

Aging with thalidomide damage: The German survey

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Hinoshita: First of all, the oral presentation will be given by Dr. Christina Ding-Greiner, she will speak about Aging with Thalidomide damage showing data of the German Contergan Study (2012) and of the Evaluation (2015). I will introduce her briefly. She got the thesis and M.D. at university of Heidelberg in 1970. She stayed in San Francisco, California in 1980 for three years. She has been working at Institute of Gerontology, University of Heidelberg. Her main topics in research in different projects: physiology of aging, stroke prevention, and rehabilitation. Ageing of mentally disabled people and patient with psychiatric illness and interaction with nurses and caregivers. Development of concepts of good care. Healthcare and prevention in elderly women. Preservation of motivation and productivity in elderly employee. Aging of victims of thalidomide. Aging processes in thalidomide affected people.

Anyway, she has so many research topics. Then Dr. Ding-Greiner, please.

Ding-Greiner: Thank you very much for your invitation. I'm very happy to be here in this beautiful city and to be allowed to speak to you.

The two studies Dr. Hinoshita mentioned give us an overview of the current living situation of victims of Thalidomide and of future health care requirements. The aim was to identify existing care deficiencies and special needs to be able to give them better care and support. Based on our results, I want to emphasize the health situation of our participants, because this is of increasing importance for the years to come, not only for Thalidomide affected people, but for all people who have to deal with health problems of victims of thalidomide.

Thalidomide affected people are quite different from other groups of impaired people, even from those, who have apparently similar malformations, because they suffered a prenatal intoxication with Thalidomide. Therefore they are a very heterogeneous group concerning their damages. The Institute of Gerontology in Heidelberg is a theoretical institute, we have no opportunity to do clinical research or even to do some diagnostics. We get all our results by questioning our participants, and our participants are the experts on Thalidomide. Our results are based on the statements of a total of 1,267 participants in two surveys, the German Contergan Study (2012) and the Evaluation 2015.

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German Contergan Study 2012

Topics of survey

- *Physical:* prenatal damages, secondary damages, pain, functional abilities and skills
- *Psychological:* handling stress, quality of life, outlook on life, self-concept, depressive disorder
- *Social:* social relationships, social network, circumstances
- *Environment:* space and infrastructure

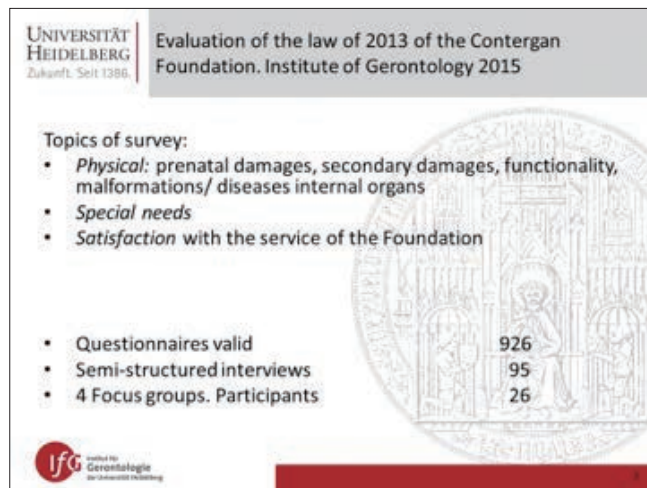
• Questionnaires valid	870
• Semi-structured interviews	285
• 23 Focus groups. Participants	112
• Questionnaires physicians	62

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In the German Contergan Study (2012) 870 questionnaires, 285 semi-structured interviews and 23 focus groups with 112 participants were evaluated and analyzed. In addition data from 62 questionnaires were collected from medical doctors experienced in treating Thalidomide affected people. The topics of the survey dealt with somatic, psychological, social and environmental issues.

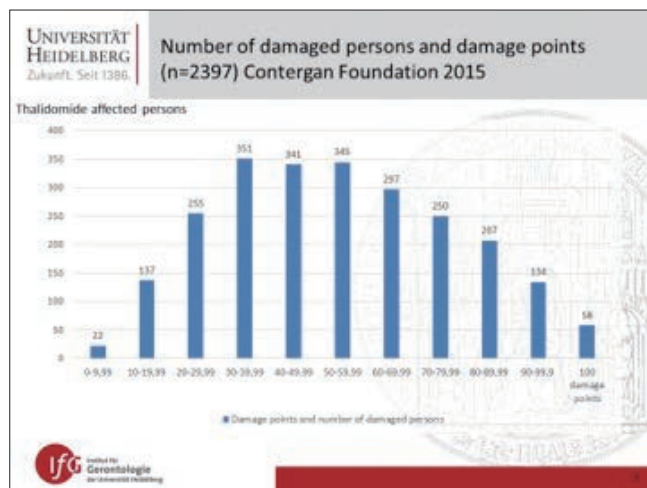
As a consequence of the results of the survey of 2012, the living situation of Thalidomide impaired people changed by modification of the Law on the Contergan Foundation for Disabled People as revised by the Third Amendments Act 2013. The financial compensations were considerably increased and in addition financial means of 30 million EUR were provided for special needs.

In 2015 the Institute of Gerontology had the opportunity of realizing an evaluation of the effects on the living situation of Thalidomide affected people induced by the new law. Questionnaires were developed. The evaluation included 926 valid questionnaires, 95 semi-structured interviews as well as 4 focus groups.



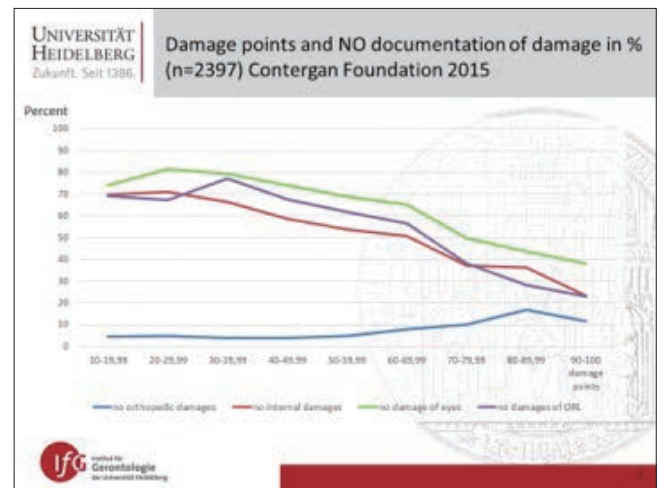
The topics of the survey were issues concerning somatic problems, special needs and satisfaction with the services of the foundation.

The foundation has its own system of evaluation of the prenatal Thalidomide damage in different organ systems. People get damage points e.g. for orthopedic damage, for damage in the eyes, in the ears, and in internal organs. Only verified prenatal damage is evaluated and gets points. The more damage there is, the more points people get up to a maximum of 100 points. The amount of damage points is decisive for the amount of the financial compensation.

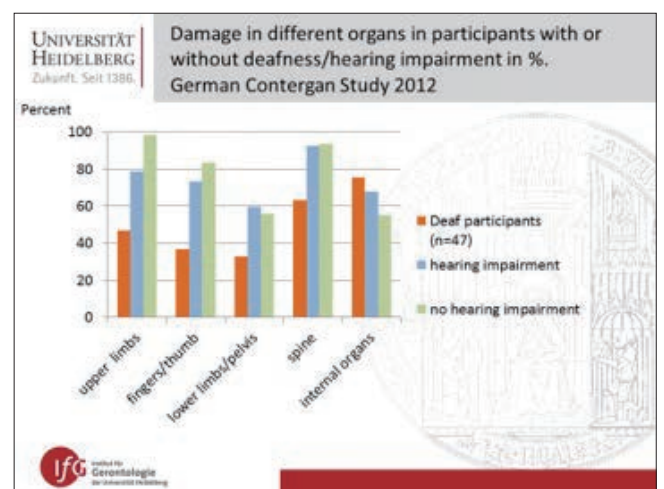


More or less half of the population of Thalidomide victims in Germany have an average of 30 to 60 damage points. Thalidomide impaired people with less than 10 points get no financial support. Today they are mostly in trouble, as they led a life as normal as possible, and up to now they developed severe secondary damages caused by physical overstrain.

The Institute was provided by the foundation with data about the recorded prenatal damages in different organs and the amount of affected people, respectively.



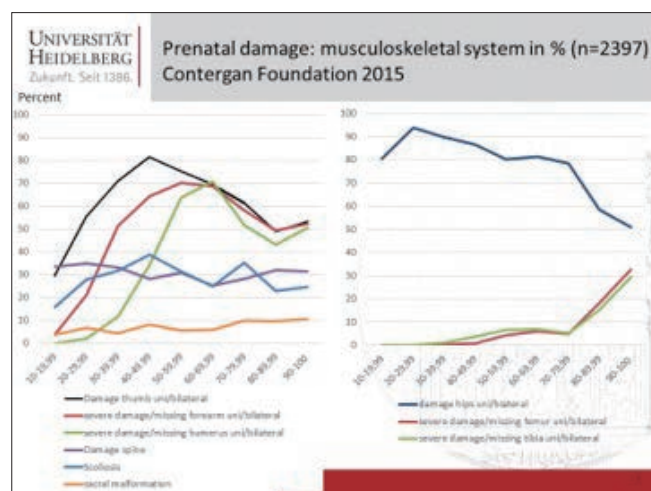
In this figure can be seen the data concerning an interesting item called by the foundation 'no documentation of damage'. As can be expected the thalidomiders with a low amount of damage points have a high percentage of missing documentation of damage in internal organs, eyes and ear, nose and throat medicine. The percentage diminishes in the groups with an increasing amount of damage points. The only exception are the orthopedic damages. Not documented orthopedic damages tend to increase the more points affected people show which means that the amount of orthopedic damages decreases in a population of thalidomiders with a high amount of points. An explanation can probably be found in the comparatively high amount of Thalidomide affected deaf people. 82 deaf people participated in the evaluation 2015 and 42 in the survey 2012. There are about 212 persons who suffer from hearing loss admitted by the foundation. In comparison to thalidomiders without hearing loss the deaf population shows a smaller amount of orthopedic damages.



This figure shows the data of the German Contergan Study 2012. Participants with hearing loss show about half

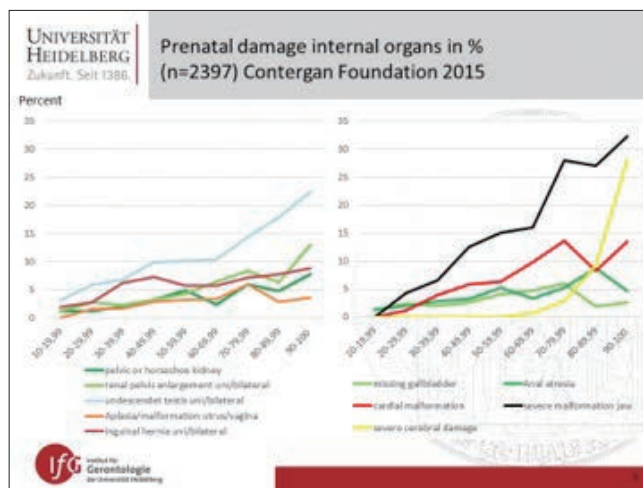
as much orthopedic damages than the group of participants with hearing impairment or without any hearing impairment. In deaf participants the spine is affected more often than the upper and lower extremities, damage of the internal organs is more frequent in this group than in the other two groups. Participants with hearing loss suffer from muscular weakness, too. They complain of severe problems when working physically, they start shaking and they need an increasing interval to recuperate, they show a high tension of the muscles. Deaf thalidomidiers may be impaired in mobility in spite of missing orthopedic damages.

The following diagrams describe the incidence of different damages in percent in relation to damage points in the whole population of Thalidomide affected people. Data were provided by the Foundation.



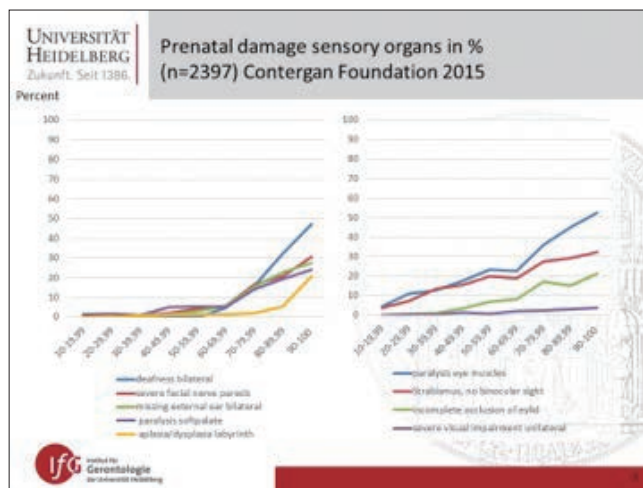
The figure on the left shows the amount of damage in the arms and the spine, the figure on the right shows data concerning damage in the hips and legs both referring to the amount of damage points. A prenatal damage in the spine is found over all groups in about 30 %. Our data in the survey 2012 show that at present about 90 % complain about pain in the spine and show damage caused by physical overstrain.

In the following figure internal organs show a different pattern, the more points affected people have, the higher is the amount of damage.



In the left diagram, e.g. the incidence of undescended testes unilateral or bilateral increases up to an amount of over 20% in the most affected group of participants. This implies childlessness, one of the gravest hardships thalidomidiers suffer. In the right diagram severe malformation of the jaw is found in almost one third in the most affected group. Severe cerebral damage which implies that those affected are not able to go to school, is found in up to almost 30 percent in participants with 90 or up to 100 damage points.

The following figure shows prenatal damage in sensory organs.



The left diagram shows data concerning prenatal malformations in ear, nose and throat. A bilateral hearing loss is found in more than 40 % of severely affected people, the amount starts to increase in the group with 50 to 60 damage points. An aplasia of the labyrinth which causes severe dizziness and restraint of mobility is found in up to 20% of the most affected people.

The right diagram shows different malformations of the eyes and impairment of the eyesight. The most common damage is the paralysis of the eye muscles which can be

found all over all groups of participants and increases up to 50% in the groups with the highest amount of damage points. It implies a severe limitation in every day's activities with secondary damage in the spine.

The next figure compares the data collected in the survey of 2012 on prenatal damage of Thalidomide affected people and today's status.

Location of damage (10 areas)	Prenatal damage	Today's status
Upper limbs	87,8%	88,7%
Phokomelia upper limbs	10,5%	10,5%
Amelia upper limbs	5,0%	5,0%
Lower limbs and hips	53,0%	59,9%
Phokomelia and amelia lower limbs	1,8%	1,8%
Vertebral column and pelvis	55,6%	91,7%
Head and sensory organs	35,4%	42,9%
Hearing organ: deafness	5,4%	5,4%
Eyes: impairment of vision, blindness	35,1%	40,6%
Malformation/dysplasia/aplasia internal organs	38,4%	62,0%

The prenatal status defines the number of the damage points, which measure the dimension of the damage. We wanted to compare the prenatal status to today's physical status. Today's physical status is controlled by 3 components:

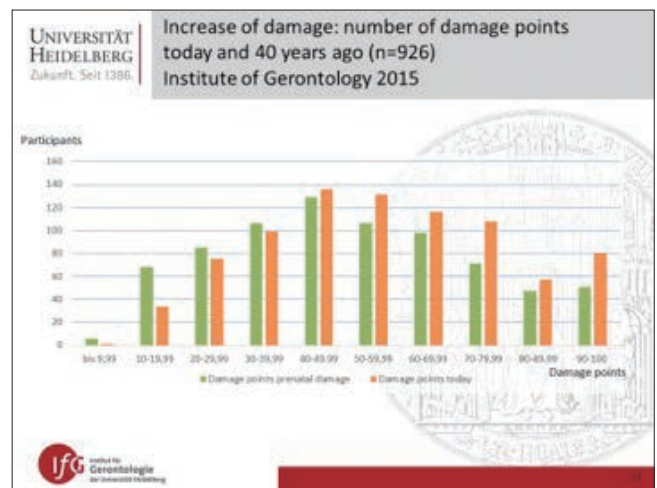
- 1st: The further development of prenatal damage and the physical impairment depend on physical overstraining.
- 2nd: The secondary damage develops in areas with no prenatal damage by pathological biomechanical stress due to compensation of restricted mobility.
- 3rd: The third component are aging processes, which begin to trouble everyone after about the 30th birthday. People without Thalidomide damage do not feel their getting older until the 60th or sometimes 70th birthday. Healthy persons have a lot of biological resources, the more resources, the longer it will last until they feel they are getting physically older. Through detailed questioning we got the impression – though we are not able to measure it – that the population of thalidomiders have only poor resources, therefore they grow older earlier than the general population.

Looking at this figure there is a shift in the amount of people damaged mainly in the spine and in internal organs. The results of our questionnaire concerning the vertebral column with pelvis show in 55 percent a prenatal damage but over 90 percent of the participants complain of discomfort and pain showing severe pathologies. The difference is

supposedly caused by overstrain on prenatal damaged organs and/or overstrain and disbalance in healthy organs causing secondary damages.

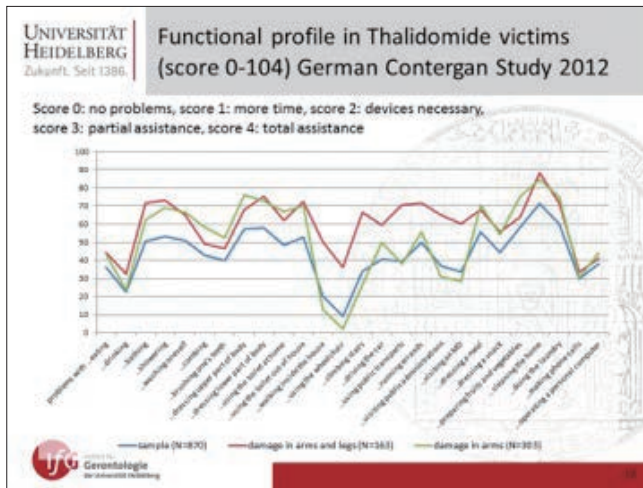
The spine e.g. is damaged following a disbalance of patterns of movement, caused e.g. by short arms or by arms with different length and different kind of damage which implies asymmetry of movements causing overstrain. Damages in different degrees and locations may develop thus in the course of 50 years. In internal organs prenatal malformations, dysplasia or aplasia were found in 38 percent, at present there are found in up to 62 percent. This increase in the amount of damage in this population is due to two factors: better clinical diagnostics with a more effective detection of pathologies and a decline of the capability of compensation in thalidomiders due to an early manifestation of the aging processes.

In the evaluation survey 2015 participants were asked to write down the amount of damage points they had in their first medical exploration 40 or 50 years ago and how many they have at present. In spite of the fact that only prenatal damage gets points, there is a shift in the amount of affected people in the different groups, showing an increase in the groups with a higher amount of points and a decrease in groups with a minor amount of points as can be seen in the following figure.



Prenatal damages were described 40 years ago, but not all of them were detected. Many of them start causing discomfort since 5 to 10 years. Diagnostic methods improve rapidly and clinical results become more accurate.

In the survey of 2012 was established a functional profile of the participants in order to specify the impairments concerning different activities of daily life. In the following figure there are the data of three groups, the overall sample, the participants with damage in the upper limbs and the participants with damage in both upper and lower limbs.



The score ranges from 0 to 104. A low score means a high level of autonomy, a high score stands for a loss of autonomy in different degrees. A participant with a score of e.g. 104 shows no independency, he needs total assistance in all activities.

A score of 0 signifies that the correspondent activity can be realized without any problems. A score of 1 means that the participant needs more time to perform the respective task. With a score of 2 the participant needs special devices to perform the activity. The score of 3 stands for partial assistance, the score of 4 defines total assistance in performing a special activity. The different scores are added to obtain the total individual score.

The diagram identifies the different levels of autonomy in the different groups of participants corresponding to activities of daily life e.g. going outside the house, driving the car, running errands, visiting a medical doctor or doing things at home, cleaning or doing laundry or bathing, showering and so on.

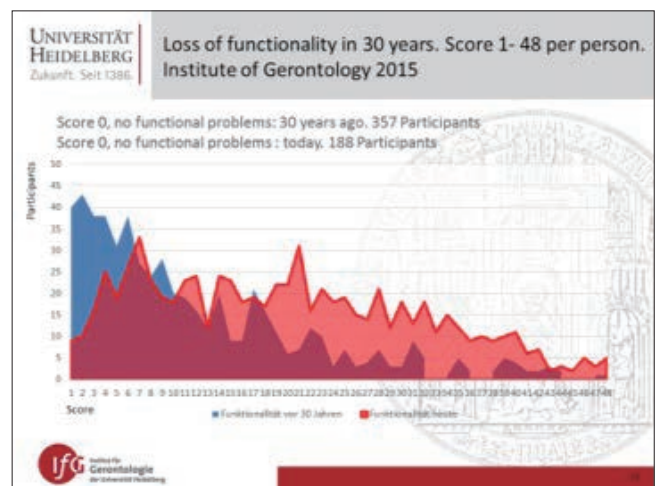
In the survey of 2015 the change of functionality was determined in the whole sample. The changes which took place over 30 years were documented in 12 activities of daily living – 30 years ago and at present. The correspondent scores defining the level of autonomy were 0 to 4, the same as in the preceding figure. The data of the following activities were collected and the value of the 12 scores were added to constitute the total individual score.

1. to shower
2. to dress one self
3. to go to the rest room
4. to walk
5. to climb stairs
6. to do small errands, to go to the doctor
7. to go by public transportation

8. to drive a car
9. to prepare a meal
10. to clean the home
11. to use a telephone
12. to use a personal computer or similar devices 30 years ago.

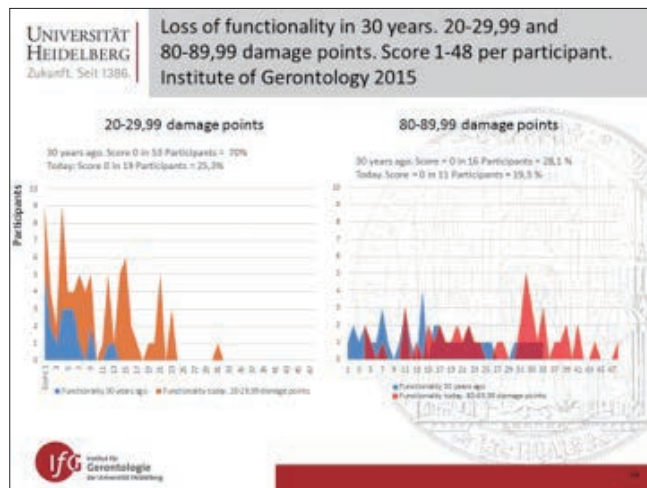
The functionality of the participants 30 years ago is marked in blue, the functionality at present is marked in red. In this figure the total score of every participant is entered in the diagram, the highest score attained was a score of 48. Every score includes the respective number of participants having attained a score of 1 to 48. A low score means a high grade of autonomy, the higher the score, the more pronounced is the loss of independency.

The score of 0 is not part of the diagram. 357 participants stated to be autonomous 30 years ago in all activities, at present there are left only 188 participants with complete autonomy.



30 years ago there were represented mainly the scores of 1 to 20 or 25. At present a higher amount of affected people have higher scores of 20 to 40. Higher scores are a measure for a loss of functionality and there is a shift to an increasing loss of autonomy in this population over a period of 30 years. This shift in functionality is possibly the expression or measure for the increasingly developing secondary damages and the progressively deterioration of prenatal damages.

In the following picture there are compared two groups of participants, one group with a low amount of points (20-30), another with a high amount of points (80-90). The collected data concerning functionality compare the situation at present with the situation 30 years ago.

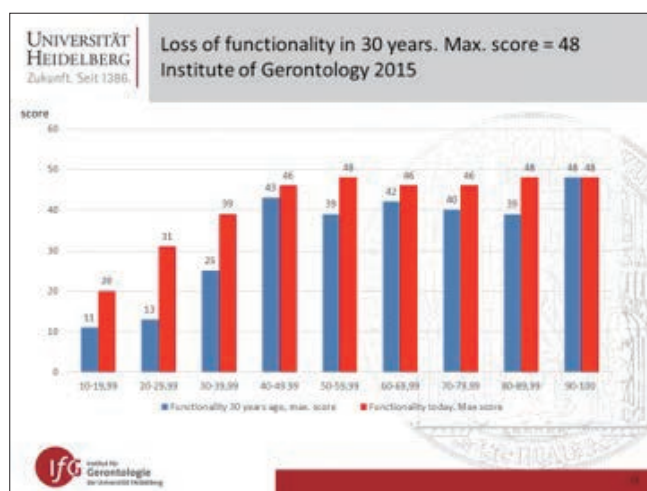


There is a bigger loss of functionality in the group of participants with 20 to 30 damage points than in the other group with a high amount of damage points. At present 19 participants are autonomous in all activities, 30 years ago they were 53.

The increase in score points which corresponds to a loss in function is considerable in the participants with low points. They had poor damage, therefore they led an almost normal life, they did a lot of heavy physical work, and they pay a high price for lifelong overstress.

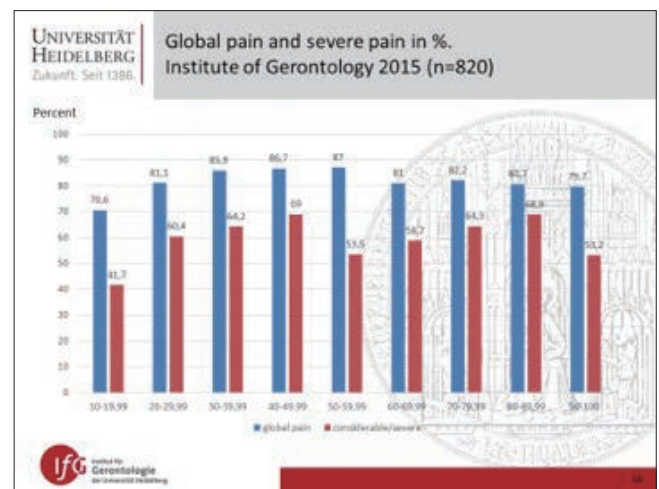
In participants with high damage points there is a loss of function, too, but the amount of this loss is not that big. The participants with a score of 0 diminish by only 9% in 30 years. There is one person with a score of 48. In this group the autonomy was already diminished 30 years ago, as they suffer from a high amount of severe physical damage of all kinds.

In the following figure the maximum scores reached by participants with different damage points 30 years ago and at present are compared.



The biggest increases in loss of functionality are seen in the participants with low prenatal damage points. Participants with 20 to 30 points show a difference of scores of 18. People with 40 points and more differ not so much concerning their scores if compared through 30 years. We find an increasing homogeneity in this very heterogeneous population. We find this homogeneity in other areas, too, e.g. pain or physical resilience.

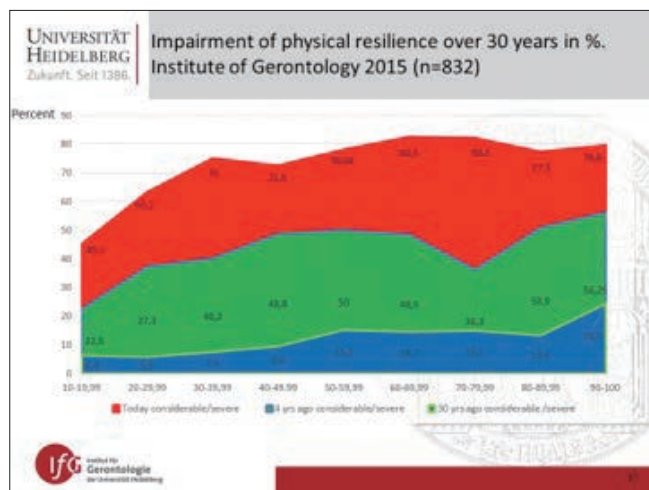
The prevalence of pain in the sample of 2012 compared to the data of 2015 show an increase. Data on different dimensions of pain were collected, too, and there could be observed as well a tendency to homogenization.



Participants with a low amount of 10 to 20 points reported to suffer from global pain in over 70 percent, they suffer from considerable or severe pain in 41 percent. Thalidomide affected people with 30 or more damage points show a mean percentage of participants suffering from global pain of 83 percent and participants suffering from considerable or severe pain show a mean proportion of 61.5 percent.

This highly heterogeneous sample shows increasingly a tendency towards homogenization concerning discomfort, loss of mobility and functionality, physical resilience and pain.

Similar findings were collected in impairment of physical resilience or fatigability. This severe symptom is due to pain, to arthrosis and to weakness of skeletal muscles. Muscular weakness causes pain as consequence of a higher tonus of muscles, a hardening of muscles and shaking. The results show that this process is increasing since 30 years and through the last 5 to 10 years this process accelerated rapidly. The data confirm that the more areas were damaged, the higher was the degree of weakness.

