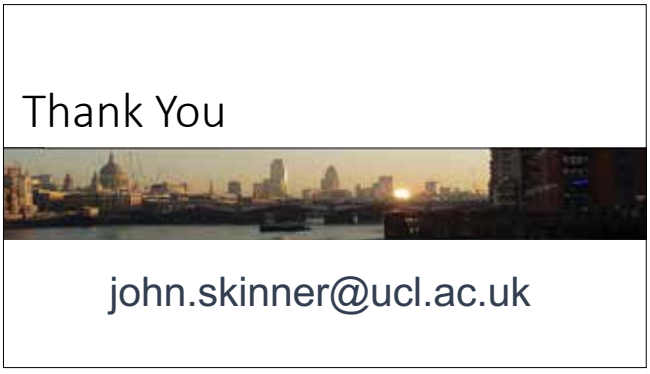


Fig. 85

and patients want equal leg length. We need to restore bone when necessary. We need to have bearings that are reliable and workable and will last hopefully the life of the patient, but certainly the life of the implant. And we know that if we get it right, these are some of the most satisfied patients. Thank you for your attention. (Fig. 85)

Q&A

Dee Morrison: Thank you, Professor Skinner. I can see why the staff think you are the best now. Any questions?

Yasuo Yamauchi: Thank you very much. Very interesting. I think I am the oldest one here in this room. I am 87 and I had a chance to visit Sir John Charnley in England. I was quite impressed by all he was doing there. First, the surgery itself, Charnley's method. Second is the operating room he was in, what we call greenhouse.

So considering that, my questions are: 1) In England, are you still using Charnley's original method, or is it sort of an old story? 2) Is his greenhouse system still popular in England? 3) Is Charnley's approach cutting the greater trochanter still valid? 4) One of the X-rays showed what my friend Tom Aitken in Grand Rapids called PFFD (proximal femoral focal deficiency). Is there any good measure to treat patients with proximal femoral focal deficiency? Thank you very much.

John Skinner: Thank you. I mean, of course, you're right. Charnley was the father of all this work and the pioneer. And he did an amazing job. Not only did he work out the materials, he found that poly(methyl methacrylate) was a way of fixing implants to the skeleton. But when he started, the infection rate was over 10%. That was a disaster, and infected joint replacement is still a disaster.

And yeah, I mean our operation theaters, we are neurotic about it, and yes, we do use, what we use is laminar flow, or ultra-clean theaters, and we have, there's a very clear system where the patient will be, where the instruments will be, and you have everything within the, it's based on the greenhouse effect. We don't actually erect a greenhouse in the theater anymore, but we do have Perspex dividers at the ceiling level that come down, so that shows where the laminar flow area is.

So you are absolutely right. All patients get prophylactic antibiotics in advance. All patients are swabbed in advanced for MRSA and Staphylococcus. Those that are positive are treated prior to surgery, and we are very meticulous about scrubbing. If the trainees don't scrub for the right amount of time, they are sent back to do it again. The next question was, I am trying to remember, what was your next question?

Yasuo Yamauch: The approach.

John Skinner: The approach. The Charnley approach with trochanteric osteotomy, I don't use, and I think people have stopped now because, I mean, it's the best approach to get you down the middle of the femoral canal. The problem was that I could not guarantee 100% of the time not to get a nonunion. We think it is very serious to have a 10% trochanteric nonunion rate, and I think that that's too much of a risk to take. So I use a posterior approach, which just divides the shorter external rotators and the capsule, leaves the gluteal medius and minimus on, and goes underneath to get into the hip. That works incredibly well. It's an extensile approach. In large patients, you can make a big incision to improve the access. So I take your point, but I don't use it. I don't think many people do now. There's a few Charnley devotees that do, but not many.

And then...

Yasuo Yamauchi: My next question was on PFFD.

John Skinner: PFFD? PFFD is a difficult condition to treat that, I work with colleagues who use techniques such as the Ilizarov technique and lengthening techniques to improve them, and they work with them; it depends on the type. But yes, sometimes you can lengthen and straighten bones using the tailor spatial frame, so you can grow them not just longer, but also straightened. If you've got a deficiency in soft bone, sometimes a bone graft, it's difficult work. Occasionally, if they've got significant improvement and restored anatomy, then I will do a joint replacement a long time down the line, but I couldn't do joint replacement in the one that I showed you, and you picked up on that.

Yasuo Yamauchi: Well, what I learned from Tom Aitken was that the enemy of PFFD is simply obesity.

John Skinner: Yeah. You are right, and this guy was mobile on that leg. He had a prosthesis and worked with it, and just got on with things, absolutely. Good point.

Yasuo Yamauchi: Thank you very much.

Dee Morrison: Any more questions?

Shadi-Afarin Ghassem: Thank you very much. Very, very interesting. Being an orthopedist, I always enjoy these kinds of lectures, really. But I noticed that you've never used any cement in any of these patients; however, they might be much younger. But having antibiotics in the cement, and you don't use it, can you just explain it a little bit more?

John Skinner: Sure. I do use cement. I tend in some cases, in some difficult anatomies with very wide femoral canals, I will use cement. The reason that I tend not to is because, in the ones where you are doing derotation or bone shortening, what you need, or what I think you need, is to be able to get rotational control proximally and distally. With the S-ROM prosthesis, the one you saw in quite a few of those, the metaphyseal sleeve gives very good rotational control of the top, and then the bottom has got flute, it's got cutting flutes on the surface. So if you jam it into the distal part, the cutting flutes will give rotational control distally. That's why my preference is actually not to use cement in younger patients. We give a high dose of intravenous antibiotics. We give teicoplanin and gentamicin prior to surgery. I don't think you need it just to deliver local antibiotics. But it's a good point.

And different people would approach these in different ways. There are people who would cement some of these shortening components, but I worry about getting cement in between the bone surfaces when I want them to heal.

Fumihiko Hinoshita: Okay, next please feel at ease after this series of very difficult, technically difficult questions. I am an internal physician. When I listened to your lecture at the beginning, at first, I thought this total hip replacement would be very difficult for orthopedic surgeons to do for thalidomiders because thalidomiders would have different anatomical problems from ordinary people. But the more and more I heard your stories and explanations, the more fully I could understand that you are very good at operating on the hip joint.

But I am afraid those highly technical operations will be done by younger orthopedic surgeons who are not so experienced. Can they do that difficult operation, total hip replacement, in thalidomiders? That is my question.

John Skinner: It's a very good question. In the UK, in surgery in general, we talk about indicative numbers. We think the occasional surgeon is almost certainly a pest. If you're not doing an operation regularly, are you doing it as well as you could, and are you doing it as well as someone who is doing it? Of course, that's an incredibly complicated question because some people, there's a different range of natural inherent abilities, and some people will be okay. But you're absolutely right. This is a complex surgery. Dysplasia surgery is complex, and the needs of thalidomiders are more complex. I mean, we shouldn't shy away from difficult problems. That's why we go to work, to solve difficult problems, but it behooves all of us to train the next generation. I don't think I would like to be the first, second, or third time someone has a go at one of these difficult hips. It's about training, it's about supervision, it's about working in teams, and it's an issue, particularly something as rare as thalidomiders.

Fumihiko Hinoshita: So you need great training experience to operate on thalidomiders for hip joint replacements, right?

John Skinner: I think you do. I mean, I think it's...

Fumihiko Hinoshita: Without any daily training, namely regular operations for hip joint surgery, it's impossible for them to operate on thalidomiders, right?

John Skinner: It's not impossible, but it's difficult. And you see that we had a very detailed pre-assessment, and we have that for all the patients because they are all different. And it's not just one surgeon, it's also the rehab team. It's also a good anesthetist. I mean, some anesthetists get terrified if you are not going to give them any arms to measure blood pressure. So it's, again, it's working the team, it's building experience. I think in the UK, we have a national joint registry, which does plot something called outlier surgeons. If your revisions are higher than average, you get told about it, and the chief executive at your hospital gets told about it. So, most surgeons are sensible. I would hope that most surgeons wouldn't take on an occasional case like this, and they do tend to refer them to specialist centers, which I think is how it should be, because specialist centers are not necessarily better, but they get very good at dealing with complex problems, because that's what they do.

I think that's the mindset we need in probably all aspects of healthcare, not just orthopedists, but also surgical specialties particularly.

Fumihiko Hinoshita: One more question, so can you accept Japanese thalidomiders who have an indication for hip replacement surgery with difficulty?

John Skinner: There will be some exceptionally good Japanese orthopedic surgeons. I am very happy to collaborate with them.

Fumihiko Hinoshita: Thank you very much.

John Skinner: Thank you.

Elizabeth Newbronner: It's more of an observation, really, Professor Skinner, than a question. But what struck me was the sort of meticulous way that you both plan the operation and the postoperative care. And sort of talking to thalidomide survivors, it strikes me that the lessons, there could

be broader lessons learned from that for more routine procedures. I think it would be great if there was some way to capture some of that and use that as advice for other doctors undertaking obviously much less complex procedures. But it's just an observation.

John Skinner: It's a good one. I think Klaus mentioned as well that thalidomide patients are at an age where they've had one doctor all their lives, and then the doctor retires, and there's no one there. And then there are other people who will say to them, I don't know anything about thalidomide. Why would you want to go to a doctor who is going to tell you that? I mean, we can find idiots anywhere. What we need when we go for healthcare problems is someone who is going to look into the problem and solve it. If that means referring to someone else, then that's what needs to happen. But it makes me cross when doctors say, I don't know anything about what you've got. Why would you stay?

Dee Morrison: Should I make this the last question?

Shadi-Afarin Ghassem: Yeah. Well, since we were talking about iliac malformations, now I wonder if you do any investigations before you have a TE-affected patient, if you look at the blood vessels before you do the surgery? I also wonder if you could think of doing bilateral surgery at the same time. Because actually, recent studies have shown that in the normal population, you can actually have bilateral surgery of the hips, and they are much, much better; they improve much, much earlier, much quicker, and leave the hospital. Those are my last two questions combined into one.

John Skinner: All of our thalidomiders have CT scans, that's cross-sectional imaging, where you can see the blood vessels, so we'll look for them. If there is anything abnormal or concerning, then we'll go on to do either a CT angiogram or visualize the vessels more often.
The second, what was the second question?

Shadi-Afarin Ghassem: If you do the procedure bilaterally?

John Skinner: Yeah, I tend not to do it bilaterally, I mean, I do some things, and certainly we've learned with patients with rheumatoid arthritis that it's better to do both ankles together, replace both knees together. Hips, you can take a view. When I've done total hip replacements, so hip replacements are quite a big insult to the patient. We don't lose much blood anymore because we give tranexamic acid, and we are meticulous about stopping bleeding, but these operations are big, and they are tiring. I think I am probably not at my best to do another complex operation just after I've done one.
So, we have done them at short intervals. We've done them in, if the patient is in good condition, done them a week later. But that gives the patient the option to say, actually, I need to go home and recover, and then they go home for 6 to 8 weeks, and then come back for the second side. Sometimes, you don't have to do the other one. I mean, the lady I showed with an awful bilateral disease, once you have one replaced, that becomes your good leg, so you offload the other one and this buys time, so that's something we see. Whereas, if it looks like it's a crisis, we must rush in and do everything today. Often, you buy time just by doing one.

Dee Morrison: Thank you, Professor Skinner.

John Skinner: Thank you very much.

Thalidomide in Brazil: Recent Experience

Lavínia Schuler-Faccini

Federal University of Rio Grande do Sul Genetics Department, Porto Alegre, Brazil

Fumihiko Hinoshita (Moderator)

Okay. Let's now proceed with the symposium, beginning with a special lecture by Professor Schuler-Faccini. She graduated from the School of Medicine at the Federal University of Rio Grande do Sul. She obtained her PhD in Genetics at the Federal University of Rio Grande do Sul. She subsequently held several postdoctoral positions and is now a professor at the Federal University of Rio Grande do Sul.

As you may know, she has carried out much research on thalidomide embryopathy (TE) in Brazil and has much experience in this area. Today, she will present a special lecture, entitled "Thalidomide in Brazil: Recent Experience." Professor Schuler-Faccini, please.

First of all, thank you very much Dr. Hinoshita, for inviting me here and to everybody, for this wonderful conference thus far. So, let's now move to a completely different reality. The title of this slide is "Gravidez Segura" in Portuguese, which means "safe pregnancy". We have a nationwide Teratogen Information Service in the Medical Genetics Service at the Clinical Hospital of Porto Alegre (Hospital de Clinicas de Porto Alegre), a public and free-of-charge hospital. We chose the term "safe pregnancy" in an effort to reach patients and the wider population who might not understand the meaning of the word "teratogen" we focus on the safe side, so safe pregnancy.

