New Drugs That Have Changed Healthcare

2. Aciclovir

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■ Fight against viruses

The representative microorganisms which cause diseases to humans and transmits infection from one person to another may be bacteria and viruses. Bacteria have tortured human beings for a long time, but the discovery of Penicillin by Fleming revolutionized the development of medical treatment for bacterial infectious diseases. After that, various new antibiotics have been developed and bacterial infectious diseases are being beaten. In Japan also, until about 1950, bacteria-caused tuberculosis and pneumonia had ranked high in causes of deaths, but they have become very rare today.

On the other hand, we were not able to beat viruses at all. Preventive vaccination is effective, but vaccines are effective for only limited kinds or viruses, and therefore it is difficult to develop a vaccine which is effective against all viruses of influenza and AIDS which change types. Moreover, even if an effective vaccine was developed, once a person was infected by the virus, there was no way to treat the disease. Why is that? Although a virus is called a “microorganism”, some people claim that a virus is not a living thing. One of the definitions of a living thing is, “it can proliferate on its own”, but that does not apply to the virus. When viruses proliferate, they do so by borrowing the power of the cell it has infected. Therefore, even if a medicine to beat a virus is developed, damages to cells will result.

■ Discovery of Aciclovir

Aciclovir which we are introducing this time is an epoch-making medicine that overcomes that hurdle. The dream of developing a medicine, which is toxic to the herpesvirus, a kind of virus, but safe for infected human, was realized. The discovery of Aciclovir was made by researchers at Wellcome Company (now, GlaxoSmithKline) in 1974. Recognized for their achievement of the development of Aciclovir and other medicines, George Hitchings and Gertrude Elion at US Burroughs Wellcome, a subsidiary company of Wellcome Company, won the

Nobel Prize in Physiology or Medicine in 1988.

The discovery of Aciclovir was not by chance. Since around 1940, Hitchings held on to the belief that “nucleic acids, like DNA or RNA, are indispensable in the life and fission of cells in living things and a chemical compound similar to the constituent of nucleic acids can become a useful medicine if blocked.” Based on this belief, he developed a wide range of medicines, such as antimalarial Pyrimethamine in 1952; the immunosuppressant drug Azathioprine in 1962, the antigout drug Allopurinol in 1966, and the antibacterial agent Trimethoprim in 1968. In spite of his over 20 years of research, he could not find an effective anti-virus medicine. While he was thinking it would be impossible to develop a medicine which had both selective toxicity against viruses and adequate safety features, in the latter half of the 1960s, there was a discovery at a pharmaceutical company in the U.S., which made him decide to resume developing anti-virus medicines. It was postulated that a derivative of the nucleic acid constituent, adenine arabinoside, had a possibility of systemic administration. Under the leadership of Elion, who was then the leader of the Department, researchers at the laboratory of the Burroughs Wellcome Company synthesized a number of compounds. After repeated efforts in ascertaining the efficacy of synthesized compounds at the laboratory of the UK Wellcome Company, in 1974, the Aciclovir compound which is a few hundred times more effective, was discovered.

■ The reason why Aciclovir is effective against viruses

Why is Aciclovir toxic only against viruses? For herpesvirus or the cell infected by the virus to be able to proliferate, DNA bearing its gene characteristics must be reproduced. DNA has a duplex structure. The task of duplication is achieved by unwinding the chain, making it into a mold and taking in a nucleic-acid constituent and linking the parts to make a replica. Aciclovir has a structure similar to the nucleic-acid constituent and when it gets phosphorylated in the cell, it is mistakenly introduced in place of the nucleic-acid constituent and the duplication process stops. Aciclovir is phosphorylated with an enzyme for phosphorylation derived from the herpesvirus in the cell infected by the herpesvirus, but it is not phosphorylated with the enzyme for phosphorylation derived from the cell. Therefore, DNA duplication in a cell not infected by the herpesvirus is not hindered. For the Aciclovir to be effective it must get inside the cell. When a cell infected by the herpesvirus is compared with a normal cell, the cell infected by herpesvirus takes in Aciclovir more easily. For such reasons, Aciclovir can be selectively toxic against the virus.

■ Diseases caused by the herpesvirus

Among herpesviruses, Aciclovir is effective against the herpes simplex virus

and varicella zoster virus. These viruses infect humans during infancy in most cases and afterwards stay dormant in the nerve and cause repeated relapses in adulthood. The herpes simplex virus infects the lips or the generative organ at first and causes a rash. Strangely enough, in the case of a relapse, a bulla is caused to appear at the same region as in the original case. When a mother catches herpes genitalis and is extruding the virus, the new-born baby may become infected by the herpesvirus and the possibility for an onset of infantile herpes which is high in mortality, increases. It has been estimated that herpes genitalis has around 72,000 patients annually. The herpes simplex virus usually infects the skin and body surface area, but sometimes infects the brain or the viscera. Herpetic encephalitis is a mortal disease.

On the other hand, the varicella zoster virus causes chickenpox in which systemic bullas appear in the initial infection. Then at the time of relapse, gives rise to herpes zoster, which usually accompanies acute pain. When herpes zoster attacks the trigeminal nerve, it may cause meningitis or encephalitis. When it attacks the eyes, the complication of keratitis or conjunctivitis may result, leading to blindness. According to a research, the incidence rate of herpes zoster in Japan is reported to be 4.33/1,000 persons a year, and the rate increases with age.

■ What Aciclovir has brought about

In the US in the early 1980s, it was said that there were 20 million patients of herpes genitalis, and was a social problem. Since the discovery of Aciclovir, however, medical treatment against the causal virus has become possible. In the case of bone marrow transplantation which is done for the treatment of acute leukemia and other diseases, the treatment is performed after completely weakening the marrow of the patient with drugs or X-rays. As a result, the immunological competence of the patient becomes extremely low, and the patient gets easily infected. Therefore, the treatment has to be done in a sterilized room. Even when the treatment is done in a sterilized room, there is no way to suppress the virus which has been dormant in vivo. Until the discovery of Aciclovir, cases in which the virus infectious disease became serious having a high death rate and a largely prolonged recovery, often occurred. Aciclovir saved many such kinds of patients. It is also reported that owing to the development of Aciclovir, the death rate of infantile herpes lowered from 90% to 30%, and the death rate of herpetic encephalitis, from 70% to 20%. Later, the improved product of Aciclovir, called Valaciclovir, was developed and recurrences of herpes genitalis came to be able to suppress.

As has been seen, the discovery of Aciclovir is as great a matter as that of the discovery of Penicillin. Thereafter, the technique has also contributed greatly to the development of treatment for virus infectious diseases, such as the world’s first medicine for AIDS, Zidovudine, developed by the Burroughs Wellcome Company.