別添資料 1

Proceedings of the International Symposium on Thalidomide Embryopathy in Tokyo, 2015

—Final Edition—

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【 Venue 】

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2F "Terrace Room"

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Dr. Janet McCredie (University of Sydney, Sydney)

Dr. Tsuyoshi Tajima (Department of Radiology, National Center for Global Health and Medicine, Tokyo)

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Dr. Fumihiko Hinoshita (Department of Nephrology, National Center for Global Health and Medicine, Tokyo)

Preface

Fumihiko Hinoshita, MD, Ph.D.
Department of Nephrology, National Center for Global Health and Medicine, Tokyo

The International Symposium on Thalidomide Embryopathy (TE) was held in Tokyo on Nov 21, 2015. This symposium on TE held in Japan was the first time for such a symposium to be held within Asia. The symposium focused on the clinical and social reports of TE in various fields, and closed with a joint discussion among the oral and poster presenters not only from Japan but also from Europe and Australia. We invited 12 special speakers who had been engaged in some respective field of work associated with TE.

The babies with congenital deformities which were induced by thalidomide (Contergan) were born in the late 1950's and early 1960's; a new clinical concept of thalidomide embryoapthy (TE) was established in the early 1960's mainly by the German pediatrician, Widukind Lenz. The more babies and infants with TE detected throughout the world, the more clinicians, mothers, researchers and mass media that became involved in this unprecedented tragedy. After it was demonstrated and confirmed that TE was definitely caused by the internal use of pregnant women, the responsible pharmaceutical companies, such as Grünenthal GmbH in Germany, which produced and sold thalidomide and the governments, such as Germany, UK, Japan and some other countries, were socially criticized and sued by the parents of the thalidomide victims. Moreover, this worldwide medical tragedy triggered great insight on how to produce a new drug and monitor its safety. Since the time of this thalidomide incident, the way of thinking of new drugs and the approach to develop and sell them have been dramatically changed throughout the world.

The thalidomide victims born several decades ago with many congenital problems and handicaps have been living through severe hardship or adversity throughout their childhood. Now they are in their 50's. Anatomical malformations, especially in the extremities, and hearing impairment as well as facial problems were likely thoroughly examined and treated in the 1960's and 1970's. And these difficulties might be overcome to some extent by the victims themselves and/or their parents and families. Nevertheless, however, unknown specific abnormalities and problems might be discovered in "thalidomiders" in the near future. In addition, clinicians, medical staff and researchers of TE should know the medical, physical and mental problems as well as bread-and-butter issues which thalidomiders have never previously experienced but are just now facing.

In recent years, our world has become very small in a sense because we can not only easily go over to far away foreign countries by airplane but we can also know the news from abroad in real time and easily communicate by telephone, e-mail or by some other modern means. Indeed, most thalidomiders are living in Germany, and next in UK as well as some in other European countries, but we should never forget that this human tragedy of TE happened globally in numerous countries including Japan, Taiwan, Australia, Canada, Brazil and so on. Therefore, it's very meaningful to think of the present problems of TE and discuss them together among experts from different countries.

Fortunately, we were able to publish this Proceedings of the International Symposium on Thalidomide Embryopathy in Tokyo, after overcoming some difficulties. I hope this record of the Symposium will be read and shared by many clinicians and researchers working on TE. I believe the Proceedings will clearly convey to the readers the achievements of each speaker, and it will certainly contribute to the clinical practice and research on TE as well as for the social welfare of the thalidomiders; further, it should help to open the future in this research field.

Finally, it is noteworthy that this symposium was supported and funded by the Ministry of Health, Labour and Welfare (MHLW), Japan. Many kind and earnest staff were assisting us, especially Secretary Ms. Aki Fujiwara and young physicians Hayato Toma, MD, and Yu Yoshida, MD. It was planned and managed by "the research group on the various problems of the health and living situation in thalidomide-impaired people in Japan" which was organized by MHLW. In this Proceedings, you might notice awkward English and grammatical errors, particularly in the sentences of non-native English speakers. I would like to ask you to overlook such small mistakes because these proceedings are literally international.

Thalidomide embryopathy in Japan

Prof. Ryoji Kayamori
Department of Physicotherapeutics, Teikyo Heisei University, Tokyo

Kayamori: Thank you, Dr. Hinoshita. Distinguished guests from abroad, you're welcomed to Japan. Ladies and gentlemen, I would like to talk on thalidomide embryopathy in Japan. At first, I'll mention demographics and a couple of characteristics on Japanese thalidomiders. This slide is showing numbers of thalidomide victims in Japan, who were born from 1959 to 1964 and later. Total number is 309 victims. Peak of birth was 1962. The number was 162. As you know, thalidomide was withdrawn from the market beginning in November 1961 in Europe. But in Japan, in September 1962, without tragic 10 month delay 50 and more victims who were born in 1963 and later might be saved from thalidomiders (Fig 1).

In Japan thalidomide was manufactured and sold by Dai-Nippon Pharmacy, independent of Chemie Grünenthal GmbH, because Dai-Nippon got the patent for thalidomide from the Japanese government with a different manufacturing method from Grünenthal's.

"Isomin" for insomnia or morning stiffness contained 25 milligrams per tablet. "Pro-ban M" for stress gastritis contained only 6 milligrams one tablet. Unfortunately, as of 2015, 15 thalidomiders are dead. The etiology of the deaths were: trains or traffic accidents-3, suicides-2, strokes-2, cardiac failure-2, hepatic failure-2, breast cancer-1 and origin unknown-3. So, 294 thalidomide victims are surviving at present. In Japan as to impairment of thalidomide victims, we classified them into two groups. Short arm group 230 people, hearing loss group 59, and mixture group 20 people. One of the characteristics of Japanese thalidomiders is that impairment of lower extremities is not so many. We speculate that taking smaller dosages of thalidomide 25 or at most 50 milligrams at once per day might be responsible for rather confinement in the upper extremities. In 2012 we carried out a study on health status and living conditions of Japanese thalidomiders. At that time, the average age was 49.9 years and 201 people answered the questionnaire.

This slide is showing subjective complaints in the short arm group. Shoulder pain, lumbago, and painful joints in hands and feet are top three (Fig 2). These complaints are outstanding. Partially because of excessive use of hands and feet, and frequently bending the spine forward to compensate short reach.

This slide is showing subjective complaints in the hearing loss group (Fig 3). Shoulder pain and lumbago are the top two, the same as in the short arm group. The third one is hearing deterioration. The fourth is blurred vision, followed by sight impairment.

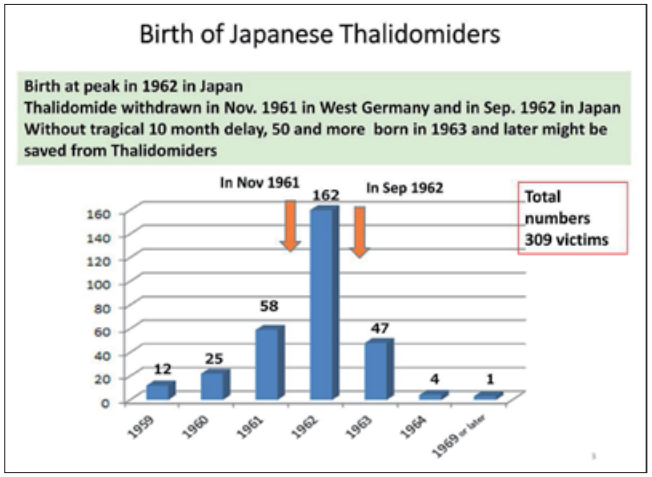


Fig 1 Birth of Japanese Thalidomiders

Subjective problems in Short arm group in 2012

N=95

	Problems	%
1	Shoulder pain	63
2	Lumbago	57
3	Painful joints in hands and feet	44
4	Numbness in hands and feet	36
5	Headache	36
6	Fatiguability	34

Fig 2 Subjective problems in short arm group

Subjective problems in Hearing loss groups in 2012

N=27

	Problems	%
1	Shoulder pain	44
2	Lumbago	44
3	Hearing deterioration	37
4	Blurred vision	37
5	Sight impairment	33

Fig 3 Subjective problems in Hearing loss group

At present, the thalidomide victims are suffering from pain, followed by limitation of activities of daily living and housework. Dizziness and tinnitus next to these. Around 50 % of the thalidomiders have disabilities in work. In the short arm group, they are feeling limitations of activities of daily living by 55 %, and housework by 42 % (Fig 4).

I'm talking about the characteristics of Japanese thalidomide victims again. Only a couple of victims were involved in the lower extremities. This slide is showing two victims involved in lower extremities. On the left, the X-ray film is showing markedly hypoplastic upper and lower extremities (Fig 5). On the right, another victim has moderate hypoplastic in the upper and lower extremities.

Instead of small numbers of hypoplastic lower extremities, we have a lot of victims who are suffering from hip osteoarthritis deformity. These X-ray films were taken 5 to 30 years ago. Acetabular dysplasia or hypoplastic acetabulum is one of the characteristics on X-ray films. Now, acetabular dysplasia changes into hip osteoarthritis deformity in time (Fig 6).

As to the classification of the severity in the short arm group, we classify four ranks (Fig 7). Most severe type is rather small minority, in comparison with severe, moderate or mild type. The rank of severity is determined in association with not only how long the arm is, but also the defective internal organs, especially congenital heart diseases. This slide is showing the most severe types. Amelia and phocomelia, in addition to hypomelia in the upper extremities. Phocomelia is defective short arms with rather normal hands attached close to the body. Prominent shoulders are likely characteristic with rather normal clavicles and scapulae. They cannot manually grip or pinch in the activity of daily living. In compensation for manual grip and pinch, they usually use their feet. Furthermore, they have to use their mouth or teeth to open a can or a bottle. It is likely that the clavicles and scapulae are normal in most thalidomiders. However, as they say, there is no rule with exceptions. This slide is showing two victims who have no clavicles with hypoplastic scapulae. Clinically they complain of pain over the shoulder and neck with droopy shoulders. Brachial plexus might be

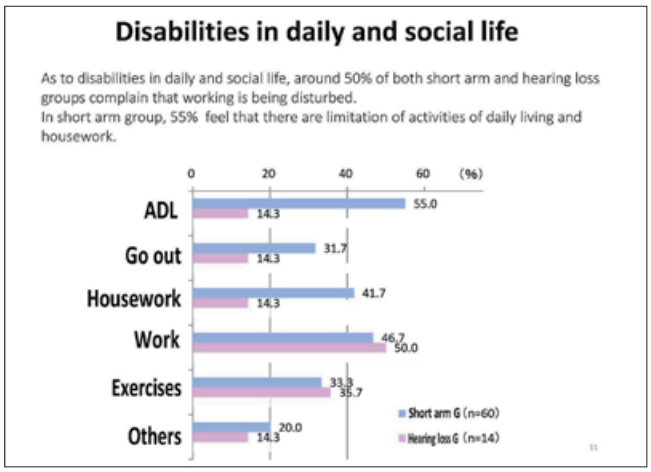


Fig 4 Disabilities in daily and social life

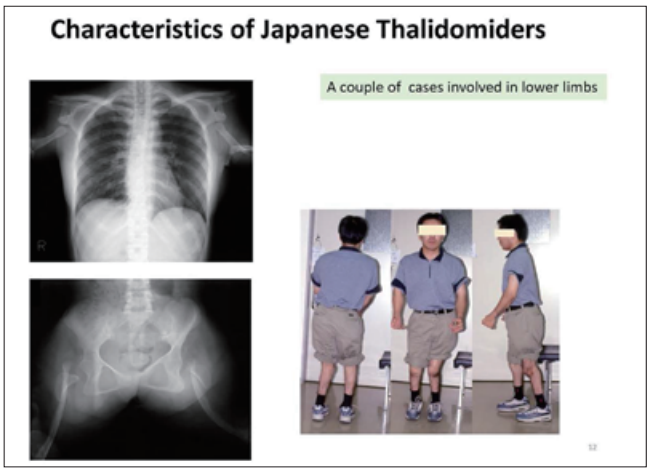


Fig 5 Two thalidomide victims with hypoplastic upper and lower limbs

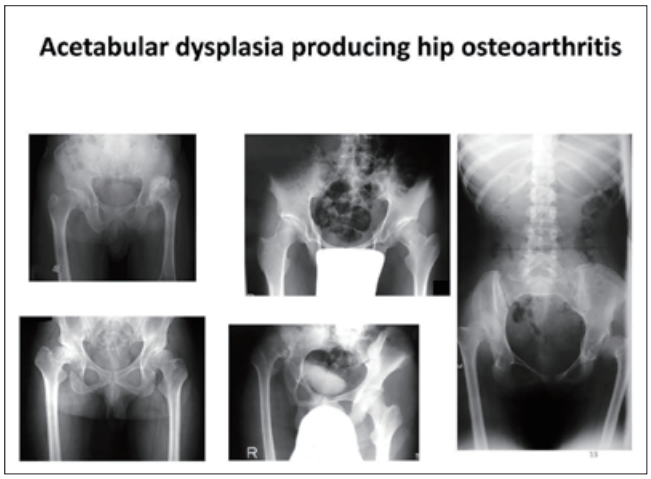


Fig 6 Acetabular dysplasia changing into hip osteoarthritis in age

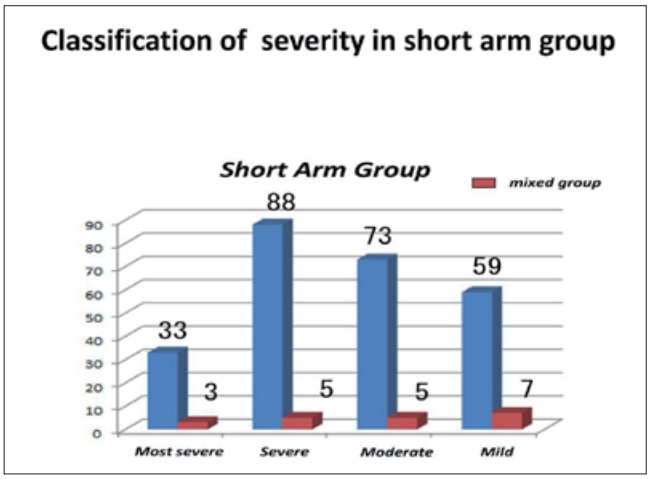


Fig 7 Classification of severity in short arm group

easily stretching or pulling downward resulting in shoulder and neck pain they are suffering at present. The severe type is characteristic with ectromelia, with clubbed hands. This type is the most common in 88 out of 230 victims with short arms. The forearm is mainly hypoplastic with radial defect. They also have curved hands and lacking of thumb.