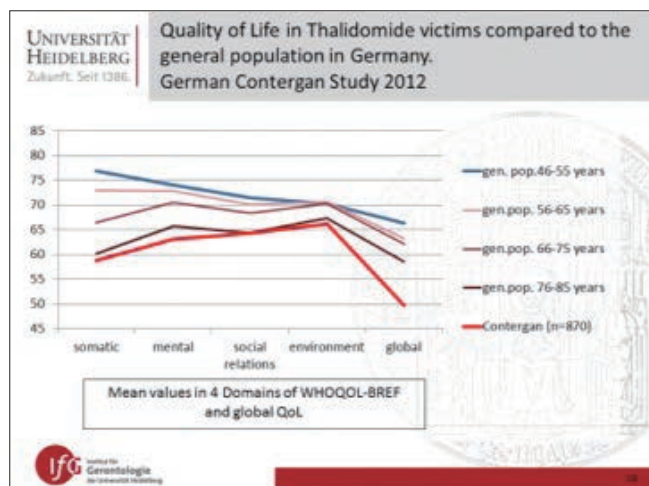


This progressive loss of physical resilience results in a decrease of daily activities, an increase of need of assistance and the participation in all kind of social activities is at risk. Participants need more rest and for a longer interval than years ago. They say that 20 years ago they were able to work e.g. in the garden for three, four, five hours and needed for recovering maybe one hour or less. At present they work one hour and need up to a 24 hour's rest to feel well again.

This process is developing through a period of 30 years. An accelerated increase is found through the last 4 years and in all damage groups. Participants with 60 to 70 damage points show an impairment of physical resilience in 14.7 percent 30 years ago, 4 years ago there were 48.5 percent and at present there are 82.5 percent.

It is impressing to witness how people affected by Thalidomide are rapidly aging and how they are losing their functionality, too. There is a decrease of autonomy in daily activities which requires an increasing need of assistance. The participation in all kind of social activities is actually at risk and on a long run maybe it will endanger affected people.

With so many different damages and disorders it is not easy to live, and even being a very brave population, quality of life is affected, too, as can be seen in the following figure.



The mean values of four different domains of QoL as well as the global QoL are compared in thalidomiders and the general population in different age groups. The QoL of thalidomiders is worse than the QoL of the general population age 75 to 85 years. Both men and women in the sample have a distinctly higher percentage of depressive disorders compared with the general population in the correspondent age group. In the interviews about a third of the participants showed depressive symptoms.

The need in treatment of depressive disorders, especially the treatment of trauma is very high in this population, as they find themselves in a state of crisis. They lived their life adapted successfully to their physical situation. Since about 5 to 10 years the development is reversed, they are losing skills and mobility, they never know when and in which amount they may lose physical faculties, whether they will be able to compensate the loss or not. They leave their jobs as they are not anymore able to attend their regular work. It is a very severe burden, they feel they cannot rely on themselves, they do not know what will happen next, where they will be next year. The more areas of the body are affected, the higher the risk of a depressive decompensation.

It is not only the physical situation that influences the mood, there are everyday problems that influence the mood, too, as e.g. the personal assistance. It is a very vital matter with a considerable impact on mental health. It is not easy to live with so many different damages and discomfort and even being very a brave population, as they are, quality of life is affected.

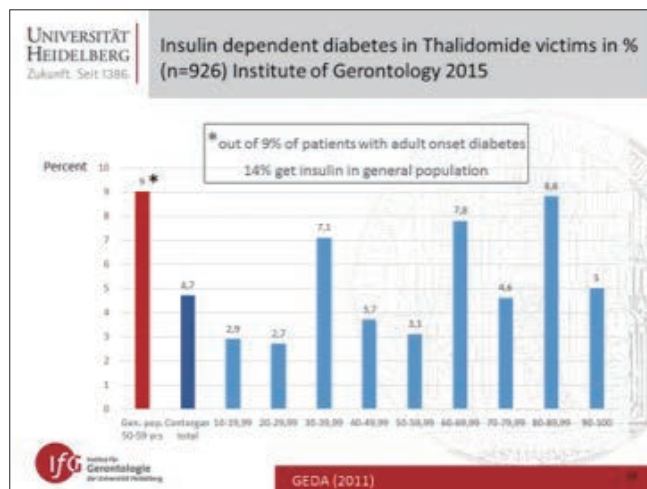
What kind of damage may be found in internal organs?

Thalidomide is a well-known inhibitor of angiogenesis and on this background most damages can be explained. The percentage of damages in internal organs increased up to today by almost 25 percent. The capability of compensation is decreasing, the damage turns up and people feel discomfort.

In the sixties everybody was impressed by the visible orthopedic malformations, therefore internal damages were often overseen and only very severe internal dysfunctions detected. At present there are better diagnostic methods than 50 years ago, the representation of small vessels, bile ducts, or of the nerve system is feasible.

The next figure shows data from the survey of 2015 concerning the prevalence of insulin- dependent diabetes mellitus, 43 participants were identified. The following samples are described: the general German population of the thalidomider's age group, the whole sample of participants in the survey of 2015 and the 43 participants suffering from insulin-dependent diabetes mellitus in relation to the amount

of damage points. Most of them were highly affected and had a high amount of damage points.

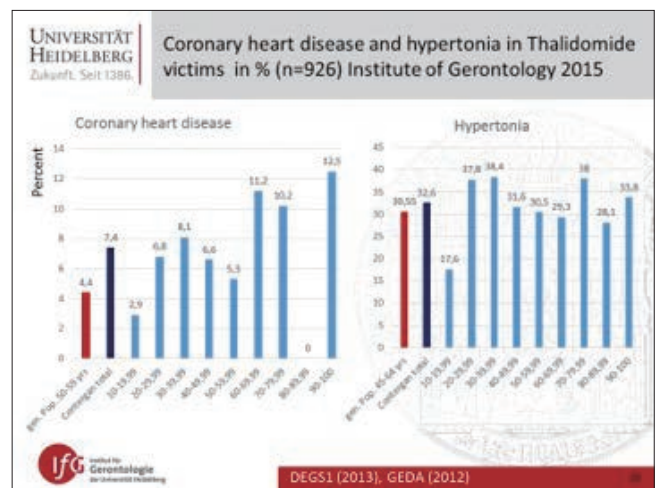


The statistics of the survey of the Robert Koch Institute GEDA (Gesundheit in Deutschland aktuell) record in the general population age 50 to 59 years 9 percent of individuals suffering from diabetes mellitus with adult onset. Out of these 9 percent a fraction of 14 percent are insulin-dependent patients, that corresponds to about 1 percent of the general population age 50 to 59 years suffering from late onset and insulin dependent diabetes mellitus.

In the total sample of the thalidomiders there were 4.7 percent, the fourfold amount. The participants with 80 to 90 damage points show the highest amount of insulin-dependent participants with 8.8 percent. The cause is unknown, there might be damages in the pancreas caused by prenatal reduced blood flow on account of Thalidomide intoxication. The participants were able to compensate as long as they had resources, getting older the resources diminished and decompensation occurred.

Two participants stated to have diabetes mellitus type 1, one of them started taking insulin with 3 years, the other with 50 years. The rest of the participants suffer from a late onset diabetes mellitus, all of them starting insulin after the age of 36 years, most of them after 48 years.

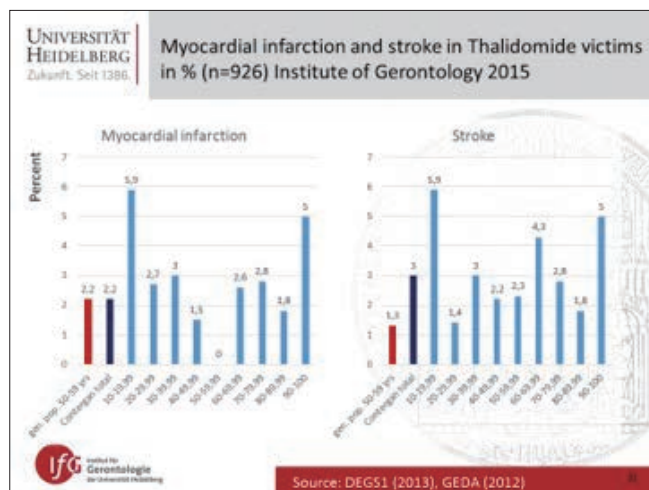
Coronary heart disease and arterial hypertonia are found to have a higher representation in the population of thalidomide affected people.



In the general population age 50 to 59 years we find coronary heart disease in 4.4 percent. In the survey of 2015 the sample shows in 7.4 percent coronary heart disease. In participants with a high amount of damage points there are documented up to 12.5 percent, which represents a three- to fourfold ratio of coronary heart disease in this population compared with the general population.

In the general population age 45 to 64 years the prevalence of hypertonia is about 30 percent. In the sample of 2015 we found a mean value of 32.5 percent. The pattern of distribution of participants with high blood pressure concerning their damage points is different from coronary heart disease. This may be due to difficulties in measuring blood pressure in this population. The usual measuring methods often are not applicable in patients with severe malformations. To prevent coronary heart disease, strokes and myocardial infarctions it is an urgent need to develop measuring methods for this endangered patients.

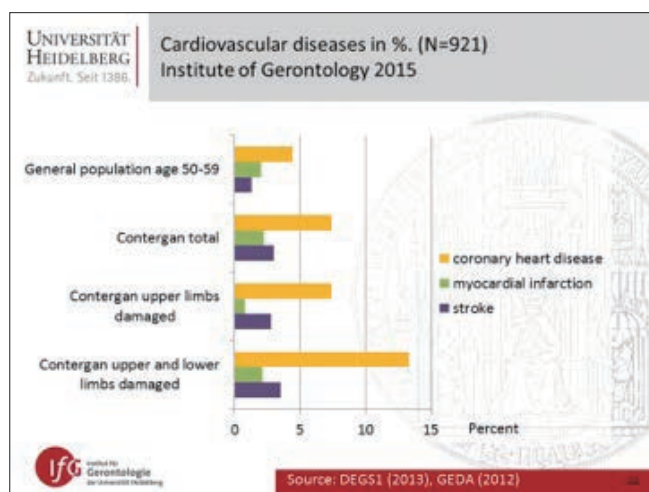
Myocardial infarction and stroke endanger thalidomiders severely. The general population age 50 to 59 years and the total Thalidomide sample seem to have identical numbers concerning the prevalence of myocardial infarction, but show an almost threefold prevalence of stroke. In both diagnosis the risk seems to be high for all participants independently of the amount of prenatal physical damage.



The participants with 10 to 20 damage points and those with a high amount of points are both endangered in a similar way. In the data of the survey of 2015 participants with 10 to 20 damage points seem to be at a similar risk as the population with 90 to 100 damage points, both showing myocardial infarction and stroke in 5 to 5.9 percent. Participants stated that they suffered their first stroke very early, with 45 or 47 years.

These data are presented to show the severe risk thalidomiders are exposed to. Health care professionals should be informed about these facts to examine Thalidomide affected patients properly, looking for vascular risks and when necessary starting preventive measures in time.

The prevalence of cardiovascular diseases in the general population and age group of 50-59 years is compared in the next figure with data collected in the survey of 2015. In contrast to the data shown until now the participants are now included according their orthopedic damage in upper and lower limbs, deaf participants are not included.



The amount of participants suffering from coronary heart disease is considerably higher in the participants (Thalidomiders total 7.4 percent) than in the general population age 50 to 59 years (4.4 percent). Participants with damage in upper and lower limbs show the highest risk with 13.3 percent. The frequency of myocardial infarction is almost the same in both populations, as we saw already, participants with upper limb damage show myocardial infarction in 0.8 percent, with upper and lower limb damage in 2.1 percent. Stroke is found to occur in Thalidomide affected people almost three times more often than in the general population. Participants with damage in both upper and lower limbs are affected in up to 3.5 percent, participants with only upper limb damage in 2.8 percent.

The Thalidomide affected population, especially the persons with damage in both upper and lower limbs, are severely endangered by coronary heart disease and by stroke, coronary heart disease being a high risk for myocardial infarction.

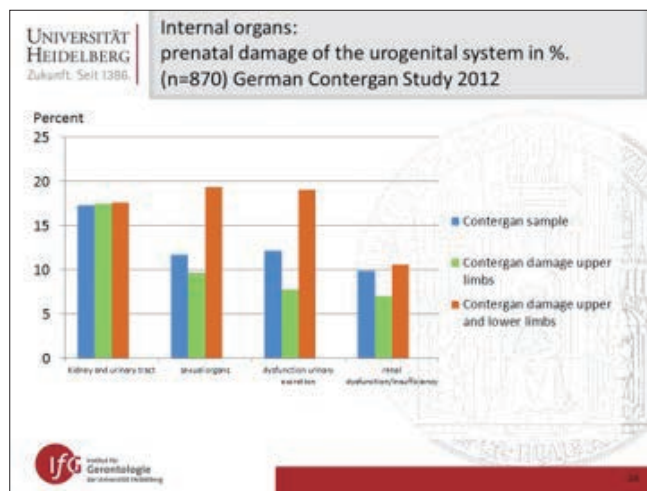
Unfortunately the causes of death of this relatively young population are not known, therefore the share of diseases of the cardiovascular system as cause of death is unknown, but due to statements of participants there is good reason to believe that they are an important cause of death. This situation makes it urgent to explore the background of these findings, to learn the possible causes of this risky situation, to study the vessels, their course, their buildup and structure all over the body to find out where the risks are and to manage either prevention or therapy.

The following figure identifies prenatal damage in the cardiovascular system and possible health effects.

Organs	Prenatal damage	Possible health effects
Heart	Dysplasia/malformation	<ul style="list-style-type: none"> Cardial insufficiency Cardiopathy
Blood vessels	<ul style="list-style-type: none"> Weakness of vascular wall (Hypoplasia of muscularis) Reduced vascularisation, reduced diameter of vessels Atypical course of vessels Truncation of vessels Missing vessels 	<ul style="list-style-type: none"> Myocardial infarction Stroke Reduced blood supply e.g. cold hands and feet, pain Dysfunction of lymphatic and venous system Dysplasia of intrahepatic ducts?

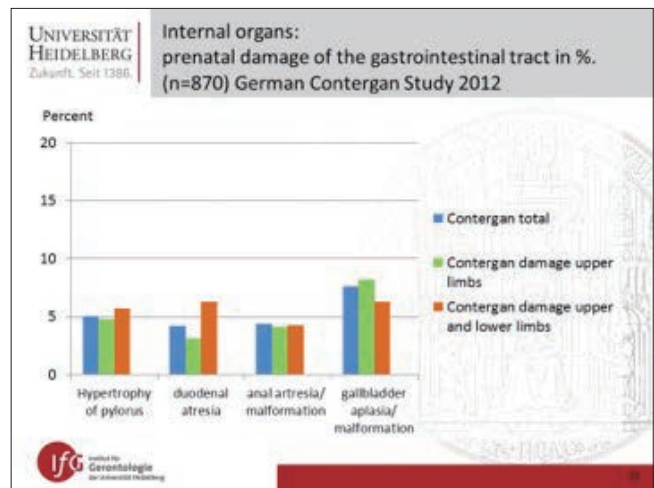
Thalidomide is well known as a substance with the property to impair the growth of blood vessels. The period of life with the fastest growth is the prenatal period. There is a solid scientific basis to verify it. There is strong evidence that Thalidomide causes the pathological changes in vessels that can be seen nowadays due to improved diagnostic methods. Impaired vessels impair the development and function of internal organs and the musculoskeletal system.

Concerning malformations and damages of the urinary tract, the participants with damage in both upper and lower limbs are the more affected group as seen before, too.



About 17 percent of the sample of 2012 show a prenatal malformation of the kidneys and/or urinary tract. About 10 percent suffer from renal dysfunction or insufficiency. Participants with damage in both upper and lower limbs develop as twice as often malformations of sexual organs and a dysfunction of the urinary excretion in 19 percent. The malformation, dysplasia or aplasia of sexual organs, the missing descensus testis cause childlessness. In about 12 % of the total sample the participants stated to be childless, childlessness being one of the most serious and straining outcomes of the thalidomide damage.

Concerning the gastrointestinal tract there are affected about 5 to 6 percent of the participants.

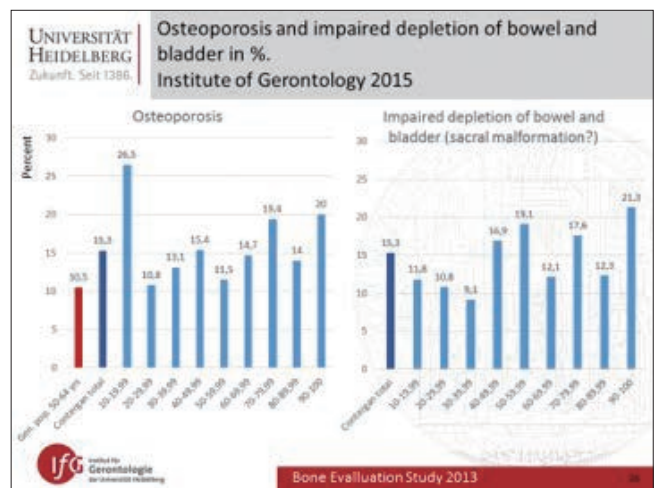


The most frequent prenatal damage is the gall bladder aplasia or malformation. There are hypertrophy of the pylorus, duodenal or anal atresia or malformation, too. Some participants report problems during colonoscopy that may give a hint to atresia in the colon.

In the following picture there are two important issues, the osteoporosis and the impaired function of the bladder and bowel.

There are more participants suffering from osteoporosis than in the general population, as is to be expected. Thalidomide affected people show functional impairment and reduced mobility, too. The most important stimulus for the buildup of the bones is missing.

In the course of the interviews questions about different body functions were asked and participants described an impaired depletion of bowel and/or bladder, problems existing since early childhood. The participants referred quite often to additional malformation of the pelvis and sacral bone. There may be a damage of the vegetative nerve system that supplies the bladder and the rectum caused by dysplasia of the pelvis.



Following the data of the survey of 2015 there are 15 percent participants suffering from osteoporosis, in the general population age 50 to 64 years there are 10.5 percent. The high amount of 26.5 percent of participants with 10 to 20 damage points is a striking result and gives a hint that there are other additional causes of osteoporosis in thalidomidiers than poor mobility and poor physical strain.

The impaired depletion of bowel and/or bladder shows up in 15 percent of participants. The data from the Foundation record prenatal dysplasia or malformation of pelvis in 10 to 12 percent. A possible connection between the malfunction since childhood and the prenatal malformation should be investigated.

The last figure describes the prenatal damages of internal organs and potential health effects in Thalidomide affected people.

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Internal organs: health effects of prenatal damage		
Organs	Prenatal damage	Possible health effects
Kidney	Malformation and/or dysfunction. E.g. Aplasia, Dysplasia, polyzystic kidney, pelvic kidney	Kidney stones, renal insufficiency as a result of <ul style="list-style-type: none"> • Malformation • Too little fluid intake
Gastrointestinal tract	<ul style="list-style-type: none"> • Hypertrophy pylorus • Aplasia of gallbladder • Duodenal, anal atresia • Malformation of pelvis and lower spine 	<ul style="list-style-type: none"> • Indigestion • Risk of incontinence after operative treatment • Partial paralysis of bladder and/or intestine • Dysfunctional sexual life
Sexual organs	Aplasia or malformation of sexual organs	<ul style="list-style-type: none"> • Operative removal • Sexual dysfunction • Childlessness • Serious psychological burden
Endocrine glands	Malformation or dysfunction of glands	Reduced hormonal production

What do we learn out of those results?

1st: Thalidomide victims are an endangered population.

2nd: Health care professionals should know more about possible pathologies due to Thalidomide to be able to provide a better health care and to minimize risks of all kinds. In addition Thalidomide affected people need a low-threshold and easily accessible psychological and psychotherapeutic support.

3rd: Society – all of us - we should appreciate their lifelong achievements, their creativity in developing strategies to adjust to all requirements, their humor.

All activities they are performing need more energy, more strength, more time and more fantasy e.g. to develop devices and strategies to maintain autonomy. More and more they need a higher amount of assistance.

We are bound to improve their situation by all means.

Thank you for your attention.

Q&A

Hinoshita: Thank you very much, Dr. Ding-Greiner. I have one more additional comment to tell you. Last year, we visited her room at the Institute of Gerontology, University of Heidelberg when she accepted us warmly, Professor Kayamori and Dr. Shiga and me. Thank you very much for it. Dr. Schulte-Hillen, please.

Schulte-Hillen: Thank you very much. Thank you very much for this fantastic presentation. I would like to know I found very frightening aspect that apparently diabetes and cardiovascular diseases seems to have higher prevalence in a premade group than in others. And can you say some, can you comment on the fact that on the idea proves this is secondary to low activity life style, like I mean somebody without legs how should he make sports?

Ding-Greiner: If you get late onset diabetes you may say it's caused by life style. But I think it's different in the case of an insulin-dependent diabetes. There may be a prenatal damage in the pancreas caused by thalidomide. We got a lot of statements from thalidomidiers suffering from damage in different organs. Diagnostic by MRTs show often unusual findings. Maybe they have a damage in the pancreas, difficult to explain in the general population but comprehensible knowing that thalidomide intoxication is the cause. We asked for insulin-dependent diabetes because it is different from the normal late onset diabetes. Clinicians should work on it, should find the underlying cause. I only have the numbers, out of the results of what people told me. But I'm sure this data are reliable. Thalidomide affected people are not lying, they do not say they have diabetes when they don't. In clinical observation and studies there will be found out more.

The other problem you mentioned is coronary heart disease. It was interesting, when participants told me they had myocardial infarction or a stroke, I asked whether doctors looked at their vessels and what they did find. Did they find advanced arteriosclerosis? Mostly they said, no, the doctor said they have very fine arteries. This is strange to me, therefore I suppose that there are other prenatal damages in the arteries. The vessels may be thinner in diameter, the walls thinner as in general population and thus they may break easier. A participant told me that she suffered from a couple of strokes. The vessels in the neck were found to be altered and very thin in diameter, so she got a stent and since then she feels better. Thus I think it is very important to look at the vessels and maybe we will find the cause of all kinds of

disorders. If physicians know about that and start looking about it, it will be possible to prevent stroke. Thalidomiders are very, very at risk concerning stroke and it is a terrible thing to have a stroke in addition to thalidomide damages.

Schulte-Hillen: Thank you very much.

Ding-Greiner: You are welcome.

Hinoshita: Dr. Ding-Greiner, as for diabetes mellitus, you think the diabetes had been caused by the original congenital defect of pancreas in thalidomiders?

Ding-Greiner: Thalidomiders run in principle the same risk to get diabetes as the general population, but not everybody is insulin-dependent. It takes a couple of years until people get insulin-dependent. Thalidomiders are quite young to suffer from insulin-dependent diabetes. Maybe there are prenatal damages in the pancreas, a destruction of tissue that causes the deficiency.

Hinoshita: So we need some body image such as CT.

Ding-Greiner: Yes.

Hinoshita: And also it's necessary to measure insulin...

Ding-Greiner: Yes, exactly.

Hinoshita: Taking blood, you know.

Ding-Greiner: Yes. And I hope these data will inspire you to look for this kind of problems.

Hinoshita: Do you have anything else? Any other question? Nobody?

Thank you very much, Dr. Ding-Greiner.

Long-term follow-up of thalidomide embryopathy in Sweden: Osteoarthritis in lower extremities, function in upper extremities, and new data on cervical spine

Dr. Shadi-Afarin Ghassemi Jahani
Sahlgrenska University Hospital, Gothenburg

Hinoshita: Then go ahead to the next presentation. The title is “Long-term follow-up of thalidomide embryopathy in Sweden: Osteoarthritis in the lower extremities, function on the upper extremities and new data on cervical spine” presented by Dr. Shadi-Afarin Ghassemi. She is a member of medical faculty, Gothenburg University from 1992 to 1998. She is now Ph.D. student in orthopedics research at the Sahlgrenska Academy at the University of Gothenburg since 2006. And she has been a professional orthopedist in Kungälv Hospital in 2006, and ongoing. Then Dr. Ghassemi, please.

Ghassemi: Thank you very much. Thank you very much for having me today. Let me congratulate you all in Japan for Dr. Omura’s Nobel Prize this year in medicine. It’s actually very

wonderful. Let me talk to you long-term follow-up of thalidomide embryopathy in Sweden, osteoarthritis in the lower extremities, functioning on the upper extremities and new data on cervical spine.

My co-authors are associated Professor Aina Danielsson, Professor Jon Karlsson, and Professor Helena Brisby. Thalidomide was used as a sedative drug for pregnant ladies in delayed 1950s and early 1960s in Sweden. It was soon proved to be a very high potent teratogenic substance and led to thalidomide embryopathy. It happened in Sweden as in the rest of the world except USA because Mrs. Kelsey did a wonderful job against thalidomide in US. Hundreds of children with thalidomide embryopathy were born. Many of them died at the birth. And the survivors are of thalidomide

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Long-term follow-up of thalidomide embryopathy in Sweden. Osteoarthritis in lower extremities, function in upper extremities and new data on cervical spine.

Shadi Afarin Ghassemi Jahani MD
Tokyo, Japan
Nov 21, 2015

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DEPARTMENT OF ORTHOPAEDIC

Co-authors

- Aina Danielsson, MD, PhD, Assoc. Prof.
- Jon Karlsson, MD, PhD, Prof.
- Helena Brisby, MD, PhD, Prof.

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Introduction:

Thalidomide was used as a sedative drug for pregnant women in the late 1950s and early 1960s in Sweden.

It proved to be a high potent teratogenic substances in medical history, leading to Thalidomide Embryopathy (TE).

In Sweden as in the rest of the world, except USA, hundreds of children with TE were born. Many of them died at birth. The survivors of TE are now over 50 years old.

At the time of our study there were 108 individuals registered in The Swedish Association of Individuals with Thalidomide Embryopathy. "Förenigen för de neurosedynskadade, FFdN."

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Study I

Long-term follow-up of TE; malformations and development of osteoarthritis in lower extremities and evaluation of upper extremities function.

Ghassemi Jahani SA et al., J Child Orthop. 2014; 8(5):423-33

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embryopathy over 50 years old. At the time of our study, they were 108 individuals registered at the thalidomide association of Sweden with thalidomide embryopathy. It's called Föreningen för de Neurosedynskadade. We did the first study which was published last year on long-term follow-up of thalidomide embryopathy malformations and development of osteoarthritis in the lower extremities and evaluation of lower extremities function. The aim of the study was to study malformation and the lower extremities, to study

osteoarthritis in the hips and the knees and clinical impact of them. And to see if the malformation of the upper all our extremities affected function as we could measure by evaluated disease-specific outcome questionnaires. 108 members of the thalidomide association in Sweden. They have very strict rules in this association. So all contacts goes actually through the association. And 24 had rejected all contact to any study whatsoever. So 84 will invite of those 33 did not answer at all, and 18 did not accept it, and 33 subjects

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Aims

- To study malformations of the lower extremities.
- To study osteoarthritis (OA) in the hips and knees and the clinical impact.
- Did malformation of the upper or lower extremities affect the function as measured by validated disease-specific outcome questionnaires?

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Material and Methods

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graph TD
    A[All members 108] --> B[Invited 84]
    A --> C[Rejected 24]
    B --> D[Not accepted 18]
    B --> E[33 subjects accepted]
    B --> F[Did not answer 33]
    E --> G[31 participants]
    E --> H[Excluded Severe mental problem]
    E --> I[Excluded Stroke]
    
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Patients

Thirty-one participants, including 13 females and 18 males with a mean age of 45.8 (SD 1.1) years were examined.

The participants came from all parts of Sweden, except 3; two who lived in Norway and one in USA.

The study was multidisciplinary, and included in addition to the orthopaedic part, ophthalmology, neuropsychology, radiology, dentistry, otolaryngology and speech pathology.

All participants were examined by one orthopaedic surgeon (SG), including a full clinical examination and measurement of range of motion (ROM) of the large joints.

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Computer tomography

All participants were also examined by Spiral Computed Tomography (CT) of the lower extremities including the pelvic, in supine position. The CT scans used for description of malformations.

For classification of OA the following scale was used:

- Grade "0", no signs of OA
- Grade "1", mild signs of OA with reduced cartilage height and/or a few osteophytes
- Grade "2", severe signs of OA with osteophytes and cysts.

For occurrence of OA:

The hip joint evaluated as one complete joint

The knee joint evaluated in three parts, medial, lateral and patello-femoral parts.

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Outcome Questionnaires

- Validated questionnaires were used for evaluation of:
 - Upper limb function: DASH: Disability in Arm Shoulder and Hand. (Atroshi 2001)
 - Lower limb function: RAOS: Rheumatoid Arthritis Outcome Score. (Bellamy 1988)
- Questions on previous treatment and surgical procedures

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Results

Other conditions

Fifteen individuals had other diseases such as asthma, hypertension, sleep apnoea syndrome and migraine.

