

Consideration of the Light and Dark Sides of Medicines: The Thalidomide Example

Fumihiko Hinoshita*

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

***Corresponding author:** Fumihiko Hinoshita, M.D., Ph.D., Department of Nephrology, National Center for Global Health and Medicine, Tokyo, Japan, Head, The research group on grasping the health and living situation as well as creating the support infrastructure for thalidomide-impaired people in Japan

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Editorial

It is easy to imagine that the use of medicines, even though primitive, started with the history of human beings. There seems to have been numerous medicines in ancient Egypt [1] thousands of years ago and also in ancient China where there were many kinds of herbal medicines [2,3]. Traces of herbal or medicinal plants, which might have been utilized, were discovered in ancient ruins in various places throughout the world. Similarly, all of the people living in the world with advanced medical and pharmaceutical sciences cannot live without the medicines of today, even though the current medicines are markedly progressed compared with those of the ancient times. In fact, we receive great benefits from a variety of extremely effective drugs. Numerous anti-retroviral therapy (ART) drugs, for example, have saved many patients suffering from human immunodeficiency virus (HIV), a virus which has afflicted tens of millions of people cumulatively since early in the 1980's. Erythrocyte stimulating agents (ESA) or artificial erythropoietic hormones have dramatically improved renal anemia in patients with chronic renal failure which had not been easy to overcome until the 1980's without such effective medicines. Obviously it is also true in the ancient times that people tried to treat medical problems they faced, although the medical problems they tried to overcome were much more primitive than today. One of these problems was pain. There is some evidence, for example, that they used opiate-like substances made from poppy seeds to treat pain in the ancient Mesopotamian civilization [4]. It is well known that Hippocrates in the era of about the fourth century B.C., Dioscorides and other prominent successors made use of the bark of the tree *Salix alba* (a kind of white willow) as an anodyne [5]. Many useful medicines, even though more primitive and less effective than modern medicines, were developed and used in the Medieval Ages both in the West and East. Thus, good medicines have consistently been indispensable for human beings throughout humanity because we would often and unexpectedly fall ill at any moment.

Therefore, have we merely received benefits from medicines? Obviously the answer is "No". It is well known that some medicines which were used a long time ago often have adverse effects and

can induce allergic reactions in at least a group of patients. Opiate-like substances, such as those used in the ancient Mesopotamian civilization, might trigger serious problems if they are inappropriately used. Salicin, which was derived from willow bark and crystallized in the 19th Century, was used as pain relief [6]. It was indeed effective. However, it had a bitter taste and frequently caused nausea and a stomachache. Based on salicin and other chemicals related to salicylic acid, acetylsalicylic acid was later developed [6], but it still has several unfavorable effects. The above-mentioned ESA improve renal anemia in almost all patients with end-stage renal disease. However, ESA might, though rare, cause hypertension and thromboembolism in some of the patients, and it may very rarely exacerbate anemia in a limited number of patients, inducing the production of autoantibodies against erythropoietin itself [7-9].

Among the long list of drug-induced adverse effects worldwide, thalidomide embryopathy (TE) has been one of the most striking disasters after the 2nd World War. The thalidomide-induced tragedy greatly influenced the policy of drug regulation, medical ethics, the means of newly developing medicines, and many other health policies as well as pharmaceutical affairs. Thalidomide, a kind of sedative and hypnotic, was produced and first sold as a safe medicine in Western Germany in 1956 [10]. Soon it was also sold in more than 40 countries throughout the world, and this medicine was particularly popular amongst some pregnant women, who readily took it to improve morning sickness or insomnia. Consequently, thousands of babies with phocomelia, congenital hearing impairments and other birth deficits were born all over the world. Moreover, it is pessimistically speculated that a high percentage of babies with TE died shortly after birth and in early infancy despite the fact that the sale of thalidomide was discontinued several years later after the etiology of TE was disclosed. Those who survived TE in their infancy and grew up with various kinds of difficulties are now living in their 50's in many countries. According to the survey in UK and Japan, approximately 460 and 290 thalidomide victims were living in 2016, respectively. In a 2010 report, it was estimated that more than 2,000 thalidomide victims might be living in Germany,