The moderate type of short arms is characteristic in unilateral ectromelia with clubbed hands or hypoplastic thumb. In this group they have a tendency of excessively using rather intact hands resulting in carpal tunnel syndrome (Fig 8). From a point of anatomy, carpal tunnel is relatively narrow, with the intact median nerve which is comparatively bigger. The average onset of the carpal tunnel syndrome was 34 years old in 19 thalidomiders out of 25. Surgical treatment completely relieved symptoms. No recurrence was reported so far. Carpal tunnel syndrome is still increasing in numbers year by year. One secondary impairment or post thalidomide syndrome is carpal tunnel syndrome on the rather intact side. This case is on the right (Fig 9). The other nerve is rather super normal in nerve conduction velocity because of shorter forearm.

Mild severity of short arms is that they are lacking or hypoplastic thumb with atrophy of thenar muscles. Some of them have triphalangeal thumbs which are not real thumbs (Fig 10). This group also has a tendency of suffering from carpal tunnel syndrome due to overuse of the dominant hand. In addition, de Quervain's disease or tenosynovitis of the wrist is frequently associated. Pain is really refractory and resistant to the treatment partially because their using hands around the clock, even with hypoplastic musculatures. This is a slide showing mild severity case who is suffering from tendonitis at least and carpal tunnel syndrome on the left. Electrophysiological findings are consistent with axonal type carpal tunnel syndrome on the dominant left hand (Fig 11). Operative findings showed constriction of rather big median nerve at the relatively narrow carpal tunnel.

The thalidomiders with short arms have limitation of range of reach with weakness of grip and pinch. To compensate short reach they have been using mouth or teeth and excessively bending spine forward with round back getting

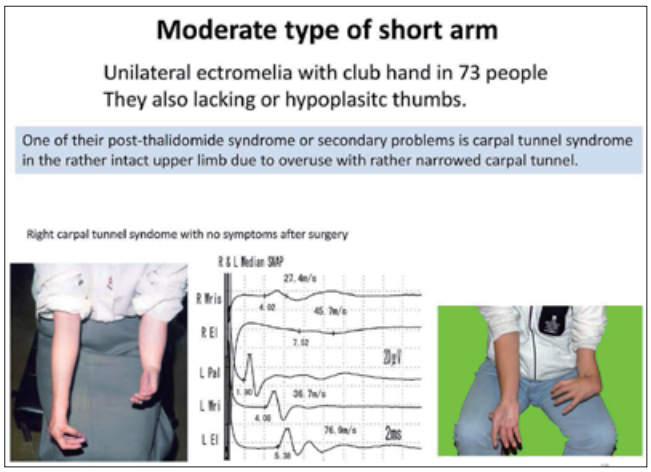


Fig 8 Carpal tunnel syndrome on the right in the moderate type

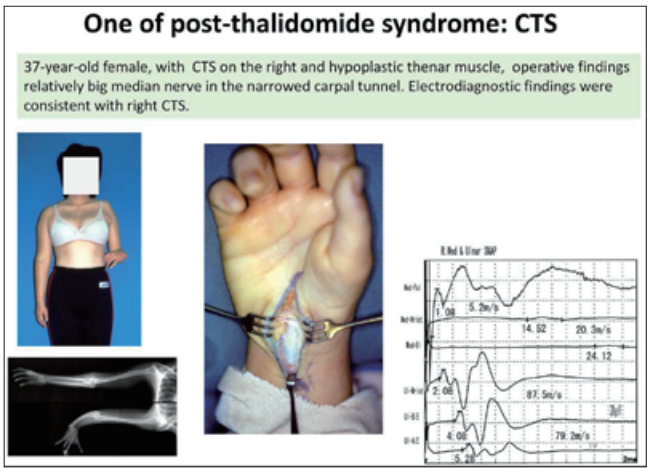


Fig 9 Nerve conduction study showing carpal tunnel syndrome

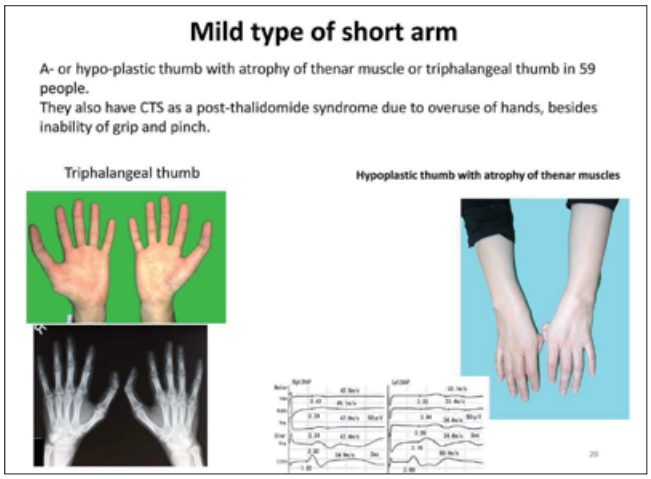


Fig 10 Mild type of short arms

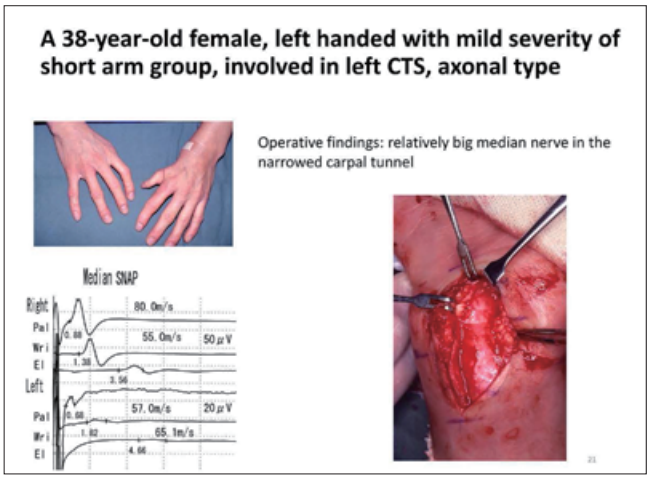


Fig 11 Rather bigger median nerve in the narrow carpal tunnel

worse in mal posture with sclerosis which can be associated with neck, shoulder and back pain. To compensate short reach they have been using body, trunk or legs, using hip joints at excessive range of motion has been getting the wear and tear in the joints. Post thalidomide syndrome means secondary impairments and disabilities. Impairment of the thalidomiders originated not only from malformed skeletal system but also from a hypoplastic muscular system. As you can see in this slide (Fig 12), there are hypoplastic skeletal musculatures around shoulder girdle and arm on the left side. They tried to make the muscles stronger, by exercises, karate, weight lifting, etc. but in vain at last. Post thalidomide syndrome might be produced by overuse of malformed joints and weak musculatures in the passage of time. This video is adopted from NHK TV "Thalidomide Drug Disaster for 50 Years," broadcasted this year.

V1-Video of Mr. M.I put on the screen
This person is living in Hokkaido and he goes to the hospital once a week. Three years ago he developed renal failure and now he is on dialysis. Dialysis usually is done using the arm but actually he does not have the arm so the artificial blood vessel is implanted to the leg and because the blood vessel is weak, the operation was difficult. And so the right leg didn't work and so he need to get the implant on the left leg. So three times a week, he has to go to the hospital and stay there for four hours. And if the life of the artificial vessel is expired, now he will have additional burden. Well, I thought the time would come at some point, so I cannot help it. So in a sense, well, I have been living a very rich life, richer than others, so I'm surviving. The question is, whether I really want to live that much. So every day I value every day of my life. I cannot think of the future. Rather, I have to have a good day every day. That's what I feel. He has been different from others. Nobody was visiting him even though he was waiting for a long time. So when I was in the grade school in the fourth year…

Kayamori: Most of Japanese thalidomiders including M.I are driving cars modify driving Franz system by feet. We appreciate Mr. Eberhard Franz for his introduction of the feet steering system in 1981. Franz system became so popular for bilateral arm amputee, as well as thalidomiders in Japan. Japanese National Police Agency and Ministry Transportation revised the ordinance and associated regulations in the International Year of Disabled People, when most thalidomiders were going to 20 years old. And this video is also adopted from NHK TV in 2015. Ms. H.N is living in Yamaguchi located in the westernmost part of mainland Japan.

V2 – Video of Ms. H.N put on the screen: This is Ms. H.N, she's living in Yamaguchi. She lacks most of the limbs. When she was born, there was no information regarding drug-induced diseases, so she didn't know why she had suffered from such impairments so she was rather trying to hide from the society when she was young. When she was small, she needed to live hiding from the society. When she was 18, she asked her parents, she wanted to go to the high school so for the first time she voluntarily went out of the house. "Well, I was afraid, when I went out. It was quite scary, so overwhelming for me." She entered some special school and so every week I tried to make a friend, whenever I go to the school. She is in Yamaguchi and from her 20s she got her job by drawing some illustrations for the advertisements. When she was small to heal for her the loneliness, her father taught her how to draw. That expanded her road. This is my corner. When I draw, there are some unexpected connections. Or sometimes her parents bring her the product, produces from the field and I draw that picture. In the past I was staying in the house and

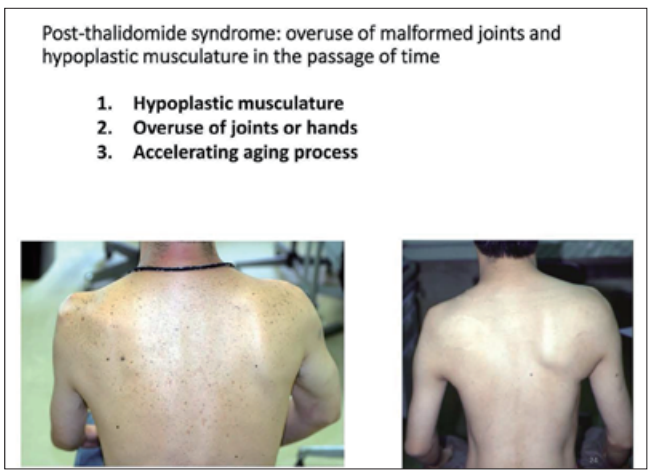


Fig 12 Asymmetric hypoplasitc skeletal musculatures

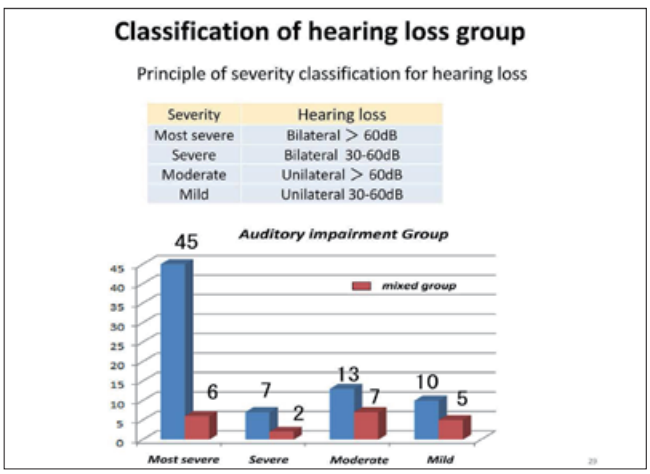


Fig 13 Classification of hearing loss group

I was drawing to entertain myself. But now I can go outside and the drawing is a tool for me to go out, and to connect with people. For her, there's one concern. For her to draw, drawing means she has to concentrate extremely. But she has the pain in the back and lower back and that's getting worse every year. She's not sure how long she can bear that pain and continue to draw.

Kayamori: As to hearing loss group, severity is classified into most severe, severe, moderate and mild. The most severe with bilateral over 60 decibels hearing loss is the most common in 45 out of 75 victims (Fig 13). In the hearing loss group there are three types of hearing impairment, conduction, sensory neural and mixed. Sensorineural type is the most common by 43 %. Facial palsy is also frequently associated in 50 %. In addition, auricular and ocular disfigurements are also accompanied (Fig 14). This is a 50-year-old female involving in bilateral hearing loss over 90 decibels with left ear disfigurement. She has also facial weakness and Duane syndrome in addition to thenar atrophy in hand.

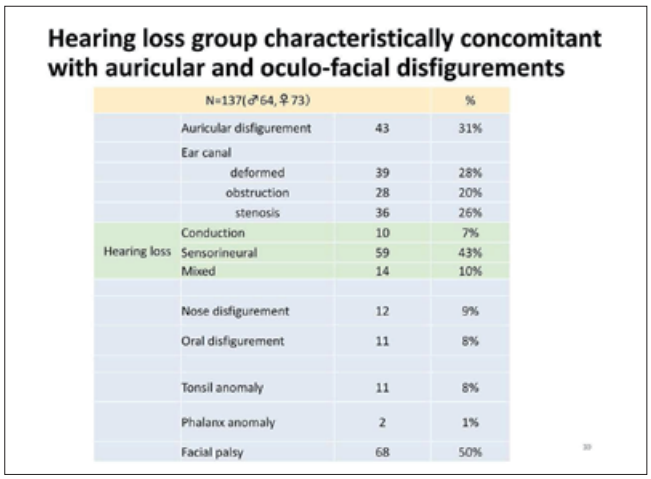


Fig 14 Oculo-facial disfigurements in the hearing loss group

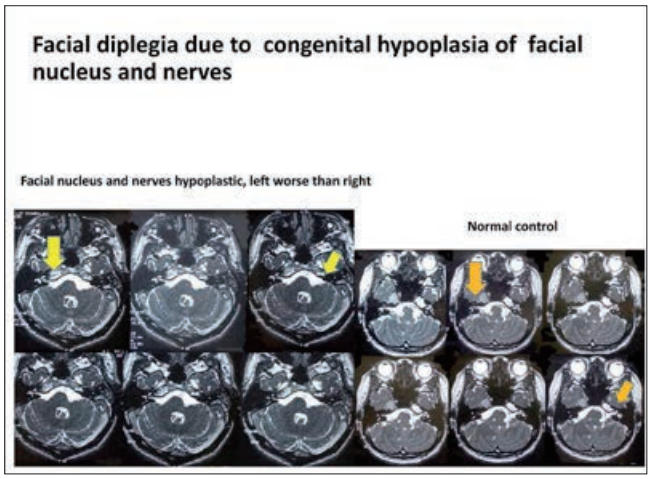


Fig 15 MRI showing aplasia or hypoplasia of facial nucleus and nerves

Kayamori: In this CT abnormal are inner middle ears on both sides. Electrophysiological findings for facial dysplasia correlated with bilateral hypoplasia of facial nucleus and nerves with mild aberrant innervation over the facial muscles. On the basis of the findings we can presume that pathology is not qualitative but quantitative in the facial weakness.
This video is showing bilateral facial weakness in association with severe hearing loss.