This service is now 27 years old and is directed at both the general population and doctors. It is open to anyone who wants any information about environmental exposures, drugs in pregnancy, infections, or other concerns. This is the reason for my becoming involved in the thalidomide problem in Brazil. (Fig. 1)

This slide shows what we expect to be Brazil. This is Rio de Janeiro, this is the Christ (statue). Here is Brazil. We are below the equator line in the Southern Hemisphere. We also have a completely different reality. (Fig. 2)

This slide shows where I live, in Porto Alegre, in South Brazil. It shows the Clinical Hospital and the Medical Genetics Service, where we work. Looking at these pictures, Brazil appears very nice and it is but one of our biggest problems is the inequality. (Fig. 3)

This slide shows that we do have good hospitals, but we also have a huge underserved population. So here you see my city, our group is working there. This is the city where I live and work. (Fig. 4)

This slide shows some important data for Brazil. We now have a population of 190 million people, and 3 million births per year. Therefore, to offer proper healthcare to all the popu-

Fig. 1

Fig. 2

lation, in a middle-income country, is very difficult. It is also difficult to have/provide good health information about the number of congenital anomalies and/or genetic diseases. In recent decades, our infant mortality has decreased mainly due to the decrease in infections and diarrhea. Therefore, congenital anomalies are progressively becoming an important cause of infant mortality. Our government is now trying to address the problem of congenital disabilities. Even so, we still face the problems of underdeveloped countries. (Fig. 5)

In this slide, we have the classic photographs of Thalidomide Syndrome that you used to see. I have included them here, to introduce the history of thalidomide in Brazil. (Fig. 6)

The first cases of malformations associated with the use of thalidomide in Brazil were reported in 1960. The official number of people born with thalidomide syndrome in Brazil prior to 1965 is about 300 cases but this is considered an underestimation. It probably reached 1000, according to the Patients Association of Brazil. This is partly because some cases were difficult to prove due to the high prevalence of self-medication. Thalidomide was an over-the-counter medication, worldwide, including in Brazil. By the time affected persons applied for compensation or to have their rights recognized, much time had elapsed between drug ingestion and diagnosis. Hence, in many instances, proof of thalidomide harm was difficult to prove and it was difficult to acknowledge individuals affected by thalidomide. (Fig. 7)

This slide is in Portuguese. I don't want you to read all this, but I have included it as it if from a newspaper. It states: "3,008,965 bottles of thalidomide drugs were apprehended in 1962, when the thalidomide was withdrawn from the market." Even so, as we heard yesterday, it was not in effect countrywide. We do know that many pharmacies still dispensed thalidomide after 1962. (Fig. 8)

Apparently, by 1965, there was not a significant amount of thalidomide available on the Brazilian market. However, as Dr. Emma Baple showed yesterday, Brazil, still today, is competing with India as the leading country in the number of leprosy cases. India probably has more absolute cases because of their huge population, but the prevalence in Brazil might be even higher than in India. (Fig. 9)

Fig. 3

Fig. 5

Fig. 4

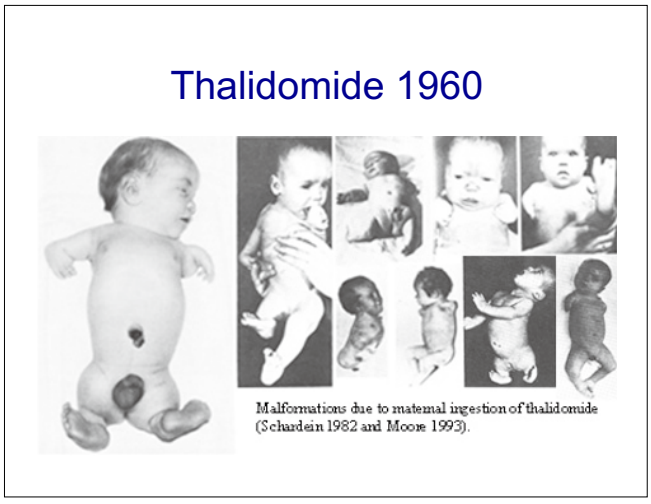


Fig. 6

In this slide, we show the number of new cases of leprosy in Brazil: almost 35,000 new cases each year. The country-wide distribution is unequal there are higher numbers in the North compared to in the South. This North–South difference reflects also the economic distribution. North is poorer and South is richer. So, we have geographic inequality related to economic inequality, and also lack of proper access to health services. In northern Brazil there is the Amazon jungle, where you have to take a boat to travel, sometimes for 2 or 3 days, to reach isolated communities. Access to modern communication systems like the Internet is also difficult. (Fig. 10)

As was previously shown "erythema nodosum leprosum" (ENL) is a common complication in leprosy. It is a very painful skin reaction, and people affected by ENL endure great suffering. It is interesting, because, in 1965, in Israel, Dr. Sheskin treated six cases of ENL with thalidomide. According to his report, he used this treatment because of the sedative effect of the thalidomide. To his surprise, he found that not only did the patients sleep well and have less anxiety, but their ENL regressed. Hereafter, thalidomide returned not as an anxiety drug or antiemetic, but as an immunomodulatory drug. ENL is a reaction that is more common in cases of lepromatous leprosy, which means a leprosy that is not treated from the beginning (it has a longer evolution). In Brazil, almost 50% of patients with leprosy have ENL due to late diagnosis. This late diagnosis if often related to prejudice against leprosy. We know that leprosy is treatable and that it is not very contagious, you do not get it from only shaking hands, for example. However, in the community, this is not known, and if someone is diagnosed with leprosy, probably he is going to lose his job and be excluded from society. Consequently, many people hide the symptoms and only seek care later. (Fig. 11)

In this slide, we show our paper published in 1996, in the journal Teratology. ECLAMC is the Latin American Collaborative Study of Congenital Malformations that registers congenital anomalies in the majority of South American countries. ECLAMC was established in 1967. Between 1969 and 1995 it registered 34 cases of thalidomide embryopathy (TE); 33 of the cases were born in Brazil all were related to the use

Thalidomide in Brazil

- The first cases of malformations associated with the use of thalidomide-based drugs in Brazil were reported in 1960;
- The official number in Brazil until 1965 is about 300 cases;
- Some cases were difficult to prove due to the high incidence of self-medication and the time elapsed from drugingestion until diagnosis

Fig. 7

Thalidomide 1960 - Brazil


Diário Oficial

ESTADO DE SÃO PAULO — (ESTADOS UNIDOS DO BR.

Sòmente na Capital

APREENDIDOS 38.964 VIDROS DE DROGAS À BASE DE THALIDOMIDA

Inutilizados, também, mais de um milhão e meio de comprimidos — Constituída um Serviço Especial de Emergência

Fig. 8

Leprosy – worldwide distribution

Fig. 9

Leprosy – Brazil

35,000 new cases each year

Inequal distribution over the country

North: 8/10,000

South: < 1/10,000

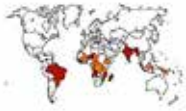


Fig. 10

of thalidomide in leprosy. At that time, thalidomide was not available in the pharmacies, but it was easily obtained by people affected by leprosy through government programs.

I had one case, and this case shocked me, still to this day. It occurred in the late 1980s, in 1987 or 1988. I was beginning my career as a medical geneticist. I had this patient with limb reduction defects. However, the patient had a brother who was affected. Therefore, to my mind, as a medical geneticist, it would be an autosomal recessive disorder. This was before we had many genetic tests available. But it caught my attention that it was not the mother that brought the child in, it was always an aunt. I then asked the aunt why the mother could not come to the clinic. They were from inland Rio Grande do Sul (my home state). She replied that the mother was ill. I proceeded to ask, "Which illness?", to which she responded "She has leprosy". At that moment, and it still shocks me, I realized that I was facing a thalidomide case. Furthermore, there was a brother that was affected. When I collected their history, I noted that the health professional that was taking care of this family had told the mother "You cannot use this medication when you are pregnant. When you discover that you are pregnant, you should stop the medication." Therefore, the woman didn't relate the problem in the baby to thalidomide, because she followed strictly what her health professional has told her. (We know that the teratogenic window for thalidomide is in the very beginning of the pregnancy when most women do not even realize they are pregnant.) (Fig. 12)

In the 1990s, many changes were made to the regulations in Brazil. Presently we have thalidomide approved officially for leprosy, lupus, multiple myeloma, AIDS, and some individual indications that doctors can apply and they have the license to prescribe. (Fig. 13)

Here is how the thalidomide is dispensed in Brazil. It is not commercialized and it cannot be bought. It is distributed only through health programs by the Ministry of Health. Herein lies the problem the problem and the solution. Because it is widely available and inexpensive, and because many patients with leprosy live far away and in places difficult to access, they may get one box containing 30 pills, or the amount required for one month of use. That means they may have 30, sometimes 60, pills at home. Thalidomide is produced only by one laboratory, under governmental supervision, and given to patients only by doctors, by the Brazilian Health Service, free of charge. Patients have to sign for informed consent, but we know that often the patient doesn't understand exactly what is written. People with low education are sometimes even unable to read. So, it depends very much on how the information is given by the health professionals. Women of reproductive age should not be prescribed, unless in special circumstances.

But again, here is a problem. Leprosy runs in families, not because it is a genetic disorder, but families do have susceptibilities. In the communities and families, generally,

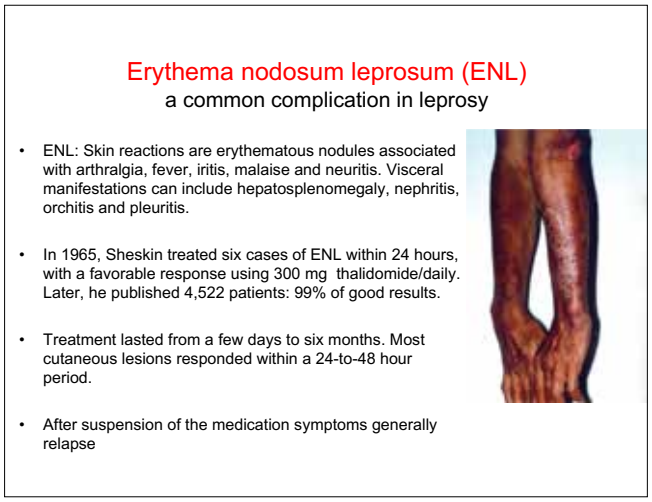


Fig. 11

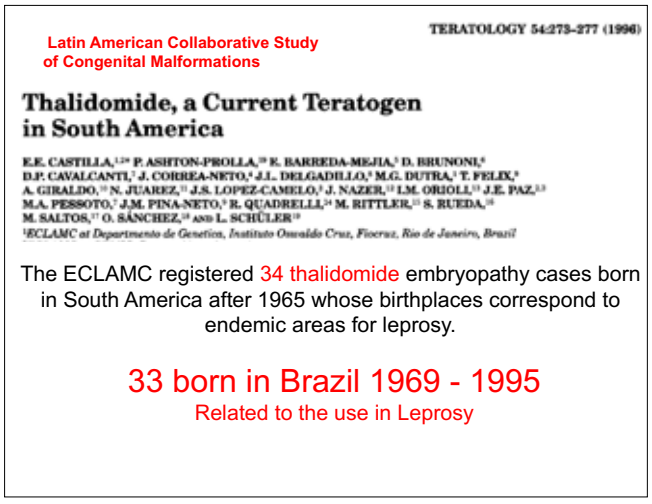


Fig. 12

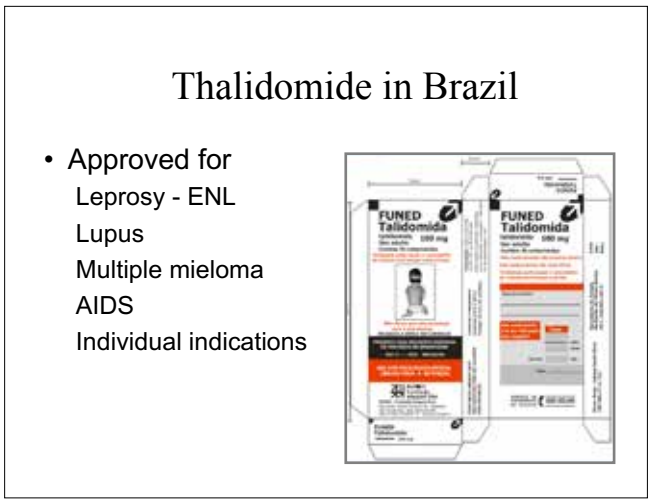


Fig. 13

more than one is affected. Women know that thalidomide is wonderful and, if they have pain, they may try many times to get the medication.

As I am going to show you later, this is like giving guns to children. It is not exactly the same, but you know that the risk is there. It is almost impossible to imagine that, during the use of thalidomide or misuse of thalidomide, we are not going to have inadvertent pregnancies in women that have a low level of education. Women with a prescription for thalidomide should use two contraceptives: one hormonal and the other by barrier. But look at that, in Brazil, 3 million to 4 million tablets of thalidomide are dispensed every year.

