

Intractable Disease Countermeasures Since 2015

1) What are intractable diseases?

When did the term “intractable diseases” begin to be commonly used in Japan? The rise of the term coincided with the occurrence of a disease called SMON (subacute myelo-optic neuropathy) in the late 1960s and early 1970s. SMON is a disease that takes over the optic nerve and simultaneously combines with myelitis. This disease was seen only in Japan and increased rapidly from around 1967 to 1968. However, at the time it was called a rare disease and its cause was unknown. Following this, the Ministry of Health and Welfare established an investigative research committee in 1969. As a result of the project’s research, the following year it was suggested for the first time that there might be a causal relationship between SMON and chinofom (also known as clioquinol), which is an intestinal medicine. Nation-wide epidemiological research revealed the possibility that the use of chinofom causes the SMON disease to occur. That same year, the Ministry of Health and Welfare halted the sale of chinofom. After this, the number of new patients with the disease rapidly fell, which proved that SMON had been caused by chinofom.

This incident, while devastating for the victims of SMON, demonstrated two things. The first is that if the cause of an intractable disease is a medicine, the national government, which approved that medicine, has a duty to provide redress. The second is that if we undertake focused and multi-angled research, we may be able to discover the causes even of intractable diseases.

During these events, the Diet of Japan held a special hearing into intractable diseases and in 1972 decided on a general policy for intractable disease countermeasures⁽¹⁾. This general policy defined intractable diseases as: 1) diseases that have an uncertain cause and have no established course of treatment, and can be feared to cause after-effects, and 2) diseases that, due to their chronic nature, are not just a financial issue but also impose heavy burdens both mentally and upon families due to the need for caretaking. To further the countermeasures for tackling intractable diseases, the following three actions were called for: 1) the promotion of investigative research, 2) the establishment of medical facilities, and 3) the reduction of patient-borne medical costs. In addition to undertaking research to discover the causes and conditions of intractable diseases and allow for their diagnosis and treatment, this also marked the first policy that sought to shift responsibility for medical expenses for intractable

diseases away from the patient and to the public instead. The original targets chosen for the investigative research were SMON, Bechet's disease, myasthenia gravis, systemic lupus erythematosus, sarcoidosis, aplastic anaemia, multiple sclerosis, and intractable hepatitis. Furthermore, medical expense assistance was made available for the treatment of four of the above diseases in particular.

Taking such comprehensive countermeasures against intractable diseases was a ground-breaking move unprecedented in the world. It is without question that within Japan, this has greatly contributed to research into the causes and conditions of rare diseases and the development of new treatments. It is undeniable that up until now pharmaceutical companies have avoided research and development of treatments for intractable diseases. This has been for reasons such as the following: 1) the market is small (due to the scarcity of patients that would use the medication and the lack of a reason for development), and 2) it is difficult to develop medication when the cause of the disease is unclear. However, thanks to the national government's comprehensive countermeasures against intractable diseases, for the first time the development of treatments for rare diseases has been brought into the spotlight.

2) Developments in Intractable Disease Countermeasures

After that, research into intractable diseases continued to progress. However, at the same time, the number of diseases to be targeted by the research greatly rose. This led to research being carried out to establish overviews and methods of treatment for hundreds of diseases. In addition to this, medical expense⁵⁶ diseases were identified as targets eligible for medical expense assistance by the Specific Disease Treatment Research Project (a project focusing on medical expense assistance) as "Diseases that have an established standard of diagnosis, as well as being both highly difficult to treat and highly severe in their nature, and are unlikely to have their causes investigated or have treatments developed without the use of public expenditure due to the comparatively scarce number of patients." Put simply, if a patient with one of these 56 diseases were to apply, have a designated physician fill out a medical certificate, and then pass the appropriate review, the medical costs would then be covered by public expenditure.

Even after that, however, not only did the number of targeted diseases grow, but the number of targeted patients also grew ([Diagram 1](#)), and by the end of 2011, 780,000 patients fell within the target. As a result, the costs required for the intractable disease

countermeasures rose rapidly during this period. Additionally, when Yoichi Masuzoe was serving as the Minister of Health, Labor and Welfare, the expenses for the Intractable Disease Elimination Program (a project focusing on medical expense assistance) had reached 10 billion yen. However, the Specific Disease Treatment Research Project (a project focusing on medical expense assistance) had an even higher budget, with its total expenditure exceeding 40 billion yen. Put simply, the funds required for medical expense assistance for intractable diseases became around four times the amount used for research into intractable diseases. Furthermore, since the main projects were managed by the prefectural governments, there were situations when the prefectures had to bear the excess costs when there was a deficit in the national budget, making it difficult to fund the necessary projects. In addition, seeking justice, patients suffering from intractable diseases and their families called for a greater expansion and review of the diseases targeted for medical expense assistance (diagram 1).

