Fig 13 Classification of hearing loss group

Classification of hearing loss group

Principle of severity classification for hearing loss

Severity	Hearing loss
Most severe	Bilateral > 60dB
Severe	Bilateral 30-60dB
Moderate	Unilateral > 60dB
Mild	Unilateral 30-60dB

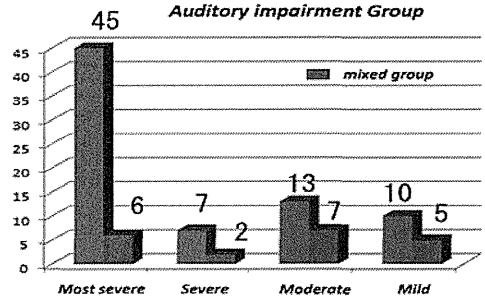


Fig 14　Oculo-facial disfigurements in the hearing loss group

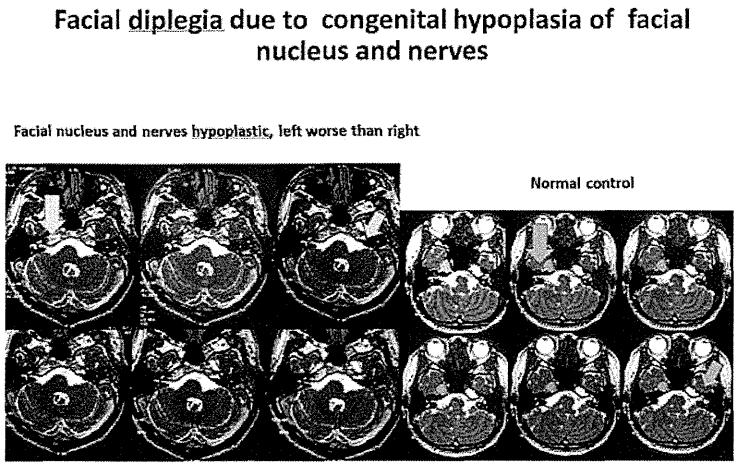
Hearing loss group characteristically concomitant with auricular and oculo-facial disfigurements

	N=137 (♂64, ♀73)		%
	Auricular disfigurement	43	31%
	Ear canal		
	deformed	39	28%
	obstruction	28	20%
	stenosis	36	26%
	Conduction	10	7%
Hearing loss	Sensorineural	59	43%
	Mixed	14	10%
	Nose disfigurement	12	9%
	Oral disfigurement	11	8%
	Tonsil anomaly	11	8%
	Phalanx anomaly	2	1%
	Facial palsy	68	50%

Kayamori： In this CT abnormal inner middle ears, both sides. Electrophysiological findings for facial dysplasia correlated with bilateral hypoplasia of facial nucleus and nerves with mild aberrant innervation over the pneumatic muscles. On the basis of finding 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 with severe hearing loss. The next video is showing bilateral abducens palsy with aberrant innervation by oculomotor nerve resulting in Duane syndrome.

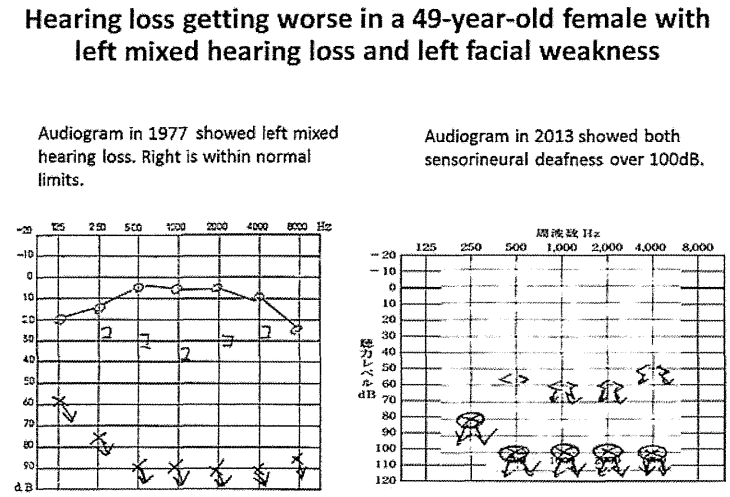
Kayamori：This is another patient, a 45-year-old man with conduction type hearing impairment, and auricular and ocular facial disfigurement. Hearing loss is getting to deteriorate in age. This is an MRI showing facial nucleus and nerves in comparison with normal control. Facial nucleus and nerves are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

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



Kayamori：This slide is the last for 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 both sides (Fig 16). CT showing both anomalies of middle and inner ears.

Fig 16　Audiograms showed deterioration of hearing loss



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

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. Any questions? OK, 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 why. 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 you're 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 the 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.