Once, an effort was made to disallow women of reproductive age to use thalidomide. However, the association of patients with leprosy complained that it was unfair for the women to suffer more consequences than men. Therefore, the Patients Association campaigned for the right of the women to have the same access to thalidomide as men. As a consequence, the regulation now doesn't exclude women of reproductive age from using thalidomide. (Fig. 14)

This slide shows our paper published in 2007. It shows that there are still babies being born with TE in the twenty-first century. (Fig. 15)

Here we show the distribution of the new cases of TE in Brazil after 2000. Imagine that in the twenty-first century everybody knows that thalidomide is a teratogen and yet we have new cases in Brazil. (Fig. 16)

This case, shown yesterday by Dr. Emma Baple, was born in 2005 in the north of Brazil. Initially, I thought it was impossible that there were still thalidomide babies being born at that time. But when the first pictures were seen, I realized that I was wrong, and that there was a strong possibility of this being a child with TE. I travelled there and we confirmed that it was indeed the case. (Fig. 17)

In this case, the mother was not affected by leprosy, but her husband was. They were very poor and illiterate, and the mother denied using thalidomide during pregnancy. So, I rephrased the question, because many women do not know that they are pregnant before they get tested. Often, when a woman recognizes her pregnancy, she is already

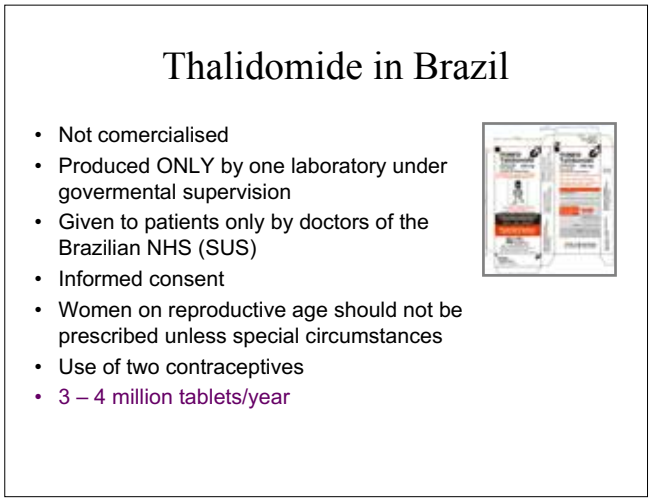


Fig. 14

Fig. 15

RECENT CASES (AFTER 2000)

Fig. 16

Fig. 17

several weeks pregnant. So, I asked her in a very polite and sensitive way (to not let her feel accused): "By any chance, have you taken this pill just before you got pregnant?" She said: "Yes. I was sick, and we have this medication at home. It was in the cupboard, beside the sugar." She took the pills and she felt better. In her mind, she was not yet pregnant. She only recognized her pregnancy when she was already 2 months pregnant.

One important thing in Brazil is that we also sometimes have cases prenatally diagnosed. However, in Brazil, pregnancy interruption (abortion) is not only medically unacceptable, it is a crime. So, anyone who performs an abortion might go to jail, both the doctor and the woman. Regrettably, it is very, very complicated. (Fig. 18)

The second case emerged in 2006. (Fig. 19)

One year later I saw this patient with upper limb defects and also cardiopathy. She died at 6 months of age. Amazingly, she was not initially diagnosed as having TE. (Fig. 20)

She was reported when she presented for the first vaccination shot (which is mandatory in Brazil). The healthcare worker didn't know where to apply the vaccine she had no upper limbs. The Ministry of Health was approached and asked how to perform a vaccination in a patient who doesn't have limbs, arms. Considering the region, where leprosy is highly prevalent, the suspicion of TE was raised and later confirmed. The mother had used thalidomide for leprosy because the doctor told her that she could not get pregnant while using thalidomide. Her conclusion was that thalidomide had contraceptive properties, which we know is completely untrue. Besides that, her husband didn't know that she had a past history of leprosy, and she didn't want to disclose it to him. So, the baby was born and died, secondary to a severe heart problem. (Fig. 21)

The third and the fourth cases were a twin pair in Porto Alegre, my home town, where we don't have leprosy. However, the grandmother of this baby was affected by multiple myeloma. (Fig. 22)

The mother of the baby was a pregnant teenage woman. She took thalidomide from her mother, thinking that thalidomide had abortive properties, because on the label it stated

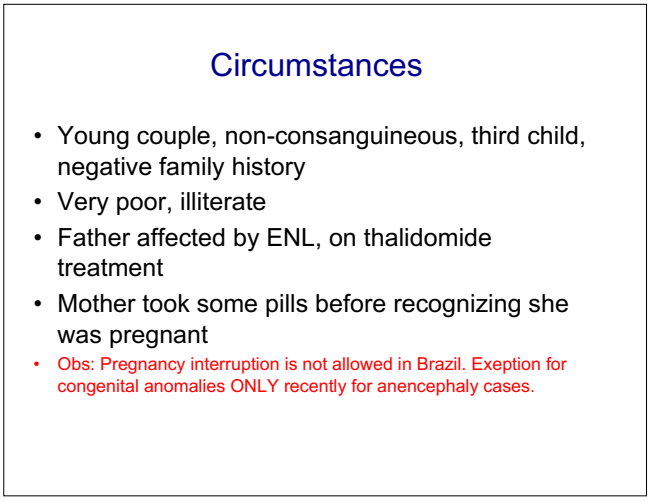


Fig. 18

Fig. 19

Fig. 20

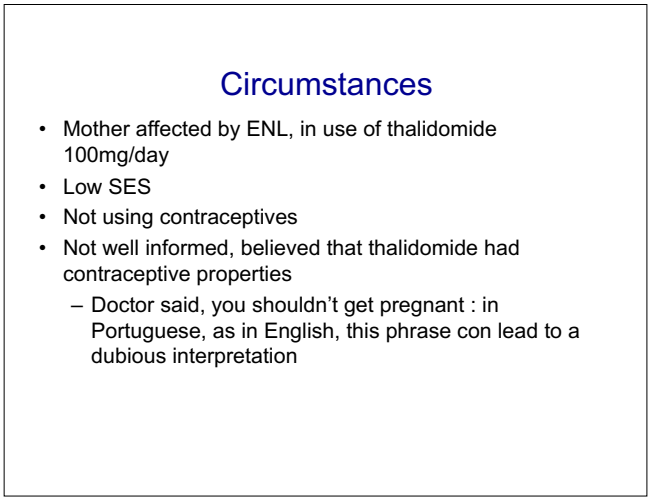


Fig. 21

the following: "Many times it causes the loss of the pregnancy." One of the twin births was a stillbirth, with the absence of thumbs, and kidney agenesis and pulmonary hyperplasia. (Fig. 23)

At this point, we started a project that focused on a follow-up of these cases and we also tried to find out if there were other cases. (Fig. 24)

Once again, we found more cases in Northeast Brazil from mothers with leprosy. (Fig. 25, 26)

In this slide, we show this small town called Cajari, where this affected girl was born. (Fig. 27, 28)

Here is the same patient showing the eye anomalies.

Here is another case, never yet reported. The child was 9 years old at the time, from a family where almost all relatives had leprosy, in the vicinity of Cajari. (Fig. 29)

In this slide, the year was 2017, and I was called to see a patient born in 2012. So, she was 5 years old at that time. Again, the socioeconomic status was very low. And look, it's interesting to find the acromion is a very prominent characteristic of TE as Dr. Emma told yesterday. She also had anal atresia. She was uncared for. The history is very sad. Prior to my visit she had obtained compensation but received inadequate care. All the money went to the parents her father took the money and bought a big car. Furthermore, even worse than that, her father used her as advertisement. He would say: "Look, I have this deformed…"apologies for the word, but"…deformed child, we are poor, we need support from the community" and placed it on social networks. It was through the social networks that we noticed this patient. She had hearing and eye problems, and was not being properly cared for.

In conclusion, we are trying to now establish some basic defects to follow and for mandatory reporting in Brazil so that these cases can be established soonest. (Fig. 30)

Here we present our decision tree, very similar to what Dr. Emma Baple presented yesterday, to define a phenotype for surveillance. (Fig. 31, 32)

We have also published a booklet, in Portuguese, available in both printed form or through a website, which is freely available to all doctors and health professionals. It

Fig. 22

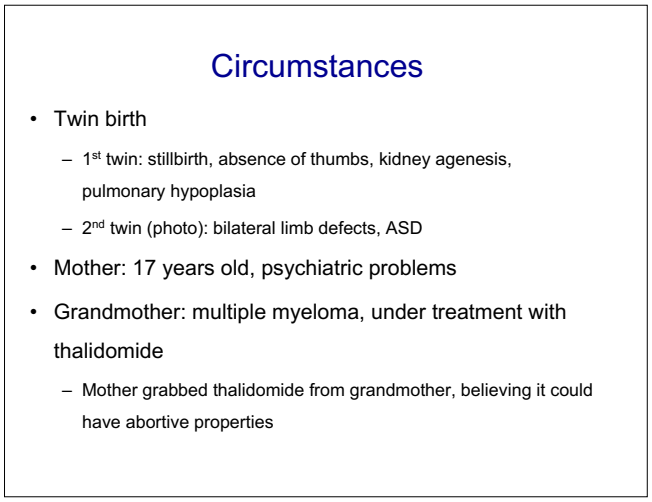
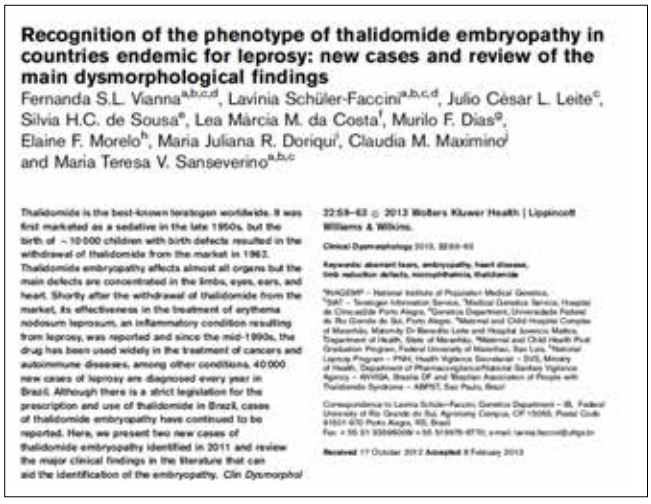


Fig. 23


Recognition of the phenotype of thalidomide embryopathy in countries endemic for leprosy: new cases and review of the main dysmorphological findings

Fernanda S.L. Vianna[a,b,c,d], Lavinia Schüler-Faccini[a,b,c,d], Julio César L. Leite[c], Silvia H.C. de Sousa[e], Lea Márcia M. da Costa[f], Murilo F. Dias[g], Elaine F. Morelo[h], Maria Juliana R. Doriqui[i], Claudia M. Maximino[j] and Maria Teresa V. Sanseverino[a,b,c]

Thalidomide is the best-known teratogen worldwide. It was first marketed as a sedative in the late 1950s, but the birth of ~10 000 children with birth defects resulted in the withdrawal of thalidomide from the market in 1962. Thalidomide embryopathy affects almost all organs but the main defects are concentrated in the limbs, eyes, ears, and heart. Shortly after the withdrawal of thalidomide from the market, its effectiveness in the treatment of erythema nodosum leprosum, an inflammatory condition resulting from leprosy, was reported and since the mid-1990s, the drug has been used widely in the treatment of cancers and autoimmune diseases, among other conditions. 40 000 new cases of leprosy are diagnosed every year in Brazil. Although there is a strict legislation for the prescription and use of thalidomide in Brazil, cases of thalidomide embryopathy have continued to be reported. Here, we present two new cases of thalidomide embryopathy identified in 2011 and review the major clinical findings in the literature that can aid the identification of the embryopathy. *Clin Dysmorphol*

22:59–62 © 2013 Wolters Kluwer Health | Lippincott Williams & Wilkins.

Clinical Dysmorphology 2013, 22:59–62

Keywords: abnormal toes, embryopathy, heart disease, limb reduction defects, microphthalmia, thalidomide

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Fig. 24

Fig. 25

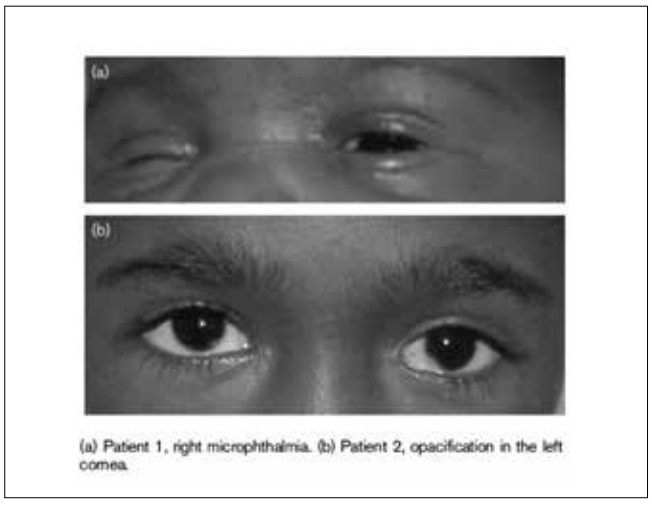
explains how to use thalidomide and all its consequences, with the aim of providing health professionals with more information about the risks of thalidomide use. (Fig. 33)

Here we show other work, similar to what is being presented here. In this paper, published by Salzano (my thesis director), 93 Brazilian teenagers with TE were evaluated during the 1980s, when they began to pursue compensation. (Fig. 34)

From 2010, we tried to recontact those who lived in our state for a follow-up. (Fig. 35)

This is the Kowalski paper published in 2015. Here, we took a picture of some of them. When we explained what the project was about, i.e., a follow-up of their health conditions, some didn't want to participate in the project. They even didn't like being recognized as a "thalidomider" they hate this word. That means that someone is defined by her medical condition and not being Paula, June, or someone who, amongst other things, has thalidomide syndrome. Here we see other project participants: Teresa, Fernanda, and this is Thayne Kowalski (all women).