V 3, 4– Video of a 50-year-old female with facial diplegia and severe hearing loss. The next video is showing bilateral abducens palsy with aberrant innervation by oculomotor nerve resulting in Duane syndrome.

Kayamori: This is another patient, a 45-year-old man with conduction type hearing impairment, and auricular and ocular facial disfigurement. Hearing loss is getting to deteriorate in age. This is an MRI showing facial nucleus and nerves in comparison with normal control. Facial nucleus and nerves are hypoplastic or lacking on the left (Fig 15). This video showing facial dysplasia and bilateral Duane syndrome type 3.

Kayamori: This slide is the last in a 49-year-old female suffering from hearing lost and mild facial weakness on the left. In 1977 her audiogram showed only left mixed type hearing loss. Right ear is completely normal. However, 36 years later, in 2013 her audiogram showed severe sensorimotor type deafness in both sides (Fig 16). CT shows both anomalies of middle and inner ears.

Kayamori: So, thank you very much for your attention.

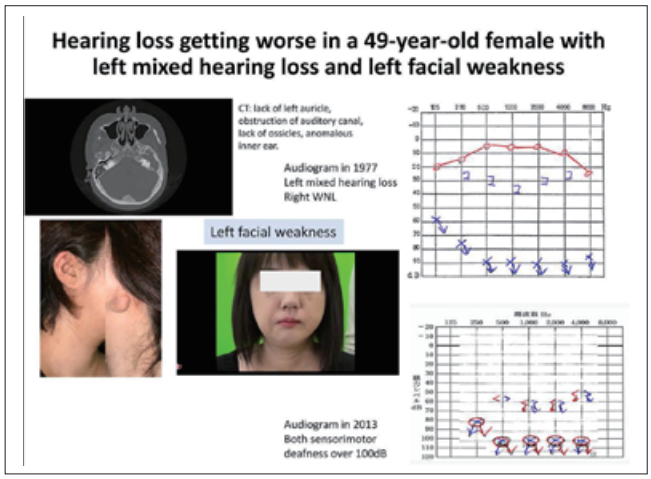


Fig 16 Audiograms showed deterioration of hearing loss

Q&A

Hinoshita: Thank you, Dr. Kayamori, for a nice lecture and the real cases shown. By the way, if you have any questions or comment about this presentation, please don't hesitate to speak out. Is there anyone? Additional comment? OK. Go ahead please. Dr. Schulte-Hillen. Sure.

Schulte-Hillen: Otherwise I can speak up. Shouldn't be any problem. Thank you very much. I would like to know the cases with hearing impairment. Do they deteriorate more than the normal population?

Kayamori: On the basis of findings showing in Fig 3, 37% of hearing loss group complained of deterioration of hearing. In general, aging process makes worse sure in the hearing. But it is likely that in thalidomide embryopathy they're going more and worse in deteriorating progressively. I think that's a big problem.

Schulte-Hillen: So it progresses more than in the compared.

Kayamori: We don't know the reason why in detail. Last slide in Fig 16 showed completely normal on the right side. Left side was mixed type deafness. The audiogram 36 years later showed sensorineural type deafness over 100dB.

Schulte-Hillen: Arigato (Thank you).

Kayamori: Thank you very much for your coming from Switzerland.

Hinoshita: OK, thank you very much, Dr. Schulte-Hillen. Now, Professor Ikezono, here? Do you have any comment about this theme? Hearing impairment.

Ikezono: Yes, I thought his question was regarding senile progressive hearing loss because of age. And his answer was about anomaly. Hearing coming from anomaly. So they're talking about different issues. That's what I understood. And he said even though the audiogram was better, in one side she couldn't understand what you said. That means she had a central processing problem, not the peripheral problem. She could understand the sounds, she could understand the words. That's what he mentioned. Am I clear to you? So he wanted to ask him if the patient has a progressive hearing loss because of age.

Staff: Please use your microphone for interpreter. Interpreter cannot hear you.

Hinoshita: Microphone, please.

Schulte-Hillen: Thank you very much. I'm sorry for the misunderstanding. My question was if the progressive loss of hearing with age is accentuated, is more severe in thalidomiders than in normal persons?

Ikezono: That his question is for the senile hearing loss, is more progressive than the general public. And your answer was regarding anomaly hearing loss. So when the person without any conduction hearing loss, he wants to know whether the progressive…

Kayamori: I did show only one case. I have no idea in detail on the mechanism of hearing deterioration. So Dr. Hinoshita asked the specialist of ENT doctor, Professor Ikezono. OK?

Schulte-Hillen: Yes. I think it's hard to differentiate whether it's normal aging progress or whether it can be attributed to thalidomide. We have in Germany the impression that many thalidomiders with only very, very moderate impaired hearing at birth tend to very severe deteriorating with age more than the normal population. And I wanted to know if that is consistent with your findings in Japan.

Kayamori: Personally I agree with you. In Japan 37% of haring loss group complained of deterioration of hearing.

Schulte-Hillen: And we do not know if it's a subtle acoustic problem or a perceptive central problem. OK, thank you very much.

Hinoshita: Maybe we don't know the reason, you know, why the hearing impairment progresses as thalidomiders age even if they had no marked hearing loss at birth. But, let's check and examine together about this theme. Is there anything else? Any other questions? About his presentation? No? OK, then the time is over.

Multicentre survey of Thalidomide Embryopathy (TE) at around 50 years of age in Japan

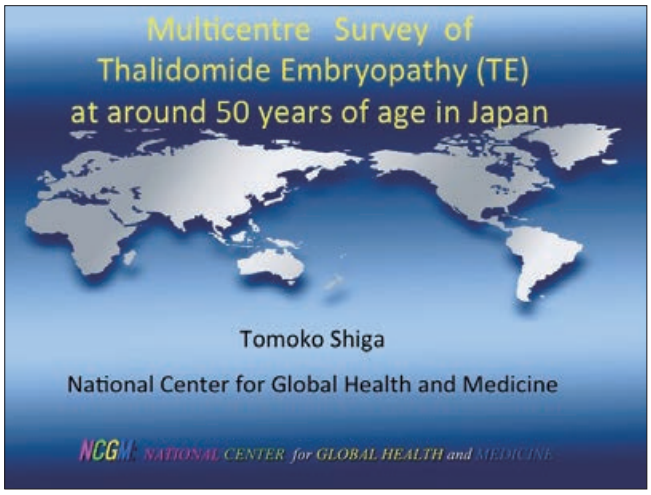
Dr. Tomoko Shiga
Department of Complete Medical Checkup, National Center for Global Health and Medicine, Tokyo

Shiga: Thank you, chairman, Dr. Hinoshita, for giving me an opportunity to give this presentation. Good morning, everyone, now I would like to talk about our research (Slide 1).

This study was funded by a Grants-in-Aid for Research on Regulatory Science of pharmaceuticals and Medical devices from the Ministry of Health, Labour and Welfare of Japan (Slide 2).

In utero exposure to thalidomide causes a wide range of birth defects, including phocomelia, hearing loss, and visceral disorders, known as thalidomide embryopathy (TE). Fifty years after the first report of TE, we conducted the first cross-sectional multicentre study to investigate the development of lifestyle-related diseases and identify risk factors for visceral disorders in subjects with TE (Slide 3).

Thalidomide was first marketed in 1957, as a sedative in Germany, where it was promoted to alleviate nausea and morning sickness in pregnant and nursing women due to its rapid onset of effects and apparent safety. Thalidomide was then made available in over 46 countries. In Japan, thalidomide was first marketed in 1958, under the trade name Isomin^{R}, as a sleep-inducing agent. Afterward Pro-ban M^{R}, containing a small amount of thalidomide, entered the market in 1960 for the treatment of digestive ulcers. Infants with thalidomide-induced defects were born to mothers who had taken thalidomide in early pregnancy. Birth defects were



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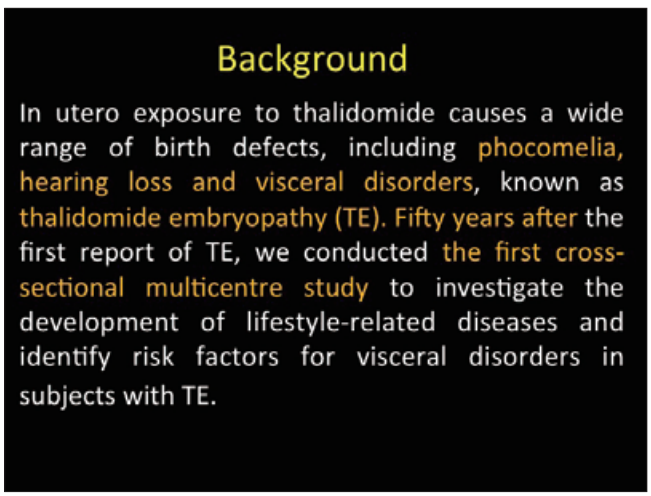

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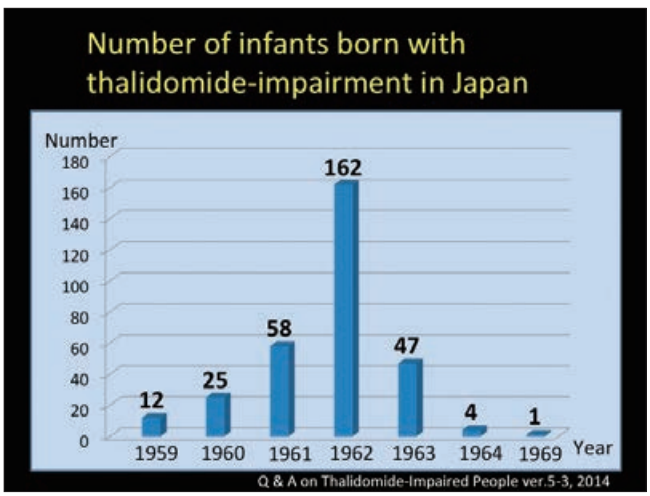


Slide 4

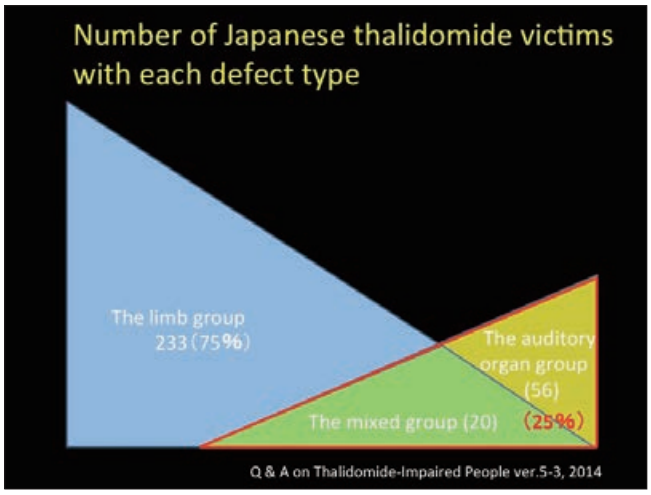
observed commencing in 1959 and reached a peak in 1962. Three hundred and nine people were recognized as being affected by thalidomide in Japan, 294 of whom were still alive in January 2015 (Slide 4). The total number of victims worldwide is estimated at 5,850.

The subjects with TE were divided into three groups: the limb group, the auditory organ group and the mixed group. The limb group contained subjects with abnormalities of the limbs. Among limb abnormalities, deformities rang from amelia, (lacking upper and/or the lower limbs) to hypoplasia of the thumb. The auditory organ group contained subjects with hearing loss (mainly sensorineural deafness or mixed hearing loss). The severity of auditory abnormalities is determined by the degree of deafness. These abnormalities are often accompanied by aplasia of the abducens and facial nuclei. The mixed group contained subjects with both limb and auditory abnormalities. The limb group accounts for 75% of the defects, with the remaining 25 % being the auditory organ group and the mixed group (Slide 5).

A multicentre survey was conducted in Japan from 2011 to 2015 by the National Center for Global Health and Medicine, Teikyo University School of Medicine and National Hospital Organization, Kyoto Medical Center. A total of 99 adults, 44 men and 55 women with TE were included in this study. Mean age was 50.7 years old. This study was performed in along with the public service corporation, ISHIZUE foundation, which is a foundation for the welfare of thalidomide victims in Japan. The ISHIZUE foundation chose the participants from 286 subjects who belonged to the foundation. The participants were chosen as 'healthier' subjects, i.e., they were healthy or out-patients (Slide 6).

Ninety-nine cases with TE were analyzed about lifestyle-related diseases and the types of thalidomide embryopathy-related anomalies (i.e., limb, auditory organs, or visceral organs).