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accepted to participate in the study. Also because of the same strict rules we were not allowed to send any reminder to this group that didn't answer. We had exclude one because of the stroke, also another one severe mental problem. So we examined 31 participants, the mean age were 46 years old, 13 female and 18 male. Participants came from all part of Sweden except three. Two were living in Norway at the time, and one is living in USA but he was visiting his home country. The study was multidisciplinary and in addition

to the orthopedic part, we had ophthalmology, neuropsychology and radiology and then otolaryngology and speech pathology. All participants were examined by me and including full clinical examination and the measurement of range of motion of the large joints. All participants were also examined by the spiral computed tomography on the lower extremities including the pelvic, and the examination was in spine position, so we didn't have any way bearing on the lower joints. CT scan was used to describe the malformations.

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Malformations of the upper limb

Location of malformation	No of extremities (%)
Shoulder	5 (8.1)
Elbow/forearm	16 (25.8)
Hand	43 (69.4)

Number of fully functional arms/hands (=palm with ≥ 2 fingers with a grip function)	No of individuals (%)
2	27 (87.1)
1	2 (6.5)
0	2 (6.5)

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Malformations of the lower limb

Five individuals (16 %) had Proximal Focal Femoral Deficiency, PFFD:

- 2 using wheel chair constantly
- 1 using wheel chair occasionally
- 2 walking with prostheses

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Two patients with PFFD

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Lower limbs of remaining 26 individuals

- All individuals had some kind of other malformations.
- 65% of the hips showed some deformity of the femoral head.
- 50% of the knees: hypoplastic lateral femoral condyle and hypoplastic intercondylar notch.
- All were independent walkers

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Slightly deformed femoral head

Slightly hypoplastic lateral femoral condyle

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RAOS: lower extremity function

	N	All	Occurrence of PFFD *		p-value
			No n=26	Yes n=5	
Pain	31	79 (21)	80 (20)	68 (24)	n.s (p=0.31)
Symptoms	31	79 (18)	80 (18)	70 (17)	n.s (p=0.20)
ADL †	30 ‡	83 (20)	87 (17)	56 (13) †	p=0.0076
Sport & Recreation	31	62 (36)	72 (36)	9 (10)	p=0.0007
Quality of Life	31	66 (26)	71 (25)	40 (17)	p=0.016

ADL score significantly lower for those with OA (79) compared with those without OA (94) in any of the hip joints (p=0.036).

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Because of not having weight-bearing, we had to follow a special scale. So grade 0 was no signs of osteo-arthritis, grade 1 was mild signs of osteoarthritis with reduced cartilage height and or a few osteophytes. And grade 2 was severe sign of osteoarthritis with osteophytes and cysts. And for evaluation of the hip joint, we had a hip joint as a complete joint and the knee was divided in three parts. Lateral, femur and patellofemoral parts. All outcome questionnaires used are evaluated questionnaires for upper limb function disability

dash all shoulder and hand. And lower limb function, RAOS: Rheumatoid and Arthritis Outcome Score. Also questions on previous treatment and surgical procedures were asked. We found as a result, 15 individuals had other diseases, such as asthma, hypertension, sleep apnea and migraine. And allergy was not considered any disease. Malformation of the upper limbs and I hope you can see. Anyway, number of extremities up on the top. I need exact number of individuals. 8 percent of shoulder malformation. 26 percent of elbow and 4 percent

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DASH: upper extremity function

- Patients with severe deformities, i.e. more than one limb with major malformation (n=15), had significantly lower DASH-scores than those with no extremities with major malformations (n=16). (25.5 vs. 14.3, p=0.0015).
- Existence/non existence of pincer grasp, did not affect the overall function of the upper limbs.

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Results OA

- Signs of OA were found in:
 - 40 % of hips
 - 60 % of knees
 despite the low sensibility of CT for diagnosis of OA

Healthy Swedish population: OA in 2%

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Conclusion

- A wide variety of malformations of the extremities was found.
- Five individuals with PFFD (severe malformations in the lower limbs) also had malformations of the upper limbs, including the hands.
- They had significantly reduced function of their lower limbs, affecting ADL, sport/ recreation and QoL, compared with those without PFFD.

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Conclusion

- Most individuals without PFFD (n=26) had some kind of minor deformity in the lower limbs as visualized by CT scans.
- Ambulation was not affected, though.

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Conclusion

- Upper extremity function (i.e. total DASH score) significantly lower in those with major deformity in more than one limb
- BUT: this score does not evaluate fine motor skills
- The differences were below the level of clinical relevance

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Conclusion

Signs of OA were more frequent In TE patients (40% hips and 60% knees) compared with general Swedish population (2%)

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of malformation. And almost 70 percent had a malformation on the hands. And the lower one is the number of individuals. 27 had two functional full arm, not full arm, so the functional hand was considered more than two fingers with grip functional small palm. So it's not shortening of the arms or also other malformations just the function. Two had no functional arms and hands. And two had only one side. Malformation of the lower limbs, we found five individuals proximal focal femoral deficiency. Two were using wheelchair constantly, and one was using it only occasionally, and two were walking with prostheses. These are the two individuals walking by a prosthesis at one side. The remaining 26 individuals had also some kind of odd malformations. Sixty-five percent had some deformity of the femoral head. And 50 percent of the knees had hypoplastic lateral femoral condyle and also patellofemoral intercondylar notch which is associated with undeveloped or lack of anterior cruciate ligament. All were independent walkers though. And as you can see this is likely deformity of the femoral head, there is a picture. In this picture the acetabulum doesn't cover the femoral head. And this is the lateral femoral condyle, hypoplastic lateral femoral condyle. These two what you can see is to draw the

arms using for doing CT in superimposition. Lower extremity function, we could compare the group it 26, we don't any P50 and 5 we P50 and they had significantly lower score for activity of daily life also sport and recreation was quite low and quality of life. Activity daily life also was quite low for those with osteoarthritis at one side comparing those we don't osteoarthritis also significantly statistically significant. Upper extremity function was measured by DASH. We could also see severe deformities those with at least one limb with major deformity and we are not considering hand anomalies. If you not considering finger anomalies but major deformities at least one limb had significantly lower DASH score than the others with not major deformities on any limb. Existence or nonexistence of the pincer grasp was not affected in this function measurement. As also as a result we found sign of osteoarthritis in 40 percent of the hips and 60 percent of the knees, and this is also despite of the low sensibility of CT for diagnosis of osteoarthritis comparing with healthy Swedish population at the same age is only 2 percent. So it's quite high. A great variety of malformation on the lower extremities were found. Five individuals P50 with severe malformation of the lower limbs and also have malformation of upper

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Study II

Degenerative changes in the cervical spine are more common in middle-aged patients with thalidomide embryopathy than in healthy individuals

Ghassemi Jahani SA *et al.*, Submitted

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Aim

To investigate the presence of malformations and subsequent disc degeneration (DD) of the cervical spine in a group of middle-aged individuals with TE and to compare with a healthy group of controls.

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Material and methods: Patients

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    graph TD
      A[Invited 31] --> B[27 performed MRI]
      A --> C[One had metal clips in the head]
      A --> D[Two had claustrophobia]
      A --> E[One rejected]
      B --- F[27 healthy controls, age- and sex-matched]
    
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27 healthy controls, age- and sex-matched

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Results Malformations

- 15 (56%) patients had deformities on 1-4 of the extremities.
- All had some function of the upper limbs, despite short arms in some individuals.
- 81% had some degree of hand anomalies
- 8 (30%) patients had a bilateral pincer grasp.

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limbs. They had significantly reduced function of the lower limbs. And it affected the activity daily life, sports recreation and also quality of life.

Most individuals with all P50 and also some kind of minor deformity in the lower extremities. We could see by CT scans. But the walking ability was not affected. So upper extremity function was significantly lower in those with major deformity in at least one limb. And DASH doesn't cover the fine motor skills. That's why we didn't consider the pincer grasp actually. The difference was in this part will be low the clinical relevance. So the sign of osteoarthritis was quite high, 40 percent of the hips and 60 percent of the knees comparing with the general Swedish population. I'm going to show a very short summary on study two which is submitted this article submitted. The general these change in cervical more common in middle age patient with thalidomide embryopathy than in the healthy individuals. The aim of this study was to investigate presence of mal-formation and subsequent disease in this generation of the cervical spine in a group of middle age individual with thalidomide embryopathy and comparing to health group. All study group was 31 participants from the study one. One rejected MRI, two had

claustrophobia, and one had metal clips in operated in the head from 80s. So it was 23 remained and DP form and MRI. The result was compared with 27 healthy controls age and sex matched. In the group of the study, 56 percent had deformities up to 4 extremities. All had some kind of function of the upper limbs. But still very short in some of the individuals. 81 percent had some degree if hand anomalies, but 30 percent had pincer grasp bilaterally. We found these degenerations in more than 1 level and 90 percent of group with TE comparing with 67 percent on the control statistically significant result. 10 patients with thalidomide embryopathy had up to 4 level and segment of this degeneration.

While in the control group, we didn't have anyone more than 3 levels, also statistically significant. In both groups majority of those degeneration where located at lower segment C5-C6, C6-C7. And only TE had in upper segments. These pathology and osteoarthritis were more often in TE than controls. Almost 90 percent in TE group has some affected for arm in comparing 44 percent in the controls. And the amount for affected for arm pair individuals TE group was also higher. So as in conclusion or finding support and earlier development of these degeneration in TE. Because of increase of this degeneration is cervical spine also increase number of affected segments in TE. Most of this degeneration located in lower segments in both groups, both TE and same their control. And if these results are because of the drug itself or because of the unusual mechanical load on the neck and cervical spine. This is something to study more if you try hopefully. Thank you very much.

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Degenerative changes

- Disc degeneration (DD) on ≥ 1 level:
89% of the TE and 67% of CTR ($P < 0.001$)
- Segments with DD:
10 patients in TE had DD on ≥ 4 levels
None of controls group had DD on ≥ 3 levels ($P < 0.001$)
- In both groups majority of DD were located at C5-C6, C6-C7.
- Only TE group had DD of the upper segments.

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Q&A

Hinoshita: Thank you very much, Dr. Ghassemi. She gave us a good insight into osteoarthritis and degenerative changes in the cervical spine. By the way, there are some orthopedists

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Degenerative changes

- Disc pathology and osteophytes occurred more often in TE than controls.
- 24 pat (89%) in the TE group had some affected foramina (controls 44%)
- The amount of affected foramina per individuals was also higher in the TE group.

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Conclusion

- Our findings support an **earlier development of DD** in the TE group due to:
increased DD in the cervical spine
increased number of affected segments
- Most DD occur at the lower segments in TE, same as in norm or control group.
- If the presented results are due to the drug itself or only the unusual mechanical load on the cervical spine needs to be further studied.

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here from Japan and from Europe. They might have any other comment or question? Yes, Professor Kayamori.

Kayamori: Differential diagnosis. This is aging process or this is particularly for thalidomide people? How to differentiate between aging and characteristic of thalidomide especially in the cervical spine? We can see the early sign of thalidomide, but aging process also we can see the same.

Ghassemi: Yes.

Kayamori: So any of the distinction between these two groups.

Ghassemi: Of course. It's also the aging process, of course. But comparing to the control at same age and sex, we also can see that thalidomiders have much higher prevalence and incidence of this degeneration. And I have to tell you that MRI done in this group is, I think, it is one of the actually first study read MRI, because ethically in Africa, he did just X-ray on the cervical spine because of the high load on the neck with the head bearing. But this is only X-ray, but MRI we use them, I don't know if you are familiar with the Pfirrmann classification tool to just see the disks and to see how early they actually changes and they get this degeneration. So comparing of course it is an ageing process but comparing to the controls we see differences. Thank you.

Hinoshita: Is there any other question? Dr. Beyer, please.

Beyer: Yeah, Rudolf Beyer from Germany. Is it possible to divide the control group in people who has lifelong hard body work like building workers? For example, find out whether it's due to overburden, overstress over the years?

Ghassemi: The control is actually was collected the whole control where collected from those MRI. We don't have any clinical problems with the, how do you say, with the sensibility or anything clinical referee. So it's picked of, picked thousand picked MRI but in other, because of other, how do you say, investigation or nothing. So they were not unusual on the load of their neck, they were not head bearing, they were, I mean this is done what on those they have whole spine MRI and we just took this cervical part.

Beyer: OK.

Ghassemi: So it's actually the very average people we don't

have any problem, clinical problem. It's very, very relevant question.

Hinoshita: Anything else? Nobody has other question? OK? Thank you very much, Dr. Ghassemi.

Then according to the time table, next we will have some intermission. Now it's just 2:20 PM, then please take a rest during the intermission to 2:40. Then, close this discussion now. Let's come back here at 2:40.

(Intermission)

Hinoshita: OK, everybody. Now it's time 2:40 PM. Then let's start the next session of this symposium.

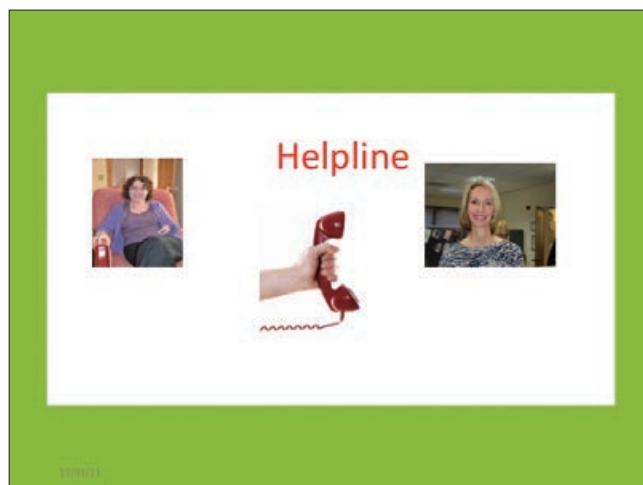
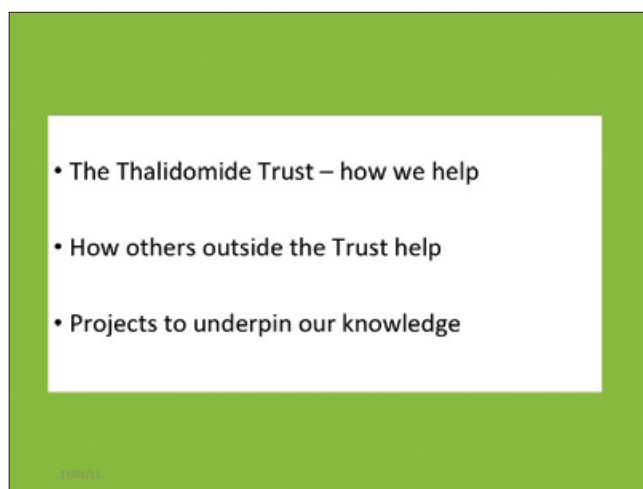
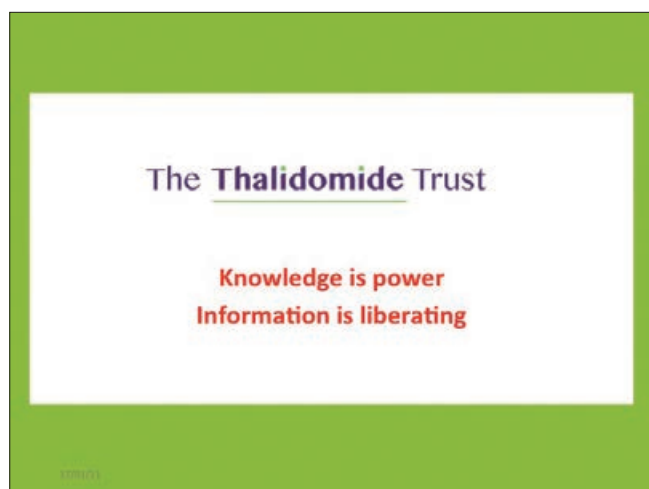
The Thalidomide Trust Knowledge is power; Information is liberating

Dr. Dee Morrison
The Thalidomide Trust, St Neots
Ms. Elizabeth Newbronner
Firefly Research & Evaluation, York

Hinoshita: As for the next presentation, here are two guest presenters. One of them is Dr. Dee Morrison over there. I should introduce her to you. She graduated from Liverpool University of medical school in 1986. Basically she has been working as partner in general practice at Walnut Tree Health Center in Milton Keynes for about 20 years. She began a medical adviser to the thalidomide trust since 2012. Since then she has vigorously been working as a medical adviser, tapering her work volume in general practice. I saw her at the Thalidomide Trust in last October. She accepted us warmly and gave us a ride on the way to and from the station in a new gorgeous car, BMW. I still imagine that she and her family might have greatly been attracted by German products,

maybe just like thalidomide. Then, Dr. Morrison, please.

Morrison: Thank you. Knowledge is power. Information is liberating. Thank you, Dr. Hinoshita for the introduction. As you have said I am a General practitioner having been a partner in a busy training practice for over 20 years. I also have 6 years' experience of helping managers understand the clinical aspects of or our work to help change the way referrals to specialists are managed. But for the last 3.5 years I have been working part time as Medical Adviser to the Thalidomide Trust for 3 days a week and now have just a small GP commitment. I am being helped today in my talk by Liz Newbronner from Firefly research and we have split



the talk in two sections with myself talking for the first 30 minutes explaining;

- The Thalidomide trust, what it is and how we help beneficiaries;
- How others outside the Trust help our beneficiaries and 2 case examples;
- 2 large research projects which have helped underpin our knowledge.


Then I am going to hand you over to Liz for the last 15 minutes to look at one further research project in more detail. I suggest we take Q&A at the end. However, please let me know if you have any translation issues as I go along.

If I turn first to the Trust, I wanted to explain what we are here for, what we can help with and who else can help. The Thalidomide Trust's main role is to look after and distribute the compensation fund set up for those affected with thalidomide embryopathy arising from thalidomide manufactured and distributed in the UK by Distillers now Diageo. Depending on their level of damage every individual receives an award. Since 2010, they have also been awarded an individual amount from the UK government called the

Health Grant. This is guaranteed for the next seven years. I mention money because it is important. It has a direct correlation with the individual's lifestyle and in turn their health. Also the Trust has had to undertake research to help lobby for increments in the award, the initial amount and its' continuance, as well as the obvious need to research to develop our knowledge of the medical issues.

So to summarize, the Trust's main role is the investment and annual distribution of the compensation fund.

So how do we help individuals? Well, for past 10 years, the Trust has operated a telephone helpline to support beneficiaries, more recently this has included email exchange. This is mainly answered by Ann Horten, who has an occupational therapist background but is also affected by thalidomide herself. She has upper limb damage. For the last three and half years I've helped as a GP. We have recently appointed a social worker as we perceive an increasing need for state benefits as individuals lose their independence as they age and need more help with state benefits. Alongside the helpline we are also able to visit and assess individuals in their own home. The wider team within the Trust helps with this particularly the overall Trust director and also the

Thalidomide damage is not unique
 International reputation
 Expert congenital deformity – custom make joint
 Complex surgery specialists
 Good bedside manners
 Seen others affected by thalidomide

Role of the Thalidomide Trust

“A quick expert opinion and treatment options from a specialist familiar with thalidomide damage”

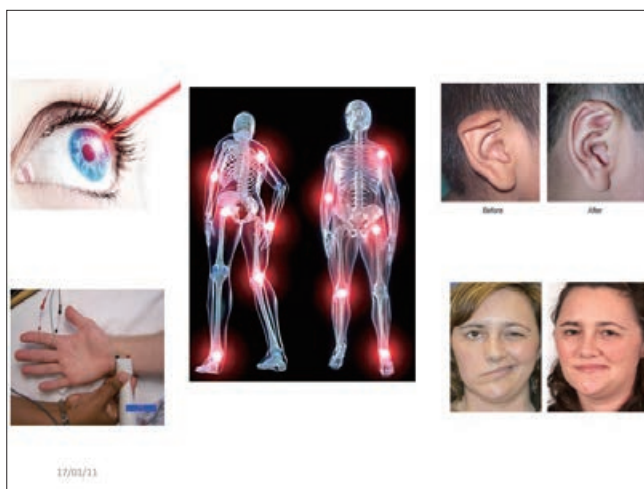
finance director. We have a pool of beneficiaries who provide much needed peer to peer support for individuals. We have an active NAC made up from beneficiaries who have been elected for a fixed term to help. We have annual meeting for the deaf community who also have a private Facebook page. We hold talks annually at the NAC meeting. This year, for example, we had a psychologist affected by thalidomide himself from Australia speaking about managing chronic pain. Last year we had a talk on cereblon and causation, a talk about the Blood pressure project and also Dr. Cowan, a neuro- orthopedic doctor talking. So we do regularly try to keep everyone updated about the issues we can help with. We also send out a newsletter. This is how we help.

So what issues do we help with? We can help with wheelchair purchase, gadgets and gizmos - I think some might call this aides, dressing sticks etc. Kitchen adaptations and home adaptations. Anne might visit the individual, or take them to see the home of another beneficiary who has had their home adapted. So it's very hands on. She is also fully knowledgeable about cars. She has visited the garages where they do the adaptations, and she will help with individual car enquiries. We also can help with car tax though we are stopping this.

As many are claiming state benefits, we can also help with the claims for this. It is a very important area. Emily, who is a social worker and new to the Trust, will be helping more with this side. We also help with finding people to help care for them and personal assistants.

We have undertaken leaflets to help with the measurement of blood pressure for those who need to take it in the leg and for those who cannot have a blood pressure taken at all. We emphasize making sure that the right size of cuff is used and that the limb with the cuff is at the same level as the heart. We are open to any suggestions to improve them. We have given the leaflets to EDRIC who have adapted them for their website and we have had enquiries from Australia and Canada and shared them with them as well. We have also a telephone counsellor, again affected by thalidomide herself, who provides private counselling by phone. This service this has been independently assessed and found to be a worthwhile service to offer.

Before I move on to other medical issues we help, I wanted to mention very quickly the style of help within the Trust. Individuals can be fiercely independent, they can resist help and up to now some have not even considered



Shoulder joint in Thalidomide Embryopathy

Affected by all same pathologies as affecting the ageing general population

Acromioclavicular joint dysfunction more common

- Reduced reach with restricted movement in the shoulder and elbow means the shoulder blade has to move further.
- Shoulder blade articulates with the clavicle so the acromioclavicular joint between the two is often a source of discomfort because it is having to move more
- The shock absorbing disc in the middle of the acromioclavicular joint has been noted to be absent in those with Thalidomide embryopathy who have had scans and operations
- With age the shock absorbing disc in the middle of the joint is often worn out in normal individuals

The Acromioclavicular joint in Thalidomide Embryopathy is worn out much more quickly than in those with normal shoulder joint function and reach.

Shoulder Joint in Thalidomide Embryopathy

- Deformity causes the humeral head to be more ovoid with a smaller, under developed glenoid
- This makes the shoulder joint rock rather than the normal rotational roll
- The range of movement is restricted and hence at the extreme range the joint actually hinges, so increasing the pressure on the margin of the joint which then becomes arthritic
- Accelerated arthritis occurs in all causes of deformity of the shoulder joint- not just Thalidomide embryopathy.
- Muscles maybe small and weak due to underdevelopment of the bones of the joint.

themselves to be disabled despite severe limb reduction. Some have a fear of medical professionals due to difficult childhood experiences from having blood taken etc. and some do not wish to take medication because of how their damage arose. They often value advice from others affected by thalidomide and peer to peer support is very important to them. Anne, our OT, over time has developed a way of working with them. If you remember she is affected by thalidomide herself, so is our telephone counsellor and so are our volunteer visitors. If you wish to learn more about this we have written articles for Pain News.

So we move now to my role and how I help. I get involved when an individual wishes to understand more about the cause of their symptoms and in particular is needing help with investigations or an opinion from a specialist. This involves liaising with the individual and their GP, to find the best opinion possible. It's very much dependent on how far the individual will travel. Our beneficiaries are spread throughout the UK and some now live across the world. We do not rely on a single center and have many hospitals which help. However we mainly liaise with the Royal National Orthopedic Hospital (RNOH) just north of London but it

has no hand specialists. So we also work with Wrightington Hospital in the Northwest of England which has all orthopedic specialties apart from spinal surgery.

When we are choosing specialists we take into consideration;

- No thalidomide damage is unique – there are other groups with similar damage
- We usually choose experts with an international reputation in their field i.e. they receive referrals from across the world.
- Particularly for limb damage they are often experts in congenital deformity with the ability to custom make a joint replacement. They are able to put a replacement joint in and out and this is called a revision specialist because of the relative young age we are dealing with.
- They are complex surgery specialists.
- They all have good bedside manners - we take the feedback from beneficiaries. This is very important because of peer to peer support.
- They have seen others affected by thalidomide and can discuss lifestyle management and the pros and cons of surgery. This is very important for individuals who are

Hence, the muscular components are still in general present in Thalidomide Embryopathy. So, whilst the bones between the joints are short and deformed, joint replacement arthroplasty can somewhat compensate for lengthening and torsional deformities and help pain and limitation of movement from early arthritis in the shoulder joint.

UK

UK

Questions in The Trust arising from the Helpline

- Symptoms - Paraesthesia, pain, numbness – but also sweating, poor healing, swallowing difficulties – autonomic nervous system
- Analogy drawn to post polio syndrome
- Known that adults given thalidomide develop a predominantly sensory length dependent axon neuropathy

using their bodies to compensate for a short reach.

Hence, the Trusts role is to facilitate a quick expert opinion with options for treatment from a specialist familiar with thalidomide damage.

We also have a neuro orthopedic doctor working with us -Dr. Cowan from the RNOH- I mentioned before North of London. He is looking at non-surgical issues. He specializes in complex rehabilitation. He looks after other groups with conditions such as post-polio patients and joint hypermobility and other complex conditions.

So how do these experts help?

Many of our individuals have physiotherapy, massage, and acupuncture locally to where they live and use their own Health Grant to pay for regular sessions. Currently Dr. Cowan at the RNOH helps individuals via their GP find therapists. However, if they need inpatient rehabilitation he can also arrange this at the RNOH.

We have helped a few individuals with laser eye surgery because they cannot manage with short arms to put glasses on and off. We have had a few enquiries about ear reconstruction. Many of them had failed ear reconstruction as children. But now there are new techniques around. We have

had one or two enquiries about facial reanimation surgery where they graft new muscle and nerve onto the face. I'm not quite sure how much we should be advertising these cosmetic techniques.

If I move now onto orthopedic issues, for hand issues we refer to Professional Trail at Wrightington Hospital. He is a wrist replacement specialist and an upper limb surgeon. He is able to help diagnose the hand pain. We also have a hand specialist in London. Regarding elbows we refer again to Professor Trail working at Wrightington but more so to Mr. Lambert at the Royal National Orthopedic Hospital (RNOH). These are the two hospitals I mentioned before for orthopedic surgery.

For shoulders we used to refer to Prof Wallace in Nottingham, but he has now retired having undertaken several shoulder replacements for individuals. We now refer to Mr. Lambert at the RNOH, more later. For the spine, we use Mr. Casey who is a complex spinal surgery specialist at the Royal orthopedic hospital. He holds joint appointments across 2 hospitals working also in one of the London neurology hospitals. For hip surgery we use Mr. Skinner again at the RNOH. For nerve conduction studies, which I

Peripheral nerve dysfunction in middle-aged subjects born with Thalidomide Embryopathy

Hypothesis - early exposure to thalidomide could damage the nerves, but with age be more sensitive to the aging process and cause problems later in life

17 individuals - upper limb damage and symptoms paraesthesia, pain numbness relatively normal lower limbs that were generally asymptomatic

- Large nerve fibres - weakness, pins and needles, Q/E abnormal reflexes
- Nerve conduction studies
- Small nerve fibres- pain and temp
- Thermal thresholds of both hands and feet
- Autonomic nerve fibres - BP, pulse, sweating, sexual function, bladder and bowel
- Sympathetic skin responses

17/03/11

Peripheral nerve dysfunction in middle-aged subjects born with Thalidomide Embryopathy

A large proportion of the 17 individuals showed had results suggestive of nerve compression - mainly wrist; nerve roots lower back, in spinal cord of the neck.

Due to the complex anatomy and difficulty interpreting the clinical and neurophysiological findings together with deciding on diagnosis and treatment options they should be referred to specialists familiar with the issues.

Hence Neurologist/ neurophysiologist and surgeon should work together

17/03/11

Peripheral nerve dysfunction in middle-aged subjects born with Thalidomide Embryopathy

Results consistent with hypothesis but other causes and issues:

- one moment in time, may have been born this way
- difficult to test the upper limbs
- not known if lower limbs nerves were in the correct anatomical place or had right connections
- other causes - alcohol, vitamin deficiencies, diabetes
- sometimes only one leg showed abnormal test results

Technical problems

- Sympathetic skin response - autonomic nerve fibres - affected by carpal tunnel
- Statistics for ANS were different in the hands and feet
- Thermal thresholds- better test would be skin biopsy

17/03/11

Peripheral nerve dysfunction in middle-aged subjects born with Thalidomide Embryopathy

Post polio analogy - concern about this analogy

- Polio - infection, clinically apparent neurological dysfunction, recovers, long period stability, further deterioration with age
- Only affects motor nerves
- Re-innervation cause giant motor units - inherently unstable and deteriorate with time

However the suggestion of deterioration with age is possible

17/03/11

will mention more about a little later with the neuropathy study, we use Charing Cross hospital in London.