Fig. 26



(a) Patient 1, right microphthalmia. (b) Patient 2, opacification in the left cornea.

Fig. 27

As we can see from the table, we registered the following as being frequent problems: deafness, hearing problems, and dental loss. We were unable to obtain good blood pressure measurements, but some cases had medical records of cardiovascular problems. This was compared with the general population; however, our sample was only 23 individuals. But just imagine, 30 years later, to get 23 individuals again

The patient's mother had leprosy in the past and was treated with antibiotic therapies (rifampicin, dapsone, and clofazimine) over a 1-year period. Eventually, she developed ENL, for which she received thalidomide 100 mg/day, and was advised to follow a contraception program because of the risk of teratogenesis. As she did not use contraceptives, further thalidomide treatment was denied. However, she took some leftover pills before realizing that she was pregnant. The exact dose and period of use of thalidomide during pregnancy was not recalled.

Fig. 28

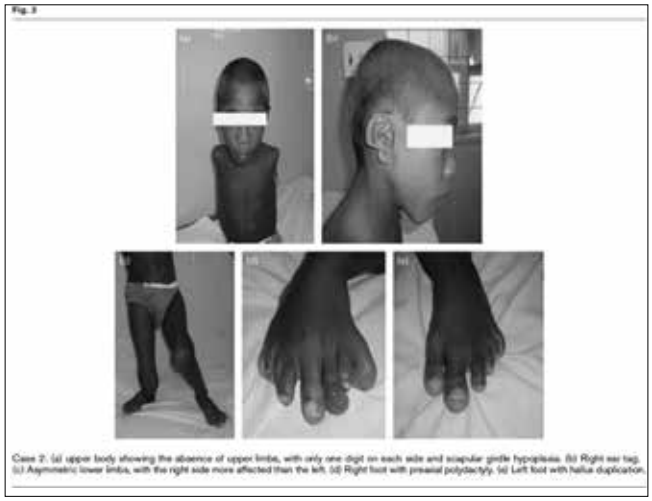


Fig. 29

During the interview, the patient's mother reported that she had had leprosy in 1995 and described the symptoms of ENL. She was treated for 5 years in different clinics until she became pregnant with Case 2. She could not recall the exact dose or period of use of thalidomide during pregnancy. Many members of her family were also affected by leprosy and reported having ENL. They live in an isolated area under very poor conditions (Fig. 3).

Fig. 30

a high proportion. We also observed a higher frequency of psychological or mood disorders, mostly stress or depression. We can guess that there is some bias since they are voluntarily participating individuals, so we might imagine that people who had endured more suffering would be more willing to participate. But the opposite could also be true. If you are too depressed, you might even think the following: "Okay, why do I have to answer all these questions for this doctor?" We therefore think that the bias of voluntarily participating is not quite relevant. And, as I have heard from you earlier, mood disorder is expected. Nonetheless, it is important that we register this disorder, and register that it is above what we see in our population.

Currently, we are trying to expand the study because the subjects are now approaching their 60s. We would like to have a group (all together), not only from our state but from other parts of Brazil, and to empower them a little bit more. I think that one of the most interesting things for me, to be here/to take home, is the sense that these women can be empowered and take care of themselves. Many of them believe that because they have a congenital anomaly there is no future for them. They feel as if they are not part of this civilization, they have felt worthless and excluded from the very beginning. Furthermore, as they do receive a compensation, they might think that they are not entitled to complain. (Fig. 36)

Finally, the conclusions. Even with stricter surveillance and regulations, indications, from case history, are that Bra-

Fig. 31

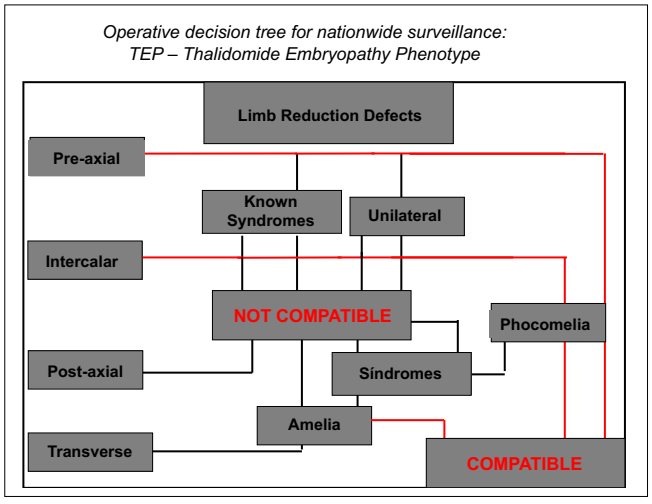


Fig. 32

Booklets produced by the Brazilian Ministry of Health to educate health professionals

92 pages

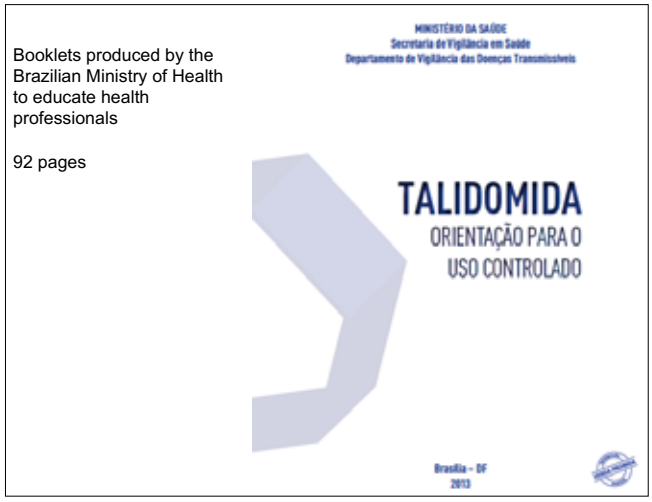


Fig. 33

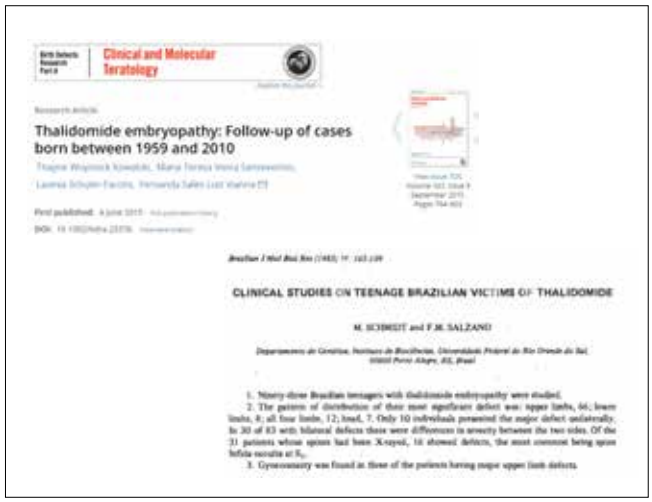


Fig. 34

Fig. 35

zil is reticent to introduce any thalidomide analogue. Lenalidomide and pomalidomide are only available through importation and are much more expensive than thalidomide. However, the inequality remains: richer people can afford to use pomalidomide and lenalidomide, which, although teratogenic, have fewer side effects. (Fig. 37)

So, thank you very much. This is our group, with all four "scientific generations" working with TE: Salzano, myself, Fernanda Vianna, and Thayne Kowalski. I wish to thank them for this collaborative work. (Fig. 38)

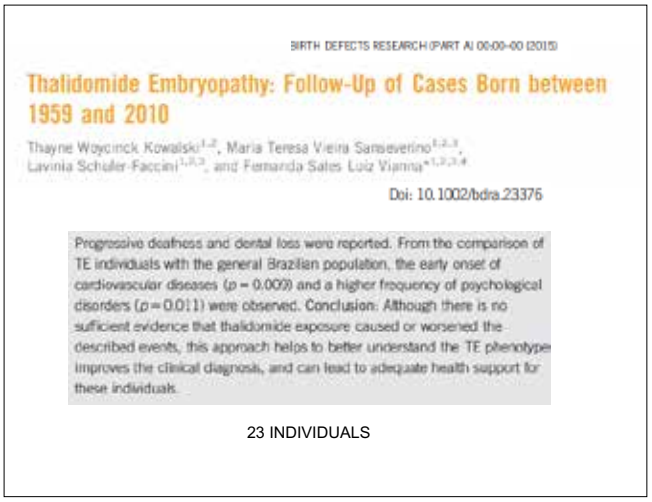


Fig. 36

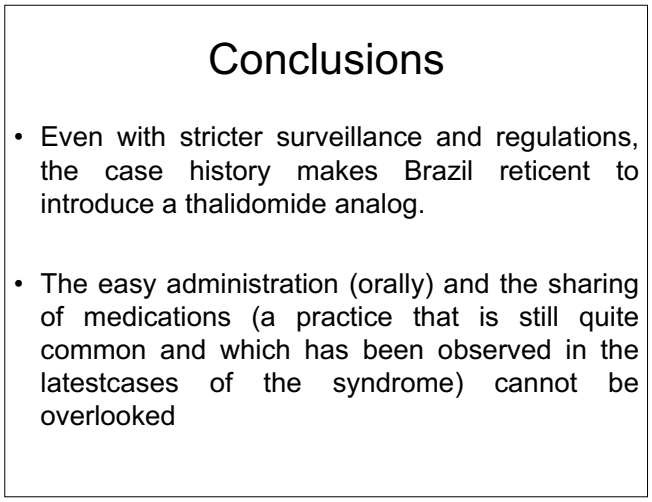


Fig. 37

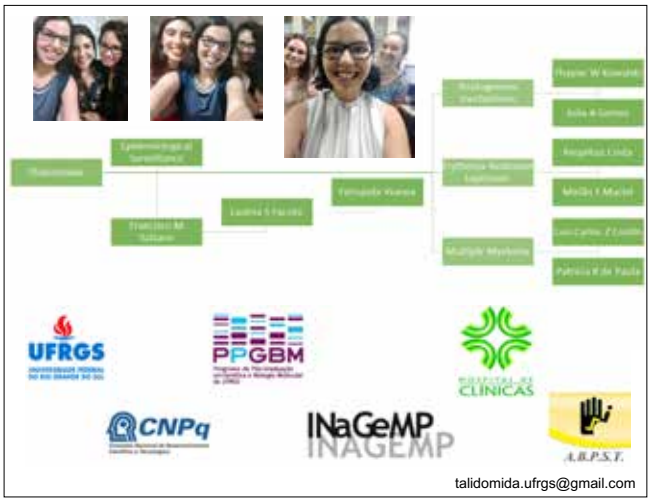


Fig. 38

Q&A

Fumihiko Hinoshita: Thank you very much, Professor Schuler-Faccini. We are now open to questions and discussion.

Tsugumichi Sato: I am Sato from the Ishizue Foundation. Congratulations and thank you very much for your impressive presentation. Yes, we Japanese thalidomiders feel very sorry about the story in Brazil. And my question is I actually have two questions. First, regarding the number of new victims after 1965 I've heard from Cláudia that there are 120 new victims in Brazil.

Lavinia Schuler-Faccini: Yes, Cláudia. Yes.

Tsugumichi Sato: Is it right or wrong?

Lavinia Schuler-Faccini: Yes, it is. However, I put this number of 34 in our paper because those 34 were the patients that we have seen. Regarding the 120, I am not sure that all of them have TE. Limb defects are quite common. But the problem is, it's quite ethic. They are receiving the compensation. They have limb defects. So, it would be harmful if we now go to them and say, "Okay, you have a genetic condition."

So what we did is, in some cases, some particular cases we have some cases of ectrodactyly that we know that are not due to thalidomide. So, we call them for a private consultation, and say "Okay". But we are mindful that some cases can be confounded with thalidomide. We try not to, you know, not make them spiteful but try to conceive that they have a risk for future generation or something. But Cláudia is mostly right. Cláudia is very, very strict in diagnosis. She is very good in diagnosis right now. She says "You are not" or "Yes, you are". Now you can call Lavinia, because she is going to tell that you are not an individual with TE or you can rightfully ask compensation for the newer cases."