3) Creation and Execution of the “Act on Medical Care for Intractable Disease Patients”

To manage this situation, the Act on Medical Care for Patients with Intractable Diseases was created on May 23, 2014 in order to promote reforms aimed at ensuring a sustainable social security system; the Act came into force on January 1, 2015 (Diagram 2)⁽²⁾. As a result, sources of funding such the consumption tax were allocated to medical expense assistance for intractable disease patients, establishing a stable system for medical expense assistance. In particular, it was specified that the payment of costs would be borne by the prefectural governments, with the national government contributing half. In other words, half of the public spending for the cost of treatment came from the governments of the prefectures and half from the national government. In addition, following the enactment of this law, the national government has encouraged the investigation and research into the mechanisms of intractable disease outbreaks, as well as diagnosis and treatment methods. This has made it possible to undertake continuing and stable projects that can create environments for recovery (Diagram 2).

4) What are Designated Intractable Diseases?

This law refers to diseases that are eligible for medical expense assistance as “designated intractable diseases”. Intractable diseases are defined by four conditions:

1) the mechanism behind their occurrence is not well understood, 2) there is no established method of treatment, 3) the disease is rare, and 4) treatment is needed over a long period of time. However, for designated intractable diseases, a further two conditions have been added: 5) the number of patients is within a set proportion of the national population (approximately 0.1% of the population), and 6) there is an established and objective standard (or equivalent) of diagnosis (Diagram 3). This means that designated intractable diseases are a category within intractable diseases that have the added requirements of not exceeding a set number of patients, as well as having an objective standard of diagnosis (in addition to belonging to a serious class of diseases and being above a set class).

There is an established process for designating any disease as a designated intractable disease. First, a committee in the Ministry of Health, Labour and Welfare's Health Science Council considers whether or not a disease meets the above requirements. The committee then discusses whether or not the disease can be classed as highly serious. Then, after seeking further public comment, the disease is recognized by the disease countermeasures committee of the Health Science Council. On top of this, the intractable disease is then designated by the Minister of Health, Labour and Welfare, completing the process. In the first round, 110 diseases were designated and medical expense assistance began from January 1 2015⁽⁴⁾. On top of this, a second set of 196 diseases were designated on May 13, bringing the total number of targeted diseases to 306, and medical assistance was given to these additions from July 1 2015⁽⁴⁾.

Following this, the number of patients with designated intractable diseases totaled around 940,000 by the end of 2015 and the scope of the medical expense assistance projects reached around 222.1 billion yen. Since then, the responsible committee has decided to add 24 more designated intractable diseases, which were appended on April 1, 2017, bringing the total number of designated intractable diseases to 330 (Diagram 4, Diagram 5)⁽⁴⁾.

5) System of Diagnosis and Treatment for Intractable Diseases

Until now, any physician could diagnose specific diseases (intractable diseases)physician. However, in accordance with the stipulations of the Act on Medical Care for Patients with Intractable Diseases, now only designated physicians for intractable diseases are able to undertake the first diagnosis of designated intractable diseases. Therefore, care must be exercised. When an application regarding an

intractable disease is made for the first time, the patient must go see a designated physician for intractable diseases. There will always be a designated physician for intractable diseases at university-associated hospitals or any large hospital. Designated physicians for intractable diseases fulfil two roles: 1) creating the diagnosis document (the clinical examination results), which is necessary for the application to authorize the payment of medical expense assistance, and 2) entering the patient data (the results of the diagnosis) into the registration system.

This ensures that not only is the accurate diagnosis of intractable diseases possible, but an accurate epidemiology database for patients with intractable diseases can be created. In the case of the 330 diseases discussed above, the standards of diagnosis and level of severity have already been decided for each of these diseases already, so a designated physician for intractable diseases would write his or her decision about the result relating those standards of diagnosis and the severity into the diagnosis document (the clinical examination results). The final decision is reached by following the relevant procedures set by each prefecture. More information about the standards of diagnosis and severity levels of intractable diseases can be viewed at the Japan Intractable Diseases Information Center website ([Explaining Disease, a List of Clinical Examination Results; Phonetic Search](#)).

The requirements necessary for becoming a designated physician for intractable diseases is that one must: 1) have at least five years of experience engaged in the diagnosis or treatment of intractable disease, in addition to being certified as a medical specialist by the relevant academic or scientific community at the time of application, or 2) have at least five years of experience engaged in the diagnosis or treatment of intractable disease, in addition to having completed a set training course (of one to two days in length). The registration of designated physicians for intractable diseases is renewed on a five-year basis.