I wanted to briefly show you 2 case examples- these are from the individual perspectives -to demonstrate where we refer to and how much they have to travel around to get the best opinion. But before I do that I first show you some information about Mr. Lambert, the shoulder consultant, gave me to share with you.

Those with shoulder deformity due to thalidomide are affected by all the same pathologies which affect the aging general population. However, acromioclavicular joint dysfunction is more common because they have reduced reach and their restricted movement in the shoulder and elbow means the shoulder blade has to move further. The shoulder blade articulates with the clavicle so the acromioclavicular joint between the two is often a source of discomfort because it is having to move more. The shock absorbing disc in the middle of the acromioclavicular joint has been noted to be absent in those with thalidomide embryopathy who have had scans and operations. With age this shock absorbing disc in the middle of the joint is often worn out in normal individuals. Hence it's no surprise in those with thalidomide

embryopathy, that this AC joint is worn out much quicker than those with normal shoulder joint function and reach. If we go to the shoulder joint itself, deformity causes the humeral head- the ball of the ball and socket joint - to be more ovoid (rather than round) with a smaller under-developed glenoid- the socket. This makes the shoulder joint rock rather than move with a rotational roll of a normal shoulder joint. The range of movement is restricted and hence at the extreme range the joint actually hinges so increasing the pressure on the margin of the joint which then becomes arthritic. This accelerated arthritis occurs in all causes of deformity of the shoulder joint- not just thalidomide embryopathy. If we note also the muscles may be small and weak but still present due to the underdevelopment of the bones of the joint.

So in summary, the muscular components are still in general present in TE. So whilst the bones between the joints are short and deformed lengthening and torsional deformities can be somewhat compensated through joint replacement arthroplasty for osteoarthritis to help pain and limitation of movement of the shoulder joint.

As said I have 2 case examples to show you how the referrals work.

Peripheral nerve dysfunction in middle-aged subjects born with Thalidomide Embryopathy

Letter

- compression of nerves common
- Such symptoms should be properly investigated by specialists
- other causes looked for e.g. diabetes, alcohol, vitamin deficiencies

When asked to help – Trust refers to centres of expertise

Autonomic neuropathy - great caution against attributing any symptoms without firm diagnostic consideration or firm evidence;

- Swallowing difficulties - number causes, not necessarily neurological and maybe treatable; not an early symptom of autonomic dysfunction
- Bladder/bowel dysfunction – prompt investigation for spinal and cauda equina causes; must be no assumption of any autonomic neuropathy

Referral on for pain management

17/03/11

Peripheral nerve dysfunction in middle-aged subjects born with thalidomide embryopathy

What are we doing?

Still some concern without further research there may be a largely subclinical generalised large and small/autonomic fibre dysfunction which over time could develop and cause clinical symptoms.

- Dr Cowan – neuro-orthopaedic doctor at RNOH – examining all beneficiaries referred to him – no clinical evidence of any such issues at present.
- BP RECALL –UK – test in check for any indication the autonomic nervous system is affected

17/03/11

UCL BP RECALL UK

17/03/11

UCL BP RECALL UK

- Different ways taking blood pressure
- Cardiovascular risk assessment
- Any need medication and why
- Best way for a future assessment
- UCL - centre of excellence for dysmelia

17/03/11

The first case is a nurse who has upper limb damage, short forearms, radial club hands and bilaterally dislocating shoulders. She was experiencing debilitating shoulder pain and increasing restriction in movement. We can see the black circle, that's where she lived. She had been to physio and had seen a local consultant a few years before she contacted us. It had been suggested she consider a shoulder replacement when she couldn't stand the pain any more. We involved her in a small project with Prof Trail at Wrightington looking at arm pain and how the Trust could help. He agreed with the diagnosis of shoulder arthritis and injected both shoulders with steroid; this didn't help and he advised her to consider shoulder replacement when she couldn't put up with the pain any longer. She returned home and several months later she returned again to see a local consultant who again suggested shoulder replacement. So she talked to the Trust after he suggested she needed to see someone more experienced than himself. She told us Professor Trail was too far away from where she lived and she also wanted to see someone who had actually operated on others within the group for this issue. So we suggested Mr. Lambert at the RNOH. He did CT and MRI scans. She remembers him telling her repeatedly she was too young for such surgery. But she wanted to go ahead. So she had a left hemiarthroplasty – in simple terms the ball was replaced. This X-ray is not hers as unfortunately the XRs did not arrive in time for this presentation. She reports that she now has more movement in her shoulder than she has had for years and her pain levels are much reduced. She is hoping physiotherapy will further improve her movement. And now four months later, she is on the waiting list for her other shoulder. She is very happy.

Second case example - again similar upper limb damage. The Individual phoned the Trust describing pain all over. It was difficult on the phone to decide what was the most important issue and he had been referred already by his local GP to a hip consultant. I suggested referral to Dr. Cowan at the RNOH for an overall assessment. There he was found to have good hip movement and it was felt the sacro-iliac joint was a problem. So he was referred back to physio near where he lived to help with this. Dr. Cowan also suggested he had hand pain and with the paraesthesia needed to see Professor Trail at Wrightington Hospital. There he was found to have weakness of flexion and abduction of the fingers particular on the ulnar side of the hand. He referred him for nerve conduction studies at Charing Cross Hospital in London where our neuropathy study took place. But as he was also complaining of shoulder pain Prof Trail also injected the shoulder joint and AC joint. In the meantime he continued

to have hand therapy and physiotherapy for his sacro-iliac joint. On review the shoulder joint injections hadn't worked. So he reinjected the joints again this time from a different approach. The nerve conduction studies came back negative, and the unit in London suggested an MRI scan of his neck. The MRI scan showed some nerve compression in the neck so he has now been referred to the spinal surgeon, Mr. Casey, back at the RNOH. In the meantime he is feeling a lot better, with the pain in his hands and back and following the second set of shoulder injections his shoulder pain has improved.

So I've explained what the Trust is, how we help and how others can help. I want to now explain about 2 of our projects. The first project, a peripheral neuropathy study came about because of questions within the Trust. Individuals were complaining about paresthesia, pain, numbness, but also they were describing sweating, swallowing difficulties bladder and bowel problems. An analogy was drawn with post-polio syndrome. We were also aware that adults given thalidomide develop a predominantly sensory, length dependent, axonal neuropathy. So the study was set up with Charing Cross Hospital in London with their neurology team. The hypothesis was that early exposure to thalidomide can damage the nerves, the nerves can heal but knowing that the function of nerves declines with age they wondered if the nerves exposed to thalidomide would be more sensitive to the aging process and result in problems in later life. So we took 17 individuals with upper limb damage and neurological symptoms with normally formed lower limbs and had controls. The paper is awaiting publication with PLOS ONE so the results etc. are not reported here. However, clinically it is important as compressive neuropathies were found to be more common. Due to the complex anatomy, and difficulty in interpreting the clinical and neurophysiology findings together with deciding on diagnosis and treatment options it was concluded that such individuals should be referred to specialists familiar with the issues. Hence, the neurologist, neurophysiologist and surgeon should work together. This is why we often refer to experts in different hospitals depending on the issues and why I showed you the case studies.

Following the study the Trust sent a letter out to beneficiaries as it was taking a long time for the paper to be accepted for publication, with a letter from the neurologist encouraging referral for such symptoms as they were potentially reversible and needed investigation. Also other causes should be excluded such as diabetes, alcohol, vitamin deficiency etc.

The second project is a Blood pressure project called BP RECALL UK. It is a research project with Professor Williams, a cardiologist and an expert in Blood Pressure and his

team in London. The project has national credibility being included in the National Institute Health Research portfolio with particular value for patient outcomes.

As you are aware many of our individuals have difficulty having a blood pressure taken in the upper limb. Though, as I have mentioned, we have written leaflets on how to take a blood pressure in the leg etc. They are not endorsed by experts due to lack of research. Also the leg is increasingly unreliable as individuals age due to peripheral artery disease. The study is aiming to take 50 individuals and look at existing ways of doing a cardiovascular risk assessment e.g. retinal photography, ECG, and 24 hour urine etc. However, it will look at other ways of taking a Blood Pressure in the upper limb, fingers and head rather than the usual way in the upper arm. It will use a specialized new MRI scanner. This will look in detail at the heart, the kidneys, the brain, body fat etc. It will match, therefore, any BP taken with damage from blood pressure in the body, e.g. forehead and finger. We have also included a test for the autonomic nerves system.

Very simply the outcomes are;

- The individual will receive their own risk of heart attack or stroke-cardiovascular risk assessment and advice as to whether they need to take medication to reduce the risk.
- It will also suggest the best way they should be followed up in the future such as different ways the blood pressure may be taken or repeat MRI scan. Due to their current age it is envisaged that if there is no end organ damage currently present then it is unlikely the individual will have to worry about their blood pressure in the future.
- It will help individuals reluctant to take medication feel more secure as to the need to take it.
- We hope it will lead to UCL being a centre of excellence for all those with dysmelia and provide advice to centres abroad.

It would take a lot more time to outline the full depth of the intended research. However, if you wish to read more you can have a copy of the full proposal.

In summary I have explained to you, The Thalidomide Trust, what it helps with and how others help and also explained about 2 of our major research projects which help to develop our knowledge.

Slide- Knowledge is power - information is liberating.

We feel it is very important to share our knowledge and to learn what others are doing so our limited resources can be used wisely. Hence we are grateful to our hosts and Dr. Hinoshita for holding this conference.

I will now pass you over to Liz Newbronner for our last very important area of research within the Trust.

Hinoshita: Thank you very much, Dr. Morrison.

Next I should introduce Ms. Elizabeth Newbronner. She is a co-speaker with Dr. Morrison. She, Ms. Newbronner, graduated from University of Cambridge majoring in geography 1982. She got MBA (Health and Social Services) at University of Leeds at 1995. Now she is studying Ph.D. course of University of York. She has owned a researching company named Firefly Research which worked for universities, government, national charities and foundations. Her main research interests are in the fears of the disability, long term conditions, self-management, old people, and family care. Then, Ms. Newbronner, please.

Newbronner: Thank you. I'd like to thank Dr. Hinoshita for inviting me here to speak. It's a great honor and I'm extremely pleased to be here. So thank you very much.

I just want to try briefly today and give you some initial result from survey of all UK thalidomide survivors we conducted the end of the summer and early autumn. The survey built on results from previous qualitative work we've been conducting for last five or six years, and the monitoring of the Health Grant to thalidomide survivors in the UK. Briefly just say the aims of the survey were – The survey was conducted for the Thalidomide Trust and it was to get a much clearer picture of the living circumstances, work situations of UK thalidomiders. To better understand the physical health problems they were experiencing and also to assess well-being and health related quality of life. So there were three main aims, and the intention is the Trust will use that information to help develop the Trust's services, as Dr. Morrison has described. Hopefully to secure the continuation of the Health Grant when the current Grant ends seven year time and also to support negotiations with the Diageo about the compensation funding for UK thalidomide survivors. So in conducting the survey we send the survey through the Thalidomide Trust to all 467 UK born thalidomide survivors. And people could respond by post or online or they could complete the survey on the telephone with support from myself. 351 people completed the survey which gave us a response rate 75 percent which we were extremely pleased with. Thirteen percent of the people chose to complete survey anonymously, but because the majority gave us the names, we were able to draw data from the Thalidomide Trust about the compensation points and to get some indication of the level of impairment they've experienced originally. 169 respondents were female and obviously rest were the male. But 11 for some reason didn't give us a gender but anyway, that breakdown of the genders is very much mirror of the

population, thalidomide population in the UK. And because we have information about people's original compensation points and we can see impairment levels in our survey group more most exactly mirror the whole population in the UK. And I can show you brief slide about that shortly.

So in terms of the survey content, we had 10 sections gathering information about the personal circumstances, work and pensions, self-reported information about their original thalidomide impairment and the health problems and also information about mobility and equipment and use help services, social care. We use two standard questionnaires to explore health related quality of life. So we used SF12 and particularly we chose that because we have used it before and we're also aware of studies using it in Germany and in Sweden. So we were quite keen to have the possibility of international comparison. And we also used mental well-being scale which was developed in the UK, and we chose that because it were able us to make comparison with the general population in the UK very easily because it's used by a national government to monitor mental well-being. The survey closed in October, so we're currently analyzing the data, so I feel a bit nervous because these are very initial results. So I'm just

going to present a few things here with particular focus on health but we'll show a little bit about people's living circumstances, and work situations. So as I said, the spread of the people on the survey very much mirror the whole UK population of thalidomiders. And I just show this slide because I think it also shows the distribution of compensation points it's very similar to the German situation. So I think that just help to think about international comparison. And for the purpose of this analysis we're going to split the group within our survey into a number of impairment groups so that we can sort of look at things in a little bit more detail. We may focus down further but for the moment we are thinking we'll have two arm group. So the first group would be people with arm shorter than their elbow and second group would be people with arms longer than their elbow. Then we also had a group for damage to legs only and people were affected both in their arms and legs. So we were sort of looking at those splits for the analysis, and then here, just showing a little bit more information about all the problems people reported including hearing impairment, deafness. So there is sort of brief breakdown there for you. In terms of people's living circumstances, we found that 64 percent of our group live

**UK Health & Wellbeing Survey
2015
Initial Results**

**Liz Newbronner
Firefly Research & Evaluation**

The **Thalidomide** Trust

Aims of the survey

Main aims were to:

- Get a picture of people's current living circumstances and work situations
- Better understand of the physical health problems people are experiencing
- Assess mental wellbeing and health related quality of life

This information will be used to:

- Help the Trust develop its services
- Secure the continuation of the Health Grant
- Support negotiations with Diageo about future funding

The **Thalidomide** Trust

Conducting the Survey

- Sent by the Thalidomide Trust to all 467 UK born Thalidomide survivors
- People could respond by post, on-line or complete it on the telephone with support
- 351 people completed the survey – a response rate of just over 75%
- 13% chose to complete the survey anonymously
- 169 of the respondents were female; 171 were male; and 11 did not give their gender
- The impairment levels of the survey respondents closely matched those of all UK Thalidomide survivors

The **Thalidomide** Trust

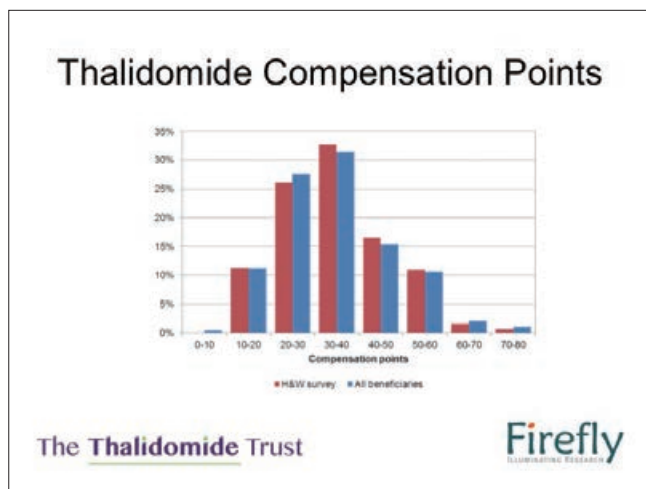
Survey Content & Analysis

- Survey had ten sections - About You; Family and Housing; Work and Pensions; Original Thalidomide Impairments; Mobility and Equipment; Health Problems; Use of health Services; Social Care Support; Mental Wellbeing; Health Related Quality of Life
- Included two standard questionnaires:
 - SF12 Health Related Quality of Life
 - Warwick Edinburgh Mental Well Being Scale
- Currently analysing the data
- Initial results are presented here with a focus on health

The **Thalidomide** Trust

with partner, or their partner and children or another family member which again I think mirrors Peter's findings in Germany. 11 percent live with another family member which could be like a parent or sibling. And 22 percent live alone and I think these are the groups that we have some concerns about. Just 10 of our sample live with paid care worker or in residential care. Interestingly 85 percent owned their own home and so have a reasonable level of security in terms of their home. The work situation for UK thalidomiders I think it's a little bit different from other European countries. We only have 16 percent of our group who are able to work full-time or who are working fulltime. And almost two-thirds are not working at all. So I think that's very different to the German situation. We also asked people about changes in the working lives. As Cristina said, a number of people said their work situation changed since 2000, and I think this might partially due to the physical changes that people experiencing deterioration in the health but also in the UK people have received much financial compensation since 2000 both their main compensation and the Health Grant, and also being exempt from taxation. So I think the financial position has changed for people. We asked people about how

the things might change in the future and a great many said they would have to make further changes to their work situation - either reduce their working hours, change their job or give up working. So I think this is a major concern for people. I'd like to touch briefly on the self-reported health problems. These are self-reported issues as we don't have clinical examinations, but 93 percent of group were experiencing a pain or loss of movement in one or more joint. So that was the overwhelming issue that they were reporting. But almost half reported generalized pain and again half reported they had one or more mental health problem, currently or recently in the last you know, few months. And nearly three quarter were experiencing neurological problems. And as Dr. Morrison says we know there maybe a variety of causes around for people but nevertheless it is major concern for thalidomiders in the UK. And this just gives a very brief breakdown for the musculoskeletal problems and again I think this Swedish study the back problems were major concern for people. Again there maybe a variety of reasons but self-reporting is significant. In terms of mental health, quite number of people reported more than one mental health problem but the key issue I think is a lot of people with anxiety closely followed

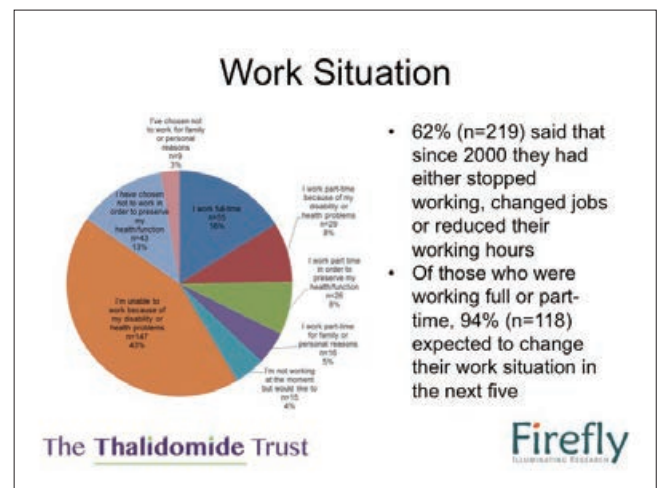


Thalidomide Impairments

Impairment	Number	%
Dysmelia – arms (major)	92	26%
Dysmelia – arms (moderate)	111	32%
Dysmelia - legs	40	11%
Dysmelia – arms and legs	65	19%
Scoliosis	77	22%
Deaf or hearing impairment	123	35%
Blind or partially sighted	40	11%
Damage to face and/or outer ear	65	19%
Damage to internal organs	110	31%

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- ### Living Circumstances
- 64% live with their partner or their partner and their children/other family member
 - 11% live with another family member/s (e.g. parents or sibling)
 - 22% live alone
 - Ten people live at home with paid carers or live in residential care
 - The majority (85%) own their own home
- The Thalidomide Trust Firefly ILLUMINATING RESEARCH



by depression. I think this is where the Trust would like to explore further the experiences people are having and look at the relationship between mental health and people's living circumstances, their work situations, and their impairment or the decline in their functional abilities. Another area is neurological symptoms although they may be a variety of causes, it is certainly a major cause of concern and I think the recent nerve study will hopefully shed more light on that.

Interestingly one of the, anecdotally problems reported among thalidomiders in the UK are problems with balance and all that did come out of survey in the self-reported health problems. And again I think that is something to investigate further because it's not quite clear and there could be multitude of causes for that. But the consequences as a whole and fractures and so on are quite serious for a lot of thalidomiders. So something to explore further. I think the other thing that quite important in the UK particularly in terms of lifestyle prevention of further problems like management issues and one of the things that trust is supporting is fitness project which has learn from Swedish, thalidomiders fitness project. So there is a lot of interesting in helping thalidomide survivors self-manage, to improve the diet and hopefully



prevent future problems.

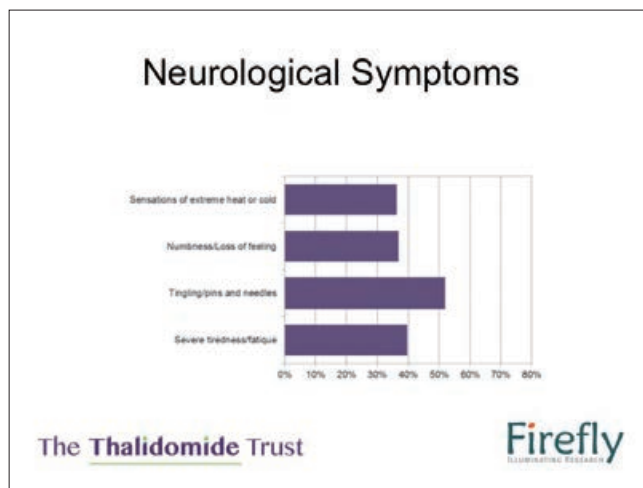
So just maybe quickly I'm conscious at the time, so I just move quickly on the work we did about mental well-being and health related quality of life. So using the standard instrument, the Warwick Edinburgh Mental Wellbeing Scale (WEMWBS) we found the mean score for UK thalidomide survivors was 43.6 whereas the UK mean score for the general population is 50. And so the early result suggest that the lower scores - the bottom 40 percent are most strong associated with living alone and not actually related to level of impairment those are the social factor seem to be very important. Another slide - this is just simple scatter plot, We need to do more work but the level of compensation points and the person's mental well-being score seems very random, but we need to do more analysis about.

So and then just moving on to the SF12 results. Here are just wanted to show the scales and subscales because as I say I know the colleagues I using this measurement. What we found in the UK consistently - this is the third time we use this method - is that the physical score is substantially lower than normalized score of 50 for the general population of similar age. Interestingly mental health score is

Self-reported Health Problems

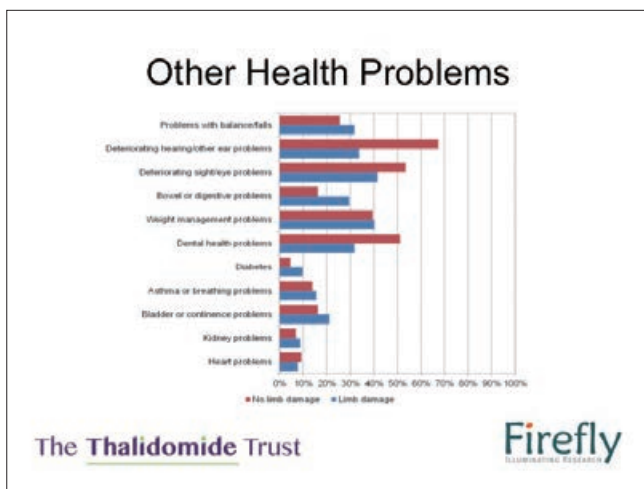
- 93% were experiencing pain and/or loss of movement in one or more joint (i.e. musculoskeletal problems)
- 48% had generalised pain (either severe and/or continuous or moderate and/or intermittent)
- 50% had one or more mental health problems
- 73% reported experiencing neurological symptoms (tingling; loss of feeling; heat/cold)



not that different from normalized score for the general population. But there are number of people, if I just move on, you see from this graph. There are a number of people who have very low scores and I think again that something that we want to try and explore further to understand why certain groups have that very, very low scores. And again, a very simple scatter plot just gives indication, but as you can see maybe not surprisingly the blue line that goes down is suggest there is a relationship between level of impairment and the score for physical health related quality of life. but curiously the red line suggest that there might also be a relationship between people who have lower levels of physical impairment but have poorer levels of mental health related quality of life. So again something we very much want to explore further. And I've just got two more slide, I should just round off by saying that I think my perception from doing qualitative work with the thalidomiders in the UK, is that many thalidomide survivors who have mild moderate levels of impairment are now reporting rapid loss of function. Many people in the UK because the financial resources in the last few years, are self-managing, taking steps to self-manage the pain and loss of function through lifestyle changes,

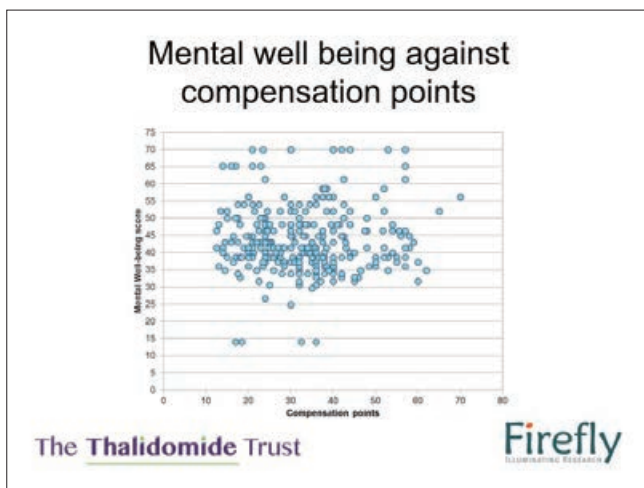
non-prescription medication, complimentary therapy. But as Dr. Morrison says that may not be enough for some people they may need more medical intervention or at least much better understanding of the problems they are experiencing. I think there is also an issue, although thalidomiders have been living with lifelong impairments. I think many people have not seen themselves really as disabled. And for those who are now losing some function, they have become newly disabled and that has important implications for people sense of mental well-being. And I think coupled with that people experiencing quite lots of problems accessing health services, particularly the local routine health services, often don't understand the problems they're experiencing, hence all the trust work to develop the network of specialist across the UK. And lastly can I just say that this is very much first impressions of the data that we have. But we hope to do much more statistical analysis and get more solid result. So the next few month hopefully colleagues and another countries to make some comparisons. So I just wanted to say thank you again for inviting me and giving me the time to speak today.



Mental Well Being Scores

- Mean score for UK Thalidomide-survivors = 43.6
- Mean score for general population aged 45-54 = 50
- Lower well being scores (bottom 40%) appear to be associate with living alone and still working full time
- No obvious relationship between mental well being sore and level of impairment

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Normalised Responses for SF12v2 - aggregate scores and subscales

Component	UK Mean	Min	Max
Aggregate Physical Health	26.7	0.5	61.7
Physical Functioning (PF)	20.9	1.7	57.6
Role Limitation Physical (RP)	36.4	21.9	55
Pain (BP)	33.6	14.2	59.2
General Health (GH)	33.7	13.7	63.7
Aggregate Mental Health	46.5	16.8	74.9
Vitality (VT)	40.4	21.3	68.2
Role Limitation Emotional (RE)	43.5	23.7	55.3
Social Functioning (SF)	34.6	2.0	55.5
Mental Health (MH)	40.7	7.4	64.5

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Q&A

Hinoshita: Thank you. Do you have any questions? Two presentations given by Dr. Morrison and Ms. Newbronner. So may I ask you, Dr. Morrison? I am thinking of chronic pain and serious joint problems. It seems you are more active for the surgical treatment and operations in your country. How do you think of it? In this respect, we are not so active to proceed the operational treatments in Japan. How do you think of it?

Morrison: I think the consultants carefully assess whether they can help the condition. As I mentioned with the nurse and the partial shoulder replacement, with her nurse training background she knew what the risks were for shoulder surgery and she was counselled that she was very young many times for this particular surgery. I think the surgeons are happy to operate when they have the knowledge to do so but it is a last resort. They're not quite so happy with a hip necessarily if the arms are short. They may be using the hip instead of their arms to eat etc. If the operation goes wrong, they are going to lose a major part of their ability to

function or the hip replacement would not allow them to be so flexible with the leg. And again with spinal fusion for pain they would carefully assess the issues as to what benefit the individual will have because they don't want to lose flexibility to compensate for other areas of the body. But certainly shoulder replacement seems to be helping – there have only been a few but so far the outcomes have been good.

Hinoshita: I see. So you have ever found the successful cases with the operation?

Morrison: Yes. Yeah.

Hinoshita: OK. Next.