But it is around 100, I guess. And even so sorry to say something more regarding these cases, I strongly believe that these cases I am showing you is what we saw just by chance. There are probably more that are not registered or reported. The regulation now in Brazil is so strict on thalidomide use that even the parents can be prosecuted or be considered accountable for their children being born with an anomaly that could be preventable. This is very, very bad, you know.

I am pretty sure that we have many more cases being born in Brazil, but we are not being informed.

Tsugumichi Sato: Thank you. And the second question is about recent cases. I have a photo yeah, this one. So, do you know the case, born in 2006?

Lavinia Schuler-Faccini: Okay. It is not ours.

Tsugumichi Sato: And this?

Lavinia Schuler-Faccini: This, was born in 2006?

Tsugumichi Sato: Swedish thalidomider gave me the photo.

Lavinia Schuler-Faccini: Okay. Yeah. It's so similar to the patient we saw in 2005. I don't know…

Tsugumichi Sato: 2005.

Lavinia Schuler-Faccini: Yeah. But I am not sure it's the same case, because there is the…
Do you know in which state or city was the case born? No? Because it's quite similar to, I looked at…
Yes. Yeah, it's my patient. Yeah. I am sorry it's my patient. It's the same one that I showed. Yeah. Yeah, I know him very well. Yeah. Yes. Exactly, yeah. I even know his name. Sorry. It's the same baby that Emma presented yesterday and I showed today; I followed him.

Fumihiko Hinoshita: Okay. Now, it's okay to confirm the case, you know…

Lavinia Schuler-Faccini: Yeah, it's a confirmed case. Yeah.

Fumihiko Hinoshita: Okay. Is there any other question or comment?

Christina Ding-Greiner: In Germany, in the scientific service from the Bundestag, I found a paper dating from 2008. There I found details about thalidomiders in Germany. They mention Brazil, and they say that there were 480 acknowledged thalidomiders in Brazil. What do you think of it?

Lavinia Schuler-Faccini: Yeah, it might be possible. Considering those born in the 1960s, before 1965 and later, I think it's accurate.

Christina Ding-Greiner: It's correct?

Lavinia Schuler-Faccini: Yeah.

Christina Ding-Greiner: Thank you.

Fumihiko Hinoshita: Okay. Do you have any other questions? You have nothing? Okay, please.

Junko Fujitani: Do new thalidomiders have some pension or compensation?

Lavinia Schuler-Faccini: Yes, they have. They have compensation because of thalidomide, because as the government gives the medication, the government is responsible. So they have a compensation, they have a moral compensation. It's a huge amount of money. The problem is like this it's like the car (the story I described earlier). The father bought a huge car let me see, in US dollars, imagine something that is around $30,000. Then, even worse than that, after buying the car he left the family. So, when I was there, they called us, because they (the family) were in misery again. So, they didn't have this huge moral compensation. The thalidomider still has a monthly, how can I say, payment. But, besides the monthly payments, any patient with thalidomide syndrome receives this, like, compensation, big compensation, and they spend it all. Yeah.

Junko Fujitani: Then, diagnosis: who diagnoses whether the baby is a thalidomider?

Lavinia Schuler-Faccini: Yes. Why this baby? Why was she diagnosed? Because she was on Facebook. As that region has a high prevalence of leprosy, we communicated with the Ministry of Health and we went there to examine the baby. Of course, there was proven exposure of the mother. She used. She was still using. We also did some medical tests, genetic tests that drill other common conditions' phenocopies.

Junko Fujitani: Thank you very much.

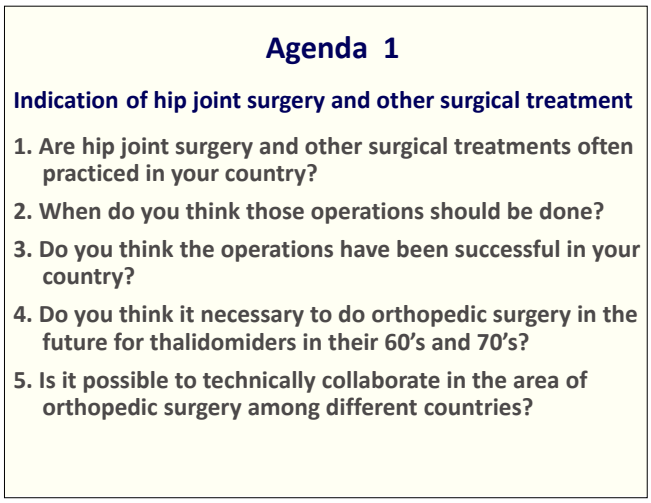
Fumihiko Hinoshita: Okay. Nothing else? So, thank you very much, Professor Schuler-Faccini. Thank you.

Staff: Thank you very much, Drs. Hinoshita and Schuler-Faccini. And now, let us move on to the panel discussion. Please first allow us a few moments to rearrange the tables.

Panel Discussion

Chairperson: Dr. Fumihiko Hinoshita (National Center for Global Health and Medicine, Tokyo)

Discussants: Dr. Ryoji Kayamori (Teikyo Heisei University, Tokyo)
Dr. Junko Fujitani (National Center for Global Health and Medicine, Tokyo)
Dr. Dee Morrison (The Thalidomide Trust, St Neots, UK)
Dr. Christina Ding-Greiner (Institute of Gerontology, University of Heidelberg, Germany)
Prof. Dr. Klaus M. Peters (Dr. Becker Rhein-Sieg-Klinik, Nümbrecht,Germany)
Dr. Shadi-Afarin Ghassemi (Unversity of Gothenburg, Gothenburg, Sweden)
Dr. Jan Schulte-Hillen (Notfallzentrun Klinik St. Anna, Luzern, Switzerland)
Prof. John Skinner (Royal National Orthopaedic Hospital, Stanmore, UK)
Prof. Lavínia Schuler-Faccini (Federal University of Rio Grande do Sul Genetics Department, Brazil)
Dr. Emma Baple (Royal Devon & Exeter NHS Foundation Trust, Exeter, UK)
Ms. Elizabeth Newbronner (The University of York, York, UK)



Fumihiko Hinoshita (Moderator): Okay, are all of you ready? I have an agenda for the panel discussion. There are three main points.

The first one is indications of hip joint surgery or hip replacement therapy, and other surgical treatment for thalidomiders. The second one is new claimers and new cases with TE. The third one is how to diagnose TE.

Let's start with point number one: indications of hip joint surgery and other surgical treatment for thalidomiders.

Professor Skinner gave a special lecture on total hip replacement surgery. So, hip joint surgery and other surgical procedures are often practiced in your country, the UK. First, I should ask the English panelists about it : how about in your country, Professor Skinner or Dee Morrison.

John Skinner: It's not commonly performed, but then it's likely to be indicated more frequently in the future as patients get older. The question earlier about 1% of patients with thalidomide having joint replacement in the UK the national averages are as follows: 0.8% hip replacements and 1.5% knee replacements. But it is age related. So, by the time you get to 80, 5% of the population has had a hip replacement and 10% has had a knee replacement. So, there is a diagnosis issue and there is also a time issue.

The commonest indication that we've seen has been dysplasia, which is probably a pre-arthritic condition. So, these patients with dysplasia do have a risk for generating osteoarthritis. The indication is always pain there has to be pain. I don't think you would perform hip replacement in the absence of pain. It is a very effective form of pain relief and it should be considered. It does often improve function, stamina, walking, and quality of life. So, it needs to be considered in those contexts really.

Fumihiko Hinoshita: Thank you. How about in Sweden, Dr. Ghassemi?

Shadi-Afarin Ghassemi: As far as I know, we have one

patient who has received a total hip replacement. He was actually displaced from the beginning. In the five PFFD individuals in our group, none of them have even asked for it. Some of them are using wheelchairs, they are not using crutches for walking. Those who have a prostheses, they haven't been, they haven't loaded that much probably. So, they haven't actually asked for it.

I mean, when we did our first study and found that they have a lot of … that they have a much higher risk of osteoarthritis in both hips and knees, that level of osteoarthritis was discovered by computer tomography. So, it was not related to how much actual pain they had. So, they haven't got these symptoms yet.

So, we are prepared. If they come, then we know that it might be because of osteoarthritis. But no, we haven't got more.

Fumihiko Hinoshita: So, do you think you will have an increasing number of chances to carry out hip joint surgery in Sweden in the future?

Shadi-Afarin Ghassemi: Yes, I definitely believe so. However, it doesn't mean that it should be for those with PFFD. It could actually be also for others.

Fumihiko Hinoshita: How about in Germany?

Klaus M. Peters: I think we have the highest number of thalidomiders in Germany. There is an increasing number of patients with coxarthrosis due to hip dysplasia and we have already done several hip replacements. I think it started in the last 10 years.

Fumihiko Hinoshita: Okay. Before the next question, how about it in Japan, Dr. Kayamori?

Ryoji Kayamori: I don't have any knowledge about that. Thank you. Dr. Skinner, in front of you are some Japanese thalidomiders waiting for your advice. They are suffering from hip pain with dysplasia. So, they want to know your advice on surgery. They want pain relief, but they don't know what to do. So, they are asking whether they would be better off going to you in the UK or remaining in Japan and waiting for a couple of years. So, could you give us, or give them, some advice for a Japanese thalidomider with a painful hip? Thank you.

John Skinner: It's a good question. For non-orthopedic surgeons, the best way to screen the hips clinically is, if the patient is supine, lying flat on a couch, if you just ask them to do a straight leg raise; that's a good screening test, because of the length of the lever arm, it puts approximately two times bodyweight force directly through the hip joint. And if that's painful, then the other test is to flex the hip up passively and internally rotate a flexed hip. If that generates pain, then, together, these are two very simple and quick screening tests for hip pathology, and almost certainly degenerative change, irrespective of whether or not there is dysplasia. And I think if we look for patients I think, if patients have got hip pain or leg pain, as they are aging, we ought to be screening them more, because we genuinely have a good treatment for those patients in pain. So, that would be my advice, to look for it. If either of those tests generate pain, or mechanical pain, that's pain on weight-bearing and with-activity, often with night pain, then those are the signs of arthritis. It would certainly be worth getting an X-ray and then evaluating from there.

Fumihiko Hinoshita: So, it's very important for us to do the appropriate evaluation before thinking of the operation. If we found some Japanese thalidomiders who were suffering from pain, and then got the results for the operational indications, we would ask you. Anyway, are there any other comments on this question?

Christina Ding-Greiner: I have a question. How many people with TE in Japan have actually affected lower limbs?

Fumihiko Hinoshita: Lower limbs?

Christina Ding-Greiner: Yeah.

Ryoji Kayamori: We have a lot of thalidomiders who are suffering from hip dysplasia, even though there are only two victims with lower limb defects. Ms. Honma, a thalidomider, is she suffering from one side or both sides?

Otomi Honma: It's bilateral.

Fumihiko Hinoshita: Bilateral, and already undergone surgery?

Otomi Honma: Right. A pelvis rotational osteotomy was conducted.

Ryoji Kayamori: How many people are there who are suffering, do you know that?

Otomi Honma: In Osaka, in Tokyo, and here, five altogether. Five patients have this dysplastic hip among Japanese thalidomiders.

Ryoji Kayamori: There are more thalidomiders who are suffering from hip problems, but they are thinking of having surgery. However, we don't have much knowledge about who is indicated. Any comments, Dr. Yamauchi? (He is the

former president of the Japanese Orthopedic Association.)

Yasuo Yamauchi: My experience is very limited. I have no definite answer. But as far as I am concerned, there is no specific type of surgery applied to thalidomiders. I think, if the patient has pain, I think we may consider surgery, as for other patients. But there is no special technique for the thalidomiders.

Shadi-Afarin Ghassemi: Can I just comment on that because, I mean, having hip displacement, it doesn't need to be related just to the thalidomide itself, and especially in women, I mean it's more common. So, it probably should be more than 10 patients in Japan with hip displacement that are not recognized at the birth.

Yasuo Yamauchi: Well, this hip dysplasia, or dysplastic hip, is very common among Japanese. But, I don't see anything specific related to thalidomide.

John Skinner: I think that's a good point. And the lady talked about the periacetabular osteotomy. There are plenty of surgeons skilled in Japan at treating dysplasia and reorienting the pelvis for dysplasia, whatever the cause. The only problem may be with thalidomide patients with short phocomelia and non-functional upper limbs, whether they can manage protected weight bearing for the longer length of time than an osteotomy may require. But that's the only difference. I agree.

Yasuo Yamauchi: Again, we had what we do for just regular hip dysplasia, the high osteotomy or rotational osteotomy. Again, I don't see anything special for thalidomiders.

John Skinner: I mean, I do agree with that. I think that the ones that I operate on-it's usually the surgery of the dysplastic hip of any etiology. I think there is no particular anatomical variance but it's the rehabilitation, the planning and what's expected, and what needs to be achieved afterwards…

Yasuo Yamauchi: Well, I think the way of rehabilitation is different. As I said about PFFD, rehabilitation is very difficult if the patient has obesity.