Blood pressure is very difficult to measure in the affected limbs of subjects with TE. Therefore, systolic blood pressure was measured in a recumbent position using this equation: prediction of upper limb = 0.86 × blood pressure in lower limb, measured by an S-size cuff. Diastolic blood pressure in



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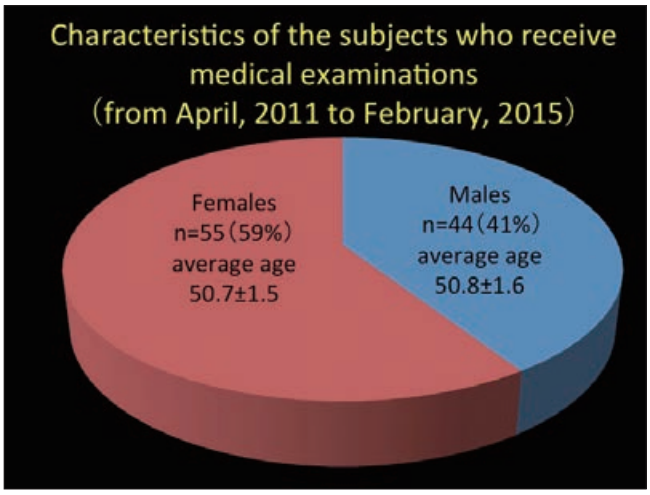

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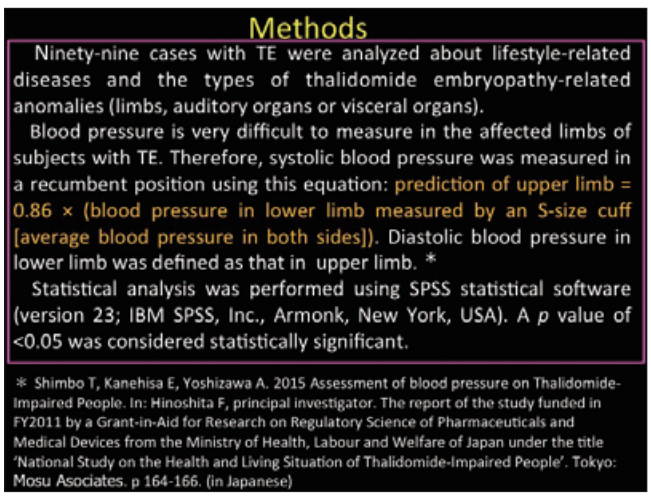

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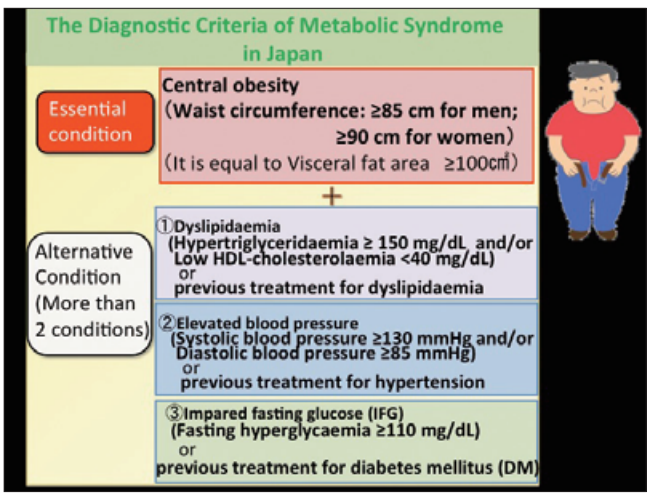


Slide 8

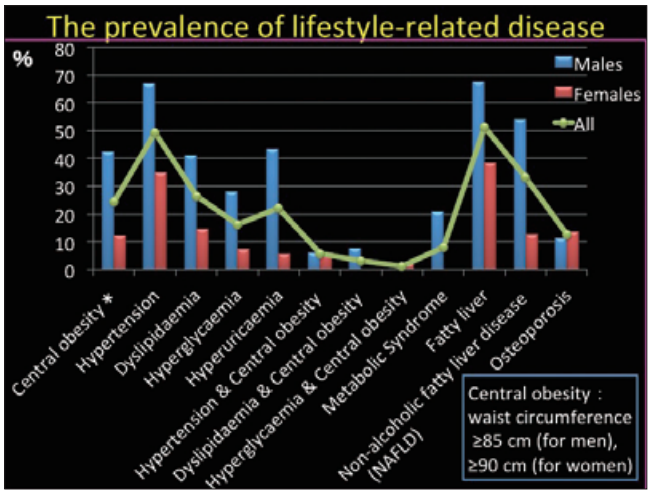
lower limb was defined as that in upper limb (Slide 7).

Metabolic syndrome (MS) was diagnosed using the 2005 guidelines defined by the Evaluation Committee on Diagnostic Criteria for Metabolic Syndrome of Japan, including central obesity. [waist circumference: ≥ 85 cm for men; ≥ 90 cm for women] and at least two of the following conditions: dyslipidaemia or previous treatment for dyslipidaemia and elevated blood pressure or previous treatment for hypertension and impaired fasting glucose (IFG) or previous treatment for diabetes mellitus (DM) (Slide 8).

The frequency of lifestyle-related diseases among male and female subjects is shown in this figure. Blue bar shows males, red bar shows females, and green line shows all subjects. Hypertension [49.4% of all subjects], fatty liver (FL) [51.2% of all subjects] and nonalcoholic fatty liver disease (NAFLD) [33.3% of all subjects] were the most common health issues encountered in these subjects. Approximately 20 to 25% of subjects had central obesity, dyslipidaemia and hyperuricaemia. In addition, hyperglycemia and osteoporosis were also major concerns for subjects with TE with frequency of around 15%. In this study only men developed MS. Taken together, these data demonstrated that men were at a higher risk than women for the development of almost all lifestyle-related diseases, including MS. Oestrogen suppresses visceral fat accumulation and increases subcutaneous fat accumulation. Therefore, gender-specific characteristics appear to play a major role in the development of MS, and there may be an association between sex hormones and MS (Slide 9).

Dyslipidaemia was checked in 41.9% of subjects with FL and 68.8% of subjects with NAFLD. NAFLD is no longer considered a primary liver disease, but rather a component of MS, insulin resistance and lifestyle-related diseases such as diabetes, dyslipidaemia, and hypertension. All cases of TE with FL confirmed by abdominal ultrasonography, which is a painless examination, should be monitored for the development of lifestyle-related diseases, such as dyslipidaemia and metabolic syndrome (Slide 10).

Therefore, multivariate logistic regression analysis was conducted to identify the risk factors for FL in subjects with



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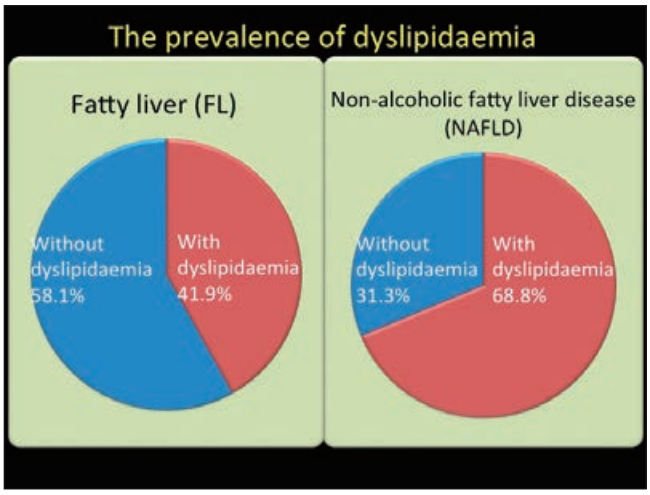

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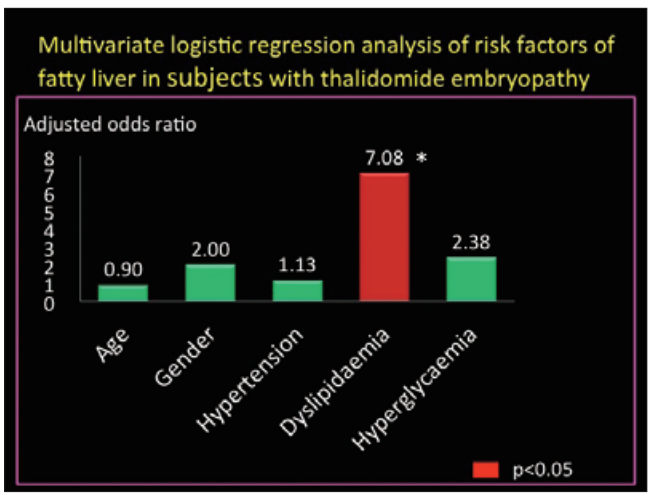

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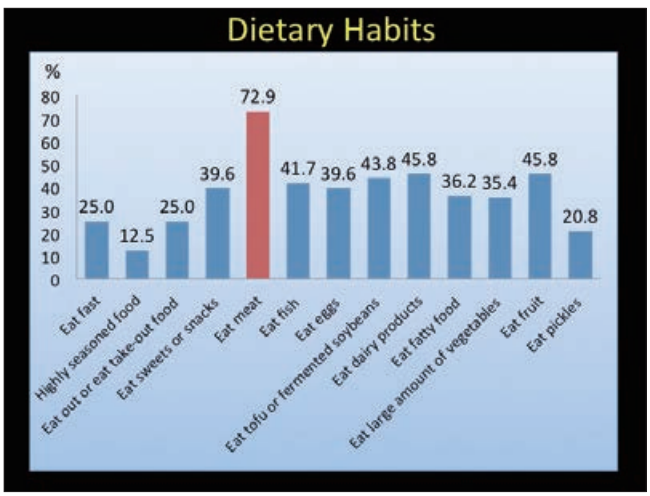


Slide 12

TE. Regression model analysis adjusted for age and gender revealed that dyslipidaemia was significantly associated with FL. Odds ratio = 7.08 (Slide 11).

Next, we analyzed the dietary habits of TE subjects. Habits of eating meat was detected in 72.9% of subjects with TE. There's no significant relationship between dietary habit and lifestyle-related diseases. However, considering the high incidence of dyslipidaemia, we recommended to eat less meat (Slide 12).

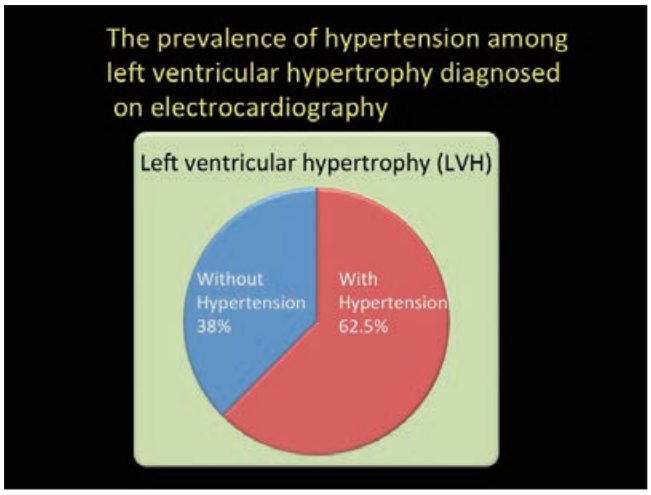
Hypertension was not significantly associated with left ventricular hypertrophy (LVH), although hypertension was detected in 62.5% of subjects with LVH. If LVH is diagnosed in a TE patient by electrocardiography, it is recommended to conduct a cardiac ultrasonography. Moreover, blood pressure must be monitored at home, and blood pressure would be controlled by a home doctor (Slide 13).

Osteoporosis was detected in 12.5% of subjects (Slide 14).

The prevalence of osteoporosis and decreased bone mass in the female subjects were more than the male subjects (Slide 15). Osteoporosis and decreased bone mass were detected in a higher incidence among those with limb deformity. Movement limitation caused by limb deformity in childhood might readily lead to osteoporosis (Slide 16).

Gallbladder development begins gestational week 4, and block vertebra (BV) is believed to be caused by blood flow obstruction from gestational week 3 to 8. Our study showed BV was significantly associated with gallbladder aplasia. Therefore, if subjects with TE with gallbladder aplasia develop shoulder stiffness and/or pain, cervical spine X-ray and MRI are recommended to investigate the presence of BV (Slide 17).

All subjects with gallbladder aplasia and 87.5% of those with block vertebra developed hypoplasia of the upper limbs. However, there was no significant association between hypoplasia of the upper limbs and visceral disorders (i.e. aplasia of the gallbladder and block vertebra). However, these data suggest new information on the teratology of TE. During pregnancy, corpus vertebra development begins during gestational week 6, whereas block vertebra is believed to be caused by blood flow obstruction from gestational week 3 to



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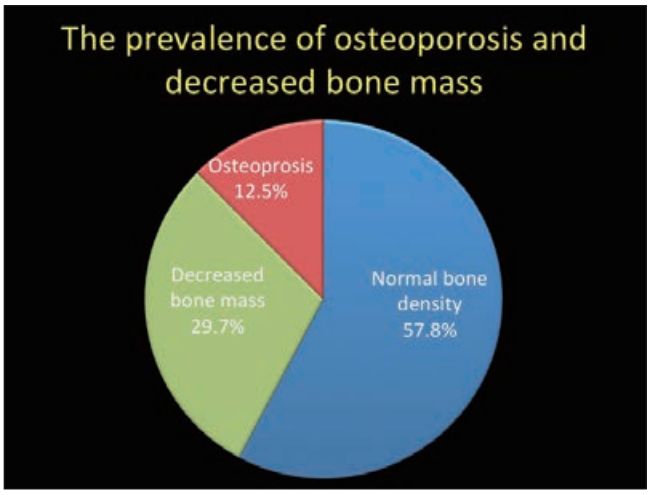

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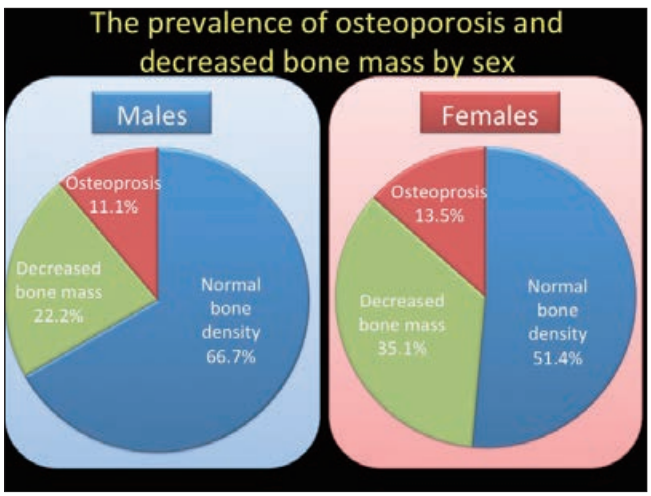

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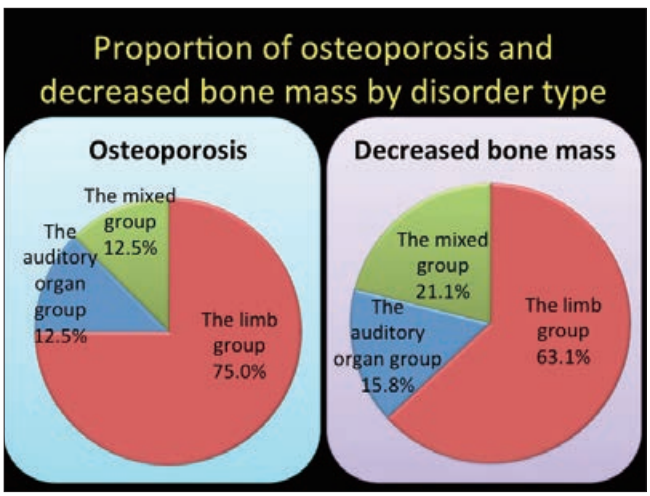

Slide 16

8. In addition, hypoplasia of the upper limbs develops during gestational week 3 to 7. The fact that TE is caused by inhibition of vascularisation establishes a causal effect for block vertebra in subjects with TE and hypoplasia of the upper limbs. Accordingly, we detected 7 subjects (87.5%) with TE and hypoplasia of the upper limbs among 8 subjects with block vertebrae. Therefore, clinicians should consider block vertebra among subjects with TE, hypoplasia of the upper limbs and shoulder stiffness (Slide 18).