Designated supporting physicians for intractable diseases are able to prepare the diagnosis documents necessary for the renewal of designated intractable diseases. The requirements for designated supporting physicians for intractable diseases are that they have at least five years of experience engaged in the diagnosis or treatment of intractable disease, in addition to having completed a set training course (of one to two days in length).

6) The System of Research for Intractable Diseases

Until now, research into intractable diseases has been overseen by the Ministry of Health, Labour and Welfare. The two projects in charge of ensuring improvements in the quality of the development of effective treatment and the diagnosis of intractable diseases were the Intractable Disease Policy Research Project and the Intractable Disease Implementation Research Project.

The Intractable Disease Policy Research Project seeks to create plans to raise the level of care available for intractable diseases by gathering information through epidemiological studies about the actual conditions of intractable disease patients, establishing diagnosis and treatment guidelines based on evidence, and undertaking the sharing and correction of relevant diagnosis and treatment standards, levels of disease severity, and diagnosis and treatment guidelines⁽⁵⁾. For this reason, the intractable disease patient database into which the designated physician for intractable diseases enters information plays a very important role.

The Intractable Disease Implementation Research Project is currently operating as the Intractable Disease Elimination Project, which is one of the nine projects operated by the Japan Agency for Medical Research and Development. The Japan Agency for Medical Research and Development is an organization that seeks to undertake top-down research based on the strategies established by the national Headquarters for Healthcare Policy. The Japan Agency for Medical Research and Development has a system of managing issues by focusing on nine projects, which each have a PD (Project Director) or PS (Project Supervisor)⁽⁶⁾. In reality, there is also a PO (Program Officer), who implements the project under the PD or PS. This means that the quality of research is managed with a top-down approach.

At the Intractable Disease Implementation Research Project, operations are undertaken including clinical research into the implementation of genetic treatments and treatment technologies for medicinal and medical equipment, as well as the establishment of practitioner-led clinical trials (such as the creation of new treatment methods and the expanded application of existing medicines). In addition, this project aims to develop a hub institution that has the technology to generate, differentiate, and analyze disease-specific iPS cells, as well as undertake research to create new medicine while utilizing medicine development support networks. It aims to get at least 11 medical products or types of equipment that target intractable diseases approved and their applications expanded by around the year 2020. As a result, it is clear that the goal of the project is not simply to conduct research on the causes and

conditions of intractable diseases, but rather to research the development of new methods of treatment.

Therefore, the two intractable disease projects are expected to work together with each other, leading to the advancement of intractable disease research and subsequently the development of new methods of treatment. From 2015 it was decided that the first of these projects will be managed by the Ministry of Health, Labour and Welfare and that the second will be managed by the Japan Agency for Medical Research and Development.

7) Efforts to Raise Awareness and Spread Information about Intractable Diseases

Various organizations seek to raise awareness and spread information about intractable diseases, such as the Japan Intractable Diseases Information Center and the Consultation and Support Centers for Intractable Diseases.

The Japan Intractable Diseases Information Center is an organization operated by the Japan Intractable Diseases Research Foundation under the support and guidance of the Ministry of Health, Labour and Welfare. Its website (<http://www.nanbyou.or.jp/>) provides the necessary information (such as information about diseases and guidance regarding diagnosis and treatment) for life during recovery and treatment to assist patients of intractable diseases, their family, and people involved in the medical field. In addition, the website also provides updates about national intractable disease policies, the overviews of the various systems and services, the intractable disease research team, and patient meet-ups. With over 2.5 million accesses per month, it is the largest website that provides information on intractable diseases.

Consultation and Support Centers for Intractable Diseases were established in each prefecture in 2003 under the support of the Ministry of Health, Labour and Welfare and are run by each prefectural government. These centers work toward alleviating the worry and anxiety felt by local patients of intractable diseases, their families and others and support their life during recovery.

8) References

1. General Policy for Intractable Disease Countermeasures:

http://www.nanbyou.or.jp/pdf/nan_youkou.pdf

2. Act on Medical Care for Intractable Disease Patients:

http://www.mhlw.go.jp/stf/seisakunitsuite/bunya/kenkou_iryoku/kenkou/nanbyou/

3. Basic Policy to Comprehensively Encourage Medical Treatment and Care for Patients of Intractable Diseases:

<http://www.mhlw.go.jp/file/06-Seisakujouhou-10900000-Kenkoukyoku/0000099473.pdf>

4. Explaining Disease, a List of Clinical Examination Results; Phonetic Search:

<http://www.nanbyou.or.jp/entry/5461>

5. Information about the Ministry of Health, Labour and Welfare's Intractable Disease Elimination Program: <http://www.nanbyou.or.jp/entry/3628>

6. Japan Agency for Medical Research and Development: <http://www.amed.go.jp/>

Copyright(C) Japan Intractable Diseases Research Foundation/Japan Intractable Diseases Information Center