John Skinner: And if there are two hips that are differently affected, it's the one that's closest to normal anatomy that's hugely relied upon as the weight-bearing joint that we tend to be replacing. In my experience, the ones with PFFD, the severe malformations of the lower limb, tend not to get joint replacements.

Yasuo Yamauchi: You are asking me? I have no answer.

Fumihiko Hinoshita: Thank you very much, both of you. Then, in Japan, we are generally likely to wait for hip joint surgery or hip joint replacement, especially among thalidomiders. You know, Professor Kayamori talked about it previously. But when is the appropriate timing to do the hip joint surgery? In the 60s or 70s, it that okay? Thalidomiders in their 60s or 70s?

Klaus M. Peters: I think it depends on the pain. As Dr. Skinner already said, if you have pain even during the night, that's the last sign, and then you should do it. And if the patient wants it to be done.

John Skinner: I'd agree with that. I don't think this is age-based at all. It's symptom-based. If the pain is bad enough, you are old enough. And it's very simple, the patients can share in decision making. And the question I always ask is "Is your pain bad enough to consider an operation?" Patients will have a view on that. It's our duty to inform them what the options are, but that's a basic step towards surgery.

Fumihiko Hinoshita: In the case of an Ishizue Foundation member, the woman was in too much pain to sleep well. Under those circumstances, the surgery might be indicated. Any comments or feedback, particularly from the President of the Ishizue Foundation?

Otomi Honma: So, in my case, maybe someday artificial joints have to be implemented, otherwise my daily life will be miserable. I understand it. I recognize it that way. However, I have already undergone the arthroplasty, which means that I am not sure whether the artificial joints fit me well or not. That is the biggest concern. So, if the surgeon can explain my concern well, if I have an opportunity to meet a good surgeon who provides me with a good explanation to overcome my concern, that might be a different story. But I understand that I am indicated for the surgery, but I have not yet been convinced. I have never yet met a surgeon that has convinced me.

This is one of the issues that I am facing right now. There is also a muscle-related issue, which is a headache for me. I am not medical expert. I am a patient with TE and my muscle power is really weak. I am deficient in terms of muscle strength, I feel I am weak. So, that is why the insertion of an artificial joint will make me walk properly, without crutches or canes. That is another concern I have right now. So having an artificial joint means having an osteotomy to remove my own bone, to make space for artificial bones. So, after an artificial joint is implanted, I realize that my native bone is better. I do not want to have that kind of regret. So before

undergoing surgery, I would like to be convinced. So, I am looking for a surgeon who will convince me.

Fumihiko Hinoshita: Well, you mean "I don't know whether I explained it well or not."
As for total hip joint surgery, without enough explanation and of course without any sophisticated technique or support, operational support, you cannot reach the conclusion "I myself should receive that operation." Is that what you wish to say?

Jan Schulte-Hillen: I would like to answer to you. Maybe, if you don't find a doctor who convinces you, I would like to show you my total hip replacement which I had 2 years ago. Prior to the op, I was walking almost like you. I think it (the op) was the best, my best decision within the last 5 years.

Fumihiko Hinoshita: Yeah, you walk smoothly. Exactly.

Ryoji Kayamori: Jan, you didn't tell me.

Jan Schulte-Hillen: I am telling you now.

Fumihiko Hinoshita: I listened to Professor Skinner's presentation. He showed us a very sophisticated example of an operation. Then we are afraid we can find such excellent orthopedic surgeons in Japan or possibly in other countries. We are also worrying about it anyway. Dr. Fujitani?

Junko Fujitani: Allow me to speak in Japanese. I have experience in perioperative rehabilitation of a patient with polio sequelae. We made plans for the surgery much earlier than in normal cases. Before the surgery, I carried out long periods of rehabilitation to build muscle strength. This is because patients with low muscle strength have low walking ability after surgery. The skills of the orthopedic surgeon performing the surgery are also important, but proper training of muscle strength in advance will increase the effectiveness of the surgery. So, I am willing to refer you to many surgeons until you yourself are convinced.

John Skinner: Your concerns are very natural and very understandable. The condition of arthritis causes pain, and the body is very good at doing anything it can at a subconscious level to minimize your pain. So quite often something happens, it is called pain inhibition, whereby if you are about to put weight on that, it's going to hurt. The body switches the muscles off and it makes it feel like you're going to give way. And the reason why people limp is because it's the body's way of minimizing the pain, subconsciously.
Furthermore, the muscles do weaken because you are not using them. You start to use different muscles; you start to use the iliotibial band down the outside. You may get knee pains or you may get outer leg pains because the body is compensating. So, a good orthopedic surgeon will have a look at you and assess what's going on. Maybe a good physiotherapist would be very helpful in looking at the muscle patterning and optimizing your function at this level. But generally, as Jan said, if you get rid of the pain, it's much easier to rehabilitate.

Fumihiko Hinoshita: Okay. Then, we move to the final question of the first agenda. Is it possible to technically collaborate in the area of orthopedic surgery among different countries? You know, in the UK, you have been using 3D copy techniques before practicing the operation of hip joint surgery. In Germany, you have maybe advanced in some respects of the operation. So, I think, and I believe, we should collaborate with the other specialists in other countries. So, let's communicate more with the specialist or surgeons in other countries. What do you say to this?

John Skinner: I think it's not only possible, I think it's essential that we collaborate and talk to each other. The world is a very small place and if we are all facing the same problems it's important that we learn from each other and so we don't keep making the same mistakes. And I think there is a lot to learn. It's small groups of patients, as we've heard; it can be broken down into small parts which are treatable. It's the rehabilitation and the expectations that may be different and we do need to fully understand them all. So, I think we can and should collaborate, and I don't see any reason why we shouldn't or why it's not possible.

Fumihiko Hinoshita: What do you think of that, Dr. Peters?

Klaus M. Peters: I totally agree with Dr. Skinner. Collaboration is a good thing, and we can learn from each other.

Fumihiko Hinoshita: Yeah. So, Dr. Kayamori, let's promote the international collaboration in respect of surgery.

Ryoji Kayamori: I am now too old. I was once retired. Rather than approach me, you should approach Dr. Nobuhiko Haga who is an orthopedic surgeon as well as physiatrist. I hope he could organize to perform orthopedic surgery for hip pain, internationally. Unfortunately, he is not present now (he has some other urgent business).

Fumihiko Hinoshita: Then, you have changed your opinion now, compared with that of several years ago. You previously said we should wait for the operation for as long as possible.

Ryoji Kayamori: Yeah. So maybe the Ishizue Foundation can take central position in organizing, internationally, discussion and cooperation for surgical treatment for thalidomiders with painful joints under the Chief Director of the Ishizue Foundation, Dr. Sato.

Fumihiko Hinoshita: And of course, the specialists in Germany and the specialist in the UK, including Dr. Morrison, please give us some information about surgeries in the future, too. Are there any further comments or opinions on this first question: indications of total hip replacement?

Yasuo Yamauchi: As far as collaboration goes, it depends on whether you are going to operate by yourself. Medical license is required in the particular country. I mean, only academic collaboration can be realized by the way of the Internet, and all kinds of things.

Fumihiko Hinoshita: Thank you. Then, let's go ahead to the next agenda. You know, we have now many new claimers for TE in developed countries, and we also still find new cases with TE, for example, in Brazil. We would now like to talk about the new claimers and the new cases with TE. So, how many people have been diagnosed with TE in Brazil, in reality?

Agenda 2

New claimers and new cases with TE

1. **How many people have been diagnosed with TE in Brazil?**
2. **Why are thalidomiders still born in Brazil? Is there good method to prevent it?**
3. **Have you recently found new claimers for TE in your country? Germany, the UK, Sweden, Brazil and Japan.**
4. **How many people have been really diagnosed with TE in your country in recent years?**
5. **Why do new claimers claim to be true thalidomiders now? Do you have any opinion about the reason?**
6. **Do you have any newly recognized thalidomiders in your country? Do they get any pension and/or compensation as thalidomidrs who were diagnosed long ago?**

Lavinia Schuler-Faccini: I think I have already addressed some of them, but, after 2000, we have confirmed seven cases. These are the ones that I presented, and one was stillborn. Okay? So, six born alive, one stillborn, and one has died, confirmed. However, as thalidomide never disappeared from Brazil, there are many claims. Many claims are from people born during the 1970s and 1980s, they are only claiming now. So, it was mentioned that for what we call the second generation of thalidomide-affected people in Brazil, which means those born between 1965 and 2000, the figure is around 120. But at that time diagnosis was not clear. Not everyone had gone through proper genetic or dysmorphological evaluation. As Dr. Emma Baple mentioned yesterday, there were some diagnoses of phocomelia that were not really phocomelia, but it was accepted. These new claimers, they don't look exactly, they only went through a legal route to get the compensation. So, it's not like a medical patient interview that you can go through. Many times, when they feel that it's not thalidomide, they say "Okay, I don't want to go further, because if you tell me that I am not, I am going to be denied the compensation." So, what I can say is that, presently, there are many new claimers, but we didn't carry out any new diagnoses, besides these 120 and the seven more after 2000. Okay?

Fumihiko Hinoshita: Okay. So, you found the true thalidomiders to be about 120, plus seven new cases.

Lavinia Schuler-Faccini: Yes.

Fumihiko Hinoshita: But there are many subjects who claim to be real thalidomiders. In fact, they may have other/different diseases, you know.

Lavinia Schuler-Faccini: Yes. Because limb defects were one of the commonest birth defects. So, a claim is just claim. So, there are many unilateral amputation defects that we know are other conditions. Ectrodactyly, Poland anomaly, unilateral, many unilateral defects. But what I want to stress is that in all these confirmed cases we are sure of the exposure because we followed the mother, we followed the baby. No one had unilateral defects. So, I totally agree we are going to go through the diagnosis of TE on DATE and ValiDATE. I totally agree with Dr. Baple that bilaterally it can be asymmetric, because we are all asymmetric. But unilateral defects are not part of the thalidomide syndrome.

And what has happened, I think because even in the Brazilian paper published by my supervisor there were some unilateral defects. I think it's the same as occurred with these patients that had children affected. Thalidomide, prior to and during the 1960s, was used by many. So, of course, by chance, even someone taking thalidomide could have a child with a Down syndrome, for example. We know that Down syndrome has nothing to do with thalidomide use. So probably there are some coincidental cases, just by chance, because after that we never saw any persons with unilateral defects with confirmed maternal exposure.

Fumihiko Hinoshita: Okay. Then, did you find any new cases in the developed countries? I mean, for example, in Germany. Dr. Greiner, how about it?

Christina Ding-Greiner: I found some data from 2017, from the Foundation, in the yearly newsletters. You can read: "Since 2009, we have had 833 new claims." Later I found that in the last 5 years, from 2014 to 2018, there were 21 claims accepted and 211 new claims not acknowledged.

Fumihiko Hinoshita: And the officially recognized thalidomiders, 10 or so, in Germany, right?

Christina Ding-Greiner: Overall, 21 were accepted in the last 5 years and 211 were not acknowledged. So, you see the proportion.

Fumihiko Hinoshita: Okay.

Lavinia Schuler-Faccini: May I just ask a question? My question is very simple. Of these 21, were all born in Germany? Because I know of Brazilians that were already confirmed in Brazil and now they are claiming in Germany. So, I am just wondering if there is superposition of cases, that we are not counting twice. Just a question.

Christina Ding-Greiner: I can't tell you. I have not had the time to check. It was the day before I started travelling. But I can look, I can ask the Foundation.

Jan Schulte-Hillen: I can tell you: there were two from Brazil.

Lavinia Schuler-Faccini: Okay.

Fumihiko Hinoshita: Okay. Overlapped.

Lavinia Schuler-Faccini: So, a double count here, because those were already in Brazil.

Fumihiko Hinoshita: Okay. Is there any opinion about it? Dr. Peters?

Klaus M. Peters: Every year I see about 10 to 15 people enquiring about claiming, but most of them are not thalidomiders. I think one or two per year, they may be possible ones.

Fumihiko Hinoshita: How about it in the UK?

Dee Morrison: We have a small number of new claimants who we do accept into the Thalidomide Trust. As I say, it's a small proportion and I've forgotten the actual statistics. In 2016, I think, we accepted six claims from the lawyers. In 2017, we had two people who came into the Trust. And we have just sent two to St George's for them to have a look at. So, the numbers are small, but they are still coming through. Some of these cases are very difficult to decide. We look at the pattern of damage, as well any history of ingestion. And then, finally, we have a committee that looks at all the information together. So, we have lawyers on that committee, and medical experts, and it's a combined decision. Some of the cases are difficult, to try and get the consensus. I think we've had 30 submissions since 2017. So, out of 30, we have put two forward. So, the numbers that actually go to committee and then get accepted are very small.

Fumihiko Hinoshita: Okay. Even after the report by the group of Dr. Emma and Professor Mansour, you can still have difficulty in really diagnosing TE in the UK.