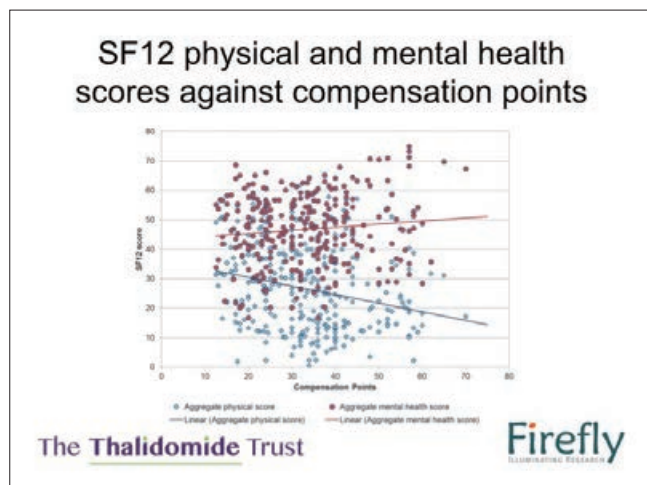
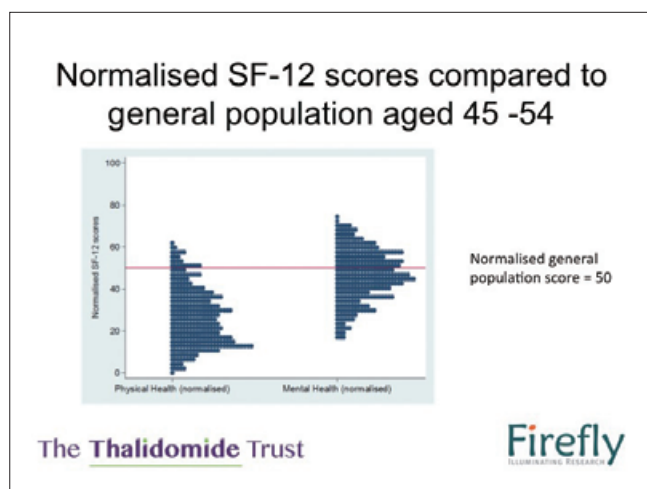
Peters: But the number of surge groups here is going up in Germany as well. But the patients have already done surgery and several ones on the waiting list will do that next month. I think because also developing osteoarthritis in hips, knees, also in shoulders.

Hinoshita: OK. In your country, there are some patients waiting for the surgeries? Hip joints, shoulder and so on. OK. All right.

Morrison: As children many had operations which didn't work so they are afraid of operations. So it's a difficult situation we have.

Hinoshita: It seems this program may be controversial. OK, doctor.

McCredie: Just to admit that we have one of a bilateral upper limb defects who has had seven hip replacements and one shoulder replacement and all failed.



Discussion

- Many Thalidomide survivors with mild to moderate levels of impairment are now reporting a rapid loss of function
- Most are self-managing their pain and loss of function through lifestyle changes, non-prescription pain medication and complementary therapies
- Despite having lifelong impairments some Thalidomide survivors feel 'newly disabled' and this has important implication for their mental well being
- The majority of survey respondents had experienced one or more problems with quality or access to health services, especially lack of knowledge/understanding of Thalidomide damage amongst health professionals
- Further analysis will use multiple regression to explore the relationship between key variables

The Thalidomide Trust Firefly

Hinoshita: Right, Dr. Kayamori.

Kayamori: I against about operation for shoulder. Just in the morning I showed the slide that means the skeletal musculatures were really hypoplastic. They tried to make the muscles stronger but in vain. So I don't think surgical treatment for shoulder joint replacement is indicated. It must be not successful. That's my opinion. Thank you.

Morrison: This is why I brought the information from Mr. Lambert on shoulder surgery and went through how they can help and why. I have two pages he actually wrote for me and which I can share with you. He is an expert in operating with congenital deformity. They see the complex cases at the RNOH which is the national center and they are specialist surgeons.

Kayamori: As long as I did a lot of patients examined with nerve conduction study, but I couldn't find evidence showing polyneuropathy except for compression neuropathy.

Morrison: Did you look at the small nerve fibers and the autonomic nervous system?

Kayamori: No, no, I didn't do that too.

Morrison: Yes.

Kayamori: Sympathetic nerve, I didn't do that. But sensory motor nerve, only I did. Thank you.

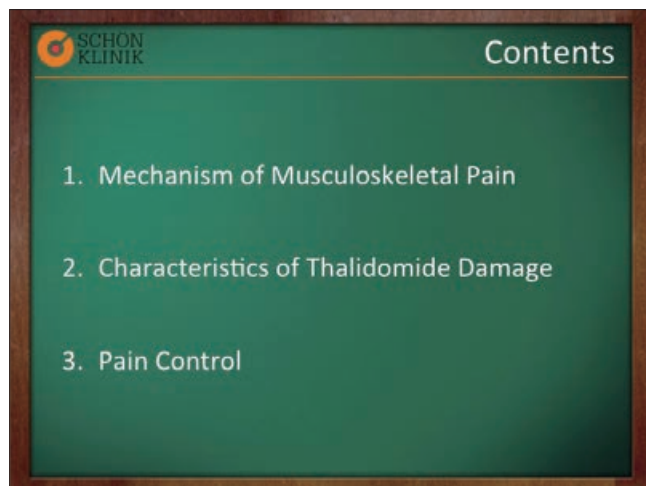
Hinoshita: It seems that Dr. Lambert has been good at the shoulder joint surgery. So if you have any patient suffering from shoulder joint pain or motion problems, how about introducing him or her to Dr. Lambert in UK? Anyway let's wait for more scientific results. Is there any other comment or opinion from German doctors about this problem? OK? Let's get back to this program later at the joint discussion or meeting.

Pain control in people with thalidomide embryopathy

Dr. Rudolf Beyer

Klinik für Anästhesiologie und Operative Intensivmedizin Schön Klinik Hamburg

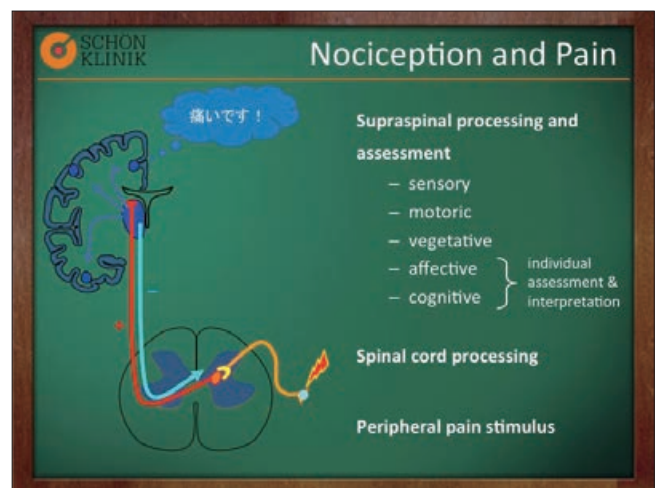
Pain is a complex output of the sensory organ and I am convinced that we need to achieve a basic knowledge in order to develop a good strategy for the treatment of pain. Therefore, I will say some words on the subject of pain mechanisms before I focus on various options of treating pain.



1. A pain stimulus is caused by a mechanical, thermal, or chemical agent in the periphery and is transferred to the spinal cord via the peripheral nerves.
2. Within the spinal cord the signal is transmitted via the tractus spinothalamicus. At this time enhancing and inhibiting influences can affect the signal and modulate the signal significantly.
3. Within the brain, a more complex process takes place that ultimately leads to the tangible sensation of pain.
4. Furthermore, what we consider to be pain could be divided in different components:

- The sensory alert notification, namely the Location and the dimension of the damage
- The direct motoric answer to get out of the danger zone
- The vegetative answer to prepare the body for fight or flight
- The affective personal emotional component
- And the Analyzing of the incident by comparing with past experience

Especially the affective component has a major influence of how we feel the pain and therefore how we express our pain to other people.



Over the last twenty years more mechanisms of pain chronification have been discovered. The researchers determined to major steps.

In the first step a long acting pain stimulus leads to sensitization and in case of ongoing pain, a remodeling of the nerve system leads to chronification as the second step.

For a better understanding I would like to explain how this is working. Even today you will find Doctors, who believe that pain processing is a matter of wiring and nerves work like electrified cables.

SCHON KLINIK Sensitization and Chronification

Sustained Pain Stimuli

- Release of neuropeptides from the nerve ending
- Increased permeability of the blood vessels leads to local edema
- Sensitivity increased by inflammatory mediators

➤ Pronounced tenderness and pain at motion

Genes: Nerve System Pain

A sustained Pain stimulus leads to a local inflammatory process which presents as pronounced tenderness and pain at motion.

After a while, structural changes of the nerve system leads to the development of new functional pathways for pain. This is basically done by changing of the properties of ion channels and by “waking up” hibernating synapses.

SCHON KLINIK Sensitization and Chronification

1. Structural changes of ion channels

- Increased permeability of Sodium and Calcium (uncontrolled neuronal „fire“)
- Activation of normally „sleeping“ synapses

➤ Development of new functional pathways for pain processing

Genes: Nerve System Pain

By altered gene encoding within the neuron, the cell properties change permanently. That means, the neuron reacts easier and stronger to stimuli even if they are sub threshold.

SCHON KLINIK Sensitization and Chronification

2. Altered gene encoding

- Synthesis of modified ion channels and receptors
- Increased number and more docking sites for nociceptive stimuli

➤ Permanent alteration of the neuron

Genes: Nerve System Pain

The endpoint of chronification consists of structural remodeling of the peripheral and central nerve system that leads to new pathways for nociceptive information and long term pain


SCHON KLINIK Sensitization and Chronification

The endpoint of chronification consists of structural remodeling of the peripheral and central nerve system that leads to new pathways for nociceptive information and long term pain

To understand what patients refers as pain, we should distinguish between chronological and biological aspects of pain.

Acute Pain is part of the live saving warning system that keeps us away from dangerous hazards.

Opposite to this, chronic pain has lost its warning function and affects mobility, psychological and social aspects of our life.



Types of Pain


Acute Pain

- is an important warning that protect us from hazards
- duration is related to tissue healing

Chronic Pain

- has lost the function of protecting
- last longer than 6 month
- affects biological, psychological and social wellbeing

Every one of us has most likely experienced nociceptive pain, so this needs no further explanation. In case of neuropathic pain the damage is in the nerve system itself and a treatment approach with common painkillers usually fails. For example phantom pain do not respond to opioids and nsais.



Types of Pain

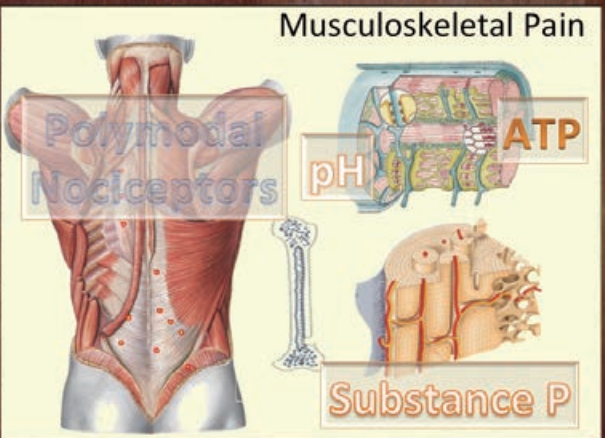
Nociceptive Pain
Tissue damage affects free nerve endings (Nociceptors)

- Bone
- Muscles
- Fasciae

Neuropathic Pain
Damage of nerve tissue (mechanic, toxic, ishaemic)


- peripheral
- spinal
- central

One could say, the fare most pain has its origin in the locomotor system and there was a lot of anatomical research on this in the last decades. They found pain processing receptors nearly everywhere.



Musculoskeletal Pain

It has shown that there is a widespread appearance of so called polymodal receptors in the connective tissue that encloses the muscles, the fasciae.




Musculoskeletal Pain

Fasciae:


Widespread appearance of sensible nerve endings, especially in the region of muscle insertion

Most nociceptors are polymodal, they simultaneously respond to different stimuli

Nociception due to mechanically, thermic and chemical stimuli



In the muscles itself there are a large number of free nerve endings which respond to products of the muscle metabolism like adenosin tri phosphat and a low tissue pH.



Musculoskeletal Pain


Muscle:

Excitation of receptive nerve endings in the muscle due to chemical stimulus:

- Adenosine Triphosphate (ATP), released by tissue injury
- H⁺-ions, pH value of the tissue

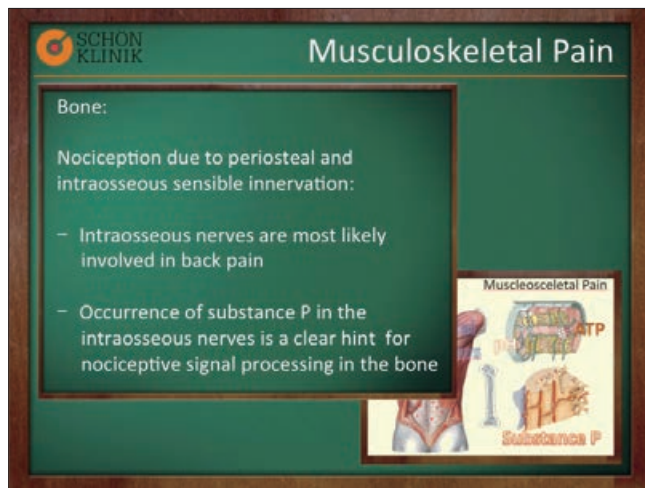
Reasons:

- Tonic contraction / tonic myotatic reflex or muscle spasm
- Overstressing by false posture



And also in the bone marone free nerve endings and Substance P where found.

At the end of the day, all these anatomic evidence shows us that the locomotor System is the perfect sensory organ for Sensation of Pain.



Beside the biological aspect, we also have to consider psychological and social aspects of pain. A chronic pain will influence your mood in a bad way and to turn it round, a manifest depression and fear will affect your personal assessment of pain strongly.

Nearly every chronic pain has an impact of your functional skills and therefore of the mobility in general. Losing mobility will determine an autonomous life and social well-being in massive way.

So, to estimate one's chronic pain, we have to keep all these aspects in our minds.

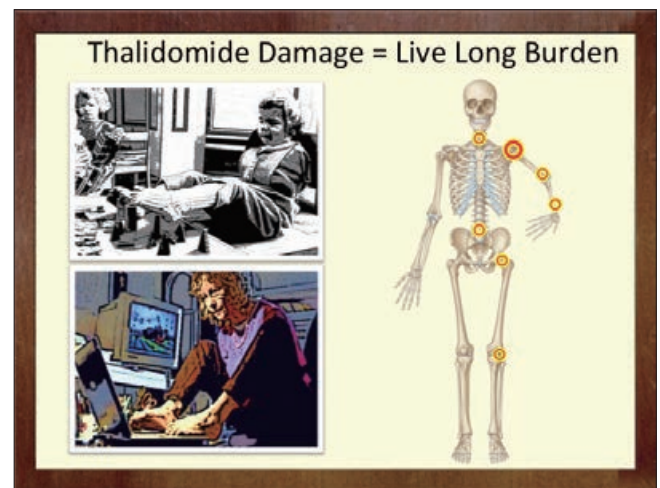


Today in Germany we have around 2,400 thalidomide survivors. They are now in their mid-50s and thus in an age in which health problems in general become more frequent. All thalidomiders had to compensate their disabilities. Unfortunately, the last years have shown, that this compensation is deteriorating and the number of consequential increases. The bandwidth of physical and psychological limitations is enormous. In addition to visible damages all other organ systems can be affected. The lifelong overuse of the body has led to considerable burdens of the locomotor system and several studies have shown that the amount of

chronic pain and the proportion of psychological impact differs significantly from the general population in a negative sense.

Unfortunately there are no readymade solutions and no magic potion for the divine sedation from pain.

So from my point of view, treating pain needs to be individual, multimodal and multiprofessional. Because pain is a complex challenge, we need a complex strategy.



It is about a strategy for solving individually different pain problems.

As a base we have three pillars that should come with each with different weightings are used.

To discuss all three pillars extensively beyond the scope of my talk with security and all take you the opportunity for coffee breaks and for collegial exchange.

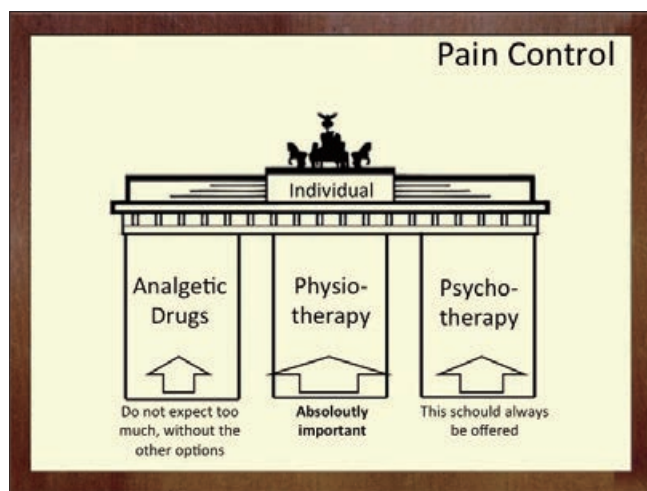
First of all we should looking for a physiotherapist and work closely with him. Regular inter-professional dialogue on the individual patient has this in my view is of central importance.

Physiotherapy should be geared more to the possibilities of the patient and includes both training and relaxation techniques.

In the medication I will go into more detail.

In addition to medication and physiotherapy and psychotherapeutic therapies should always be attempted, because pain always affect the mood and mental well-being, and vice versa, the mood plays a significant role in the assessment of their own pain.

In addition, people have unfortunately often experienced considerable trauma by doctors and around, sometimes even by their own parents' house with thalidomide damage already in their childhood. The prevalence of depression and anxiety are significantly increased in this patient population.



The medicinal pain therapy can be based on the WHO pain ladder, but this should be extended with coanalgetics, adjuvants and invasive procedures.

For each group I want to say only this:

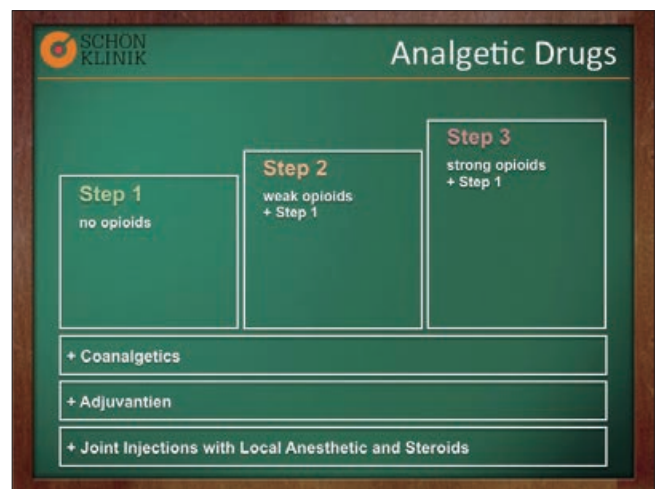
The non-opioids include a variety of substances which are either ineffective, such as paracetamol, or which may cause various complications of long-term use.

The classical NSAIDs and the newer coxibs should be applied in particular with regard to stomach bleeding and kidney damage only under strict medical supervision. The most effective analgesics in musculoskeletal pain.

Dipyrone is effective and has comparatively low organ toxicity. However, independent of dose, there is a possibility of a bone marrow depression with agranulocytosis. For this reason, dipyrone is controversial in many countries and not admitted. In Germany, it is often used and this clinically relevant agranulocytosis seems to be rare.

Opioids are the strongest painkillers currently known to us and are probably due to its similarity to endogenous substances (endorphins) the least organ toxicant. However, they appear to be for patients with obstructive sleep apnea and coronary heart diseases a certain risk in terms of nocturnal hypoxia.

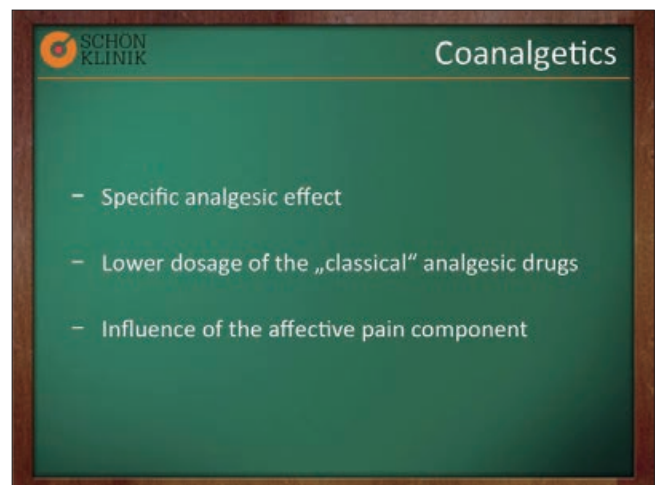
Although the proven potency, opioids are not always superior to musculoskeletal pain compared to NSAIDs.



In order to implement a mechanism-based pain management, it makes sense to extend the classical stage scheme.

In particular, the importance of physical therapy, strength training, balance training is in my opinion too little stressed.

A pain therapeutic concept should be considered in addition to the use of analgesics and physiotherapy also psycho-social factors.



I would now like to respond to the so-called coanalgetics because they have a major role in drug pain management

Some antidepressants have since decades a firm place in the pain medicine, they have partly self-analgesic properties, and some of them can also affect pain modulation, the so-called descending control positive. Antidepressants certainly change the affective component of pain.

The antiepileptic drugs gabapentin and pregabalin are especially effective in neuropathic pain and also have a strong anxiolytic effect.

Particularly in the dose-finding with gradual up-titration strong sedation and dizziness can lead to discontinuation of therapy. Seeking development and pronounced settling phenomena may also occur.

In my view, muscle relaxants have a prominent role, for painful muscle spasms are common in patients with dysmelias of the upper extremities. Since the lack of arm's length is compensated by movements of the shoulder girdle, shoulder and adjacent regions are considerably overloaded.

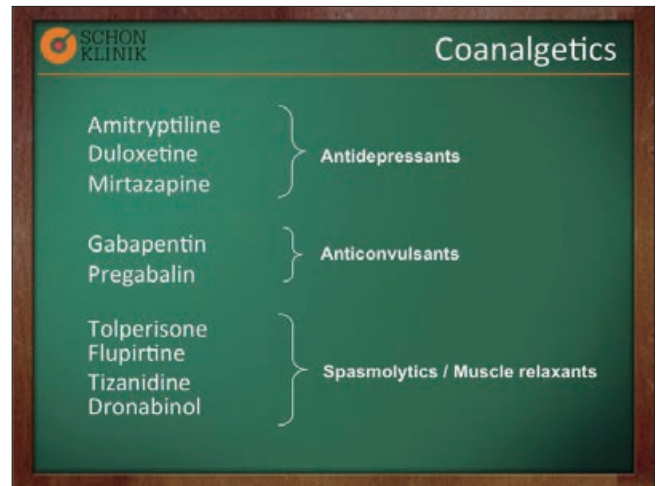
Benzodiazepines should where possible not be used because they have a significant potential for addiction and there is the suspicion that the inhibition of pain is worsened by a total of benzodiazepines.

Flupirtine is centrally effective and it has a peculiar analgesic and a muscle relaxing effect. In Europe, cases have occurred sporadically from serious liver damage and liver failure. Therefore, close monitoring of liver function tests during therapy is required.

Dronabinol, a cannabinoid is authorized in Germany and America for some indications, such as painful muscle tension in multiple sclerosis. There are some thalidomide patients who clearly benefit under an illegal self-medication of cannabis. I believe that the off-label prescription of medicines available on the market to be justified and reasonable. Of course, it should not all patients would be made to addicts, but an objective substance comparison would turn out between the muscle relaxants in favor of cannabinoids, for there are both benzodiazepines, as well as for flupirtine (and tolperisone) clear warnings on the potential for addiction.

When prescribing documented agreements with the patients and controls by the prescribing physician are writing urgently needed.

To increase compliance when taking the patient to the sense and the regulation needs to be explained in detail in each case.



“You need to stop flying and start jogging“

- Exercise programs – posture retraining, muscle strengthening, fitness training, hydrotherapy and stretching
- Manual therapies – stretching, joint mobilization and manipulation, massage
- Fascial manipulation

Thalidomide Clinic Hamburg (Contergansprechstunde Hamburg)

In our hospital, we provide a wide range of outstanding specialist treatments.



After a year of planning, we developed a concept which aims at providing acute medical services. It consists of three coordinated services and shall be the first step for a regional healthcare network.

The basic consideration is the interdisciplinary treatment at one location.

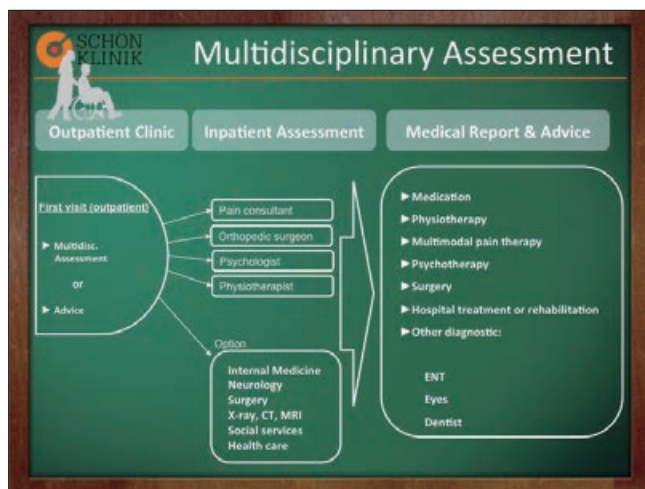
During the first consultation in our outpatient clinic, all patients see a pain consultant and an orthopaedic surgeon. Beside pain- and orthopaedic assessment, all patients will be

examined for general risk factors – like diabetes or cardiovascular diseases.

In case of more complex health problems, there is the opportunity to admit these patients to the hospital for several days.

At the end all patients receive a comprehensive medical evaluation and a detailed advice for further medical treatment.

For the implementation we have a consultation room refurbished and rebuilt, a patient room with a special sanitary area. This enables people with short arms to use it largely independently.



Q&A

Hinoshita: Thank you, Dr. Beyer. Maybe we have some questions, OK? Any question or comment or opinion? I have two or three questions. First, you explained about the merit of the co-analgesics. Is it really effective for the thalidomiders? The thalidomiders can gladly accept taking many kinds of drugs? Because they dislike taking drugs in general.

Beyer: Yes. I have made the same experience, and I personally do not have the opinion that just prescribing a drug is an appropriate solution; I don't believe that this will work out. From my point of view, the biggest pillar of the three pillars is physiotherapy. And I know that drugs only have a limited effect especially with their side effects. I mean that thalidomiders maybe don't go often to the doctor, we don't really know how is their kidney function or if they are suffered from diabetes. When I prescribe non-steroidal-anti-inflammatory-drugs, I'm afraid of kidney failure. So again, I say I think the biggest part of the therapy should be based on physiotherapy and also psychotherapy. But sometimes we need to prescribe something, and it's a matter of starting on the lowest level and to control it very good.

Hinoshita: I see. One more question. I have ever heard it from some specialists on the thalidomide embryopathy in different countries. The massage, the limb massage would be very effective to suppress uncontrollable pain in thalidomiders. How do you think of it?

Beyer: I think that in every patient this is needed to find out which kind of therapy works best. And we can have some patients who are very well in warm water, and some of them are very well in cold water. We have to find out to try it weekly. And I think massage is a really good thing but you need also try to have muscle exercise especially for the rotator cuff. Quite few of them are suffered from, how to say, a de-central shoulder position, and they could benefit from muscle strength and special exercise. Thank you very much.

Hinoshita: Danke schön.

Beyer: So I think it's a matter of not only lay down for massage also do excise.

Hinoshita: Thank you. OK. Liz, please.

Newbronner: I just wondered with you explained the physio is really important. Have you found that physios you work with local physios? Have the skills to work with thalidomide survivors or they needed additional training or understanding of the thalidomide embryopathy?

Beyer: Many of the thalidomiders came from far away to our clinic, and they have their special experience with their own physiotherapist at home. But some of them reported that physiotherapists now at the point they don't know what to do, I think there is a need to have a conference or symposium on this subject especially for orthopedic surgeons and physiotherapists to find out what kind of treatment should be apply to or not. I mean there is this new concept of fasciae training or fasciae therapy. I don't know if you've heard of it. But it's based on manipulation of the fasciae. I think it could be very effective but if it is applied the wrong way, it could be very painful.

Hinoshita: OK, please.

Peters: We have special exercise teams in all clinic, competent teams depending on this physiotherapist and doctors and even psychologists, and a special trainers for the thalidomiders. Because it's really important for the thalidomiders. And to have therapists, which even more the same as they

know we need more. Most things with thalidomiders know more about his disease or his MTE and doctors and therapists. That's a problem. That problem is solved by competent teams.

Hinoshita: Thank you, Dr. Peters. Do you have any other question? Dr. Schulte-Hillen.

Schulte-Hillen: Thank you very much. Does a traditional Chinese medicine play a role like acupuncture? Not yet?

Beyer: I have not found all yet. But if a patient came to me and asked me and say "I have a good experience of this." I have no problem to prescribe it. And to get a feedback how does it work, I'm not sure, I think there are no limitations in manual therapy, Chinese medicine, and acupuncture. You have to try it. And I'm sorry this is maybe not good message these is no ready-made solution. You have to find out individually.

