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Achievement:
The Discovery of the Statins and their Development.

THE BIRTH OF "STATINS", NATURE'S GIFT OF CHOLESTEROL-LOWERING AGENTS

A therapeutic drug for high blood cholesterol

Blood contains lipids such as cholesterol and triglycerides. Excessive concentration of blood cholesterol is a condition known as hypercholesteremia. This illness affects more than twenty million people in Japan alone. Excess cholesterol gradually adheres to the interior of blood vessels leading to hardening of the arteries which in turn causes blood vessels to become clogged and increases the risk of diseases such as myocardial infarction and cerebral infarction.

During my research, I discovered "ML-236B" (often called compactin) from blue-green mold that lowers blood cholesterol levels, and directed my energies into making it into a medication. This research garnered considerable attention, resulting in research commencing worldwide. Subsequently several breakthrough drugs for hypercholesteremia appeared from amongst this compactin group. These are known collectively as statins and are currently used by approximately thirty million people around the world and have helped to prevent cardiac disease,strokes and other illnesses.

Developing a new-acting medication

Since boyhood, I had been interested in mold and fungi and during my time at university I read the autobiography of Dr. Alexander Fleming who had discovered penicillin from *penicillium*. At that time I decided that I too wanted to undertake research that would make use of mold. After graduation I joined Sankyo Co., Ltd. and was involved in research to find substances from mold and fungi that would be useful in food processing. While studying in the United States from 1966 to 1968, however, I learned that a very large number of people develop myocardial infarction from hypercholesteremia and determined to develop a therapeutic drug for it.

Around that time there were three main medications used in the treatment of hy-

percholesteremia. One was a special type of fine resin powder called negative ion exchange resin. Cholesterol converts bile acid in the liver and is used in fat absorption. This powder binds bile acid in the intestines and forms faeces that are eliminated from the body. As bile acid thus decreases, the body tries to compensate for that lost portion by converting cholesterol to bile acid with a resulting drop in the level of blood cholesterol. This however had very little effect in preventing myocardial infarction, and difficulties in ingesting this medication made it onerous for patients.

The remaining two medications included a nicotinic acid derivative and something known as a fibrate-type drug. Neither of these acted on cholesterol and their cholesterol-lowering action was also limited. Fibrate-type drugs in particular demonstrated a variety of side effects including liver damage, vomiting and diarrhoea, while muscular impairment (striated muscle myolysis) sometimes occurred as a serious side effect.

While these drugs were gradually improved and are presently used by some patients, I was aiming for a drug that acted differently from these. I knew that cholesterol is produced within the body more often than it is ingested as food. Therefore, I thought I would try and produce a drug that reduced the amount of cholesterol produced in the body.

The human body contains a multiplicity of enzymes that work to change substances. Cholesterol is formed when approximately thirty types of enzymes successively act on the substance that makes up its raw material. I hypothesized that if the action of one of these enzymes could be inhibited, this would impede cholesterol production and therefore the cholesterol level would likely drop. Therefore, I set about searching for a drug that would inhibit the action of an enzyme called hydroxymethyl-glutaryl coA reductase.

A discovery in mold

Upon my return to Japan, I confirmed a method which enabled the efficient investigation of whether a particular mold or fungus culture medium contained a substance with the desired action, and proceeded to investigate 6,000 strains. In 1973, when trying to taper off research that had remained fruitless for two years, I [RGM1]finally found compactin, a substance that exerts a powerful inhibiting action on enzymes, from *penicillium* which formed on rice produced in Kyoto (Fig. 1).

This was the beginning of all statins. However, as blood cholesterol levels did not decrease when compactin was administered to rats, its development as a drug was not commenced. I did not give up though, and after two years' further persistence, identified that blood cholesterol in chickens decreased by close to 50%. Further trials with dogs and monkeys confirmed a dramatic lowering in blood cholesterol levels.

Although my team and I commenced drug development in this way, toxicity tests in rats revealed a toxic effect on the liver and, consequently, development once more came to a halt. Then, in collaboration with Dr. Akira Yamamoto, a lecturer at Osaka University at the time, using compactin in pa-

tients with critically high levels of blood cholesterol, we were able to confirm a conspicuous decrease in blood cholesterol and also its outstanding safety.