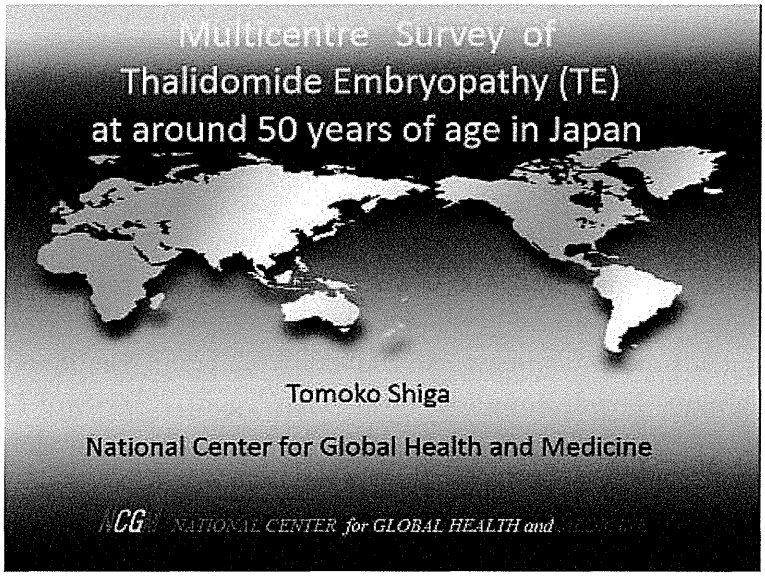
Hinoshita： Maybe we don't know the reason, you know, why the hearing impairment progresses as thalidomiders age. Even if they had no marked hearing loss at birth. But, let's check and examine

together about this theme. Is there anything else? Any other questions? About his presentation? No? OK, then the time is over.

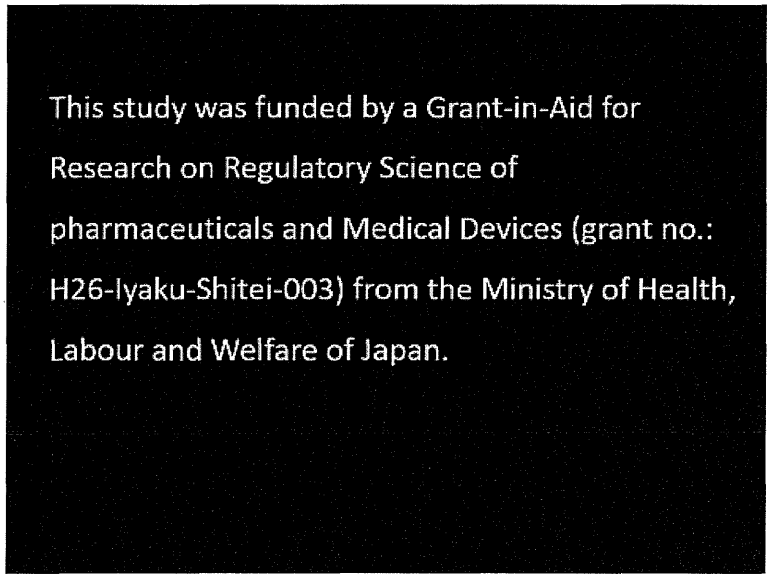
②Dr. Tomoko Shiga

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

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 research (Slide 1).



Shiga： This study was founded by a Grasnt-in-Aid for Research on Regulatory Science of Pharmaceuticals and Medical devices from the Ministry of Health, Labour and Welfare, Japan (Slide 2).

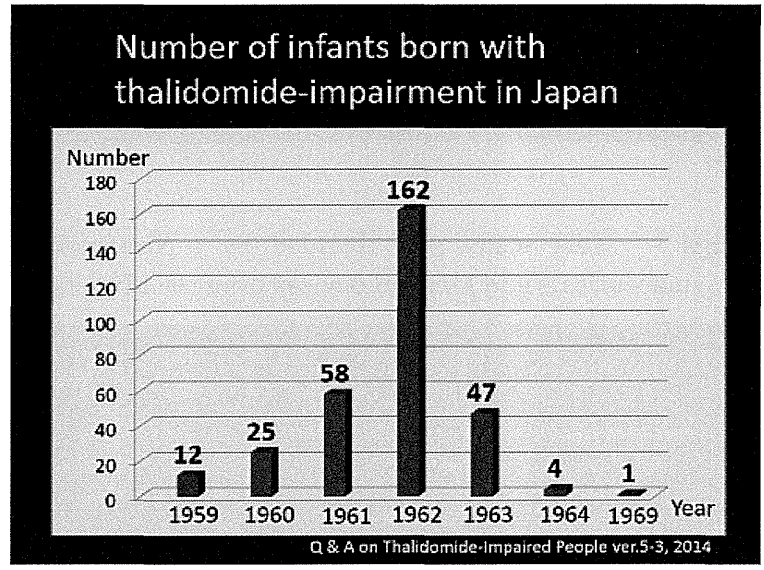


Shiga： In utero exposure to thalidomide causes a wide range of birth defects, including phocomelia, hearing loss, and visceral disorders, known as thalidomide embryopathy (TE). Fifty years after the first report of TE, we conducted the first cross-sectional multicentre center study to investigate the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

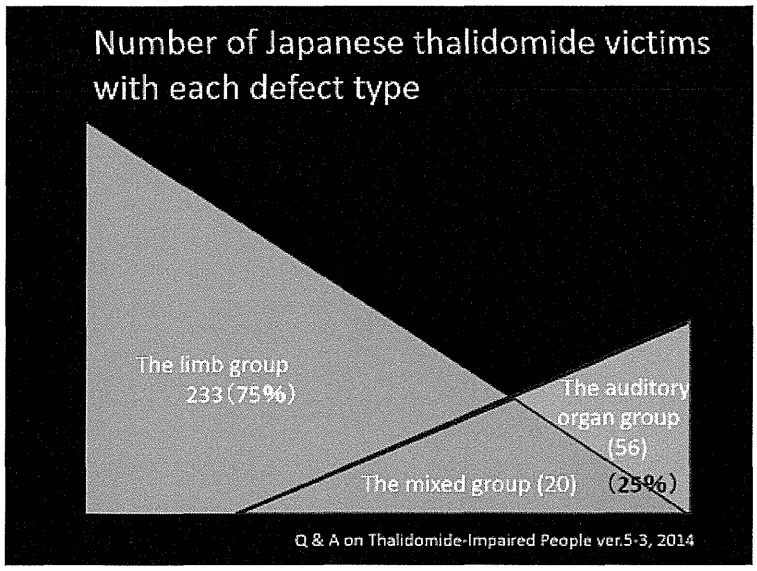
Background

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.