Schulte-Hillen: It is a good message whatever helps going to be applied. That's a good message.

Beyer: Yeah. I think that's the way.

Hinoshita: Any comment? Dr. Peters.

Peters: I think we have got very good experience with acupuncture at our clinic. A part of our pain control and therapy.

Hinoshita: Basically acupuncture with herbal medicines, it's very popular in Japan. How do you think of this, Dr. Kayamori? Have you ever experienced it? Acupuncture for pain control.

Kayamori: The important thing is, how do I say, relationship between person and patient. Acupuncture is only intermediate, so it's up to the patient if relationship between the doctor and the acupuncturist is good and the patient. So I think a little bit effective. But there is no scientific knowledge of acupuncture.

Hinoshita: Thank you. Dr. Ghassemi, OK?

Ghassemi: I just want to give a short comment because in every year, a part of diseases or organ problems, of course, I mean physiotherapists in general are very well working with, but it's always important to send him to the special person. That is more convenient with that special organ to work with. And especially when it comes to thalidomiders, I mean we have today seen that both their posture and direction they have

so many problems, so many other malformations that maybe we don't know. So it's even more important, not to send him to just every physiotherapy. Because we have all the effects of them, you have it, also I know you have it in Sweden. Its orthopedic parts that they do some manipulation of the neck which could be actually disastrous result in not only thalidomiders but even in others. So that was just a comment.

Hinoshita: Do you have any comment against Dr. Ghassemi, Dr. Beyer? Final comment, please.

Beyer: There is no scientific research about the result of the spine surgery because you can't double blind it. At my clinic, I have a famous orthopedic surgeon who is doing spine surgery. And he says 90 percent is to make the right indication. And another one says every spine surgery has the indication apart from the first.

Hinoshita: Thank you very much anyway. Thank you. Sorry, the schedule is just behind the timetable, but I don't want to shorten the afternoon teatime. Then what do you say to starting the next session from 4:35? The next part would start at 4:35 PM. Then please relax yourself and take a rest.

(Intermission)

Primary and consequential disorders in people with thalidomide embryopathy: Results from the thalidomide study of North Rhine-Westphalia (Germany)


Prof. Dr. Klaus M. Peters

Dr. Becker Rhein-Sieg-Klinik, Nümbrecht

Hinoshita: OK, then let's start again. The next speaker is Professor Dr. Klaus M. Peters. His presentation title is 'Primary and consequential disorders in people with thalidomide embryopathy. Results from the thalidomide study of North Rhine-Westphalia in Germany'. Then I will introduce him to you with his individual or personal history. He graduated from University of Cologne and Basel in 1986. He studied his surgical work at University of Cologne. After he worked at two orthopedic clinics, he became senior consultant of orthopedic and osteologic department of Rhein-Sieg Clinic, Nümbrecht, since 1995. He specializes not only in orthopedics but also rheumatology and osteology. He has been a super numeral professor RWTH Aachen since 1999. Then Professor Peters, please.

Peters: Yes. First of all, Dr. Hinoshita, thanks a lot to you to invite me to Tokyo and to give a possibility to present my results. We performed the study in the north of Westphalia, the biggest county in Germany with most inhabitants, and about 837 thalidomiders are still living in North Westphalia. And the study targeted all people living in North Rhine-Westphalia, and we got 202 people with thalidomide embryopathy that means 24 percent of all living patients. What we did with the paper in this people is that we had thalidomide-specific questionnaire with 34 items. We performed the pain-detecting questionnaire, we performed MPSS reminds model of pain chronification people forms 36 questionnaire, we did skit interview with all the thalidomiders. And we did systematic physical examination in

International Symposium on Thalidomide Embryopathy. 21.11.15, Tokyo

Dr. Becker  Klinikgruppe


Primary and consequential disorders in people with Thalidomide embryopathy. Results from the Thalidomide study of North Rhine-Westphalia (Germany)

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Klinisches Schwerpunktzentrum DVO

www.dbkg.de

Setting

The study targeted all Thalidomide-affected people in North Rhine-Westphalia:
n=837
202 people with Thalidomide embryopathy (24%), born or living in North Rhine-Westphalia, were recruited (female:male= 115:87).



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Methods


- Thalidomide-specific questionnaire with 34 items
- Pain DETECT-questionnaire
- MPSS (Mainz Model of Pain Chronification)
- SF 36 questionnaire
- SCID-interview
- systematic physical examination
- X-ray, ultrasound (in selected cases)

⇒ Individual treatment recommendations for physical and mental disorders for every participant

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Pattern of skeletal damages (n=202)

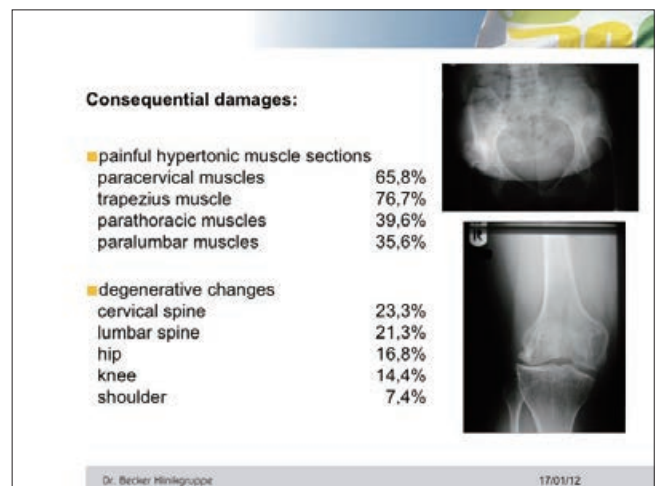
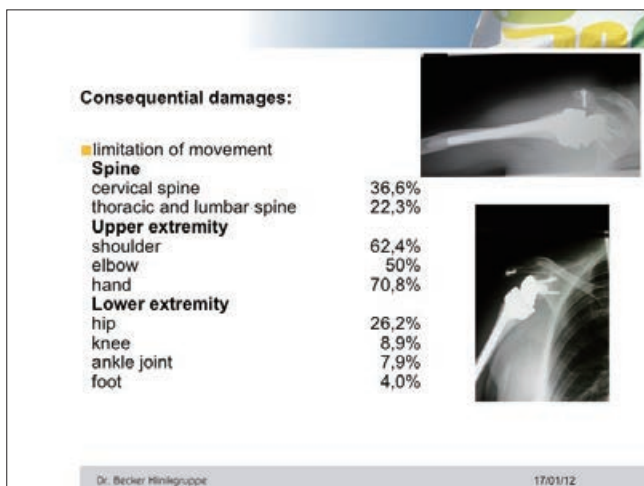
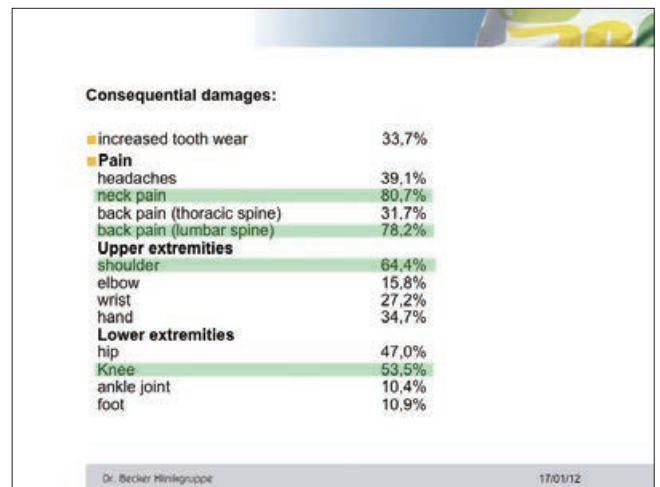
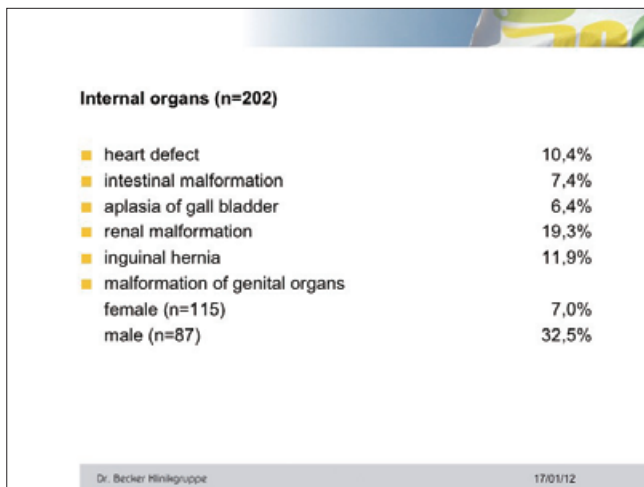
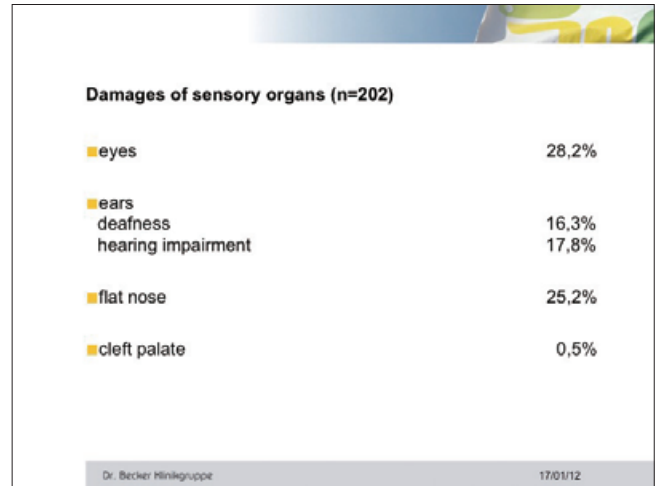
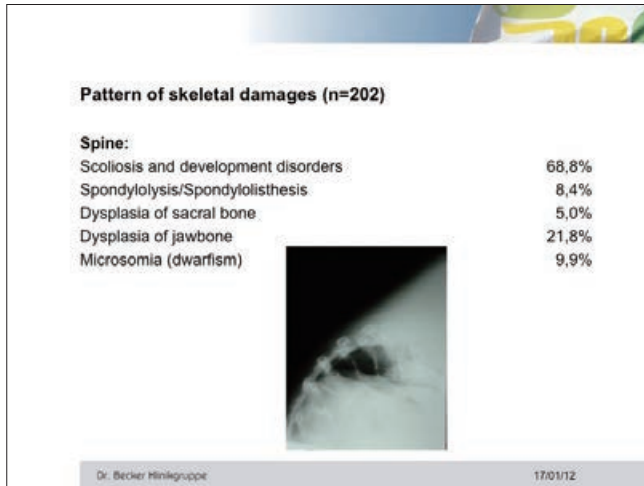
Twofold damage (dysmelia of upper extremities)	89,6%
Fourfold damage (dysmelia of upper & lower extremities)	9,9%
Concomitating damages:	
Hip dysplasia	57,9%
Hip luxation	7,4%



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all of the 202 patients. And we did further X-ray and ultrasound diagnostic in selected cases. After our examinations every patient got individual treatment recommendation for physical and mental disorders. What's the pattern on our skeletal damages twofold damages is about in 90 percent of our thalidomiders. And the fourfold damage is about 10 percent. That's a bit less than its collective off of mark-word in 70s. Concomitant damages were hip dysplasia this in about 58 percent and additional hip luxation is about 7.4 percent.

What about spine? Scoliosis and development disorders is about nearly 70 percent of all thalidomiders. Spondylolysis and spondylolisthesis 8.4 percent. Dysplasia of sacral bone of sacra l bones 5 percent, Dysplasia of jawbone in 21.8 percent. And microsomia that means dwarfism about 10 percent of our people. What about damages of sensory organs? Damages in the eyes about 28 percent, according to deafness, deafness in 16 percent and hearing impairment in about 18 percent. So called flat nose in about one-quarter of our patients.




Cleft palate in 0.5 percent. What about the internal organs? 10 percent of them have heart defects, 7.4 percent intestinal malformation. Aplasia of gallbladder was in 6.4 percent.

Renal malformation is about 20 percent, inguinal hernia is about 12 percent. What about malformation of genital organs, the females 15 patients namely in 7 percent, and males 87 patients namely in 32.5 percent. Now to the consequential secondary damages we discuss already a lot of them doing day to day, we have increased tooth ware. The mouth

and teeth problems in about one-third of all patients. What about pain? We told you already about a lot of pain. And the most dominating pain is neck pain. It's about 80 percent. And the back pain about 78 percent. If you see the upper extremities, the pain of the shoulder joints dominating with 64.5 percent, followed up by the pains of the wrist. In the low extremities it's not the pain of the hip but it is pain of the knee dominant. It's the most common pain in about 54 percent. What about consequential damages due to the limitation of

Chronic pain

MPSS Stage II + III (Gerbershagen) **62,45%**
 PainDETECT-Questionnaire
 nociceptive pain **50%**
 neuropathic pain **50%**



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Prevalences of mental disorders

Disorder or disorder group (ICD-10 code)	4-Week prevalence (total, n=193)	4-Week prevalence (women, n=109)	4-Week prevalence (men, n=84)
Neurocognitive disorder (F0x) ²	1 (0.5%)	1 (0.9%)	-
Substance-related disorder (F1x) ²	16 (8.3%)	3 (2.8%)	13 (15.5%)
- Alcohol-related disorder (F10)	12 (6.2%)	2 (1.8%)	10 (11.9%)
- Medicine- and drug-related disorder	6 (3.1%)	1 (0.9%)	5 (6.0%)
Psychotic disorder (F2x) ²	1 (0.5%)	1 (0.9%)	-
Affective disorder (F3x)	44 (22.8%)	25 (22.9%)	19 (22.6%)
- Unipolar depression	32 (16.5%)	18 (16.5%)	14 (16.7%)
- Dysthymic disorder	3 (1.6%)	1 (0.9%)	2 (2.4%)
- Minor depression	10 (5.2%)	6 (5.5%)	4 (4.8%)

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Prevalences of mental disorders

Disorder or disorder group (ICD-10 code)	Lifetime prevalence (total, n=193)	Lifetime prevalence (women, n=109)	Lifetime prevalence (men, n=84)
Neurocognitive disorder (F0x) ²	1 (0.5%)	1 (0.9%)	-
Substance-related disorder (F1x) ²	29 (15.0%)	4 (3.7%)	25 (29.8%)
- Alcohol-related disorder (F10)	26 (13.5%)	3 (2.8%)	23 (27.4%)
- Medicine- and drug-related disorder	9 (4.7%)	2 (1.8%)	7 (8.3%)
Psychotic disorder (F2x) ²	1 (0.5%)	1 (0.9%)	-
Affective disorder (F3x)	76 (39.4%)	42 (38.5%)	34 (40.5%)
- Unipolar depression	64 (33.2%)	35 (32.1%)	29 (34.5%)
- Dysthymic disorder	3 (1.6%)	1 (0.9%)	2 (2.4%)
- Minor depression	11 (5.7%)	6 (5.5%)	5 (6.0%)

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Prevalences of mental disorders

Disorder or disorder group (ICD-10 code)	4-Week prevalence (total, n=193)	4-Week prevalence (women, n=109)	4-Week prevalence (men, n=84)
Neurotic, stress, and somatoform disorders (F4x)	52 (26.9%)	33 (30.3%)	19 (22.6%)
- Phobic disorder (F40)	24 (12.4%)	14 (12.8%)	10 (11.9%)
- Anxiety disorder (F41)	5 (2.6%)	4 (3.7%)	1 (1.2%)
- Panic disorder	4 (2.1%)	3 (2.8%)	1 (1.2%)
- Generalised anxiety disorder	1 (0.5%)	1 (0.9%)	-
- Obsessive-compulsive disorder (F42)	2 (1.0%)	1 (0.9%)	1 (1.2%)
- Post-traumatic stress disorder (F43)	6 (3.1%)	5 (4.6%)	1 (1.2%)
- Dissociative disorder (F44)	-	-	-
- Somatoform disorder (F45)	27 (14.0%)	18 (16.5%)	9 (10.7%)
- Pain disorder	24 (12.4%)	17 (15.6%)	7 (8.3%)
- Other somatoform disorders	4 (2.1%)	2 (1.8%)	2 (2.4%)

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Prevalences of mental disorders

Disorder or disorder group (ICD-10 code)	Lifetime prevalence (total, n=193)	Lifetime prevalence (women, n=109)	Lifetime prevalence (men, n=84)
Neurotic, stress, and somatoform disorders (F4x)	99 (30.6%)	37 (33.9%)	22 (26.2%)
- Phobic disorder (F40)	27 (14.0%)	16 (14.7%)	11 (13.1%)
- Anxiety disorder (F41)	10 (5.2%)	7 (6.4%)	3 (3.6%)
- Panic disorder	9 (4.7%)	6 (5.5%)	3 (3.6%)
- Generalised anxiety disorder	1 (0.5%)	1 (0.9%)	-
- Obsessive-compulsive disorder (F42)	3 (1.6%)	2 (1.8%)	1 (1.2%)
- Post-traumatic stress disorder (F43)	8 (4.1%)	7 (6.4%)	1 (1.2%)
- Dissociative disorder (F44)	1 (0.5%)	1 (0.9%)	-
- Somatoform disorder (F45)	27 (14.0%)	18 (16.5%)	9 (10.7%)
- Pain disorder	25 (13.0%)	18 (16.5%)	7 (8.3%)
- Other somatoform disorders	4 (2.1%)	2 (2.8%)	2 (2.4%)

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Prevalences of mental disorders

Disorder or disorder group (ICD-10 code)	4-Week prevalence (total, n=193)	4-Week prevalence (women, n=109)	4-Week prevalence (men, n=84)
Eating disorder (F50)	5 (2.6%)	5 (4.6%)	-
- Anorexia nervosa	3 (1.6%)	3 (2.8%)	-
- Other eating disorder	2 (1.0%)	2 (1.8%)	-
Personality disorder (F6x) ²	15 (7.8%)	6 (5.5%)	9 (10.7%)
Mental retardation (F7x) ²	4 (2.1%)	1 (0.9%)	3 (3.6%)
Presence of at least one mental disorder	91 (47.2%)	51 (46.8%)	40 (47.6%)
- One diagnosis ²	50 (25.9%)	29 (26.6%)	21 (25.0%)
- Two diagnoses	25 (13.0%)	14 (12.8%)	11 (13.1%)
- Three or more diagnoses	16 (8.3%)	8 (7.3%)	8 (9.5%)

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the movement. In the spine, you have the limitation of the movement cervical spine is about 36.6 percent, lumbar spine is 22 percent. What about the upper extremities? Here is a hands dominating limitation of the movement of the lists in about 70 percent. That's due to the primary damages. And then followed by the shoulder about 62 percent. What about lower extremities, here is a hip joint are dominating with 26 percent followed by the knee. Knee is painful but the movement are not so limited. Only limitations in nearly 9

percent of the participants. What about the muscles? Painful hypotonic muscle sections as we heard already several times, paracervical muscles about 66 percent, trapezius muscles about 77 percent, parathoracic muscles about 40 percent, and paralumbar muscles about 36 percent. What about degenerative changes? You see degenerative changes. You see we have degenerative changes in the cervical spine about 23 percent followed by lumbar spine about 21 percent. Degenerative changes of the hip, osteoporosis of the hip in about 70

Prevalences of mental disorders

Disorder or disorder group (ICD-10 code)	Lifetime prevalence (total, n=193)	Lifetime prevalence (women, n=109)	Lifetime prevalence (men, n= 84)
Eating disorder (F50)	7 (3.6%)	6 (5.5%)	1 (1.2%)
- Anorexia nervosa	3 (1.6%)	3 (2.8%)	-
- Other eating disorder	4 (2.1%)	3 (2.8%)	1 (1.2%)
Personality disorder (F6x)¹	15 (7.8%)	6 (5.5%)	9 (10.7%)
Mental retardation (F7x)²	4 (2.1%)	1 (0.9%)	3 (3.6%)
Presence of at least one mental disorder	115 (59.6%)	62 (56.9%)	53 (63.1%)
- One diagnosis ³	51 (26.4%)	30 (27.5%)	21 (25.0%)
- Two diagnoses	36 (18.7%)	17 (15.6%)	19 (22.6%)
- Three or more diagnoses	28 (14.5%)	15 (13.8%)	13 (15.5%)

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Summary physical disorders

More than 50 years after the withdrawal of Contergan painful consequential damages dominate the condition of Thalidomide survivors:

Thalidomide survivors:
62,4% pain chronicity of MPSS stages II + III
50% possible or probable neuropathic pain

Pain localisations:
neck > back
shoulder > knee > hip

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Summary of mental disorders

47,2% of Thalidomide survivors with one mental disorder (four-week interval) versus 27,7% in German general population

Depressive disorders (22,8%) > somatoform (pain) disturbances (14,0%)

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- physical quality of life ↓
- mental health ↓
- care needs ↑

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Medical care system in North Rhine-Westphalia/Germany is not prepared for these problems !

⇒ consultation of doctors ↑
hospital care ↑

but treatment of consequential damages is not successful!

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Reasons

- inadequate knowledge about the Thalidomide embryopathy and its consequences among general practitioners and medical specialists
- complex patterns of damage in Thalidomide survivors
- „orphan disease“ (837 Thalidomide survivors in NRW)
→ only a few individual patients per practice
- lack of training opportunities for general practitioners and medical specialists regarding initial and subsequent damages
- excessive distance from drug pain therapy among Thalidomide-affected people resulting in insufficient treatment

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percent, that's much rarer as in Sweden. And as the knee in about 15 percent but only extra examination those patients were painful joints. It's different to you. You did the CT scans all of your participants. That may say the differences. What about chronic pain? What we did find about chronic pain, 63 percent of all our thalidomide patients have chronic pain as stage 2 and 3 of Gerbershagen. There is chronic pain, and used the pain detection questionnaire only have still nociceptive pain. And the other patients, the other 50 percent have already neuropathic pain. That's a lot.

Now to mental disorders. Due to ICD code, you see, substance related disorders are really common and all that four-week prevalence so called point prevalence. In the point prevalence you see substance related disorders are in about 15.5 percent of all of men. The women are less in only 2.8 percent. Effective disorders are very common in all groups. In men 22.6 percent and the same percentage in women. That's a four-week prevalence. If you see in the lifetime prevalence, substance-related disorders, for example, especially alcohol related disorders are common in men 75 percent, in women only in 2.5 percent. The men are much more affected by alcohol related disorders in Germany than women. And medicine and drug-related disorders also men are more common than in female. 8.3 percent versus 1.8 percent. Another group of mental disorders as effective disorders is especially the depression. You see the lifetime prevalence of all people both genders about nearly 40 percent of all thalidomide survivors in the study had effective disorders. And nearly equal in n men and women. You see in women 38.5 percent versus 40.5 percent in men especially depressions. What about neurotic stress and some other stress disorders? Also a huge amount in the four-week prevalence, you see about 27 percent of all, and the women a bit more than the men. That's the four-week prevalence. And if you see the lifetime prevalence, it's even higher, it is normal must be. So,

30.6 percent of the whole collective. And the women a bit more than the men 33.9 percent against 28.2 percent. And here you see especially phobic disorder as the problem. And some matters of the disorder about 14 percent of lifetime prevalence. Eating disorders are very rare and only in female. Men have no eating disorders. And if you see personal disorders, in 7.8 percent and bit more in men in the lifetime prevalence than in the women. And if you look at the presence of the mental disorders, admit the one mental disorder in about 47 percent in the four-week prevalence, and that's nearly equal if you compare women with men if you have one diagnosis. If you have two diagnoses in another 13 percent in three of more mental diagnoses in about 8.3 percent of the participants. And if you see here in the lifetime prevalence, you have already nearly 60 percent of all thalidomiders have at least one mental disorders, that's a lot. You see the men are a bit worse than the women. And if you see one diagnosis, two diagnoses, three and more diagnoses you see 26 percent one diagnosis even 18 percent have two diagnoses, and another 14.5 patients have even three or more mental disorders. That's a lot, much more than in the German community. Now we come to the summary of the physical disorders. More than 50 years after the history of Contergan (thalidomide) painful secondary damages dominate condition of thalidomide survivors. To the pain chronicity 62 percent of the patients have chronic pain of the MPSS stages 2 and 3. And in half of them pain is already neuropathic pain. And if you look for the pain localization you can say neck is more than back. And if you see the joints, shoulder is more than knee and then hip. Some other mental disorders, 47 percent of thalidomide survivors have one mental disorders in the four week prevalence that means point problems versus 27.7 percent in the German general population. You see the point prevalence is much higher in the thalidomide survivors in the general German population. And the depressive

Strategy of centres of excellence:

1-2 in NRW

several functions, e. g.

- build up peer-to-peer programs
- make treatment paths of existing treatments visible for patients and doctors
- serve as centre for the screening of vulnerable groups

The EX-Centre in Stockholm is a good example of the successful establishment of a superregional centre of excellence for patients with dysmelia.

EX-Centre will be a model for a German institution for Thalidomide-affected people.

disorders dominate before against some other form pain disturbance as you see 22.8 percent versus 14 percent. What is the other result physical quality of life also thalidomide survivors becomes worse. The mental health becomes worse, and their care needs increase. Our problems in Germany, that's medical care system is not prepared up to now for these problems. Although we have increased consultation of doctors and increased hospital care of the thalidomiders. But the treatment of the secondary consequential damages is not successful up to now. What are the reasons of set situation? We have nowadays inadequate knowledge about thalidomide embryopathy, and its consequences among the general physicians and medical specialists in Germany. Why? We have a complex patterns of damage in thalidomide survivors. They are not unique, they're very different. And TE isn't an open disease. You see only 837 thalidomide survivors in North Rhine-Westphalia about 2,500 in all Germany. And as a specialist or a general practitioner, you have only a few individual patients every practice. That's a problem. And we have lack of training opportunities for the general practitioners and medical specialists regarding initial and subsequent damages. And on the other hand, even excessive distance from drug pain therapy among thalidomide-affected people resulted in insufficient treatment especially in pain. What is the strategy and results of our study regarding North Rhine-Westphalia? We want to establish centers of excellence and also in Westphalia we want to establish one or two of these centers, these centers should have several functions. We want to grade up peer to peer programs. We want to make treatment path of existing treatments visible for patients and doctors. And we want to serve as a center for screening of one of groups within the thalidomiders. The EX Center of Stockholm as you visited in September is a good example for the successful establishment of super regular center for excellence for patience of Westphalia. And the excellent model of our German institutions for thalidomide affected people. And that's our clinic and I think it's a lot to do in the future for the thalidomide survivors, and we have to do it. Thanks a lot.

Q&A

Hinoshita: Thank you very much, Dr. Peters. Do you have any question? Dr. McCredie.

McCredie: You have an alarming number of mental diseases.

Peters: Yes.

McCredie: Is that largely reaction to the situations they're finding themselves in or something else?

Peters: I think it's a lot of them were not detected up to now. I think its percentage is much higher than they knew. Because all these patients were examined by the skit interview, and also systematic very intense interview about three hours last to put these diagnoses together. And it's a moment a lot of people didn't have these examination, therefore the numbers we know are much lower. But in reality, they are higher. And we have to do, we have to come to these patients.

McCredie: I think in Australia we are getting it at sideways because I've been told by those who lumbar thalidomide association of the other. Almost all the thalidomiders are in anti-depressants. That's a sort of sideways look as the same thing.

Peters: Yes.

Hinoshita: OK. Is there any other question? Dr. Schulte-Hillen.

Schulte-Hillen: Thank you very much for this presentation. I want to make a remark on tooth and teeth wear. I think the name [inaudible] 2008. They had a similar approach and they wanted to find out whether the teeth, the very bad teeth of the thalidomiders came from abuses as beer can opener, something like that. And they found out not to be the case but they found out that 42 percent of the thalidomiders had gastric regurgitation. And they thought that could be the explanation, so maybe somebody in your clinic has very bad teeth. It could be a good idea to perform gastroscopy to find out he has a reflux problem.

Hinoshita: What do you say to this, Ms. Newbronner?

Newbronner: Just a brief comments to follow on from that. Our UK survey found that dental problems were common amongst Thalidomide survivors, including those with no limb damage which perhaps suggests that there are other causes including poor dental hygiene for people with facial disfigurements. So I think that was borne out by the Swedish study, wasn't it?

Hinoshita: Anyway, the mouth or a dental problem has not been focused so far. Then it's a new theme to treat thalidomiders from now and near future. Anyway, Dr. Maruoka.

Maruoka: My name is Maruoka. I belong to the same hospital as Dr. Hinoshita. Please let me speak Japanese. OK? For the regurgitation and bruxism are related, and because of the regurgitation there are some acids. And the acids are just cause of the decay of the teeth, and that's quite plausible.

Hinoshita: He said regurgitation might influence the teeth, maybe. We should start think of this further. OK. Any other question? Yes, please Dr. Kayamori.

Kayamori: I would like to ask prosthesis inserted in the shoulders. Could you comment on the insertion of artificial joint? Your opinion?