Development was recommenced and at the end of 1978, when I considered that clinical trials were on track, I left Sankyo and joined Tokyo University of Agriculture and Technology. In the following summer, development was once more suspended due to flaws in toxicity tests on dogs.

Separate to these developments, at the end of 1978, Merck & Co., Inc. in the United States discovered a second statin, "lovastatin", that was very similar to compactin. (Actually, I had also discovered a substance the same as this at Tokyo University of Agriculture and Technology). Merck commenced clinical trials in 1980, obtained Federal Drug Administration approval in the U.S. in 1987 and started marketing the drug.

Meanwhile, Sankyo developed Plavastatin, which was a partially modified compactin, and this went on sale in 1989. As its appearance coincided with the emergence of high blood cholesterol as a major health problem in Japan, it was widely used.

Statins continue to evolve

Numerous companies apart from Sankyo and Merck then took up statin development. Lovastatin and pravastatin were followed in the market by simvastatin and fulvastatin, and recent years have seen the emergence of atorvastatin, pitavastatin and rosuvastatin (Fig. 2). The last three of these are particularly effective in cholesterol-lowering capability and currently constitute a triumvirate of drugs to combat high cholesterol.

The origin of all these drugs was "compactin", the first statin discovered by me. In fact, the same substance had been discovered at the British company Beecham (now Glaxo-Smith-Klein). Beecham, however, did not direct much attention to this substance because of its weak antibiotic effect. Later, despite administering it to rats, as it still did not lower blood cholesterol, the company gave up on developing it as a cholesterol-lowering drug.

Compactin also proved very useful in research into mechanisms controlling the amount of intracellular cholesterol when cells incorporate and produce cholesterol. Dr. Michael S. Brown and Dr. Joseph L. Goldstein, U.S. researchers who accepted my offer to use compactin in collaborative research with me, were awarded the Nobel Prize for Physiology or Medicine in 1985.

Thus, my discovery of statin, was not only able to save countless people from the burden of illness but also was able to make a significant contribution to advances in learning.

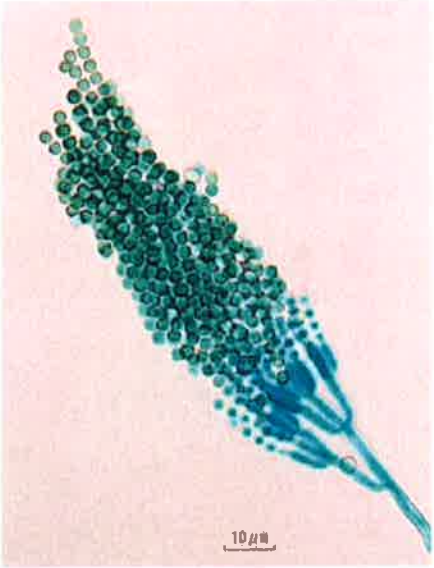

Fig. 1. Microphotograph of *Penicillium citrinum* in which the first statin (compactin) was discovered.

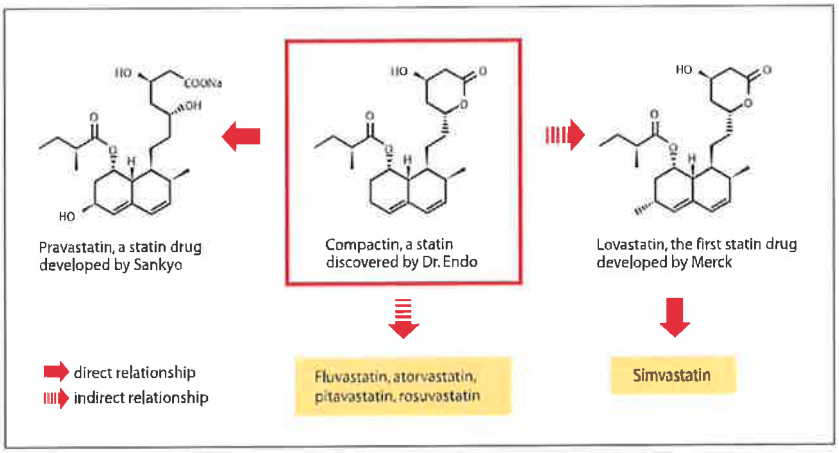

Fig. 2. The various statin-type prescription drugs developed on the basis of the statin.