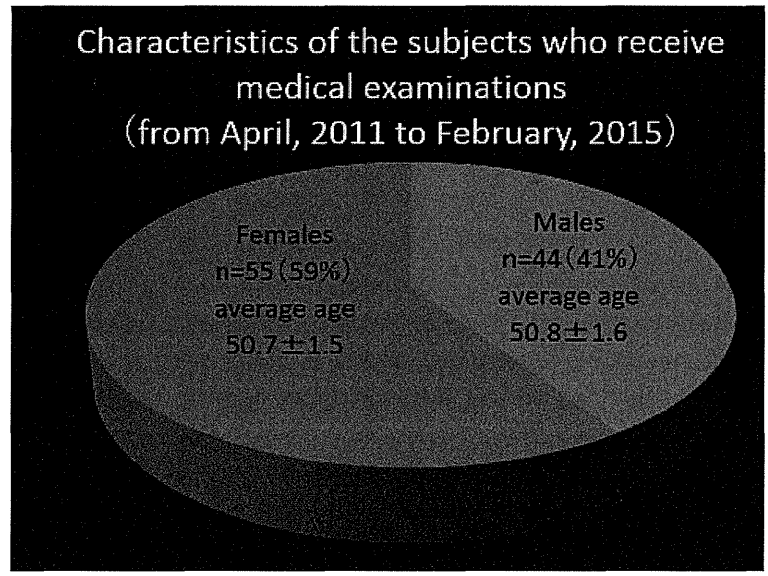
Shiga： Thalidomide was first marketed in 1957, as a sedative in Germany, where it was promoted to alleviate nausea and morning sickness in pregnant and nursing women due to its rapid onset of effects and apparent safety. Thalidomide was then made available in over 46 countries. In Japan, thalidomide was first marketed in 1958, under the trade name IsominR, as a sleep-inducing agent. Afterward Proban MR, 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 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. The total number of victims worldwide is estimated at 5,850 (Slide 4).



Shiga： 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 nucleai. 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).



Shiga： 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. That is, they were healthy or out-patients (Slide 6).



Shiga： Ninety-nine cases with TE were analyzed about lifestyle-related diseases and the types of thalidomide embryopathy-related anomalies (that is, 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 lower limb was defined as that in upper limb (Slide 7).

Methods

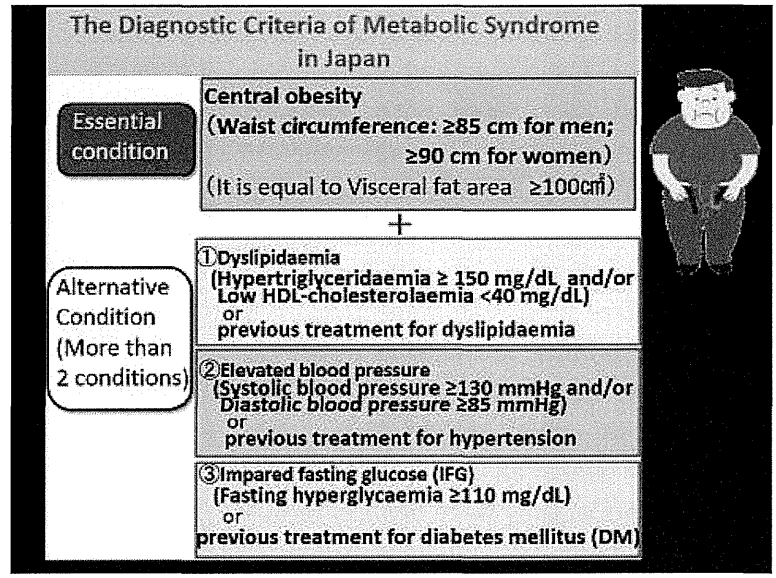
Ninety-nine cases with TE were analyzed about lifestyle-related diseases and the types of thalidomide embryopathy-related anomalies (limbs, auditory organs or visceral organs).