There are 4 conclusions.

(1) First

Subjects with TE also have a risk of lifestyle-related diseases similar to that of the general Japanese population. Dyslipidaemia was significantly associated with FL. All cases of TE with FL confirmed by abdominal ultrasonography should be monitored for the development of lifestyle-related diseases, such as dyslipidaemia and metabolic syndrome.

Specifically hyperuricaemia and dyslipidaemia are risk factors for arteriosclerosis and renal dysfunction. It is important for TE subjects to detect them at an early stage. It is difficult to introduce hemodialysis among TE. So it is important for TE to protect renal function. If hyperuricaemia and dyslipidaemia are detected, early therapy which includes diet therapy, is also important.

(2) Second

If LVH is diagnosed in a TE patient by electrocardiography, it is recommended to conduct a cardiac ultrasonography. Moreover, blood pressure must be monitored at home and blood pressure would be controlled by a home doctor. Catheter therapy is difficult for the limb group due to depressed angiogenesis. So control of blood pressure is important to prevent vascular diseases, such as cerebral infarction and coronary heart diseases and so on (Slide 19).

(3) Third

Osteoporosis was detected in 12.5% of subjects with a higher incidence among those with limb deformity. The prevalence of osteoporosis and decreased bone mass in the female subjects were more than the male subjects. Bone fracture is the main cause of becoming bedridden. It is important to prevent bone fracture.

Multivariate logistic regression analysis of risk factors of gallbladder aplasia in subjects with thalidomide embryopathy

	Gallbladder aplasia (n=10)	No gallbladder aplasia (n=89)	Adjusted OR (95% CI)	*p* value
	Number (%)			
Age			0.73 (0.42–1.28)	0.272
Male	5/10 (50.0%)	39/89 (43.8%)	0.98 (0.23–4.22)	0.981
Female	5/10 (50.0%)	50/89 (56.2%)		
Block vertebra (BV)	4/10 (40.0%)	4/89 (4.5%)	12.58 (2.41–65.71)	0.003

Slide 17

Proportions of disorder type and gallbladder aplasia

	The limb group and The mixed group	The auditory organ group
All	78/99 (78.8%)	20/99 (20.2%)
Male	33/44 (75%)	10/44 (22.7%)
Female	45/55 (81.8%)	10/55 (18.2%)
Gallbladder aplasia	10 (5 males, 5 females) (100%)	0 (0%)
Block vertebra (BV)	7 (4 males, 3 females) (87.5%)	1 male (12.5%)

Slide 18

Conclusions

(1) Subjects with TE also have a risk of lifestyle-related diseases similar to that of the general Japanese population. Dyslipidaemia was significantly associated with FL. All cases of TE with FL confirmed by abdominal ultrasonography should be monitored for the development of lifestyle-related diseases, such as dyslipidaemia and metabolic syndrome (MS).

(2) If LVH is diagnosed in a TE patient by electrocardiography, it is recommended to conduct a cardiac ultrasonography. Moreover blood pressure must be monitored at home and blood pressure would be controled by a home doctor.

Slide 19

Conclusions

(3) Osteoporosis was detected in 12.5% of subjects, with a higher incidence among those with limb deformity. Bone fracture is the main cause of becoming bedridden. It is important to prevent bone fracture.

(4) In addition, cervical spine radiography and magnetic resonance imaging (MRI) are recommended to assess block vertebra (BV) in subjects with TE with gallbladder aplasia who develop shoulder pain.

Slide 20

(4) Fourth
In addition, cervical spine radiography and MRI are recommended to assess BV in subjects with TE with gallbladder aplasia who develop shoulder pain (Slide 20).

Thank you for your attention.

Q&A

Hinoshita: Thank you, Dr. Shiga. Do you have any question about this presentation? Is there any? Please raise your hand. Japanese or English, either will do.

Tagami: Tagami from Kyoto Medical Center. Thank you for a nice presentation. I have one question about dyslipidaemia. What characteristics of dyslipidaemia such as high triglyceride or low HDL cholesterol or both? And how about the LDL cholesterol?

Shiga: We checked dyslipidaemia according to metabolic syndrome definition. So we checked hypertriglyceridaemia and low HDL cholesterol.

Tagami: They have both.

Shiga: Yes, both or one.

Tagami: How about the percentage? Make sure.

Shiga: I'm sorry. I checked hypertriglyceridaemia and/or low HDL cholesterol. I didn't check each subject, so I will try.

Tagami: Because you presented how to revise the problem with dyslipidaemia so maybe high triglyceride is worse for their disease.

Shiga: My impression is hypertriglyceridaemia is more than low HDL cholesterol.

Hinoshita: Thank you. Maybe in Dr. Tagami's opinion, triglyceride would more strongly influence the genesis of fatty liver, right? So we need to classify dyslipidaemia into specific types according to the levels of cholesterol and triglyceride. OK? Is there any other question? Please.

Ikezono: Did you include audiometry in your medical checkup protocol?

Shiga: Yes. Audiometry. 1,000 hertz and 4,000 hertz. Only medical checkup level.

Inozuka: Actually I didn't know the hearing loss progression related to age in TE patients was the problem, because you mentioned so. I think we should do a thorough audiometry, not the simple one but the thorough audiometry in the next protocol.

Shiga: Thank you.

Ikezono: Thank you.

Hinoshita: By the way, when you speak out, please identify your name and affiliation. Then, thank you very much again, Dr. Shiga.

Shiga: Thank you very much.

Pathology, radiology and pathogenesis

Dr. Janet McCredie
University of Sydney, Sydney

Hinoshita: OK, let's go ahead to the next presentation. The next presentation would be given, using a video, and I first introduce Dr. Janet McCredie. She graduated from a medical school, Sydney University, in 1959. She was a fellow of Royal Australian College of Radiologists in 1976. Next, she got a Doctor of Medicine, University of Sydney, with a thesis, Neural Crest Defects, presenting evidence that many congenital malformations are the result in injury to the embryonic neural crest. It was reported in 1979. Next, she retired from Sydney University in 1990. She has got many glorious medals and achievements so far. She also published a great book entitled, "Beyond Thalidomide in 2007." Then please start your presentation.

McCredie: Thank you very much, Dr. Hinoshita, and good morning, ladies and gentlemen. I'd like to thank Dr. Hinoshita and his team and the translators for all the work that they've done and it's a very promising meeting to have. As you can hear I've got laryngitis, which is why Dr. Hinosohita's given me permission to present through the video because I don't think my voice would last for 20 minutes. Perhaps I should be wearing a white mask.

Hinoshita: We Japanese love masks. Don't worry.

McCredie: I'd like to pay tribute to Professor Nishimura, the late Professor Nishimura, who was one of the great embryologists who came out of Japan. And the very first photograph that I'm going to show you is a photograph that he gave me of a 28 day human embryo. And later on in my talk I will furnish some advice he gave me. So, I just like to mention his name just now because he was one of the greats. I think I'll sit down now, and let the technicians take over.

Hinoshita: It's OK to sit down there, all right? Uh-huh.

* Dr. McCredie gave us a video presentation in the symposium because she was sick as mentioned above. Several months later, she sent the edited record of her presentation for the official proceeding which will be published by the research group on the various problems of the health and living situation in thalidomide-impaired people in Japan. Instead of her video presentation recorded, the edited presentation of her own making is shown as follows.

Introduction

Over 50 years ago, thalidomide (when used as an anti-nauseant for pregnant women) attacked human embryos and caused an epidemic of birth defects. How the drug acted within the embryo can be deduced by analysis of these birth defects, using the medical sciences of human anatomy, neurology, radiology and pathology, and by reviewing past research by many doctors and scientists. Details are published in my book "Beyond thalidomide: Birth defects explained" (1).

We start by looking at the attacker, thalidomide - and then at the victim, the normal human embryo. Early research established that teratogenesis was due to exposure to the thalidomide molecule itself, not to breakdown products. On contact with fluids (e.g. serum) the thalidomide molecule hydrolysed into any of 12 products of hydrolysis, none of which proved to be teratogenic. Schumacher et al (2) showed that oral thalidomide was rapidly absorbed, with peak at one hour, and half-life at 3 hours after ingestion, falling to zero at 12 hours.

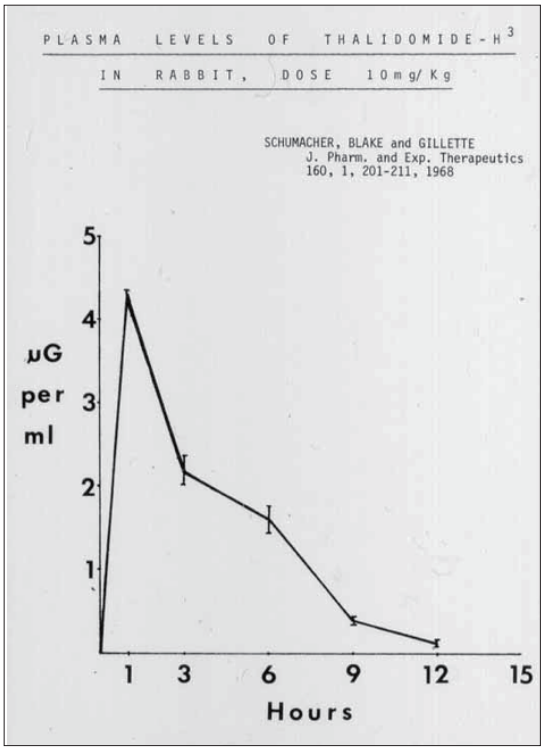

Figure 1

Thalidomide's pharmacokinetics show that it inflicts a rapid "stab injury", a sharp attack in a short time, the first important fact.

Equally important was the fact that thalidomide attacked sensory nerves in adults using it as a sedative. This was revealed before the drug was deployed as an antinauseant for pregnancy. Adults using thalidomide sedation complained of tingling, numbness and shooting pains in feet and hands. German and British neurologists diagnosed sensory peripheral neuropathy of the axonal degenerative type, a "dying back" of axons from the distal tips of the longest nerves (3, 4, 5).

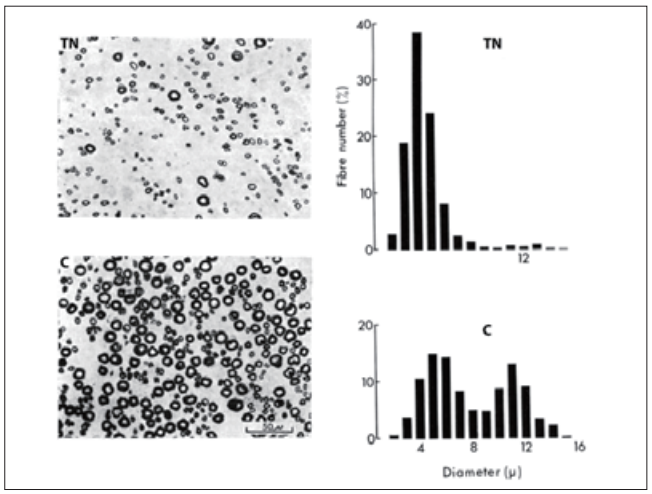

Figure 2

Six years later, 75% of damaged adults still had symptoms, like this woman (top of fig 2) whose sural nerve biopsy, 6 years after stopping thalidomide, shows almost complete destruction of large diameter nerve fibres (type A fibres that carry touch sensation). Her histogram of fibre sizes shows that large fibres have been practically eliminated by thalidomide's neurotoxicity (6). Compare with the biopsy of a normal, age-matched control sural nerve (below), where large diameter axons are normal and abundant, and there is a normal bimodal histogram of axon sizes (6).

This is the second important fact: that thalidomide attacks sensory nerves. Therefore when we come to examine what thalidomide does to the embryo, we must look closely at the embryonic sensory nervous system.

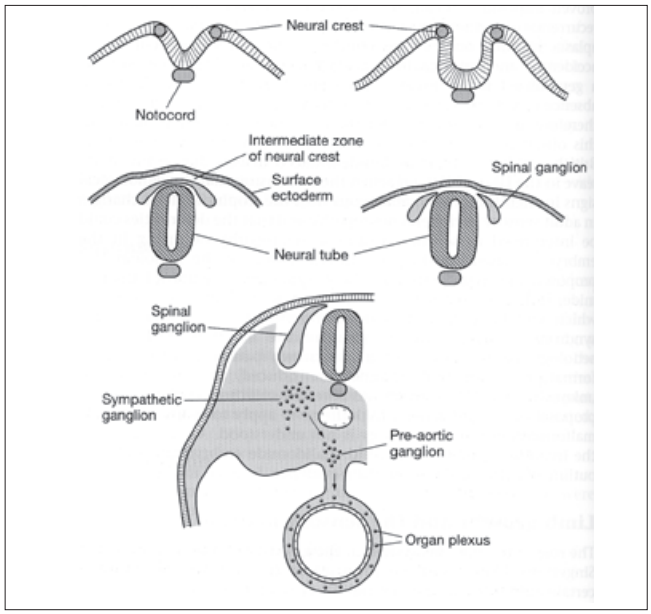

Figure 3

In the human embryo, sensory and autonomic nerves develop from NEURAL CREST, a primordial ectodermal tissue (7), the first differentiated tissue to appear in the human embryo, at day 18 of gestation. It is highly active. Neural crest cells rapidly multiply, migrate and sprout axons as they evolve into neurons. Their cell bodies aggregate into ganglia, while their axons branch out into the undifferentiated mesenchyme of the embryonic disc. Axons always precede differentiation. They are abundant within undifferentiated limb buds (8, 9, 10).

Axons are very delicate strands of unmyelinated cytoplasm, easily destroyed by poor tissue preparation or overlooked by inadequate microscopy. They require tissue preparation as used in medical neuropathology laboratories, and meticulous electron microscopy (8, 9, 10).

Neural crest is a ubiquitous tissue with many progeny. In addition to the sensory and autonomic nervous systems, other derivatives of neural crest include connective tissue and bones of face and skull, cranial nerve nuclei, septum and conotruncal structures of the heart. Thalidomide damages ears, eyes, facial structures, cranial nerves, and causes septal defects and cono-truncal heart deformities.

How does thalidomide cause birth defects? What is the pathogenetic mechanism of its teratogenic action?