where thalidomide was originally developed and first sold [11]. There have been some official foundations or groups to financially support, medically help and examine the people with TE in some countries such as Germany, UK, Japan and Sweden. As the head of “The research group on grasping the health and living situation as well as creating the support infrastructure for thalidomide-impaired people in Japan”, I have twice visited European countries, such as Germany, UK, and Sweden, where I could actually meet some people with TE who are working and positively living, even with various hardships; I also met with physicians and health-care workers specializing in TE in each country. In 2015, we held a small international symposium on TE in Tokyo with the members of our Japanese research group as well as the specialists from other countries [12]. Through all of these activities, I came to recognize that the thalidomide tragedy did not end but rather it still continues. The people with TE who could overcome the physical disabilities in their youth are now suffering from physical, mental and socio-economic problems which they had not experienced as a young adult: overuse syndrome with unbearable pain, lifestyle-related diseases such as hypertension, diabetes mellitus, obesity, fatty liver and dyslipidemia, further impaired body motion, peripheral neuropathy, anxiety for the future, depression, hard elderly care for their parents, financial difficulty and so on. The social welfare and medical care they receive, their financial situation, and physical disabilities as well as the happiness they feel vary by individual and from place to place. The situation of national or public support and compensation offered by responsible enterprises for thalidomide victims might differ in Japan, Germany, UK and in many other countries where people with TE have been identified. However, we should never forget struggling and suffering that people with TE must bear; it is absolutely not their responsibility as it was undeniably caused by a terrible “medicine of the devil”, thalidomide, produced by humans.

Paradoxically, however, thalidomide has recently become a “medicine of the angel” in another way and came into the spotlight. Namely, the favorable effects of thalidomide and its analogs have been recognized in leprosy, multiple myeloma (MM) and in a few other diseases [13]. Thalidomide was approved and licensed around the world, and is used for leprosy and resistant MM in many countries now. Naturally, the new sale of thalidomide was resisted by most victim groups of TE and then required additional expenditures to ensure the safety. Thus the drug price of thalidomide became higher than expected. A very strict regulation for the use of thalidomide was set for patients with MM, and both physicians and pharmacists in charge in Japan [14]. I think there have been many regulations and rules to ensure the safety and to prevent possible disasters by thalidomide in most of the countries where thalidomide is used and sold today. However, many survivors with TE have been detected in Brazil even after the initial sale of thalidomide was discontinued in developed countries in 1960’s [15] because thalidomide has been available in some districts with endemic leprosy. Actually, Brazil approved its use for the treatment

of erythema nodosum leprosum in 1965 [16]. Consequently, thalidomide has continuously and overtly been obtainable since that time. In addition, strict drug control for thalidomide was not practiced in the endemic regions with leprosy in Brazil where the drug was frequently used. These are thought to be the reasons why new babies with TE were born in the 1970s through 1990s [15].

Taken together, the tragedy of TE did not end considering the many victims greatly suffering now, as well as the new births of babies with TE in Brazil although the favorable effect of thalidomide for some specific diseases was definitely identified. According to the famous philosophy statement “Analects of Confucius” in the ancient times of China, it says “To err and not change one’s ways, this is what it is to err”. Human beings might commit great faults at times. For example, we have experienced tremendous train and airplane accidents, great financial system failures as well as atomic bombings at Hiroshima and Nagasaki. If some war with atomic and hydrogen bombs should happen in the future, we would see the unprecedented tragedy of human beings in the world. Therefore, we should ourselves reflect and revise our ways so as not to repeat such great faults. In this respect, we need to learn from the history of various types of great tragedies. Conclusively, we must not forget the precious lessons of the thalidomide tragedy. Therefore, I believe we should always deeply consider and strictly check the dark side as well as the light side of medicines.

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