Peters: Yes. Here, several cases this osteoarthritis of the shoulders will be put in inverse prosthesis. Then we have no problems of this rotator cuffs.

Kayamori: I was asked to have a Japanese thalidomider want to have a surgery in the shoulder. But I don't think artificial shoulder is not effective for pain, because shoulder girdle is so weak, besides the exact site is not responsible. So that's a reason why I don't recommend the surgery for the patient.

Peters: We are different. It depends on the joint. If it's a complete joint. Lots of them have new complete joint and no joint arthrosis, that's easy. But if you have a complete shoulder joint, and opportunity to do that joint but then you should do inverse prosthesis not only most cases, it's not sufficient to do a plastic joint because of the muscles. Must have muscle to do the Swedish solution. Otherwise you won't be successful.

Kayamori: Probably the problem is what calls a pain. That's a problem. Joint arthrosis is mainly a problem, that's one I think needs to have a surgical treatment. But pain is questionable one cause hypoplastic muscle, weak muscle.

Peters: Have you differentiated in advance before? You have to see if it's arthrosis pain or it is cause be the muscle. Then you can do by injections for example to see it comes from the muscles or comes from the joint.

Kayamori: But that one is normal person. So there are lots of factors or contributing to the pain in the thalidomiders. That's, if we are familiar with whole thing, we comprehensively understand what the problem is existent.

Peters: To see comes from the joint, it's you have to make injection in the joint. And if the pain wait about 24 hours, then you know main pain comes from the joint.

Hinoshita: OK, then Dr. Beyer, please.

Beyer: So that is what I think, too. I'm with you in this part. In this region, you have really multi-reason having pain, from the bones, from the joints, from the muscles, from the fascia. And I think it's really a good idea to distinguish between these different tissues by injecting local anesthetic in the joint because local anesthesia will work if it's a problem link to the joint from my point of view. And if you are sure that you are in the joint by ultrasound controls or whatever. I'm quite sure if the problem comes from the joint, you can solve it for 24 hour or maybe 10 hour. But you can't distinguish very good between muscles and joint itself.

Peters: Yes. Most of the problem is muscular problems. You see you have about 80 percent, 60 percent of our patients had shoulder problems. And you have done shoulder prosthesis up to now about five or six. You see its minority, only few cases. Most of them have muscular problems, and then you have to clear this problem. But one of them is osteoarthritis and therefore artificial joint can be benefit for this.

Kayamori: Chronic pain you're thinking of is due to arthrosis. Patients complain of chronic pain. That means we have been doing the treatment for a long time. But still patients complain about pain. That is chronic pain, so we use a lot of medication and physiotherapy. But we reserve an operation. So if we are familiar with choice of chronic pain. But so far we don't know.

Peters: I think it's depends on the history also pain. You can have a chronic pain, but suddenly pain of the shoulder comes worse and worse. Then you have to look.

Kayamori: Do you have to consider whole thing? Just we are talking about only one place. That is a shoulder pain. But patients complain about back pain, neck pain, lots of things. But even though we do surgery for the shoulder, but still patients complain about pain, other place. That is true.

Peters: But the solution is to replace their shoulder, you can only have solution for shoulder pain, not for the back pain. That's normal. But if you have severe problems with the shoulder and can't sleep any night because of the pain of the

shoulder, then shoulder joint surgery can be a solution for that pain.

Kayamori: So you came from North Rhine-Westphalia. That is I think Aachen is a capital. So I visited once while, I visited Aachen where I found head of Grünenthal is over there. They are producing a good medicine named analgesia. That's good one. Grünenthal is just producing and selling drugs.

Peters: Right.

Kayamori: Yeah. So if you think pain is due to arthrosis, if you prescribe good analgesia before doing surgery, how about prescribe good medicine.

Peters: You see you do before surgery long distance of other treatment before you said. It's the end of the story. This is the end of the story.

Hinoshita: OK. There seems to be a great gap between both of your opinions. Anyway, after this symposium please individually discuss it. And then, is there anyone who can have any other short comment about this program? Doctors from England or Dr. Nakamura, or someone else?

Newbronner: I can give you the letter that a consultant gave to me. I did the slide on. So you can have a little look at his comments again on wide shoulders causes the problem.

Peters: Can you do that tonight?

Hinoshita: OK. Anyone else?

Newbronner: I was just interested, because your findings in relation to prevalence of mental health is very similar to our self-reported findings. And I wondered if you, that strategies you are using to help thalidomide survivors who have mental problems. Furthermore what approaches you're using because I think that is difficult issue for us in England.

Peters: Different approaches, most of them have ambulance psychotherapy in the ambulance setting.

Hinoshita: OK. Dr. Beyer, please.

Beyer: So I think it's a good idea to admit every one of them psychotherapists to find out whether he needs help or not. I mean it's a difficult thing, because there is a high barrier to

go to a brain doctor. Because everybody says "No, I'm not crazy." But I think you should convince your patient to do so. Even if you find mild depression, maybe this could be helpful for the patient. And in cases of major depression or other mental disorders you need an expert to classify whether this needs for example, to be treated in a hospital or in an ambulance setting even if you have the feeling something is not OK there, you can't name it really good.

Hinoshita: OK. I have one question. In Germany, you have so many thalidomiders. There're the most over the world. But you have found so many specialized hospitals. And you are talking about the strategy of centers of excellence. Also in England, Dr. Morrison and other staff are trying to make the specialized hospitals for the thalidomiders. Wrightington Hospital and Royal National Orthopaedic Hospital, for example. And in Japan, we have seldom specialized hospitals exclusively for thalidomiders. May I ask you how to deal with thalidomiders to do some specialized operations? Or to control pain or to support dental problems or so? I mean for the patients far away from the specialized hospitals, it's difficult for them to go to the medical centers. So do you have any good idea about this program?

Beyer: Yes. They can come as outpatient. Then he or she gets examination and proposal what to do, and can do as ambulance patient at home. Or if you have a severe problem, you can come as inpatient to our clinic. If he or she has to have surgical procedure, there is a specialist in clinic. I and our team do surgical procedure.

Hinoshita: So you think one of the best ways is to establish the specialized hospitals.

Beyer: Yes.

Hinoshita: Even if a few in each country? The same idea as in the United Kingdom?

Morrison: We don't have a single specialist centre because one hospital would not be able to cover every issue. So we refer to individual specialists which is what I tried to show this means the individual has to travel. But as I said, some hospitals have more specialists than others. So if a patient has a problem I just try to find the best person around the area they are willing to travel to. But quite often they like to see a specialist who has seen others like themselves - they don't like doctors who are not used to their damage and make

comments when putting X-rays up and seeing the unusual anatomy which is not unusual when the individuals go to the local hospitals. Communication between beneficiaries as to how they have been helped is important and hence Facebook. But you often meet individuals who do not want help and I think Christina said or Janet said this, a certain group who do not want operations, and don't want to have anything done. And maybe you have to wait for them to be ready. And try to work with them slowly so they will accept help.

Hinoshita: Thank you very much. How about in Switzerland, Dr. Schulte-Hillen?

Schulte-Hille: Thank you very much. I come from Germany. But I moved for job purposes for Switzerland. I know that the German thalidomide trust aides pensions to exactly nine patients in Switzerland. And I have so far tried to invent to contact them. They are absolutely no way organized.

Hinoshita: So if somebody has any serious problem which needs operations or so, they might visit some hospital in Germany?

Schulte-Hillen: Sorry, I did not understand this.

Hinoshita: OK. If thalidomiders living in Switzerland should go to Germany for some operations, specialized operations or so?

Schulte-Hillen: This should be possible on any account, but I don't know very much that any Swiss patient would go to Germany for any treatment. I'm sorry they are very special.

Peters: But I think there is international exchange also to get patients from Beijing or Netherlands for example for doing surgical procedures.

Schulte-Hillen: Of course I would advise them to go to and see you, too, because I know there are very capable specialists if I was asked but so far I have not been asked.

Hinoshita: OK. Will you understand the situation in each country? Any other question or opinion, or comment? Nothing? Thank you very much, Dr. Peters. Then, let's have a brief intermission until 5:25 PM. From 5:25, we will start the joint discussion. Thank you.

(Intermission)

Joint discussion

Hinoshita: All of you are ready? Get your own receiver. All right? Then let's start the joint meeting or discussion finally. Actually I have ever given the symposiasts several main topics for the joint discussion. First, I will show them the question. What are the key problems thalidomiders are medically facing now? Today, we could listen to the basic and detailed reports in the general survey in Germany, United Kingdom, Japan, and Sweden. How can we overcome these problems? Then, first of all, can we hear from Dr. Kayamori or Dr. Shiga as for the situation in Japan? What are the most serious problems the thalidomiders are now facing?

Shiga: I think the most important problem is pain. I met about 20 TE subjects in a hospital, for medical check up. Then I analyzed lifestyle-related diseases and so on. When I talked with them, they always said "We have pain." So please solve this problem.

Hinoshita: Do you agree to this opinion, Dr. Kayamori, now in Japan?

Kayamori: Yes, we carried out a survey that is a study on health status and living condition of Japanese thalidomiders in 2012 in accordance with that survey that Japanese thalidomiders complain about shoulder pain, 44 percent and lumbar pain always 44 same in the short arm groups as well as hearing loss group. So chronic pain is one of the most troublesome problems in the Japanese thalidomiders.

Hinoshita: How about in Germany, Dr. Peters or Dr. Ding-Greiner?

Peters: I think it's the same in Germany as well. Most problems are the chronic pain.

Hinoshita: The same opinion, Dr. Ding-Greiner?

Ding-Greiner: I think of pain as an additional cause of loss of motility and of functionality. We do not have enough professional personal assistants in Germany and the nurses give a different kind of care thalidomiders do not need in this situation. They have the somatic problems of 80 year old persons, but they are only 50 years old and they have a young mind. I think there is something they even don't want to think of, that is to be forced by the circumstances to go

to a nursing home. Nursing homes cannot be adapted to an individual situation of physical impairment. Therefore they will lay on the bed, they will sit on the chair, and that's all they can do. There will be no normality. I don't think it's the life they deserve. This is a very, very big problem. Thalidomiders are more open for technical innovations than elderly people in Germany, because they see it is the only way of preserving some autonomy.

Hinoshita: OK. Most of the thalidomiders have great anxiety for the later life, right? Then, also the ADL, Activity of Daily Living, is now poor, and we should improve the housing condition or the living environment, right?

Ding-Greiner: That's a financial problem.

Hinoshita: Yeah, financial problems.

Ding-Greiner: A very big financial problem. That's what the problem is. Because it's high cost.

Hinoshita: But in UK, the government had decided to give a great benefit, you know? How about the situation in UK?

Newbronner: In the UK, because the financial situation for thalidomiders has improved substantially since 2000. In particular from 2010 when people received the health grant. And in the UK, the health grant is 75 percent of people's annual compensation grant. So it is big improvement in people's financial situations. And what we found in the UK is that people make different choices when they have the resources to make choices about how they want to live and how they want to spend their money and preserve their health. They make different choices. Some people choose to adapt their homes or buy equipment, other people buy assistants. And they pay for all kind of health care. And I think giving people the freedom to make those choices is really crucial alongside of the knowledgeable of special medical treatment and health care. But in their daily lives people need the financial resources to decide themselves what will make their lives better.

Hinoshita: I see. How about in Sweden? Now pain and the house living have been focused on. Pain is a great problem in Sweden, too?

Ghassemi: Yes, I believe so. In the beginning, when I started a study, we didn't have so many responses as I showed you before. Now I think because it was they were so independent, and they didn't even want to be part of any studies. But when we were in Stockholm at the entry meeting, first thing I heard that "Can't you start these your study again?" They preferred the CT again because I think now they are dealing with problems with pain. I totally agree with you. Because not only pain it's just concern about being very dependent future. And it's the [inaudible] case just to accept for many of them. And it comes to the economy and I know that is in Sweden, the stage has agreed with the almost huge sum of money for the whole association. I think it's as the president was telling me I think it's something like 1.8 million euro which is, and as you say they are trying to divide their money not exactly equal, because it depends on how many points of impairment they have. And I think they are going to use that money for the tentative house or cars.

Hinoshita: Financial aid and support.

Ghassemi: Yeah.

Hinoshita: Thalidomiders accept it, too.

Ghassemi: Yes. That is actually a part from the monthly grant. The monthly one they have from AstraZeneca.

Hinoshita: How about in the Switzerland or the area around you? And you yourself how do you feel about it?

Schulte-Hillen: Personally I think the most burning question of the thalidomiders is the question of relieving pain and the question of loss of autonomy. Because they have led the life a lot of autonomy and a lot struggle until now. And they see themselves impaired by age but we as doctors should not forget there is another burning problem which is not heard, that is, hypertension, there is no way to measure correctly hypertension in these people. That is Dr. Ding-Greiner pointed out earlier today. These people are in danger for cardiovascular disease. And there must be every effort I think should be taken to find a device that permits measuring blood pressure correctly.

Hinoshita: From the standpoint of thalidomiders, pain is a very important problem for you?

Schulte-Hillen: For me, personally not. Because I do not have pain.

Hinoshita: But other thalidomiders?

Schulte-Hillen: As far as I know them, yes.

Hinoshita: In the latter part of discussions, pain was discussed very hotly. How would you solve the pain control, Dr. Beyer?

Beyer: I would like to analyze but I can't take everyone's pain. But you wouldn't be able to take part of life, so I think it's important to see pain therapy has always to focus on mobility. In first instance, if you prescribe medication which cause severe dizziness in a patient, you might danger him for falling down or breaking bones whatever. So I think it all need to be rational for the individual problem of this individual patient. And individual patients have to agree with it. Because if you prescribe pills he doesn't want to have, he never takes it. And you always have to find individual solution, otherwise it will not work out at all. And I'm sorry to say this. No medication or whatever you can give for completely pain relief. And you have to take everything, otherwise you can't get. Acupuncture, fascial manipulation, you have to try everything. And maybe there is strategy to start with more harmless therapies to find out whether it helps, together with others. Then to start with, a harmless therapy. So it takes time. You can't do at once. You can't predict how it works out. Take time, and you have to discuss this with the patient to let him understand. There is no solution for this. Sometimes operation might be good.

Hinoshita: Systematic strategy is needed for pain. Dr. Ding-Greiner.

Ding-Greiner: This is a very important point. To discuss therapy with the patient takes time. And this amount of time we do not have in our health system in Germany, neither in hospitals. At the Hospitals of the University of Heidelberg we have five minutes per patient. In five minutes per patient you can't do a good job. Thus patients often go home with their unsolved problems. Considering this situation we think it's important to have centers as Dr. Beyer is establishing, as he manages to have time for the patient. But it's a financial problem, too. The time it takes you to care for one thalidomide affected patient, in this time maybe you would examine and medicate 10 other patients. I think this is a very important point, too.

Hinoshita: OK. Is there anyone who has any good positive plans or schemes to support the thalidomiders in the near future? In the United Kingdom, the government or the Thalidomide Trust has given much financial support. But in other countries, that's not enough or well organized maybe. How to solve this problem?

Kayamori: I don't have any idea, but we don't know about the financial problem in Japanese thalidomiders. That's a secret. That one is difficult to know. So in terms of money, we don't have any idea for Japanese thalidomiders. I have no idea that they are lacking of money or have enough money to have a treatment.

Hinoshita: Do you think it necessary to build up some specialized center for the thalidomiders?

Kayamori: No, I think most of the thalidomiders are against that opinion. Because they are comfortable in living in outside of Tokyo. The important thing is that they are in their own houses in which they are living for a long time. The rest of their life must be spent there. That's the best way. So even if we build a new hospital where we have comprehensive treatment for thalidomide victims, I don't think it a good idea for Japanese thalidomiders.

Hinoshita: OK. How about in Australia? Thalidomiders are satisfied with pain control and with living in Australia now?

McCredie: No, they have exactly the same problems as we have heard from the patients today. They complain of pain, premature aging and all that comes with that. In 2010 we reviewed all Australasian thalidomiders and they were given substantial sums of money to support them for another 10 years. But they wonder what will happen after that? Meantime the government has decided to create a National Disabilities Scheme on which the thalidomiders would be able to draw. That is some years in the future at this stage. The cynical thalidomiders think government is putting off the date of the scheme's institution until some of them are dead. So it is not well sorted out in our country. We also have the problem of our huge geographic area. The whole of Europe would fit inside Australia with some space left over, and our Australian population lives around the edge of the continent with a big desert in the middle. National travel is very expensive. The 60 odd thalidomiders are scattered through country towns and villages as well as the cities, so it is very difficult to create a clinic that can deal with them, let alone a dedicated hospital,

which would not be feasible in Australia. Klaus Peters said that one of the problems is that a lot of young doctors are not aware of thalidomiders' current problems. One result of taking thalidomide off the market for 30 years has been that its lessons dropped out of medical education.

Hinoshita: OK. When it comes to pain control, there was hot discussion before, namely whether surgery is good or not. But anyway, since we have such an international symposium let's exchange information about the good way to operate or the good way to control pain. Please let us know Dr. Peters and Dr. Beyer because you are specialists about those. Please.

Peters: Yes, I think pain control, pain management should be multidisciplinary, that is important and multifunctional different methods, and drugs may or must be only one part of. And physiotherapy, acupuncture, several other techniques around the pain, and the operation is only the last step of long journey through a pain control.

Hinoshita: OK. Do you agree with Prof Peters?

Beyer: Yes. From my point of view, I totally agree with this, and I have two eyes on it. One eye as anesthetist, one eye as pain consultant. And my clinic I established when operation is needed, there should be a conference interdisciplinary different doctors. And orthopedic surgeons are very cautious with doing something which does not fit and normally working day. So they take care of it and plan it very well even rehabilitation afterward plan very well because if we have our patient out hospital and he exceed the time of day, it will lower the economic at the end of the year, and they will be remembered to this point weekly by the day managing director. So they take care of this, and I think it's not a decision of one. Specialists should make a decision in a couple of specialists.

Hinoshita: How about the cost-performance problem?

Beyer: What? I didn't get that.

Someone: Namely, was this cost too much for this result or performance?

Beyer: How many costs I produce by doing what I'm doing?

Hinoshita: Yeah.

Beyer: I have no clue. I tried to calculate this. There are so many people involved in this. It's really, really hard to estimate, and if you pay one trained consultant, you pay 180,000 euro. If you have a physiotherapist part time, you pay maybe 40,000 euro. So you can exceed easily limitations they usually have. And up to now, my managing director allows me to do so. But I don't know how long it will go.

Hinoshita: Yeah. A tough role. From a different point of view, Dr. Morrison, do you have any comment on this pain control and the premature problem?

Morrison: I think one of the things I'd like to develop on our website is a pain leaflet specially tailored for our individuals. The British Pain Society has a good one. Unfortunately it is sponsored by Grunenthal. As I have mentioned I think peer to peer support is very good and quotes from other beneficiaries as to how they have been helped could be included in any such leaflet. So I think if we try to get very good information on the website as well as showing them what interventional therapies can help e.g. hugging a pillow at night can help those with short arms, pacing activities during the day to help with fatigue.

Hinoshita: In Japan, we don't know exactly the information given by the Thalidomide Trust or the English staff in UK. In other western countries, European countries, do you know the solutions or some good information given by the Thalidomide Trust? Do you see such information and understand it? Please, Dr. Ghassemi.

Ghassemi: I think the most information actually goes to the EX-Center in Stockholm. They don't deal only with thalidomiders but also with dysmelia. Unfortunately the information is not spread out over the country. Many times when I had my study group and they complained on something I wrote the letter to the general practitioner because they are also a matter of financial problem. So I wrote to doctors, hoping that they will send these people to the EX-Center. But I know that it didn't happen. So I gave my opinion to the EX-Center by myself actually and gathered more information about what they're doing and they also want the information to be strict. So I have a good idea when I go back home to Sweden what to do actually after this.

Hinoshita: Anyway, you have various opinions or ideas to control pain and support premature problems in the thalidomiders. But anyway I think it is important to ask to exchange good information or better innovation if someone or some

center might find or spread in each country. So let's exchange good information between these countries. Then let's take good measures or ways to control pain or support the thalidomiders. So, just after you go home, let's introduce our website addresses or so mutually, OK? One more comment.

Ding-Greiner: Yes, speaking only about pain control is not enough, there are more problems. You need cardiologists, gynecologists, urologists and all kinds of physicians, but there are not enough for thalidomide affected people to run a big hospital exclusively for them. So I think Mr. Beyer's project of a virtual clinic is very good because there are all kinds of physicians accessible as needed. Also they are physicians who are interested in thalidomide embryopathy and the long-term outcome. Patients know where to go, they can just give a call and get a reasonable treatment. I think it is very important to focus not only on pain but on the problems that are coming now as they are getting older. There are more deficiencies at present than 20 years ago and all the diseases and impairments of old age make an appearance, too.

Hinoshita: You mean more and more physicians needed in other fields.

Ding-Greiner: Yes.

Hinoshita: We must be more interested in these problems.

Ding-Greiner: Yes. You can't go to every physician as a thalidomider who has a specific problem. Physicians and therapists need some information about the causes of the prenatal damage, the development of the damage through lifetime. And there is almost no literature about thalidomide. In our surveys the experts on thalidomide were the participants. You need time seeing patients and learning about their strategies handling their discomfort and their impairments, they have a lifetime's experience in doing so. The best therapy is conceived together by thalidomiders and their physicians and therapists.

Hinoshita: Thank you. Finally.

Beyer: One short comment. The websites supported thalidomiders in Hamburg or elsewhere also in English, and the barrier-free version. So you can choose.

Hinoshita: We have a great barrier, language barrier, sorry. In your country, everything is broadcast or spread in English?

Beyer: Usually not.

Hinoshita: Let's exchange messages in English just as we are doing now. Dr. Nakamura, please.

Nakamura: Thank you very much. Very interesting discussion I heard from you all. They are the very specialists on the thalidomiders. I'm very curious about the more modern technique of the data on pain assessment, for example, functional MRI data. Do you have any those kind of the data on the thalidomider's pain issues? Anyone has any opinion?

Beyer: I have no data from technical investigations like functional MRI. I think up to now, it's not known what means functional MRI for the individual person, I don't know. But I'm collecting data on a questionnaire in Germany like every other countries I suppose. There is a pain society. And they have established questionnaire with many, many items. And I uses patients to, let's say, compare at the end of the day with normal chronic pain patients, and these questionnaire contains, I think everything is needed for the assessment of pain and also demographic data, general health data and social data, and for example, some kind like SF-36 of life quality and activity of daily life. So this data I collect. But I have a very small number up to now.

Nakamura: So, for example, in the orthopedic field and pain control societies to save lumbar and low back pain patients. There are many information coming from fMRI observations. So I think it could be feasible for you or us to collect the data. On the chronic pain basis in thalidomiders, the investigation, we could get the image of it from fMRI. If we can have very good candidates and collaborators for the assessment.

Beyer: But I think before you put persons in MRI which is inconvenient, you need to have really good reason for this. I think good reason means it changes maybe your decision for the therapy. But I'm not sure about this.

Nakamura: I'm not so acute about the remedy exploitation. But just I want to know the condition of the thalidomider's pain, chronic pains. What is going on there? Is it possible to explore or to extend our understanding form the kind of the general population data or not? I'm just curious about it.

Hinoshita: Thank you very much. Maybe Dr. Nakamura is talking about subjective evaluation of pain control. It is one of the good measures to use the fMRI.

Then let's go ahead to the next question. What kind of orthopedic problems are important now? And how to solve? First, Dr. Peters. Do you have any keen programs you are now most interested in.

Peters: It's a variety of problems there. Muscle problems and joint problems due to osteoarthritis. It's a pain problem, problem of activity of daily living. I think they have to perform several procedures. Physiotherapy programs and pain control programs, even in a few cases, operations, and assisted living problems for the people in the future. I think that will be a big topic.

Hinoshita: OK. Then first, let's focus on osteoarthritis which does not need any surgery or so.

Peters: We have some of those..

Hinoshita: Those pathological changes are progressing now in thalidomiders.

Peters: Is it. Yes.

Peters: Especially the last five years. That's progressing a lot. With conservative treatments, however, it's becoming worse and worse because we have no original treatment to cure arthritis. And I think in the next years the number of thalidomiders who have to get surgical procedures will increase.

Hinoshita: Yes. Then the percentage of that way in thalidomiders is much greater than in the general population?

Peters: Yes.

Hinoshita: Do you have any comment, Dr. Ghassemi?

Ghassemi: Yes. Actually we have. Because the orthopedic problem is as it is for all of us. It may be not the problem at home, it's at work. I know that some of the thalidomiders just stopped working because this is a way to help them with the many more symptoms of arthritis. And of course as Dr. Peters are saying the operation is the last session or most for those joints. And before that I also could show all studies. Their sport and recreation was quite effective in these groups, which makes even difficult for them to convince them to go to physiotherapy, because it's just like post-polio syndrome or so. They just get more and more tired. And they don't have the trend as they should.

Hinoshita: Is there any other good method to disturb or slow the progression of osteoarthritis or similar changes in thalidomiders? Dr. Morrison, please.

Morrison: I think the controlling of their weight is very important. Individuals who have lost weight have improved their flexibility and improved the pain control. The Swedish study on lifestyle management very much showed this. We have had the team over to talk through their findings in this study and they have a book which they used to help with the study.

Hinoshita: Dr. Peters.

Peters: We perform one more very intensive rehabilitation program for these patients, two or three weeks as inpatients and they have therapy every day. We keep down the pain and disabilities for certain time.

Hinoshita: When I talked with Dr. Graf in Nürnberg, he said if thalidomiders are really painful, they should stop working. And he said they don't need to do hard exercises or training to soften the pain. Do you agree to that opinion?

Peters: I think going away from drugs is not always a solution. Because they will have the pain also besides work, therefore we try to make patients doing rehabilitation to put them out of the normal environment, put them the places where they can do the exercises and programs all day long for certain time, two, three, or even four weeks. That will largely give good benefit for them.

Hinoshita: OK, is there any other opinion about this problem, osteoarthritis?

Beyer: I think it's largely dependent on what you are doing on the work. And if you are forced to do things that you don't like or that are very static, for example computer work, or I had one patient to be employed in the street working, and this was definitely not good for the locomotor system. And I think one solution could be to retrieve these people from work and to retire them if they can afford it, and if the pension is high enough for this. And there is a clear evidence that there is a link between sports and recreation and a low number of pain. So you should motivate patients to do so. But not good as a street workout from my point of view. I think it's a good idea to keep them in mobility anyway.

Hinoshita: And then Dr. Ghassemi.

Ghassemi: That was almost as you were saying because in Sweden there is a possibility if your work is too static and you cannot manage that. There are always ways to adjust your work to your anatomical ability. And I think after that, mostly after that because people are trying not to retire as much as they can because of the mental healthiness, you know. You want to be in contact with social life. That is why and just not to feel pain even more if you are sitting at home all alone after these helps from this day and from your local job basically if he doesn't work. Then I think it's a good way to just offer them as, yeah.

Hinoshita: And Ms. Newbronner.

Newbronner: Yeah. We just support that you know it is working UK, I think we have found that for the people who feel that they have no choice but to give up work because of the health problems and loss of function, that can be very negatively associated with poor social life and socialization. I think when Dr. Beyer said that people are helped to either change their work or give up working in a more positive way, and perhaps replacing that with recreation or volunteer work which they can regulate more easily. Then you can have very positive benefits but it can be negative when people feel they have no choice and they forced to give up work and possibly don't have the resources to continue a good quality of life.

Hinoshita: To completely stop jobs is not always a good way. Thank you. Is there anyone who would like to comment? OK, Dr. Kayamori.

Kayamori: Just I'm facing troublesome cases with tendinitis which really causes intractable pain. So I want to know any idea. How about Dr. Peters? Do you have any good idea to treat tendinitis which is intractable and really painful? Is there any good treatment for that?

Peters: In most cases you can only do is to do preservative treatment with bandages. Our thesis, for example, is local physiotherapy and physical therapy. Combination. I think for anatomic changes you should immobilize the overused joint, and sometimes if it's a working hand of the patient, you get into other trouble. And you must try with physical therapy and physiotherapy and local pain control.

Kayamori: But the patient has had intractable pain over 30 years, she is working as a housewife. She is using the hand 24/7 or around the clock. So no rest. So do you have any experience to have surgery for that?

Hinoshita: OK, Dr. Ding-Greiner.

Ding-Greiner: I think the best support you will find first in assistance for relief. If physiotherapy doesn't help any more, then surgery is left as the last chance.

Beyer: So one last comment, I have seen quite a few patients and went surgery for this problem and at the end, they always had more pain. And it's just a matter of surgeon to say, "I can help you." "I will help you." But I have never seen it worked out.

Hinoshita: We may have some candidates of thalidomiders who should or might be operated for the hip joint program. But some of the specialists including Dr. Kayamori or Dr. Greiner or so would say the operation would be the final solution. Then, one might refrain from operating him or her for the time being to wait. Do you agree to the idea or opinion on the hip joint program? Dr. Peters, please.