Any hypothesis of thalidomide's teratogenic activity must explain the following 12 phenomena observed in the embryopathy:

1. Drug action predates existence of limb buds.
2. "Sensitive period" of 21 – 42 days gestation, established early in the epidemic (11).
3. Cranio-caudal sequence of defects in time shown by Lenz and by Nowack in 1965 (12)

4. Symmetry in majority but not all.
5. Upper more commonly afflicted than lower limbs.
6. Sparing of Central Nervous System.
7. Longitudinal reduction defects of limb bones.
8. Triangular bone remnants,
9. Dislocated joints, and
10. Synostoses or fused bones and joints.
11. Associated visceral defects.
12. No bone histopathology, but neuropathology found.

This paper examines these twelve phenomena.

1. Drug action predates existence of limb buds

Timelines in human embryogenesis reveal this important phenomenon, as follows in figures 4 – 6.

Fertilization is at zero time.

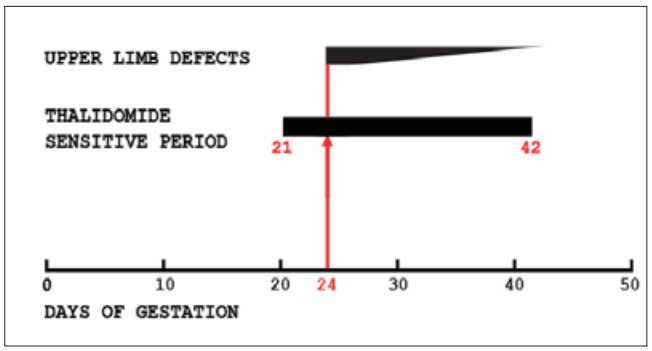

Figure 4

2. The "sensitive period" was established by Lenz as 21 to 42 days gestation (11). It possibly extends longer, but its commencement is not debated. Lenz emphasized that upper limb defects resulted from exposure from day 24 onwards, day 24 being the earliest date of exposure recorded with arm defects (arrow).

All embryology textbooks state that the upper limb bud does not appear until day 28.

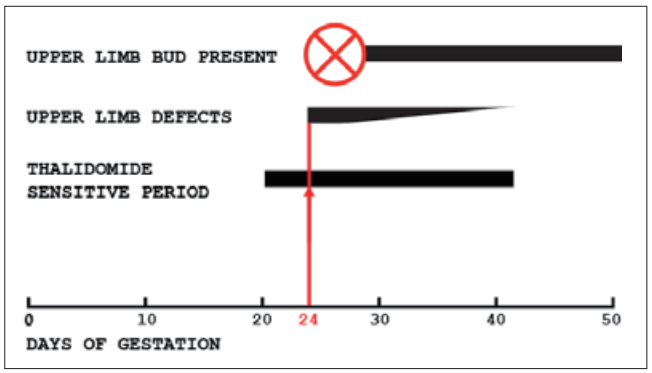

Figure 5

Therefore thalidomide cannot act within limb buds – because they do not exist for another four days! It follows that any hypotheses that are set within limb buds are refuted by these facts. Molecular and vascular hypotheses fall over because neither limb buds nor forelimb arteries exist when the drug attacks.

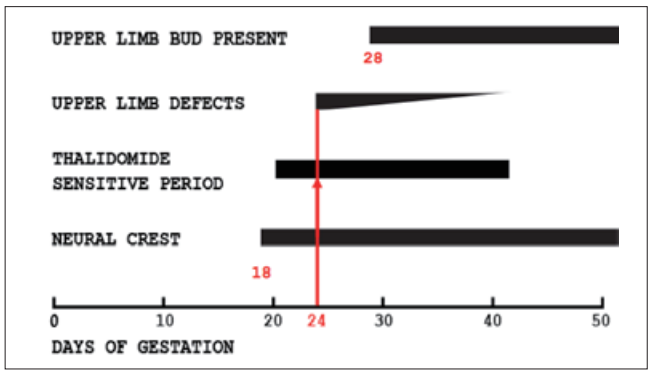

Figure 6

Neural crest, however, is present from day 18 of gestation (13) and is highly active during the thalidomide-sensitive period, dividing, migrating and sprouting axons (14). These activities make neural crest cells highly vulnerable to injury at this time.

3. Cranio-caudal sequence of thalidomide damage

Lenz recognized that a wave of sensitivity swept down the embryo from head to tail between 21 and 42 days of life. Particular defects followed thalidomide exposure on particular days (12):

- between days 21 and 24 resulted in eye, ear, cranial nerve and other head and neck defects;
- exposure from day 24 resulted in arm defects;
- exposure from day 27 caused leg defects as well.

Nowack and Lenz concluded that "the morphological type of the birth defect was essentially a function of the TIME of exposure, not the dose" (12).

This data from humans is replicated in laboratory primates. Neubert's laboratory in Berlin found the same cranio-caudal sequence of occurrence in primates exposed to thalidomide. Upper limb defects resulted from exposure before the limb bud existed (15).

Neubert et al concluded that thalidomide must act within the torso of the embryo, deep to the site of the future limb bud. This is exactly where neural crest axons are infiltrating undifferentiated mesenchyme – axons of naked cytoplasm, unprotected and highly vulnerable.

4. Symmetry versus asymmetry

Publication of large series of thalidomide cases in the aftermath of the epidemic proved that the majority were bilaterally symmetrical (16). But all series had 15 – 25% of cases with asymmetrical or even unilateral deformities.

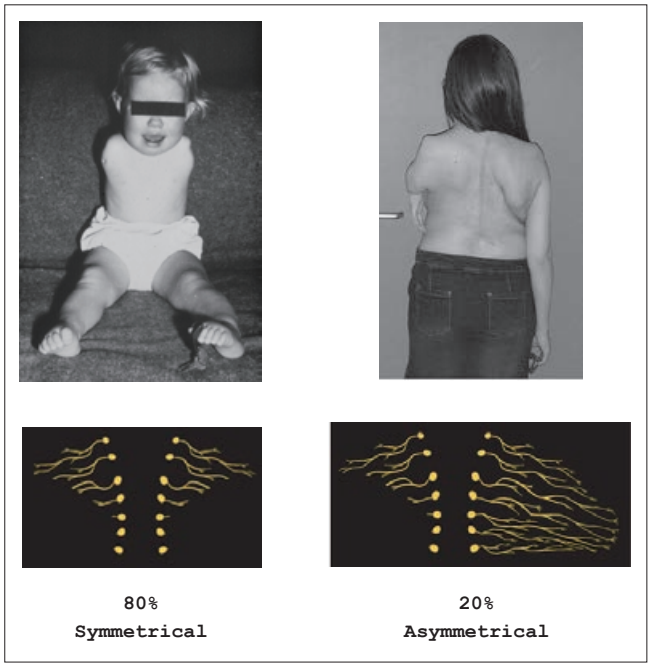

Figure 7

I sought advice from Professor Nishimura, who had studied and staged thousands of normal Japanese abortuses. I asked him whether all human embryos develop the left and right sides of the body at the same time, in unison. He said that they do not! Professor Nishimura told me that 80% of human embryos develop symmetrically, but in about 20%, the left and right sides are out of step, by up to 4 embryonic day's difference (17). This means that neural crest must develop asymmetrically in such embryos. It follows that 80% of thalidomide defects should be bilateral and symmetrical, and that 20% should be asymmetrical with a few even being unilateral.

5. Frequency of upper > lower limb defects

This master diagram is from Henkel and Willert's landmark paper of 1969 (18) that defined the pattern of dysmelia in over 200 German thalidomide children.

Upper limb defects were most numerous, especially absent radius and thumb. Perhaps this is because nausea of pregnancy is characteristically early, sometimes the presenting symptom, around the time of the missed period.

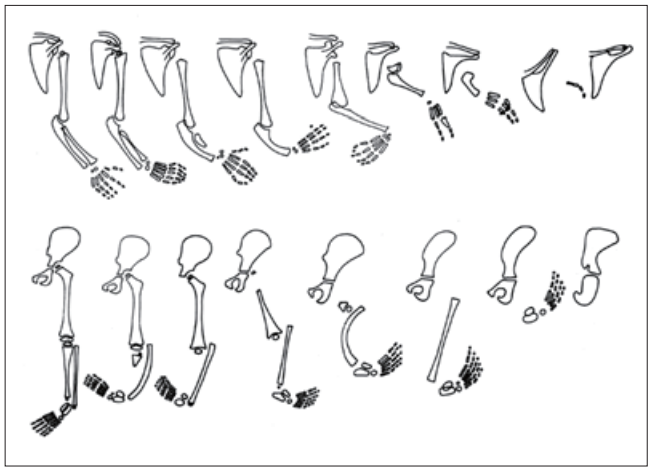

Figure 8

Nausea is usually short in duration, and a woman may take only one or two tablets, sufficient to target the neural crest at about day 24, causing arm rather than leg malformations.

6. Sparing of central nervous system

The brain and spinal cord in thalidomide were usually normal, but the peripheral nervous system (outside CNS) was not. The immense network of nerve fibres of peripheral nerves extend to every part of the body. Peripheral nerves have evolved for the purpose of signalling and communication throughout the bodies of all animals, including man. The basic cell in the sensory division of the peripheral nervous system is the bipolar neuron. As shown in the introduction, in human adults, thalidomide attacks this group of sensory neurons (derived from neural crest) not brain cells (derived from neural tube). In human embryos, thalidomide also targets neural crest, not tube. The target is consistent throughout life from embryo to adult.

7. Longitudinal reduction deformities of the limbs

In the limbs, thalidomide deleted longitudinal bands of bone, and such defects were classified as "longitudinal reduction deformities". This distribution of disease, subdividing bones, is not consistent with bone pathology. On the other hand, skin is innervated in longitudinal strips called dermatomes, each dermatome supplied by one spinal segmental sensory nerve.

C6 Dermatome Subtraction

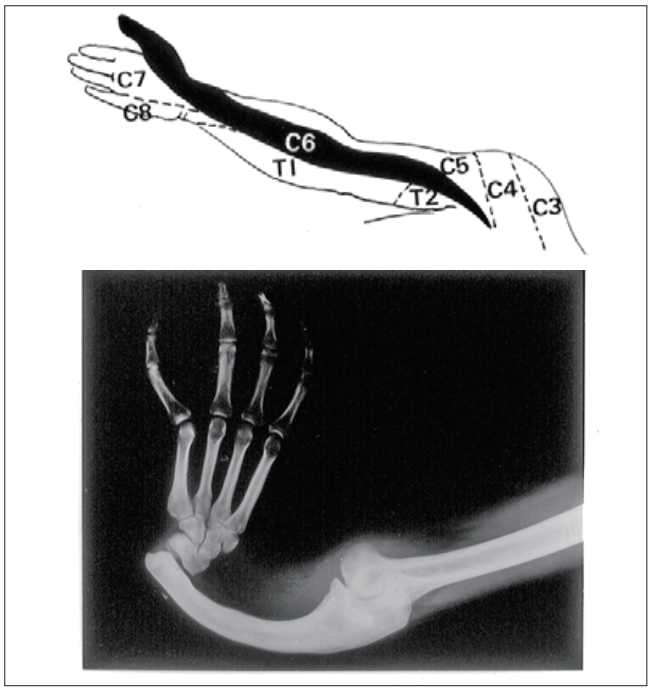

Figure 9

Here the dermatome of the 6th cervical nerve is black. If it is excised together with the underlying bones, radial aplasia and absent thumb would result as shown in this Xray film of the most common upper limb defect in thalidomide embryopathy.

The skeleton has similar (but less well-known) segmental sensory innervation. The strips of segmental nerve supply of bones are called "sclerotomes". Based upon past literature plus their own experiments and clinical observations, Inman and Saunders of San Francisco drafted these maps of the segmental sensory nerve supply of the limb skeleton in 1944 (19).