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* [average blood pressure in both sides]). Diastolic blood pressure in lower limb was defined as that in upper limb. *

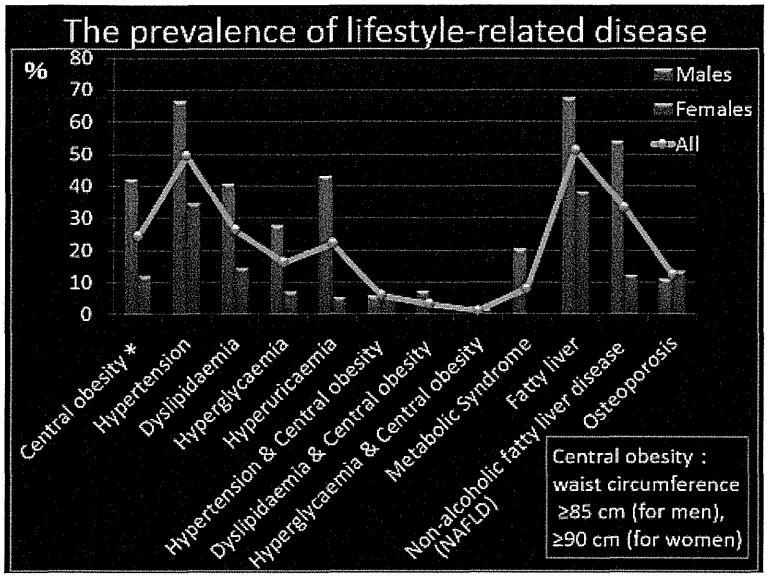
Statistical analysis was performed using SPSS statistical software (version 23; IBM SPSS, Inc., Armonk, New York, USA). A p value of <0.05 was considered statistically significant.

* Shimbo T, Kanehisa E, Yoshizawa A. 2015 Assessment of blood pressure on Thalidomide-Impaired People. In: Hinoshita F, principal investigator. The report of the study funded in FY2011 by a Grant-in-Aid for Research on Regulatory Science of Pharmaceuticals and Medical Devices from the Ministry of Health, Labour and Welfare of Japan under the title 'National Study on the Health and Living Situation of Thalidomide-Impaired People'. Tokyo: Mosu Asociates. p 164-166. (in Japanese)

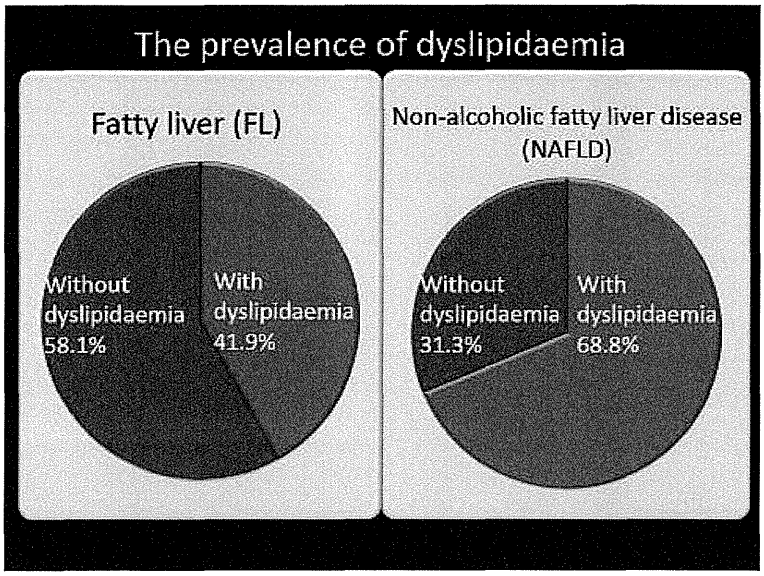
Shiga： Metabolic syndrome (MS) was diagnosed using the 2005 guidelines defined by the Evaluation Committee on Diagnostic Criteria for Metabolic Syndrome of Japan, including central obesity. [waist circumference: ≥ 85 cm for men; ≥ 90 cm for women] and at least two of the following conditions: dyslipidaemia 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).



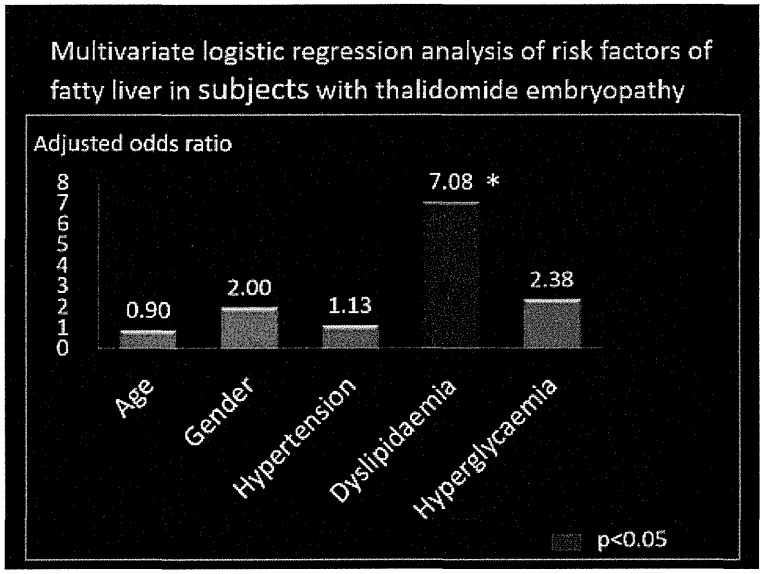
Shiga： The frequency of lifestyle-related diseases among male and female subjects is shown in this figure. Blue bar shows males, red bar shows females, and green line shows all subjects. Hypertension [49.4% of all subjects], fatty liver (FL) [51.2% of all subjects] and nonalcoholic fatty liver disease (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. Estrogen 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).