Dee Morrison: Yes, and we are quite favorable in our approach. If it's 51% more likely than not that a new claimant has a pattern of the damage consistent with that caused by thalidomide and if it is likely that the mother had access to thalidomide in the susceptible time period during pregnancy, we will accept the claimant into the Trust.

Fumihiko Hinoshita: How about it in Japan, Dr. Kayamori?

Ryoji Kayamori: Just yesterday, I presented my two cases. So far, we don't know that these cases are really thalidomide embryopathy (TE), or not. Judging from DATE, a diagnostic algorithm for TE, with an emphasis on the epidemiological point of view, the first case is more likely to be a thalidomider. However, the second case was born in 1971, nine years after recall of the drug, even though her malformations really fit TE, with agenesis of the right kidney.

Fumihiko Hinoshita: Okay. What is the reason, why would those people in Japan claim to be thalidomiders themselves? The reason, why? Could you comment on the reason? Why would they claim to be real thalidomiders? I mean new claimers.

Ryoji Kayamori: Yeah, new claimers. Dr. Sato, as Chief Director of the Ishizue Foundation, could you explain this to us? These two cases were referred from the Ishizue Foundation, were they were involved in TE?

Tsugumichi Sato: In the first case, the mother said to him that his disability is due to thalidomide, but his parents did not claim at the time of the resolution of the court in 1974. Furthermore, his mother had health problems. In his family, talk about a thalidomider is not allowed. So now he has decided, by himself, to claim; he has claimed whether he is a thalidomider.

Fumihiko Hinoshita: How about another one?

Tsugumichi Sato: Another one, the second case. I don't know much about the second case. Yeah, the second case is similar. In the second case her parents also did not claim,

they were worried about discrimination in the rural area in Japan.

Fumihiko Hinoshita: I see.

Tsugumichi Sato: In the third case, her or his mother could not write characters. She was unable to fill out the claim form.

Fumihiko Hinoshita: So, it appears that in Japan there are no new claimers who would like to get, or who would like to seek, some compensation or monetary gain. Is that right?

Tsugumichi Sato: Not yet.

Ryoji Kayamori: All the Japanese cases are too modest to ask their mothers or fathers whether they are suffering from TE or not; they are not moneywise. So, that is the one of the characteristics of the Japanese new claimers.

Fumihiko Hinoshita: But in Germany and Brazil there are so many new claimers. I am afraid that, among them, there are some cases with the deformities who would simply like to get some monetary assistance or compensation. How about it, Dr. Ding-Greiner?

Christina Ding-Greiner: I don't have any statistics, but as far as I have spoken to people, I found many people with hearing loss, with deafness, without orthopedic damage. They didn't know that they were thalidomiders, and they oriented themselves to associations of deaf people. And now they are growing older. They are more vulnerable, too. They are starting to have problems with arthrosis, with the spine, and with internal damaged organs. And they remember what was said in the family - maybe they could be thalidomiders.

The other group that I spoke to were people with a low extent of damage and disablement. In some families, it was taboo to speak about thalidomide and, if almost no bodily deformities were to be seen, children weren't told. Now these people are getting older, and they are suffering pain and becoming increasingly disabled. They are asking more questions in order to find out about thalidomide.

All others who were severely damaged, I suppose, were screened out as children. They were examined and officially acknowledged. The new claimers are mainly people who, at first glance, do not appear to be thalidomide-affected people. For the families, it is difficult to live with the idea of having a thalidomide-affected child, but for the mothers it is even worse: it is very difficult to say "I took thalidomide, and therefore I have such a child." Most of them feel very guilty.

Fumihiko Hinoshita: Okay. In Brazil, there are many new claimers who would be absolutely free of TE, right?

Lavinia Schuler-Faccini: I am sorry? In Brazil?

Fumihiko Hinoshita: In Brazil there are so many new claimers, but in reality, free of TE at all, right?

Lavinia Schuler-Faccini: Yes, very few, I think, although I must say something. There are two different things. One is the medical diagnosis and the other is the law. Okay? So in Brazil, if you cannot prove if it's a compatible case, and if you cannot prove other cause, and it's compatible with TE probably he is going to be recognized. So what I know is that some cases are accepted in Brazil as having TE, while in Germany they have refused to be recognized. But what I am saying is the same. Now, like 60 years later, it's very difficult. If it's not the complete, the characteristic, case, it's very difficult to know whether the mother took thalidomide or not. So, in these less-characteristic cases, if it's not another genetic syndrome, it's difficult to say. But what I am saying is that for those born in the 1970s, 1980s, and even 1990s, it's really, really rare to have a new case. There are many claimants but very few are considered compatible. Now, we have many other opportunities of genetic testing, so we can now rule out Holt–Oram syndrome, which we were unable to do earlier.

So, I know that in this group of 120 there are some patients with Holt–Oram syndrome. They might also have Okihiro syndrome. So, recently, because of oriented genetic screening, not full genetic screening, but oriented by diagnosis, we were able to diagnose more genetic conditions.

Fumihiko Hinoshita: I see. Okay. Do you have any further comment?

Ryoji Kayamori: Excuse me. May I ask Professor Faccini? You mentioned, as an indication for a thalidomide drug, you mentioned the lupus, AIDS, and individual indications besides leprosy and multiple myeloma. So, I wonder if they/ the new claimers complained of AIDS or the other indications.

Lavinia Schuler-Faccini: No. It's interesting. That's interesting. Because of those, among those claimers, no one specified these diseases that you have mentioned. It's not possible-thalidomide is not in the drug stores, it's not in the pharmacies-it's the government. So, to have a patient using thalidomide, the doctor has to fill in a form and say I am going to give this patient this medication. So, if there is now

any claimer, it may be that our patient is related to someone who is registered. But not one of these obscure cases was registered, besides those ones I presented. I was clear.

Ryoji Kayamori: Almost all new claimers include leprosy?

Lavinia Schuler-Faccini: No. That's interesting. It's very important. These cases were not claimers. We diagnosed them. We went there and said "Okay, this is a thalidomide case." The claimers are different. They are in the population, and they enter as a claimant, yeah, for the legal system. It's very important, because these new cases, we ascertain them. It was not true. But the last patient truly obtained thalidomide though, that's the reason why she was certified as a thalidomide victim. There are two realities. The last patient, I saw her only for the past 5 years. She got the compensation. Because she went through the legal system, she got the compensation. But she didn't get the medical attention. That is quite schizophrenic. Double reality. You can receive the compensation yet you are not receiving the proper medical care. But the claimers, the other claimers, none are in these special programs.

Ryoji Kayamori: Could you give us individual indications, what kind of individual indications?

Lavinia Schuler-Faccini: Yes. You know, the number of diseases potentially treatable by thalidomide or its analogs is about 400, including immunological conditions, cancer, and skin disorders. So, the doctor has to show that there is literature evidence, and he can then request medication from the government for a specific patient. The request is going to be reviewed. It's not like its immediately approved. It is a process. But it's possible. Okay?

Fumihiko Hinoshita: Okay. Do we have any comment from the UK side? I mean, Dr. Baple and Ms. Newbronner or Dr. Morrison, comments regarding new claimers in the UK?

Dee Morrison: No. I've just passed on two cases in the last 18 months. So then, we had six in 2016, two accepted in 2017 whom we haven't seen, and the two going forward now.

Fumihiko Hinoshita: So, in the UK you have recognized two thalidomiders? New cases, I mean, recently?

Dee Morrison: Yes. We've had two cases accepted in 2017.

Fumihiko Hinoshita: Just two cases.

Dee Morrison: And then we've got two that we have just passed on to St George's, just recently, that they haven't looked at yet. Previously we may have asked St George's if we weren't sure about the pattern of damage. And that's maybe where the confusion is lying. But we've certainly got two cases that they haven't seen yet, that they are about to see.

The pattern of damage will be looked at but also how much access the mother had to thalidomide, it's not just the pattern of damage. We don't ask for proof, but we do consider the history. The timing is also very important.

Shadi-Afarin Ghassemi: How old are they?

Dee Morrison: They will be in the age range; these are in the age-specific range. Yes. There would have to have extremely good evidence of proof of access to thalidomide if they are outside the age range by about 10 years, because the drug was withdrawn.

Fumihiko Hinoshita: Are there any new claimers in Sweden?

Shadi-Afarin Ghassemi: No. In the beginning, when the government, except the monthly payments that they receive, according to their reports, and it depends on how malformed they are, how many malformations they have. It was also at the beginning of the century that the government paid, well, quite a high amount as one payment.

Then there were some people coming. Actually, a woman born in 1957 was recognized, which is very, very early, because there was no thalidomide in Sweden before 1959. But, as you said Dee, it was because of the history, because the father was a chemist and visited Grünenthal in Germany. So, he took the medicine with him. And I think the mother never told anyone that she actually took it. I mean, the parents probably agreed not to say anything. So after that payment, she submitted a claim, and she was actually approved as well. So, the highest number of TE individuals in Sweden has been 115.

But when we started it was 108. There has been a death and actually one murder, and some that, I mean, I think some just move on and never have any further contact, so they are no longer members. But after that, no, we haven't had any new claimers.

Fumihiko Hinoshita: Okay. Then you have newly diagnosed TE, two people in the UK, and more than 10 people in Germany. Then, your government or the trust would compensate him or her, just after the recognition of TE in Germany and in the UK?

Dee Morrison: Sorry, you are talking about compensation?

Fumihiko Hinoshita: Yes, compensation started.

Dee Morrison: Yeah. Okay. What we'd do is, if they are accepted into the Trust, they would receive compensation from Diageo, a drug company responsible for those who distributed thalidomide in the UK. They would receive a lump sum and they would then receive an annual allowance, the same as everybody else. What they've missed out on is the annual grant every year, up to now. But the lump sum they still get and they still get the annual grant. And in addition, they will then get the health grant every year annually, from the government.

Fumihiko Hinoshita: And in Germany?

Klaus M. Peters: In Germany, we have some medical commission of the proper diagnosis. They decide. And if they decide "no" in the first round, maybe that claimer has to seek justice.

Fumihiko Hinoshita: Okay. The reason why I choose this agenda, for new claimers and new cases with TE, is partly because it's very tough and difficult in some cases to diagnose TE. So, we proceed to the final agenda: How to diagnose TE? Now, we are accepting new panelists this time in this symposium. For example, Dr. Baple and Professor Faccini. Then, let's talk about how to diagnose TE.

Agenda 3

How to diagnose TE?

1. **Can you summarize the essence of DATE again, Dr. Baple?**
2. **How do you diagnose TE in your countries?**
3. **What do you think of DATE proposed from the UK?**
4. **What do you think are the essential and/or important items to correctly diagnose it?**
5. **Are you planning to newly determine how to diagnose TE in Brazil and Germany? We just started to think of how to diagnose it in Japan.**

First of all, can you summarize the essence of DATE again, Dr. Baple? And then. do you think it's a final version of diagnosing TE?

Emma Baple: So, the premise of 'DATE' or 'ValiDATE,' as we are calling it nowadays, is that it can potentially provide a numerical score for the likelihood that an individual's congenital abnormalities were caused by thalidomide. So, that's the premise of it. And what we did to arrive at that weighted score was to look at the different abnormalities that are seen as part of thalidomide, and characterize those as abnormalities that are found very commonly in TE and that are not found commonly outside of TE. Those would get the highest scores.

There are certain abnormalities that are more commonly found together, and they would get an enhanced score. And at the other end of that spectrum, we have abnormalities that we felt are not part of TE. These included isolated unilateral limb defects, as Lavinia mentioned earlier. So, we put the diagnostic aid or algorithm together and presented, at the WHO Conference in 2014, the features that we felt would fall into those different categories, to try and reach a consensus on what we now have included in the manuscript. We want ValiDATE to be available to all clinicians seeing patients with possible TE. So, it will be available through a Web-based interface. There will be a small cost associated with using it, but it's not-for-profit. It will be maintained by an independent trust that's overseen by the Thalidomide Trust. It will be called the 'ValiDATE Trust', so that the algorithm can be revised in the light of any new knowledge and it can also be maintained.

Fumihiko Hinoshita: Good news. Anyway, I should ask the same question to other specialists in other countries. For example, in Brazil, Germany, Sweden, and Japan, how do you diagnose TE in your country? For example, in Germany, do you agree with the proposal of 'DATE' from the UK?

Klaus M. Peters: Yes. I think it's a good new tool. We haven't used it yet because it's relatively new, but I think we will also use it in future because I think it's very helpful. Up till now, we have a criteria catalogue for the damages. We use clinical examination, X-rays, and ultrasound, for example, missing kidney and also gall bladder, and so on. A definitely defined catalogue.

Fumihiko Hinoshita: Okay. What do you think of it, the 'DATE' from the UK? Dr. Ghassemi from Sweden?