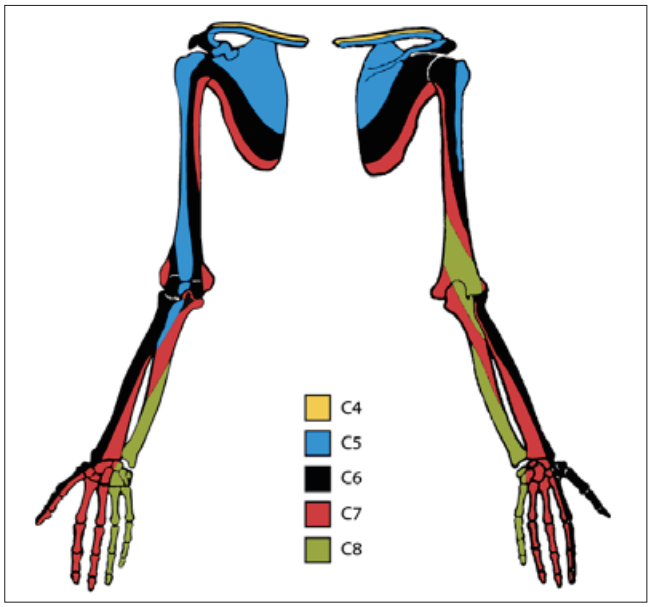

Figure 10

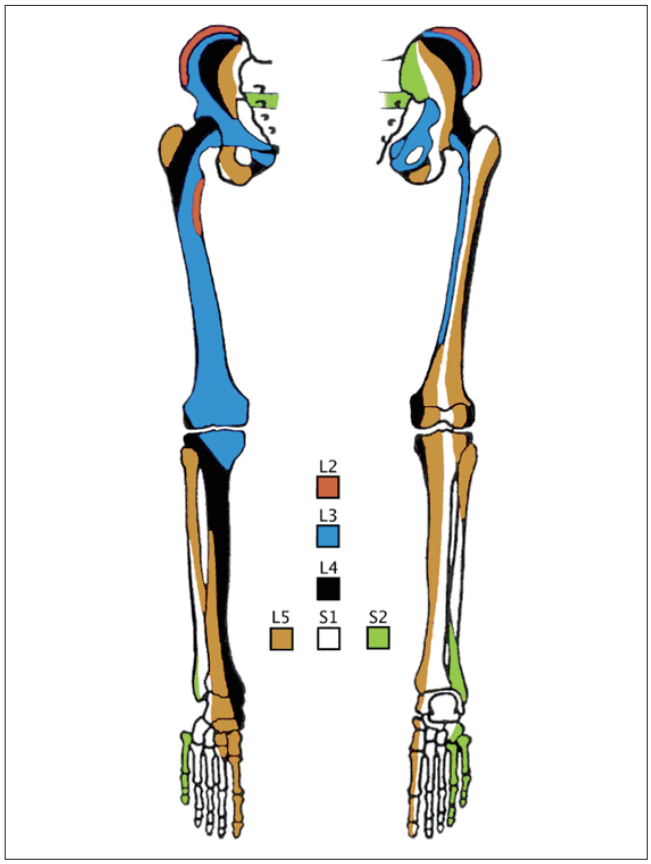

Figure 11

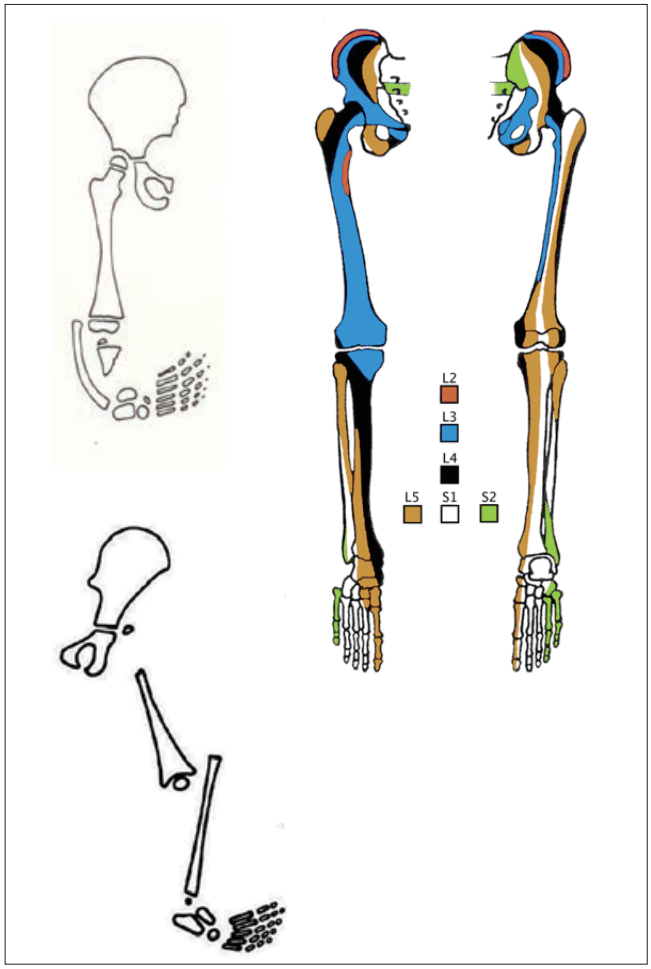

Figure 12

When I applied the sclerotome maps to the radiographs of thalidomide cases, the deformities emerged as failure of formation of sclerotomes (20).

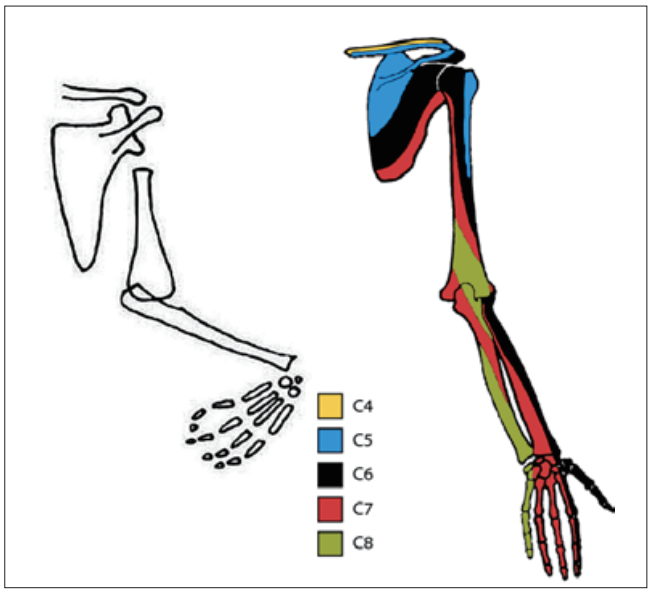

Figure 13

That indicates some connection between sensory nerves and limb growth. Is there such a connection? There certainly is, as has been proved in regeneration biology (21, 22, 23).

Sensory nerves possess an ability to make other cells divide. This particular ability is called "neurotrophism": neuro = nerve, trophism = growth.

Regeneration biologists know most about neurotrophism because limbs will not grow without sensory nerves (21, 22, 23). In studies of amphibian limb regeneration, these biologists have shown that sensory nerves stimulate mitosis of undifferentiated cells (21, 22, 23). Through neurotrophism, sensory nerves recruit mesenchyme cells by making cells divide, repeatedly, until a heap of undifferentiated cells creates a limb bud. This recruitment through mitosis was shown to begin from the inception of limb formation (22, 23, 24). The conclusion is that sensory nerves drive mitosis/cell division.

Although the biological principles were established in amphibia, the findings can be translated to human embryos, because the pentadactyl limb that results is similar throughout the vertebrate kingdom (25).

It follows that if a segmental sensory nerve is damaged, its neurotrophic ability fails, and mitosis of mesenchyme will fail downstream. This would cause one or more sclerotomes to drop out of the blueprint of the limb, along with any other structures supplied by the damaged nerve.

I took the sclerotome maps to Göttingen, where Professor Willert and I re-examined his collection of Xray films of over 200 thalidomide children. We wanted to see whether or not the maps of segmental sensory nerve supply could explain the pattern of thalidomide malformations. The sclerotome maps and thalidomide defects coincided

- exactly in 80%,
- fairly well in 15%,
- poorly in 5%

We concluded that (26)

Both patterns are expressions of the underlying sensory segmental innervation of the skeleton, and that

- the sensory nervous system is involved in limb morphogenesis and teratogenesis.

8. Triangular residual bone remnants:

These triangular remnants of tibia, femur and humerus were frequent. Only the sclerotome maps can explain them (26).

TIBIA: The most curious remnant was a triangular piece of upper tibia bearing the tibial articular surface of the knee joint. The maps show that this is the distal end of the 3rd lumbar sclerotome. It lies beside the most vulnerable 4th lumbar sclerotome that is commonly deleted from the leg by thalidomide (26).

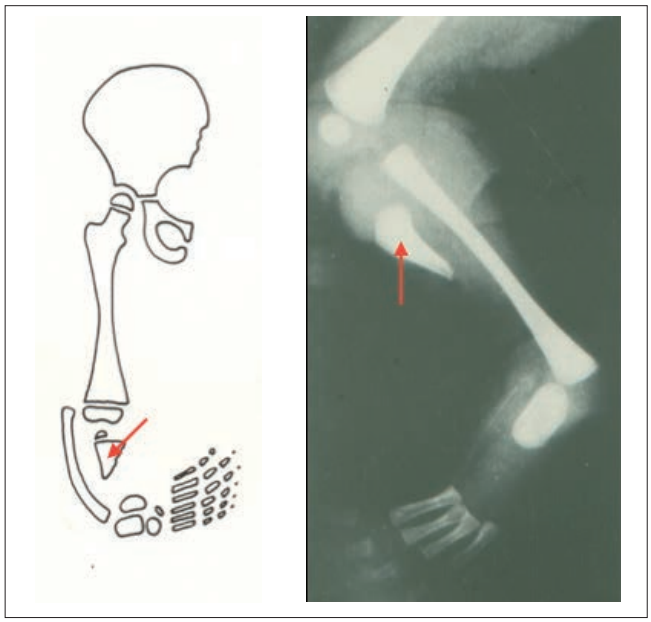

Figure 14

FEMUR: Proximal focal femoral dysplasia was common in thalidomide embryopathy but not confined to it. It occurs in other conditions. Loss of proximal femur (vulnerable 4th lumbar nerve) leaves an isosceles triangle of femur based at the knee. It matches the residual 3rd lumbar sclerotome of distal femur. So lumbar nerve 3 appears to resist thalidomide while lumbar nerve 4 is affected (26).

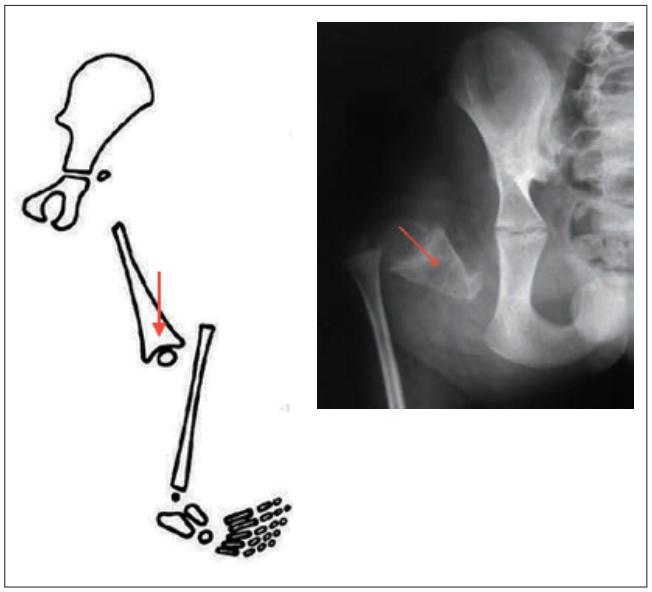

Figure 15

HUMERUS: Phocomelic arms present variants of this particular complex. The humerus is reduced to a distal triangle based at the elbow. The upper humerus has failed to form. This happens when thalidomide deletes both 5th and 6th cervical nerves. What remains of the arm is supplied by the 7th and 8th cervical nerves. The humerus is so reduced in length that the forearm and hand move up towards the shoulder. This is phocomelia. It has different degrees of reduction depending on the amount of a sclerotome removed (26). The external shape of the shoulder is pointed because of absence of musculo-skeletal tissue at shoulder and upper arm.

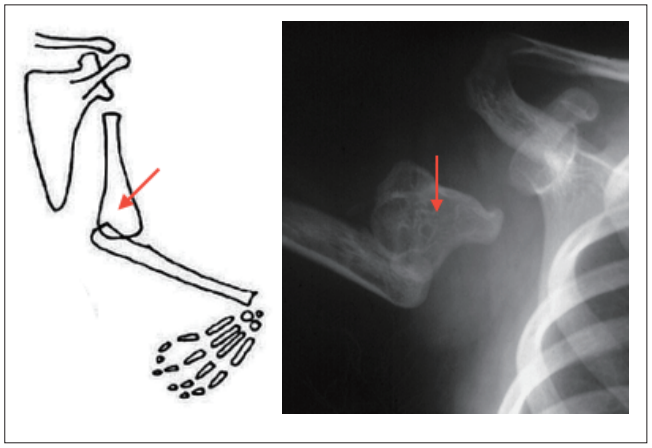

Figure 16

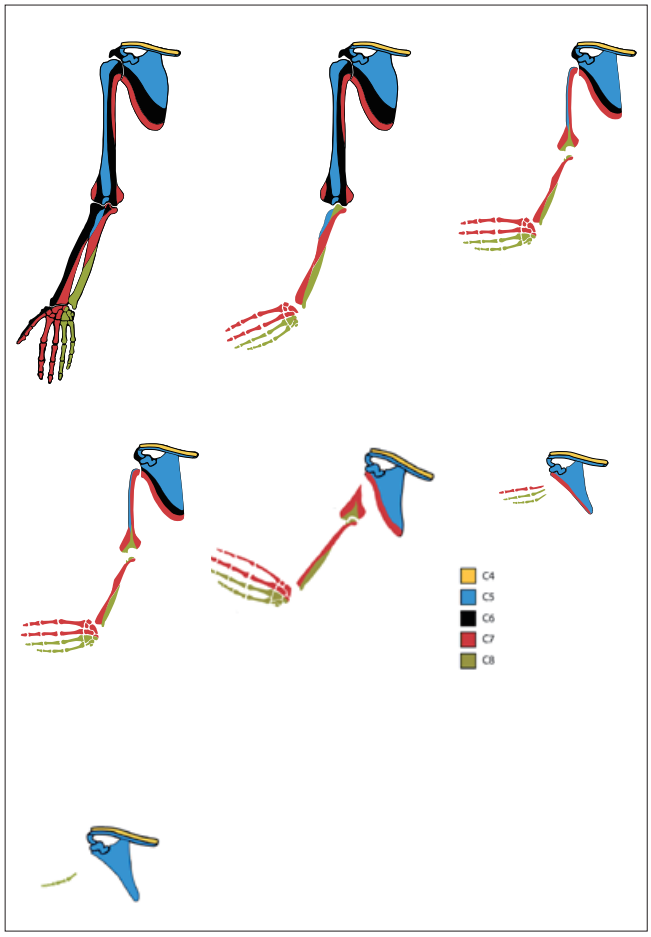

Figure 17
Progressive subtraction of sclerotomes in the arm by thalidomide to form phocomelia.

9. Dislocated joints

These were common in thalidomide embryopathy, and they had characteristic signs of neuropathic joints in their radiographs.

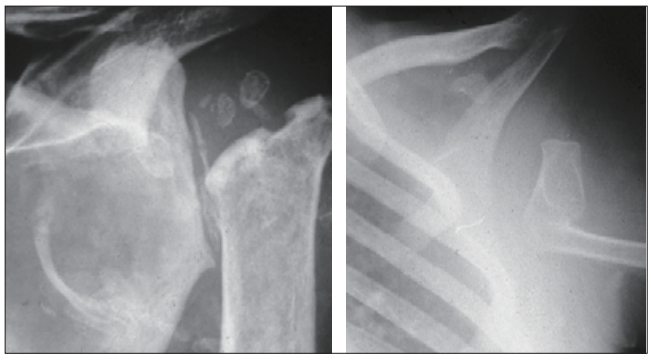

Figure 18

On the right is the shoulder joint of a thalidomide child. On the left is that of a woman with syringomyelia. Both show

- flattened joint surfaces on both sides of the joint
- with no loss of bone density and
- painless dislocation

Adult neuropathic joints occur in long-standing sensory peripheral neuropathy (due to diabetes, syphilis, leprosy, syringomyelia and other conditions). That neuropathic joints appear in thalidomide embryopathy (27) is further evidence that sensory nerve damage occurred in the early embryo.

10. Synostoses

Fusion between bones was common in thalidomide embryopathy (28). Failure of neurotrophism in damaged nerves reduces the number of mitoses downstream.