Peters: As for the hip joint operation should be always the last solution for every patient. You should use all conservative treatments before. And when this is finished and there is no choice at all, then you can discuss it with patients and see the benefit and risks.

Hinoshita: OK, when it comes to this program, almost the same opinion as ours.

Peters: Yes.

Hinoshita: Thank you. Is there any other comment or discussion about the orthopedic problems? Please, Dr. Schulte-Hillen.

Schulte-Hillen: I would like to ask a question concerning total hip replacement. Do the hip implants allow for the same range of motion as normal hip because thalidomiders deeply depend on a big range of motion?

Peters: That can be a problem in a single case if you find very much lateralized mobility of the hip, but otherwise most of them are normal range and the normal collective of the patient. The mobility can a bit go down. For example if you

have retention of 60, 70 degrees internal external retention can have as the thalidomiders, you born to achieve that was a Fischer joint. Otherwise you have the risk of luxation.

Schulte-Hillen: So this has to be taken into consideration when we're talking with the patients before they decide to have hips replaced. Sorry. For example, somebody comes for this feet probably not going to be able to do so after total replacement

Peters: That's correct, yes.

Schulte-Hillen: Thank you very much.

Hinoshita: OK, there is little time left for the question 2. Then, let's go ahead to question 3. How should we solve the specific pain problem, so called post-thalidomide syndrome in thalidomiders? But as for pain control, we have already discussed it so much. So is there anyone who would like to give some comment on the post-thalidomide syndrome? Please, Dr. McCredie.

McCredie: I refer to my last two slides which graph nerve fibre populations over a lifetime. Numbers of nerve fibres on the vertical axis against age in years on the horizontal. Birth is at zero, death at the far end. The first graph is of normal people with no nerve damage, like most of us, showing that we have surplus nerve fibres from birth to death. We go through life without symptoms of nerve damage. The horizontal line represents the symptom threshold : if the number of nerve fibres drops below that line, symptoms such as pain, tingling, numbness occur. In a normal lifetime this never happens because of the normal surplus fibres we are born with. It is normal to have a physiological loss of fibres in middle age as part of normal degenerative changes at that age, but this normal reduction of fibre numbers is insufficient to cause symptoms : the total population of fibres remains well above the baseline symptom threshold. So we carry on a pain-free life. Now look at the second picture : Underneath the normal curve is the situation for thalidomiders. In embryonic life their sensory nerves were damaged by thalidomide, a sensory neurotoxin. So they go through life with a reduced number of sensory nerve fibres, what neurologist call a "sub-clinical neuropathy", at risk of further damage. When they reach middle age, the thalidomiders suffer exactly the same loss of fibre numbers as we normal people do, only because they started with as much lower total number, their nerve numbers drop below the pain threshold and they get pain and other sensory symptoms.

Thalidomiders cannot buffer the degenerative loss of nerve fibres in middle age. That is what we are taught in neurology in our Medical School.

Hinoshita: OK. If I follow your opinions straight, the sensory and the motor system of the nerves would go quite worse in their later lives of the thalidomiders. Right? Do you feel the great damage of the peripheral nerves in your consultation with thalidomiders in each country? Dr. Kayamori.

Kayamori: From my experience, I don't think peripheral nerve is involved. So, in my opinion, peripheral nerve is judging from nerve conduction study. I don't think peripheral nerve is involved. At first, axonal of type of peripheral neuropathy used be one of the side effects of thalidomide. But I don't have any experience having patients with peripheral neuropathy.

Hinoshita: Dr. Morisson, maybe you are interested in peripheral nerve neuropathy.

Morisson: As I said, we have a neuro-orthopedic surgeon, a doctor who is used to treating patients with post-polio and used to examining for generalized neuropathies. So far, there is no evidence at present any of our beneficiaries have a clinical generalized neuropathy. They do have compressive neuropathies (but there may be some possibility of an underlying more generalized subclinical neuropathy which the nerve study showed).

Hinoshita: Just now, some other doctors are studying the peripheral nerve.

Morisson: Yes. Seeing people to assess them. At present there is no evidence of a clinical generalized neuropathy. As I have said the nerve (peripheral neuropathy study) says that there is some evidence of concern regarding the possibility of a subclinical neuropathy but they didn't do progressive studies with age. The study was static (at one period of time only). They didn't know whether the nerves had been damaged at birth. And been that way ever since. But often nerves decline with age so without doing a study over a period of time we do not know. So whether they will in the future develop a clinical generalized neuropathy we don't know. At present, we are safe that if there is an issue it is subclinical. We need to be cautious about trying to raise awareness of this area as there is very little we can do to help and we know compressive neuropathies are common and are treatable. Hence we may miss something that is treatable if we focus on any underlying

issue. So it is important to look for compressive neuropathies and causes which can be treatable before looking at options for pain management. We are looking at this are with further research in mind. We will see what happens.

Hinoshita: How do you think of or feel for peripheral neuropathy of thalidomiders in your clinics? Dr. Ghassemi or Dr. Beyer, Dr. Peters?

Beyer: I think two ways of neuropathy. Maybe some patients have experiences for a long time, and they have compensated anyhow, terms of balance problems or weakness, maybe it's new to neuropathy. And now they come to point where this compensation does not work any longer. And for neuropathic pain, I would say if you have nerve tightened syndrome, it is neuropathic pain. If you have cervical spine, it's neuropathic pain. If you have [inaudible], it is neuropathic pain. Maybe you have found a special solution by operation maybe.

Kayamori: It is true that patients complain of numbness in the extremities. I mean the foot and the hand. Patients complained such problems so that I did the electrol physiological examination. But I couldn't find polyneuropathy. So that's the problem. As patients complain of numbness and pain in the hands and the feet, but we have to consider another reason, not neuropathy. That's my opinion.

Beyer: But you still find some patients who has a patchy operation of the spinal tracts. And it was also mixed with multiple sclerosis. But the clinical way is completely different, so I assume it isn't thalidomide damage which was compensated for a long time. And now this compensation does not work any longer. And it's neuropathy. And I think the hand and the foot are the part of the body where you can see it first, because it's a last meadow, could you say so? Germany, we say so.

Hinoshita: Dr. Ghassemi.

Ghassemi: I always say some of our patients have done the surgery for the release of the median nerve at the carpal tunnel. And I believe this is the most performed surgery actually in this group. And having the surgery on the early age, unfortunately I don't know if they had the sensory problem before the surgery. I don't have more experience of that actually in my clinic.

Hinoshita: Then, let's go ahead to the next question. Number 4 will be lifestyle disease. Obesity, cardiovascular disease, and

stroke markedly increase in later lives of them. What do you think of them? Dr. Greiner, you have partly talked about it.

Ding-Greiner: I think you have to treat these diseases in every person, there shouldn't be differences in society. Thalidomiders have a problem going to see a doctor because they were in hospitals as children where they made bad experiences. Hospitals in the 60s were not a good place to be. So a lot of them say that they don't want to see a doctor. It's one side of the problem. But at present a lot of them are dying as Dr. Schulte-Hillen told us. Something has to be done. I don't think we can solve all existing problems. The very important thing we can do is to give them good living conditions and a good health care. The time which is left for them to live should be a good time for them.

Hinoshita: OK. In Japan, our research group have examined more than 100 thalidomiders to check if they have a lifestyle related disease or not, or the levels of their cholesterol, triglyceride, fasting blood sugar or so. So far in other countries, you didn't check such parameters. Then will you be interested in the lifestyle diseases in the near future in Germany or in United Kingdom? How about this?

Peters: We checked it all in our study, too, but I didn't present these data because of a large number of data.

Hinoshita: OK.

Morrison: Everybody in the UK is invited for a health check by the GP once they are over 45. So these individuals will be invited and it's usually the GP who deals with those problems. If an ECG or MRI showed that even if their blood pressure was normal but that body is not coping with the blood pressure (target organ damage) then their blood pressure needs to be treated or an opinion from the specialist is needed. Obviously this is a group who may not like doctors or taking medication and our blood pressure study may not reach those individuals as they may not wish to take part. It was for these individuals in particular we were doing the Blood Pressure study. We will see what our study shows.

Hinoshita: Do you feel if thalidomiders have more cardiovascular attacks or incidents? I mean compared with the general population in UK or in Germany.

Morrison: I'm suspicious, a lot of them on the helpline seem to be on blood pressure treatment. So I wouldn't like to say

without more research but I have a suspicion that this may be an issue. But obviously lifestyle factors are very important. And they need to be considered when treating the individuals.

Hinoshita: How about in Germany, Dr. Greiner?

Ding-Greiner: We have similar problems, but we have no means to force thalidomiders to make a checkup, everyone is free to do it or not. I guess, if we had physicians and therapists with good knowledge of thalidomide damage, maybe it is easier for them to go to a consultation. But the big problem begins with taking blood. Lots of thalidomiders told me that it is not possible to take blood under normal conditions. There are a lot of barriers for affected people for going to seek medical help.

Hinoshita: Dr. Morrison, please.

Morrison: I think if you are highly suspicious of a problem and feel they are at high risk a way forward is to put them on treatment with medication that doesn't need blood tests to monitor it. Or you can refer give them to a specialist who can do this.

Hinoshita: How about in Australia? There may be less thalidomiders in the country. How about cardiovascular attacks or stroke, something like that?

McCredie: I've heard of 3 or 4 who have died. Two were certainly from coronary disease, and one had a stroke. There are about 60 thalidomiders in my country that are known. There may be some others that have not been counted or verified.

Hinoshita: Dr. Shiga? You have examined it.

Shiga: In Japan, there are many patients with fatty liver and hypertension, but in this medical checkup, we can check thalidomiders. But I heard that many thalidomiders don't want to go to hospital, so some of them don't check the blood pressure. So it is difficult to order them to go to the hospital. I think it is good information about checking the blood pressure is good for you by internet or some leaflet and so on. The information is good thing I thought.

Hinoshita: All right. Do you have any other comment? Anyone else? OK, then let's go to the next theme. Number 5. How about the anatomical problems or bone defect? How about depression and/or other mental problems? First, anatomical problems or bone defect. Dr. Tajima, do you have any comment? He is a radiologist.

Tajima: I want to talk about undescended testis. Someone talks about undescended testis. This is a very important problem. That can cause testicular malignancy. So we have to follow these patients. Also I think spina bifida is another important problem. It has been reported that patients with spina bifida have strong influence on neurological deficits. So for someone who have neurological symptoms we have to follow and perform CT or MR in the area of lumbar spine or sacrum. How about spina bifida in your country?

Hinoshita: Two problems. First, undescended testis. Next, spina bifida, right? So first, let's focus on undescended testis. Maybe Dr. Peters has mentioned about abnormalities in the sexual organs among your patients.

Peters: That's not a rare condition as we thought all of the undescended testis have to be treated in childhood. But spina bifida, I think it's not more common in thalidomiders. I think it's not a typical anatomical problem of the thalidomiders.

Hinoshita: How about it, Dr. Greiner? Undescended testis and spina bifida?

Ding-Greiner: Participants told me they had undescended testis, they were operated in childhood but it was too late. The doctors didn't take notice of it. Patients have higher risk of developing cancer of testes. We have in our first survey of 2012 about 10 to 20 percent of participants who were childless of this and of other causes.

Hinoshita: You noticed the number of the patients with undescended testis was greater in thalidomiders. More than in the general population. Anyone else? Spina bifida or something else. Anatomical problems.

Schulte-Hillen: To my knowledge, spina bifida is not a part of thalidomide syndrome. Undescended testis is, I say in Germany, at least 30 to 40 with that condition, and we have at least one who developed carcinoma of the testis, and survived.

Hinoshita: OK. Thank you. Is there anything else which we didn't know as anatomical abnormalities but you know or just found?

Peters: I think slight hypoplastic changes of the knee joints are not often seen, and that's also primary damage of the thalidomiders. But in a lot of cases it's not seen and not diagnosed. And they might result in severe secondary knee arthrosis.

Hinoshita: OK. Do you have any idea for those cases how it was derived of or it was caused by thalidomide itself?

Peters: I don't think so, like the hip dysplasia as the same dysplasia of the knee joint.

Hinoshita: I see.

Schulte-Hillen: Two years ago, we found out that many of the thalidomiders with the ear damage also have complete missing of stato-acoustic organ which means particularly dangerous for the people with short arms because they cannot go out themselves when they fall. They changed the law in Germany. This defect is generally accepted as part of the thalidomide syndrome and compensated for.

Hinoshita: We also expect there might be more anatomical deficit or problems in the face or near the mouth or near the ears, bone defect or something which nobody have ever discovered, maybe. So Dr. Maruoka. Now we are starting to check the mouth and the jaw joint in our medical checkup. Do you have any comment?

Maruoka: So far, I've never seen such a disorder. But from now, I will investigate such types of disorder.

Hinoshita: All right. Is there any other anatomical problem? OK, please.

Ghassemi: I have one of our patients, actually a woman. It was shown that she didn't have any internal genitalia. So no uterus. That's only thing I know which is the only person also I know. And you don't know if it's because of the thalidomide or not.

Hinoshita: I see.

Schulte-Hillen: Can I answer to the question?

Hinoshita: Yes, sure.

Schulte-Hillen: Malformation of the internal sexual organs is considered as part of the thalidomide syndrome. And we have quite a few of them. I don't remember what I could have said here. I would simply leave this out since the sentence before and after absolutely make sense and are complete sentences. I think that's the name for it are completely missing aplasia or complete atresia of...

Ghassemi: Because that was complete aplasia.

Beyer: That is in Germany definitely part of the thalidomide syndrome.

Hinoshita: Aplasia of the gallbladder is also famous. Next number 6 question. There're still many problems to be solved on the thalidomide embryopathy, TE. Does your country fully train young physicians treating TE? How about this?

Beyer: I think in Germany there are a very low number of specialists because in the normal clinics today, nobody would like to spend the time or exceeding the time for this topic. And I found out I do my clinic together with orthopedic surgeons which are under the state of registra or special registra and what they are normally doing is assessment for hip replacement or shoulder surgery, and they are doing this very quick and very fast. And they like to come to my clinic to make an assessment of people whether they can assess the whole people with all joints because I forced them to do so. And they always get one and half hour and they are off duty or reward this time. So they like it. And I tried to help them little bit by what I found out how to classify the dysmelia because nobody has analogy of this.

Hinoshita: OK. Ms. Newbronner.

Newbronner: We also found in our survey in the UK that many thalidomiders had problems with a lack of knowledge of thalidomide damage or the specific impairments when they saw health professionals. And I think people are realistic. They appreciate their doctors or other health professionals cannot know everything especially if they are generalist. But I think what often people say is that they would like people to listen more carefully to their own knowledge of their bodies. And so to have that time as Dr. Beyer said to discuss things more thoroughly with them. And also not to rush to treatment but to seek advice ether from the Thalidomide Trust or from specialist. So I think it's about taking that time and listening to the thalidomiders themselves. Because it is not possible of every doctor and every nurse too understand thalidomide.

Hinoshita: Maybe it is a universal or general problem over the world. If we examine the thalidomiders, it will take much longer time for that patient. Dr. Graf in Nürnberg did say the similar thing to us when we visited him. No many orthopedists or specialists don't like to gladly examine the thalidomiders.

Now we have a few Japanese people with TE in this place. So Ms. Masuyama, what's the situation in Japan? Do you have any reliable physicians or physicians who would listen to your complaints or problems in Japan?

Ms. Masuyama: Well I am not an expert on this topic, so this is my personal impression actually. But on the Ishizue foundation I am working as supportive or supporting staff members. So through this capability I have seen or contacted many people with TE. And actually some people were deteriorating their physical conditions rise quickly. I have seen such people in most recent several years in particular. And I hear some physicians just declined their treatment for such people because some physicians are feeling that this is a completely unknown condition for them. And further it's an unknown condition even to ourselves. Generally speaking, physicians might be afraid if this is a completely new condition which might require surgery and if the patient might be dying after the surgery. So there might be some cases actually I often heard of that some patients were actually referred back and forth among different physicians.

Hinoshita: Anyway, to support thalidomiders, our research group of Japan has determined to make some medical network. I mean the specialists or physicians who can take care of the thalidomiders. I mean in other word we are preparing a list of the specialists or physicians who can take care of them. Now I am arranging it. In a few months we can complete the list up. But anyway, sorry to say however, I have asked more than 70 doctors, and only 30 or 40 doctors have said yes to be involved in that network so far. Anyway, is there any other comment? Dr. Nakamura.

Nakamura: I would like to know what the different face of the investigation of the thalidomiders. We have got many new information regarding the biological assessment. So I would like to ask Dr. Morrison if you can. I know that UK has started the genome-wide analysis. 100,000 genome projects here supported by NHS. Dr. Mark Williams studied that project. I mean the investigation of your British people to gain the British people's standard genome profile.

Morrison: You mean regarding blood pressure?

Nakamura: Yeah. Oh, everything. Genome-wide analysis.

Morrison: You mean over 45?

Nakamura: Yeah. Everything. I hear 100,000 genome projects, it said.

Morrison: All right. I don't know.

Nakamura: Uh-huh.

Nakamura: This is my personal view, but the conventional investigation has come to the kind of the limited now. So we should employ much more innovative methods to investigate the pathology of thalidomiders. So if possible, we need to consider genome-wide analysis of the gene information, and to compare that kind of data with the general population. That might be giving us very good clue to know or to extend more about the pathology and pathogenesis of our concerning condition. So just I want to know your British status because I hear that your British data are very good, greatly advanced on the GWAS genome-wide analysis.

Morrison: No, I don't know about it.

Nakamura: OK.

Morrison: I couldn't comment.

Nakamura: Thank you.

Hinoshita: Is there any other comment or opinion? OK, Dr. Greiner, please.

Ding-Greiner: I guess the secret to be a good doctor for thalidomiders is to forget part of everything you know concerning your ordinary patients, to listen to the patient because those patients and their ailments are different from other people's as the cause is an intoxication with thalidomide. You have to invest a lot of time listening to them and thinking about possible causes, about which therapy might help, and the most important problem is which kind of therapy or support they will accept.

Hinoshita: Thank you. Finally we would like to go to the next question. Today, we gathered from several countries. Can you show us strong or good points as well as bad points of the support system and the social system to assist thalidomiders in your own country? Could you show us in detail in each country? Then Dr. Greiner? No, sorry, Dr. Morrison.

Morrison: I think there is financial pressure to reduce

everywhere costs to support individuals. Theoretically our individuals should be able to claim from the government in addition to the compensation they receive to help their daily lives. However, a lot of them are having the amount they receive reduced. And hence we are trying to support them and to help them answer the questions and to fill in the questionnaires to help them get the money they should be entitled to. And it's partly why we have increased our team to try to give more individual support. We've also discussed assessing everybody in the trust with a needs assessment to look at all the different factors and trying to see where we can help. So I think the good thing is we have the Trust to help. The bad thing about it is the waiting list and prioritizing individuals.

Newbronner: I think the other thing in the UK is in our social care system. Actually a relatively small proportion of thalidomiders in the UK get social care support - less than 20 percent. This is partly because they're working and they have more income, so they are not entitled to it. But also many people don't want to be part of the social care system. Because they had bad experiences in the past of being told what to do or having restrictions placed on the kind of support and care they can receive. So I think firstly they want to have control over the personal kind of support they have. And I think particularly people who are upper limb affected. The social care system doesn't really understand that type of disability. They understand people who use wheelchairs but they had a limited grasp of the implications of upper limb impairment. And we have the Trust's work to comprehensively document upper limb impairment, something called Upper Limb Statement that colleagues are really working on. I think it is something that eventually could be turned into information for health and social care professionals. So they perhaps will better understand just how many problems life presents people with upper limb damage.

Hinoshita: In your country UK, you have the great financial support from the government or the Thalidomide Trust. It is a good point and also now you are making up a list to specialized medical centers, Wrightington Hospital and the Royal National Orthopedic Hospital (RNOH) to treat thalidomiders especially for pain control or surgical operations, right? These are good points I think. Anyway, let's go to Germany, and who would answer.

Beyer: So, I think the support by Conterganstiftung für behinderte Menschen is really poor in Germany. There are no definite medicals as decision-makers from my point of

view, and I see you say to grasp of what disability means to people is not very good there. And everything has been built up in Germany is without the support of the trust, I would say. It's just a kind of treasurer for the money which is...

Hinoshita: So you mean you are lacking of decision-makers to financially support individual thalidomiders?

Beyer: Yeah, I think there is no central navigation by the trust (Conterganstiftung). You have to do everything on your own, and invent on your own, and you have to ask for money. It's not easy. And there is no one who is doing a kind of central navigation.

Hinoshita: But you have the Conterganstiftung.

Beyer: Yeah.

Hinoshita: Conterganstiftung is not functioning well you mean?

Beyer: I think the Conterganstiftung, they just take care how to spend the money without really having medical knowledge. And they decide by formal things, not by medical things. This is my personal view. So thalidomiders need to go to hospitals and ask if they could imagine to build up a clinic or something. They have to do on their own. They are not supported by anyone. I think there is a lack in Germany. If you compare it with the rich country and if I look through England or through Sweden, I think it's much better.

Schulte-Hillen: I would like to respond to that.

Hinoshita: Yes.

Beyer: One of the members of the medical committee of the Conterganstiftung of the thalidomide trust in Germany, and by law that the task of the thalidomide trust was to distribute the money. And they have developed beyond that and they are starting to assemble database for physicians. We are capable of, we have special knowledge and they found database for content management. So, for example where to drop that from the thalidomiders, for example where to measure the blood pressure. As you know, Germany has changed in the last decade. Big changes in the health system, and everything is managed-care. People we have one of 5 big diseases like diabetes or breast cancer and hypertension very well taking care of. This went to great extent Germany was forced

be the European Union to find that is called national union for people with rare diseases. And thalidomiders have one of those rare diseases considered as one rare disease. And we are just starting, you might say.

Hinoshita: OK. Thank you very much. Is there any comment from other German doctor? Dr. Peters or Dr. Greiner.

Peters: I think it's improving because financial support has improved in the last years. But it's the way, the way it's not the end up to now. I think one of the main point is future secondary damages. It has to be notified, seen as a problem. That's not a problem in the focus at the moment. I think that will be noticed as the next step. Secondary damages are important. That decrease quality of life. That has to put it in the financial support, I think for the people. That's not up to now. And we have to build up a network for specialists all over the country. That will be one of the next aims.

Hinoshita: Anyway, you yourself just started to build up a good center for the thalidomiders? Then also Dr. Beyer vigorously deal with pain control in thalidomiders. Please spread those movements all over the nation. Anyway, next, how about in Sweden?

Ghassemi: In Sweden, the good point is that thalidomiders actually are not forced to work 100 percent. They can choose if they want to work 100 percent. But they can actually choose to work only 50 percent if they want to. I need to say the time when they need to work. And the bad point is as you said, it's [inaudible] also they have to stand in line. Because they are also connected to the local practitioner, general practitioner. If they are lucky to get contact with the EX-Center they will do that. And I think when the problem is getting in many areas and more severe that they are forced to. And I think the information will also go from their president of the association that actually can ask for that at least give the information to the general practitioner.

Hinoshita: OK. In Japan, the number of the specialists or the experienced doctors for TE has been decreasing, such as Dr. Kayamori. Some of the doctors are interested in and dealing with the TE. The Ministry of Health, Labor and Welfare has been interested in supporting thalidomiders who are over 50 years old. But any totalized medical network has not been built up so far. In my idea, as I said before, we should make up the medical network with the physicians who have been interested in TE and can take care or treat the thalidomiders

over the nation. And also we noticed that at least in Japan, we have increasingly more patients or thalidomiders with lifestyle related diseases such as hypertension, obesity, fatty liver or some kidney dysfunction. We also should focus on such life-style related diseases from now on. Is there any other comment, Dr. Shiga or Dr. Kayamori about the situation in Japan? No?

Shiga: No.

Hinoshita: OK. How about Dr. McCredie? Is there any additional comment?

McCredie: In our country, because of the geography, and because the majority of people are computer-literate, it would be a great help if some of the information from the German groups and the UK Thalidomide Trust was transmitted to us.

Hinoshita: Thank you. We did not discuss the mental problem, depression or something else. Anyway, Dr. Imai, do you have any specific comment?

Imai: Allow me to explain in Japanese. I work at the same hospital with Dr. Hinoshita. I'd like to say a few words as psychiatrist. I'd like first talk about pain. If drugs and surgical treatment are effective it should be treated. However, it's a big problem that pain would often become chronic. When the pain becomes chronic, people feel that without such pain, I could do more and I could do this. In addition, people are likely to think too much about pain. And consequently their way of thinking would easily deviate. Then psychological treatment may become important. And when that happens Cognitive Behavioral Therapy CBT, would be effective. That's I think very useful. CBT would correct this biased thoughts in foundation. What is important is that you should not tell them "You are in such situation. Therefore, do like this". You shouldn't not say in that manner to the patients. You need to encourage patients to recognize their biased recognition on their own. Therefore the treatment is to support patients understand the bias problem. That's the first topic I'd like to talk about. Second according to the Thalidomide Trust in UK and the report in Germany, there are researches on the mental problems in which more than 200 people had been surveyed. And I think it is a very good data that you have identified many people with mental problems. But I am a little concerned I am in the practice and I'm afraid because we are not speaking up the information from everybody. For example, in the UK, only 75 percent of the patients had been surveyed. They have complied with a survey. But I believe

there are many people with obviously mental problems who were in the rest of the surveyed. Therefore, what is important is that we tried to pick up the people with mental problems who have fallen in out of the survey data. Another point, there is the German survey where more than 50 percent of the people among disabilities their percentage of mental problems seem to be very high. But as the anesthesiologist reported, how to use benzodiazepines or minor tranquilizers should be very careful because people want to move away from pain. They frequently tend to rely on alcohol or such psychotropic drugs. And we have always this problem in Japan. It may be also true in non-psychiatrists. Whenever patients claim insomnia or anxieties, we would very easily prescribe benzodiazepines. It's been the case today, but when benzodiazepines are prescribed very easily dependency becomes a problem. So that's one thing we need to be careful about in drug treatments. And that is also for pain whenever there is a problem, you need to think of other treatment, alternative treatment. Now about statistic depression or emotional problems and anxieties, we have seen fairly good number of patients complaining these symptoms. And they are not just transient symptoms, but they are probably secondary pain based on that they are victimized. So these are often secondary to what had already happened and if you can treat with the patients or be involved with the patients, I think those are the problems which may be deduced. And now, we will also need to work on this more.

Hinoshita: Thank you very much for the comment. OK, Dr. Beyer.

Beyer: So one comment. Maybe it was misleading what I was talking about, but I do not recommend benzodiazepines at all. I have met patients who took benzodiazepines for over 20 years. And they are nearly untreatable in terms of pain. So I would never prescribe this. I'm against it.

Hinoshita: OK. So, finally, any comment about mental problems? OK, thank you very much. Now it's 7 PM. Then let's finish this hot and fruitful discussion now. Please get back to your seats, the original seats for the symposiasts. Thank you very much.

Staff: Thank you very much, all the participating doctors on the symposium. So could you return to you own reserved seat now? Thank you.

So, Dr. Hinoshita would be giving us the closing remarks. Dr. Hinoshita, please.

Closing remarks

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The time has now come to close this international symposium. Although a symposium from 10 AM to 7 PM may seem long, in fact it was very short, because today we have come to realize that we still have many unresolved problems. As “thalidomiders” age, we are certain that they suffer from more and more serious physical, mental and medical problems which they had rarely experienced at a younger age. Fortunately, however, today we were able to discuss and shed light on these problems among physicians and researchers from different countries. I think it is very important to bring these discussions home for re-consideration and to make efforts to improve the situation associated with thalidomide embryopathy in each country. Indeed, there are a few experienced, able and earnest clinicians and researchers for thalidomide embryopathy in each country, but they may be outnumbered by the great needs of the thalidomiders.

There is a very famous old proverb in Japan, when translated into English it is: “The frog in the well does not know the ocean”. I hear there is also a similar English proverb. “He that stays in the valley shall never get over the hill”. It seems that, to date, there has been little international exchange

on the various problems of thalidomide embryopathy, at least between the West and the East, or the southern hemisphere. I hope and believe that this symposium will become a great trigger for further international communication and cooperation among different countries. Also, it may serve as a medium to find and develop good measures in the medical, physical, orthopedic, and mental areas or even in other specific fields. In addition, discussing and refining the compensation scheme and the administration policy will help to resolve the current and future problems that thalidomiders face.

Finally, I would like to thank you very much for joining us today. In particular, I would like to express gratitude for the great assistance of the Ministry of Health, Labour and Welfare, Japan, and for many managing staff. I also want to express our thanks to the guest symposiasts, especially those who came from abroad, for participating in the symposium. Now I would like to conclude my remarks by wishing everyone here good health, prosperity and safe travels. Thank you again.