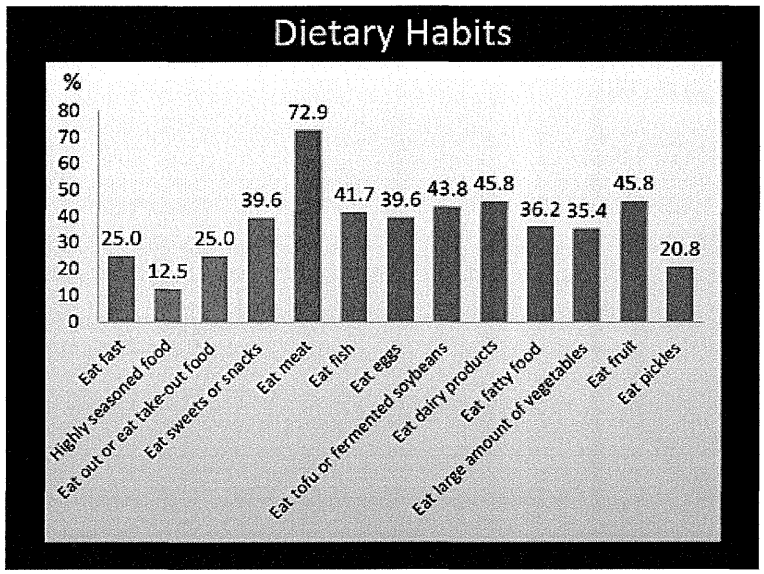
Shiga： Dyslipidaemia was checked in 41.9% of subjects with FL and 68.8% of subjects with NAFLD. NAFLD is no longer considered a primary liver disease, but rather a component of MS, insulin resistance and lifestyle-related diseases such as diabetes, dyslipidaemia, and hypertension. All cases of TE with 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).



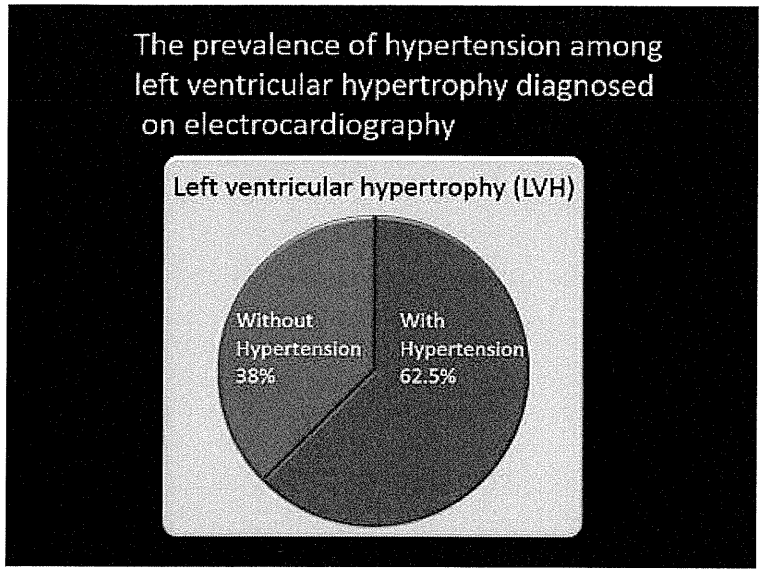
Shiga： Therefore, multivariate logistic regression analysis was conducted to identify the risk factors for FL in subjects with TE. Regression model analysis adjusted for age and gender revealed that dyslipidaemia was significantly associated with FL. Odds ratio = 7.08 (Slide 11).



Shiga： 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).

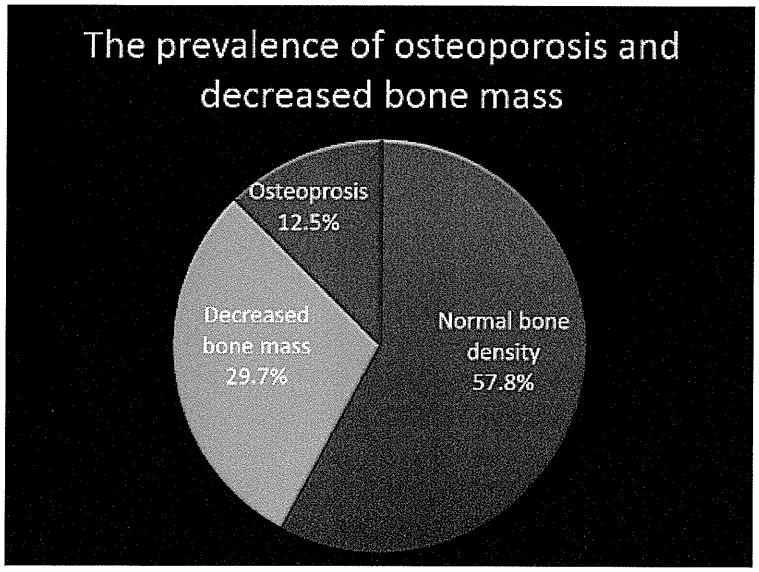


Shiga： Hypertension was not significantly associated with left ventricular hypertrophy (LVH), although hypertension was detected in 62.5% of subjects with LVH. If LVH is diagnosed in a TE patient by electrocardiography, it is recommended to conduct a cardiac ultrasonography. Moreover blood pressure must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