Shadi-Afarin Ghassemi: Well, 'ValiDATE' is, I think, going to be a very, very useful tool really. I think it's just amazing. Because I know that at the Ex-Center in Stockholm they also use X-rays. Many individuals actually got their diagnoses during childhood. And those who came later on, as adults, have X-rays. That was very convincing at the time. But then I realized that it maybe shouldn't be so. Even only triphalangeal thumbs have been a reason to be approved as a thalidomider (actually there are a couple).

So, I think these tools are very, very nice. But God forbid if new cases emerge in Sweden. I must say, because it's so, so restricted using, I mean, all the fertile women, and even men, they go through, they have to write a consent how to

use, how to behave. And women who are using thalidomide, especially with some blood cancers, they have to go through pregnancy diagnoses every 6 weeks. So, it's nothing that, we don't have the crime of abortion of course in Sweden.

Fumihiko Hinoshita: What do you think of it, Dr. Schuler-Faccini?

Lavinia Schuler-Faccini: Okay. In Brazil, the diagnosis is stepwise. It has changed over the years, but of course it's mostly clinical. It involves exclusion criteria. First, there are some basic things that it's more likely to validate. Unilateral – out. Ectrodactyly – out. There is a panel of various experts that receive photographs and X-rays. That's the first step: photographs, X-rays, any type of evidence, the history, year of birth, and all. The evidence of exposure is, I must say, useless, because it's very difficult to be confident and reliable. So, I am going to say something that is very interesting; you might say it's true or not. The people who have proven maternal exposure, the guilt from parents, and even from the child that learns as an adult, that says, okay, like open to public, that the mother took or something. Nowadays, it's very, very difficult. So, in the majority of the cases, the claimants are not certain that their mothers took (the drugs). It's like a history that has become repeatedly established, or instructed by the lawyer. And because it's very similar, different claimants come with the same history, without any confirmed evidence.

So, what I mean is the diagnosis is mainly clinical, but it includes which type of exposure, if there is anyone in the family with leprosy or multiple myeloma or AIDS. We begin with X-rays and photographs.

If there is enough basic evidence that it's compatible, it is referred to a medical geneticist. These consultations can be paid by the government. So, the government pays because the legal system requires it. Later, they also pay for genetic tests. In Brazil, if you are poor, you have access to a lawyer, free of charge. So even if they don't gain the cost, they won't be paying. If you are richer, you have to pay for these things and if you gain the cost, you refund it. So, what I mean is that it's stepwise, involving mostly clinical criteria, and you are using almost the same algorithm as Dr. Emma presented, more intuitively (but not very strict in the sense). If I cannot prove that there is another genetic condition or another environmental condition, and the case didn't fit any of exclusion criteria, it is going to be accepted. Okay? So if there is doubt, the claimant has the benefit.

Fumihiko Hinoshita: Thank you. In Japan, the Japanese research group has just started to determine the diagnosis criteria or conditions to diagnose TE correctly. By the way, Professor Kayamori, do you have any comments about how to diagnose TE?

Ryoji Kayamori: Yeah. I want to ask Dr. Schuler-Faccini. She showed us an algorithm, a diagnostic algorithm, not DATE, based on the preaxial or morphological characteristics. You showed us one slide. It is very good. In Brazil, it's difficult to use the DATE system because it looks like it is easy to obtain the thalidomide drug. So, in that situation, the DATE system cannot be used. So, we want to know what is the minimum characteristics in TE.

Lavinia Schuler-Faccini: Yes. This flowchart that I showed is what we developed before ValiDATE, before the WHO meeting. So, it has to be bilateral. It has to be preaxial. Or a thumb or radial X-ray needed. But if you don't have the confirmed exposure, only an ear defect, at this moment it's not going to be accepted. You have to have some orthopedic malformation.

But as far as I know, in Brazil, to date, only ear anomalies are not asking for compensation, it's more related to limb anomalies. We now presently carry out molecular testing, for Holt–Oram, Roberts, and SALL4, because it's impossible to make a differential diagnosis and, in some cases, a specific diagnosis. But these three conditions are likely to the basics; they must be present, to qualify for compensation. So, you have to have negative test results for these three genetic conditions before being eligible to receive the compensation.

Ryoji Kayamori: May I ask one more question?

Lavinia Schuler-Faccini: Yes, of course.

Ryoji Kayamori: If you have a patient requiring a differential diagnosis, for instance, for Okihiro syndrome, the absence of radials, and Duane syndrome, is it easy? We don't have any knowledge about genomic diagnosis, so, is it easy, or how long does it take to get the results?

Lavinia Schuler-Faccini: Okihiro, there is one gene, SALL4, and we sequence the gene. We didn't have many patients for differential diagnosis. Presently, there is a student of mine carrying out these tests. When we have one Variant of Uncertain Significance (VUS). If we find a VUS, we don't roll out because we are going to say: "Okay, we have not enough evidence that this VUS is the cause." So, only if you have a pathogenic or possible pathogenic, according to these international criteria, to rule out/to confirm Okihiro.

Ryoji Kayamori: We understand your situation. The important things that make a diagnosis of TE comprehensive with the clinical history and findings, X-ray films, and other imaging. Genetic testing is not indispensable, but a final approach to make a differential diagnosis.

Lavinia Schuler-Faccini: Yeah, the genetic test is done…

Fumihiko Hinoshita: Now, we have the advanced technique of genetic or genomic analysis. So, what or how should we use or utilize the genetic or genomic analysis for the new claimers or the people suspected to have TE?

Lavinia Schuler-Faccini: It was my question to Emma yesterday, and then we agreed. We use the genetic test only if we have a phenotype, then I say it's thalidomide or Okihiro or Holt–Oram or Roberts. So, I never use like a screening test. It's going to be a headache and it's impossible. So first, a very clear clinical description. Because these three syndromes are very much alike in terms of the genetics. Sometimes there are other congenital abnormalities, but it depends, you know, on your medical assessment. It starts with a very good medical consultation, and then you proceed to the other tests. Sorry.

Fumihiko Hinoshita: Is there any other opinion from the specialists in other countries? Okay. Dr. Baple?

Emma Baple: I completely agree with that consensus. I think there is a move to do more complicated genomic testing, so exome or genome testing. Certainly, I know people who have done whole exome sequencing and trawled through all of the variant data, which I think is actually quite dangerous. And some people would argue for an extended panel, but I think that, in reality, you have to get back to your clinical skills, examine the patient, determine a differential diagnosis, and test them for the disorders that you think that they might have. I would probably add in, and I presume you also do, a microarray for some patients.

Lavinia Schuler-Faccini: Yes. Yeah.

Emma Baple: Yeah. So, I would also add in a micro and I would do SALL4, as well as SALL1. Would you agree with that if you had it available, Lavinia?

Lavinia Schuler-Faccini: Yes.

Emma Baple: Yes, I would do SALL1 and SALL4.

Lavinia Schuler-Faccini: Yeah, SALL1, too. Yes.

Emma Baple: Because Okihiro and Townes–Brocks are pretty difficult to differentiate from each other. So, yeah.

Fumihiko Hinoshita: Dr. Schulte-Hillen?

Jan Schulte-Hillen: I just wanted to ask if there is any new test available for Holt–Oram syndrome, because, as far as I know, it has a sensitivity of only 0.3. That means two-thirds of the cases remain undetected. So, the test could not be used to actually rule out the Holt–Oram syndrome. Are there any new developed tests, or is that still the situation?

Lavinia Schuler-Faccini: I am going to ask Emma later, but to my knowledge, no. And we know, that's the reason we say it in doubt, the claimant has the right. So, what I mean is that there might be some Holt–Oram cases that we were not able to diagnose, and then the doubt goes in favor of the claimant. But I don't know if you have more information about the molecular tests for Holt–Oram.

Emma Baple: No. Except that I guess we can do more accurate copy number variant analysis nowadays than probably that number indicates. And I guess the other thing I would say is there are some clinical differentiators. So, I think there are some aspects of Holt–Oram that clinically are slightly different from thalidomide, and that you wouldn't necessarily see in thalidomide, like the particular EKG or ECG abnormalities you sometimes see in the shape of the shoulders is quite characteristic.

Lavinia Schuler-Faccini: Yes. Yes.

Emma Baple: So, whilst saying that any reasonable doubt is in favor of the claimant, I think there are some clinical indicators. And it is a diagnosis that you'd want to get correct.

Lavinia Schuler-Faccini: Yes. You know, that's the question I mentioned when we have a separation between the legal and the clinical sides. I have a patient, rather, I had a patient ("had" because she abandoned me). But I am going to tell you why because I was pretty sure that it was Holt–Oram. There was no evidence. And she was born in a place that had no thalidomide. The phenotype was more Holt–Oram than TE. So, I counseled her as Holt–Oram. But she was really angry, saying "Okay, you are denying me the right I have for this compensation." So, I said "Okay, it's different information. I am your doctor. You have the right to approach the legal system." She went and she was successful, not with my report, because of the legal system she entered. It was before having the test. And now that she has the compensation, she no longer wants to be tested. Sometime, when I met her, I told her "Okay, you are protected by the secrecy of the medical system. So, if you want …?"
But she doesn't want. It's too risky for her to have a test that

might be negative. So, the only thing I said is "Okay when your child is grown up, please tell her that perhaps it's good to have a genetic test or something. That it's protected. But it's a question because it's autosomal dominant." So, for her, okay. But for your grandchildren, there might be a risk. So, okay, that was how our medical doctor–patient relationship ended. But I do think I tried to convey the message. She probably understood. She was a patient with a good education.

Emma Baple: Let's hope so.

Fumihiko Hinoshita: Okay. Thank you very much. Anyway, to diagnose TE correctly and genetically, it is a delicate problem. Anyway, the hot discussion continues, but I think the time is over. Finally, are there any other comments from other specialists or from the floor? Final comments?

Lavinia Schuler-Faccini: I have just one final comment.

Fumihiko Hinoshita: Okay.

Lavinia Schuler-Faccini: I think my final comment is addressed to Dr. Handa who spoke yesterday, and to all the biochemists. We have to find a non-teratogenic drug. Because thalidomide is important. You are on this side, but I have friends with multiple myeloma, and multiple myeloma was a death sentence until some years ago. Now, they are living more than 5 years. Even in Brazil that it's underdeveloped. And when I see these patients with leprosy, they are suffering. So it's not possible to say "Okay, you must not take this medication, but the men can take it."

Regarding the future there is one question here: how to prevent? We need to find a drug that has the therapeutic potential and non-teratogenic potential. But, that's my opinion.

Fumihiko Hinoshita: Okay. Thank you very much for collaborating together with us for the panel discussion here. We have heard many good results and conclusions here in this panel discussion. And, of course, all of us came to mutually know the real situation in other countries regarding TE.

Anyway, thank you very much again to the panelists and to the audience. I would now like to close this panel discussion. Thank you.

Closing Remarks

Fumihiko Hinoshita, MD, Ph.D.

Staff: Dr. Hinoshita, all the panelists, thank you very much. At the very end, we would like to receive closing remarks by Dr. Hinoshita. So, let's continue in this way.

Fumihiko Hinoshita (Chairman): Well, thank you very much for the in-depth discussion on important themes in thalidomide embryopathy or TE over the past 2 days. In fact, investigations and research for the Japanese thalidomide victims have continued since the 1960s, originally by the Teikyo University group and recently by the research group of Ministry of Health, Labour and Welfare (MHLW), first organized in 2011.

However, leading up to the time of the first international symposium on TE in Tokyo, held in 2015, we Japanese group members only knew of a few or several who were engaged in the research activities and support for the thalidomide victims throughout the world.

I believe that our vigorous international activities and the first International Symposium on TE, held in Tokyo in 2015, and in particular the presentations of the invited European speakers have greatly influenced the TE researchers, not only in Japan but also in Europe.

These activities have played a role in promoting international collaboration and exchange of valuable information between the specialists in Europe and Japan. In addition, these international activities might facilitate clarification of more specific TE-associated problems and promote future consideration of specific measures to overcome such problems.

Together, these activities progress clinical research on TE in countries such as Germany, the UK, Sweden, and Japan. Moreover, I feel now that the researchers would be more stimulated, and learn more things from colleagues abroad. Therefore, the present international symposium is very valuable in many senses. We have newly invited guest speakers. Professor Handa spoke on teratogenicity and the pharmacological mechanism of thalidomide. Professor Skinner spoke on total hip joint replacement. Professor Faccini reported new cases with TE in Brazil. Dr. Baple reported on how to diagnose TE. All of the themes they discussed are very important. They are fresh topics that were not included in the previous symposium.

Next slide, please.

Though we have not completely resolved all of the difficult TE-associated problems, all of us continuously work towards a resolution. Importantly, it is imperative that we do not forget that we have great colleagues worldwide, not only in Europe and Japan, but also in Brazil and other countries. And I really hope that this global network on TE will successfully push forward and function well in the future, too.

Finally, I would like to thank you all for joining us yesterday and today. In particular, I would like to thank Ministry of Health, Labour and Welfare for their great assistance, and everyone here. Moreover, I want to wish you safe travels back home. I also welcome those of you who will be touring Japan from tomorrow. Thank you very much again, and so long.

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