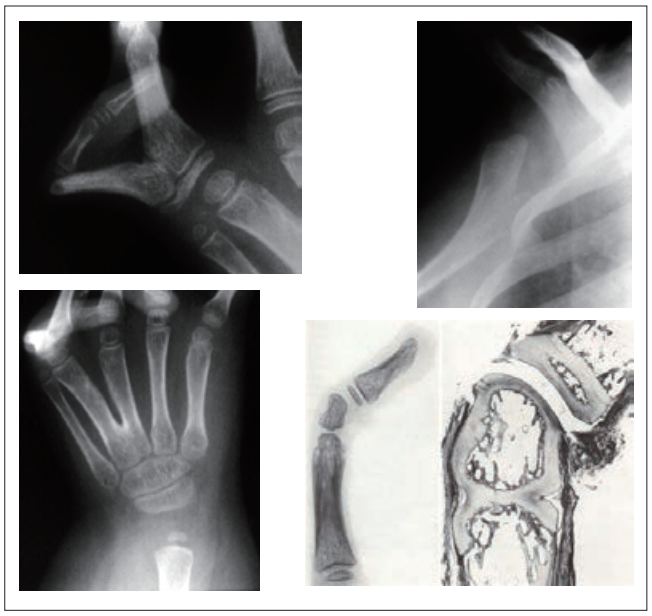

Figure 19

There is reduction in the final number of cells that are destined to differentiate into bone, so the final formation of the bone is reduced in mass in the area supplied by the damaged nerve. Incomplete formation leaves some bones unable to separate. This results in

- transverse fusion between paired bones (e.g. radio-ulnar, inter-phalangeal, carpal coalition), and
- longitudinal fusion between serial bones (e.g. humero-ulnar, interphalangeal).

11. Associated internal defects

This large complex subject could easily fill a whole lecture. Here the autonomic division of neural crest comes into play, often associated with sensory lesions at the same spinal level.

One toxic assault upon early neural crest could injure both sensory and autonomic branches, with damage to internal organs as well as to limbs that share their nerve supply. This indeed occurred.

Evidence of such associations emerged in data published by the British Ministry of Health (29) in 1964. Over 90% of children with congenital heart disease also had upper limb phocomelia of major or moderate degree, indicating damage to cervical sympathetic as well as peripheral sensory nerves at the cervical level.

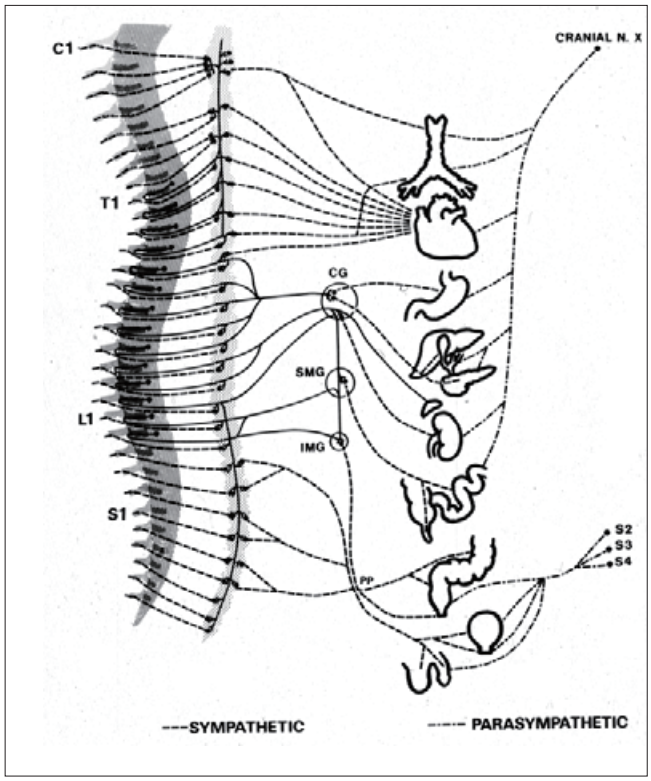

Figure 20

Similarly, leg reductions were associated with ano-rectal and genito-urinary defects, sharing lumbo-sacral nerve supply.

12. Pathology

a. Thalidomide children:

Specimens of bones and joints from autopsies and amputations in thalidomide children were examined by Professor Willert and colleagues in pathology, searching for histopathology in bones and joints. However, no abnormal cells could be found in the skeletal tissues. The architecture of the skeleton was clearly abnormal, but no disease was found in bone or cartilage cells (30).

This is an important negative finding. The conclusion is that the primary pathology is not in the skeleton, but in some tissue outside it, with secondary effects upon the skeleton, consistent with primary nerve damage resulting in disordered skeletal architecture, as proposed by the theory of neural crest injury.

b. Adults with sensory neuropathy caused by thalidomide showed destruction of large diameter axons and abnormal histograms consistent with sensory neuropathology (figure 2) (see introduction).

c. Rabbit fetuses exposed to thalidomide showed similar loss of large diameter axons in sciatic nerves, worst fetuses with absent tibia, and less severe in treated fetuses without skeletal defects (31, 32). North demonstrated that nerve damage preceded skeletal damage in thalidomide embryopathy.

d. The "post-thalidomide syndrome" can be explained by quantitative neuropathology. All humans possess a generous surplus of axons in peripheral nerves, enough to buffer considerable axon loss without suffering any symptoms. All humans sustain a physiological loss of axons at middle age as part of the normal aging process. But they do not experience symptoms of neuropathy because the surplus axons buffer this physiological reduction. (figure 21) (1).

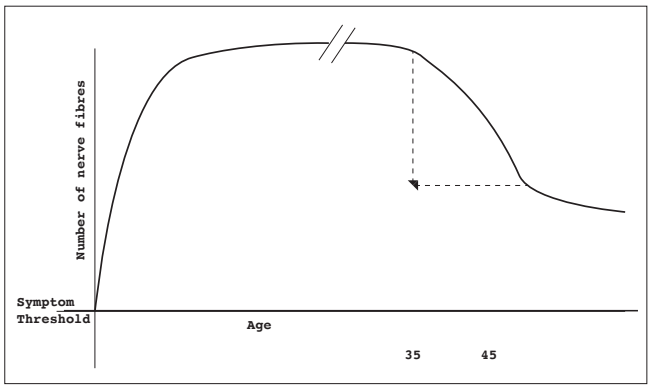

Figure 21
Normal aging causes loss of axons but no symptoms

However, a symptom threshold does exist: a minimum number of axons below which neuropathic symptoms occur - pain and paraesthesia in sensory nerve damage, and weakness, wasting or paralysis of muscles supplied by damaged motor nerves. Normally this threshold is never reached in undamaged nerves.

But the "post-thalidomide syndrome" now besetting middle-aged thalidomide survivors can be explained by quantitative change in axon numbers, with pathophysiology similar to that of "post-polio syndrome". Of course polio affects motor nerves, whereas thalidomide affects sensory nerves. However the quantitative mechanism is the same in each group: two episodes of axon loss in each case. First, there is severe loss of nerve axons in early life (in infancy or embryo) due to a pathological process (polio virus infection or intrusion of a neurotoxin). Second, at middle age comes an additional loss of axons, a physiological process common to all peripheral nerves. In previously damaged nerves, the second bout of axon reduction cannot be absorbed. Surplus axons are all used up and the symptom threshold is breached. Symptoms of neuropathy erupt (see figure 22).

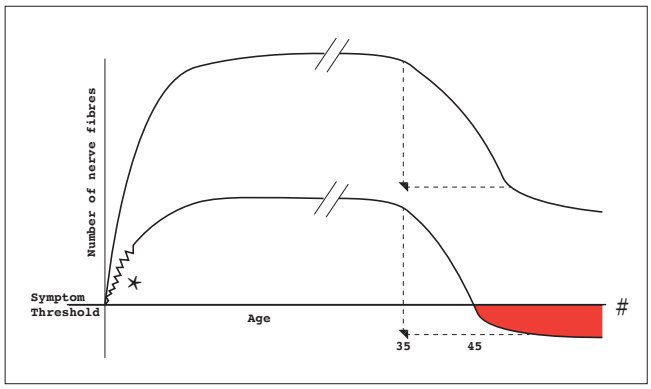

Figure 22
Previous damage * to peripheral nerves, plus age changes, results in neuropathy in middle age #

Conclusion

Neural crest injury explains all features of thalidomide teratogenesis. Consistent quantitative neuropathology has been found in adults, children and animals damaged by thalidomide. Conversely, no bone, cartilage or other histopathology was found to indicate primary skeletal disease. Disordered skeletal architecture in the absence of skeletal histopathology is consistent with primary nerve damage causing secondary skeletal growth disorder.

Skeletal morphogenesis emerges as a 2-stage process:

- an initial undifferentiated stage of high nerve-dependency associated with neurotrophism, and
- a second stage of differentiation with reduced nerve-dependency.

Thalidomide acts in the nerve-dependent stage before differentiation, i.e. in the first stage, not the second stage of morphogenesis. Thalidomide poisons neural crest/sensory nerves during their early embryogenesis, disabling all nerve functions, including neurotrophism. This halts mitoses, which reduces the mass of undifferentiated mesenchyme within bands of segmental nerve supply.

Thereafter the second stage proceeds. The rest of the limb differentiates, minus the damaged neural segment/s. The size, shape and architecture of the limb is altered, but not the skeletal cells.

Neural crest defects comprise a large collection of various disparate birth defects, adjacent to the well-recognized group of neural tube defects.

Within the large lexicon of medical diseases, thalidomide embryopathy belongs within the group of sensory and autonomic peripheral neuropathies. To suggest that

thalidomide does not attack the neural crest is seen as absurd by informed neurologists, pathologists, pediatricians, radiologists and other medical practitioners who realize that neural crest injury explains the embryopathy.

The neural crest theory will not go away. It has a life of its own because it explains observed facts.

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Q&A

Hinoshita: Thank you very much, Dr. McCredie. As she said she suffered from a little bronchitis. Because of her problem she decided to give this presentation using the video. She focused on pathology, radiology and pathogenesis of thalidomide embryopathy. By the way, do you have any questions? If you have, please raise your hands. Yes, Dr. Morrison, please.

Morrison: Hi, I'm Dr. Morrison, Medical Advisor to the Thalidomide Trust. I just wanted to say we are all entitled to have different opinions. However, in 2014 the World Health Organization held a convention in Geneva for medical experts to try to reach a consensus regarding the causation and diagnostic criteria for thalidomide embryopathy. With regard to causation there was most interest in the work around cereblon. This was the theory the experts chose to take forward. In addition regarding the classification of damage the medical experts proposed to support an algorithm. Hence The Thalidomide Trust currently supports the work of cereblon going forwards as causation of the embryopathy not the neural crest origin. The Trust also, when we look at new claims, understand that upper limb damage is bilateral, although there can be differences between the limbs. The medical experts at the WHO conference in Geneva discussed this aspect and agreed that if one upper limb was affected that the other limb would also be damaged. And lastly, just looking again we have an eminent neuro-orthopedic doctor working with the Trust. He is examining many affected by thalidomide embryopathy and he very much states that he can find nothing to support the view of the neural crest origin causing the problems from thalidomide. He felt it should be obvious when he examines them and though he has looked he cannot find any evidence that the neural crest is the causation. So, though I appreciate we all can have different opinions, at present this is the belief at the moment within Thalidomide Trust.

McCredie: Well, I agree with you that there's plenty of room for other opinions. But I'm disappointed that the Thalidomide Trust is going to open a molecular hypothesis because I think it's going to be a waste of time. It cannot explain the 12 facts of thalidomide embryopathy that I have just explained through neural crest injury.

Morrison: OK.

McCredie: I must say most of the work I've done has been done with the Department of Neurology in Sydney University, which at that stage was heavily geared up to examine peripheral neuropathies and had all the laboratory tests ready to run on peripheral neuropathies. And that team entirely believed what we were saying. So, two different opinions.

Hinoshita: Uh-huh. It seems she has made much of the malfunction for the injury of the neural crest. And recently, the mechanisms of thalidomide have been researched in detail, and the drug also influence the new angiogenesis in our bodies. So, is there anyone who'd like to give some comment on the pathogenesis of thalidomide embryopathy? How about Professor Kayamori?

Kayamori: It is popular to believe that pathogenesis of the thalidomide embryopathy might be angiogenesis prevented from new formation by thalidomide. Thus, they are trying to treat cancer by using thalidomide medicine at present.

McCredie: In the timelines that I showed you, Lenz's sensitive period for arm defects begins on day 24 of gestation. The arm bud does not emerge until day 28 according to Professor Nishimura. In that 4 day period from day 24 to 28 there is no arm bud, and no limb blood vessels. But the nervous system is there proliferating and extending out from the neuraxis. So that is a problem for people who want to postulate that thalidomide acts on blood vessels. There are no blood vessels to act on. But nerves are there to act on, That is fact number one.

Fact number 2 is that the angiogenesis theory became popular because oncologists and their cancer patients are desperate to get new drugs to treat cancer, and are willing to try thalidomide despite its dangers. If you follow up these cancer patients treated with thalidomide, you find the neurology journals full of reports of another epidemic of thalidomide polyneuropathy, with concerned neurologists in attendance.

Fact number 3 is that when German and British doctors originally used thalidomide as a sedative, it caused sensory neuropathy. It did not produce any vascular pathology. There was never any angiopathy reported. Thalidomide can stop cell division, but only by halting neurotrophism by killing the sensory nerves.

Kayamori: I want to ask about one thing. You mentioned about sparing of central nervous system. Could you give us knowledge of peripheral nerve involvement? For the first time

of thalidomide scandals, they reported lots of involvements of peripheral neuropathy axonal type. But we didn't get such evidence in Japan. And from a point of electrophysiology just examining patient whether patient is involved in peripheral neuropathy or not, I couldn't find generalized neuropathy except for entrapped neuropathy. So we considered there was no pathology in the nervous system, in the peripheral as well as the central nervous system.

McCredie: The bi-polar neuron has two arms. That diagram of the withering nerve fibres, they died back, from the distal end. There's also some withering in the central end going up to the central nervous system. MRI of spinal cord has shown depletion in volume of the posterior columns going up to the brain. And so, undoubtedly in the brain, there are going to be effects which weren't reported at first of course in the babies:- autism, perhaps an increase in the incidence of epilepsy. These things creep in and out of the literature. There is obviously going to be some effect up there on the other end of the bi-polar neuron.

Kayamori: Someday, if you will come to us again, I have a discussion, I would like to discuss more and more. Thank you.

McCredie: OK. I have two graphs to show you then too.

Hinoshita: Is there any comment or opinion from German researcher or physician? Professor Peters, do you have any comment or opinion about the pathogenesis of thalidomide embryopathy?

Peters: No electric involvement as well as no angiogenetic involvement. Maybe it's both. Depends, difficult.

Hinoshita: Is there any other question about her presentation? Then, thank you very much, Dr. McCredie. OK now it's a little behind the schedule, but we will start our lunch time and poster session. When it comes to the poster session, the discussion will be done during the time from 12:15 to 13:10, OK? Please stand by the posters for the poster presenters. Anyway, until 13:10, I would like to have lunchtime. Thank you very much for the former part.