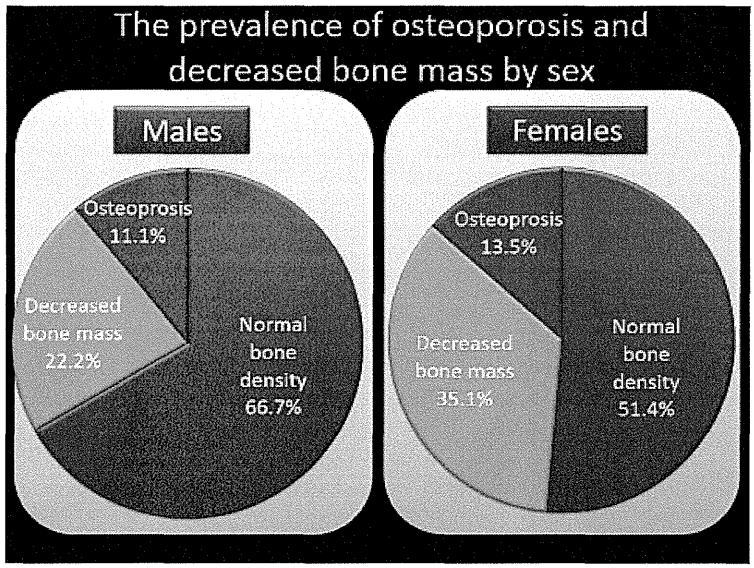


13).

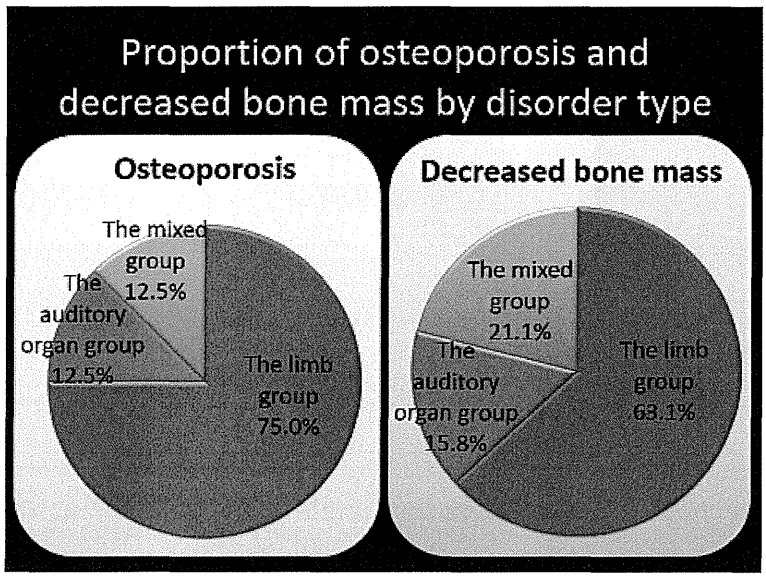
Shiga： Osteoporosis was detected in 12.5% of subjects (Slide 14).



Shiga： The prevalence of osteoporosis and decreased bone mass in the female subjects were more than the male subjects (Slide 15).



Shiga： Osteoporosis was detected in 12.5% of subjects. The prevalence of osteoporosis and decreased bone mass in the female subjects were more than the male subjects. 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).



Shiga： Gallbladder development begins gestational week 4, and block vertebra (or 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).

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%)

Shiga： 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.[that is] 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 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 block vertebrae in 7 out of 8 subjects (87.5%) with TE and hypoplasia of the upper limbs. Therefore, clinicians should consider block vertebra among subjects with TE, hypoplasia of the upper limbs and shoulder stiffness (Slide 18).

Proportions of disorder type and gallbladder aplasia

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Male	33/44(75%)	10/44(22.7%)
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Gallbladder aplasia	10 (5 males, 5 females) (100%)	0 (0%)
Block vertebra (BV)	7(4 males, 3 females) (87.5%)	1 male (12.5%)

Shiga： There are 4 conclusions.

(1) First

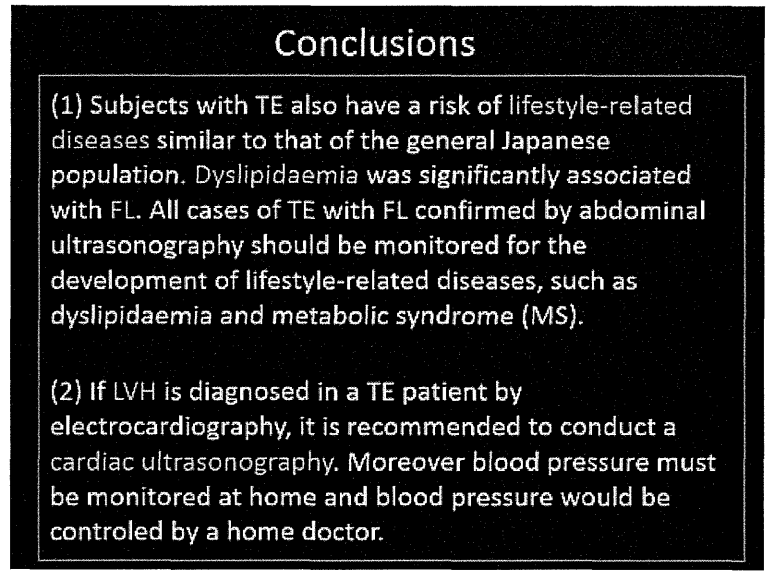
Subjects with TE also have a risk of lifestyle-related diseases similar to that of the general Japanese population. Dyslipidaemia was significantly associated with FL. All cases of TE with FL confirmed by abdominal ultrasonography should be monitored for the development of lifestyle-related diseases, 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 controled 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 disease and so on (Slide 19).

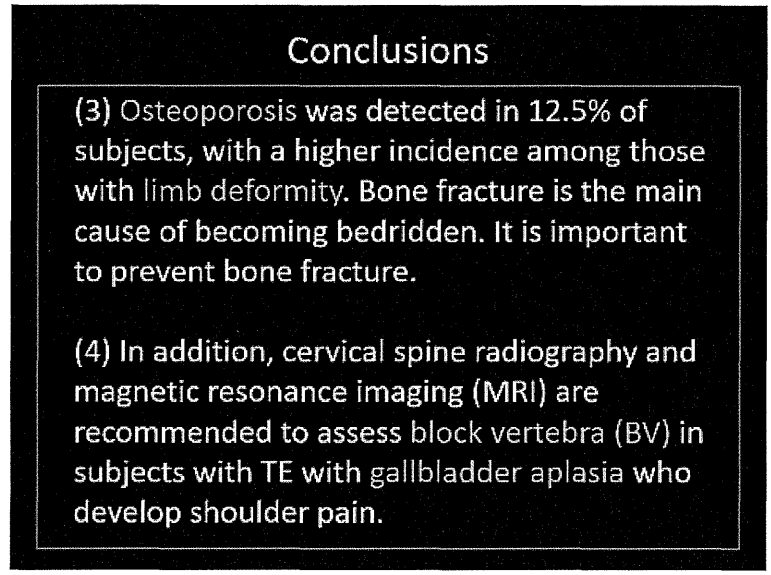


(3) Third

Osteoporosis was detected in 12.5% of subjects, with a high er 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.

(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.

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 dyslipidemia. What characteristics of dyslipidemia such as high triglyceride or low HDL cholesterol or both? And how about the LDL cholesterol?

Shiga：We checked dyslipidemia according to metabolic syndrome definition. So we checked hypertriglyceridemia 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 hypertriglyceridemia and/or low HDL cholesterol. I didn't check each subject, so I will try.

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

Shiga： My impression is hypertriglyceridemia 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 dyslipidemia into specific types according to the levels of cholesterol and triglyceride or so. 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 what 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.

③Dr. Janet McCredie
" Pathology, radiology and pathogenesis."

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, presented evidence that many congenital malformations are the result of 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 24 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 monthe 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. In stead of her video presentation recorded, the edited presentation of her own making is shown as follows.

PATHOLOGY, RADIOLOGY AND PATHOGENESIS OF THALIDOMIDE EMBRYOPATHY.

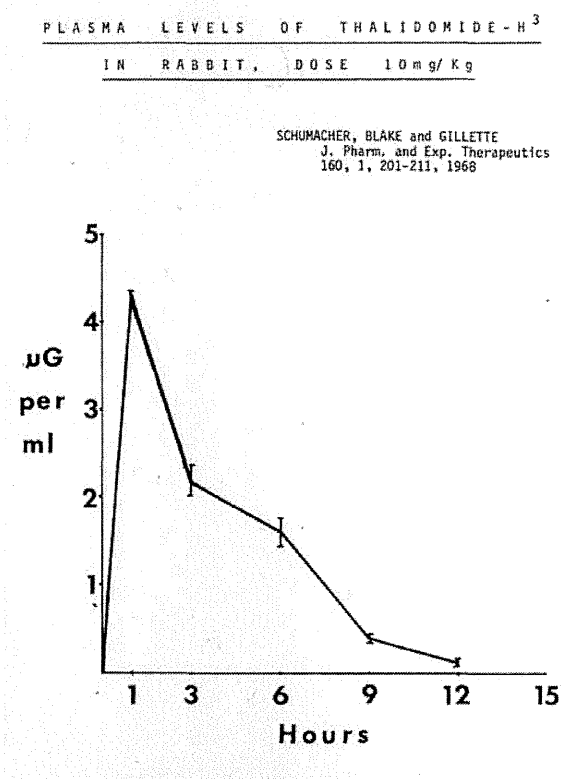
Professor Janet McCredie, AM, MD,
Faculty of Medicine,
University of Sydney,
New South Wales 2006,
AUSTRALIA.

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

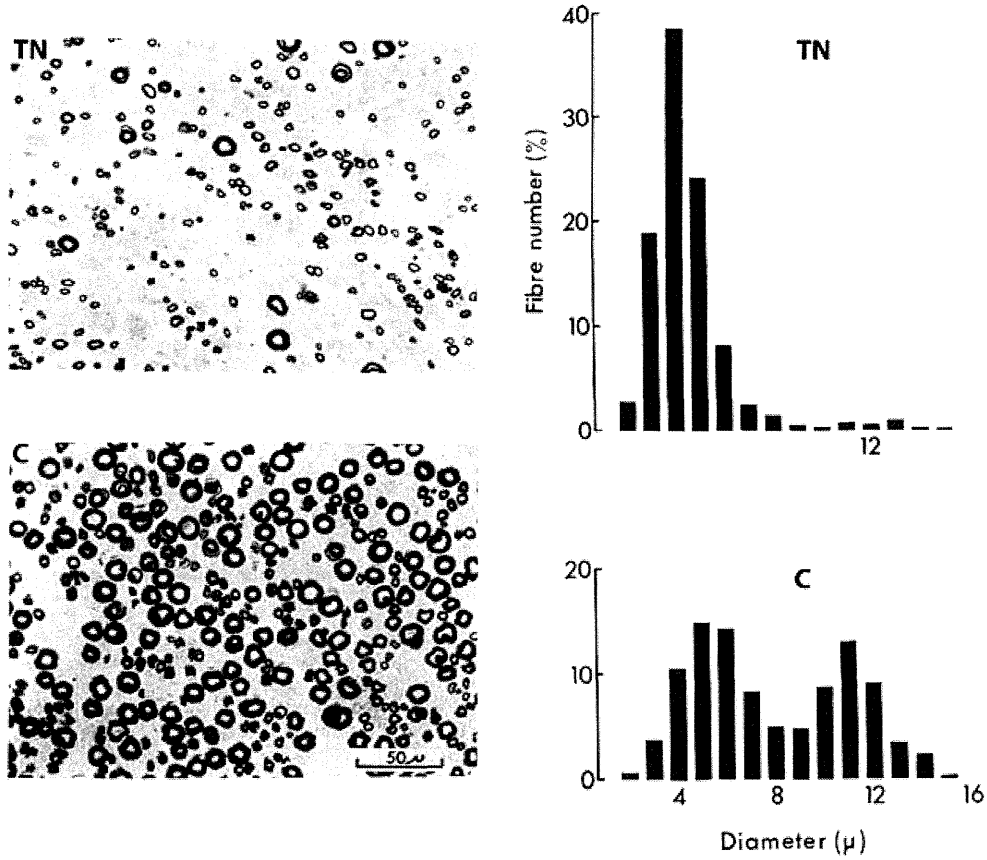
contact with fluids (eg serum) the thalidomide molecule hydrolysed into any of 12 products of hydrolysis, none of which proved to be teratogenic. Schumacher et al (2) showed that oral thalidomide was rapidly absorbed, with peak at one hour, and half life at 3 hours after ingestion, falling to zero at 12 hours.



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

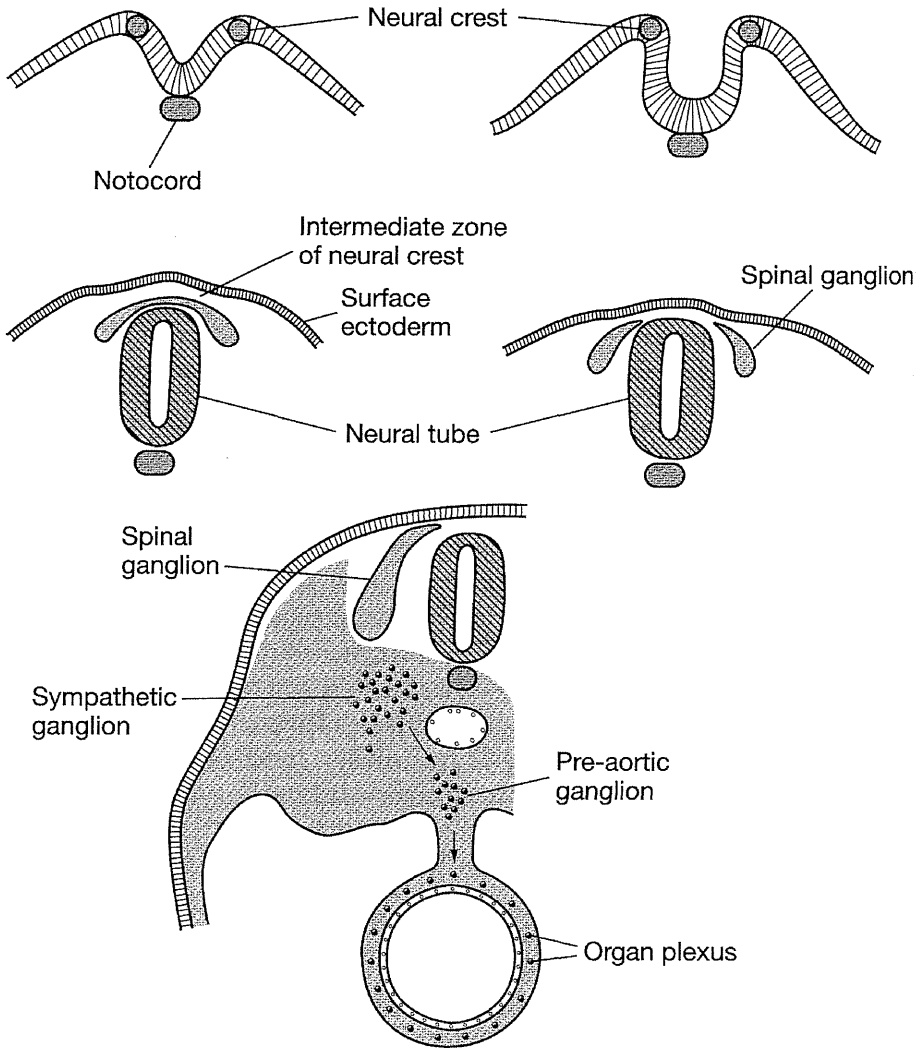
Equally important was the fact that thalidomide attacked sensory nerves in adults using it as a sedative. This was revealed before the drug was deployed as an anti-nauseant for pregnancy. Adults using thalidomide sedation complained of tingling, numbness and shooting pains in feet and hands. German and 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.



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 3 - 5.
Fertilization is at zero time.