Hayashibara: Hamsters and Hotels

By Hidemasa Saito

Hayashibara Corp. Ltd. is probably the most financially secure venture business in the world. It possesses enormous financial assets accumulated over the century since its establishment and is able to lavish huge real estate earnings on biotechnological research. Located about 170 kilometers west of Kyoto, Hayashibara Corp. is the nucleus of the Hayashibara Group, which plays a powerful role in the regional economy of Okayama Prefecture in western Japan. The company annually invests ¥2 billion ($8.3 million), or about 20% of its annual sales of ¥10 billion ($41.6 million), in research and development.

Ken Hayashibara, the fourth-generation president, is a young 43. A karate expert with a disarming personality, he says without hesitation, "I am not cut out for business. I always weigh the right or wrong of an issue before thinking of its profitability." Although he is one of the few multi-billionaires in the Chugoku Region around Okayama Prefecture, he is not speaking in jest.

Ken graduated from the law department of Keio University, a prestigious private university in Tokyo. Although he is an amateur when it comes to technology, he has learned the basics of chemistry, physics and biology through the "learn-while-sleeping" method. His brain is packed with knowledge and ideas.

Ken became president of the company immediately after graduation when his father suddenly passed away. In the 20 years since, he has made one bold decision after another, and has turned a small manufacturer of starch syrup, glucose and candies into a highly diversified modern company.

President Ken Hayashibara of Hayashibara Corporation Ltd.

Hayashibara Corp. has always been Japan's foremost producer of starch syrup from rice, but none of Ken's predecessors imagined even in their wildest dreams that the company's starch syrup manufacturing technology would someday blossom into biotechnology. Yet today the expertise in fermentation, microorganism culturing and refining acquired in the production of sugar and starch has made Hayashibara Corp. the world's largest producer of interferon and intravenous maltose for diabetics.

In addition, the company produces food ingredients, additives, pharmaceutical and chemical materials, reagents, diagnostics, and photosensitizing dyes. It has diversified its business by branching out into the leisure industry, real estate, gasoline stations, and trucking. The annual turnover of the Hayashibara Group exceeds ¥30 billion ($125 million). As a major shareholder of the influential, regional Chugoku Bank and owner of four million square meters of real estate throughout Japan, the group enjoys the absolute confidence of Japan's financial community.

If there is an element of art in business management, Ken Hayashibara's management philosophy displays it to perfection.

Real estate and R&D

In the suburbs of Okayama City he has established Hayashibara Biochemical Laboratories, Inc.—what he calls the company's "active bioreactor"—where 50,000 hamsters are raised for cell culturing. At the same time, he has constructed hotels and office buildings all over the country. But he has no intention of saving the income from these real estate holdings to build up his own fortune. Rather, driven by a sense of mission, he is channelling this cash flow into biotechnology,

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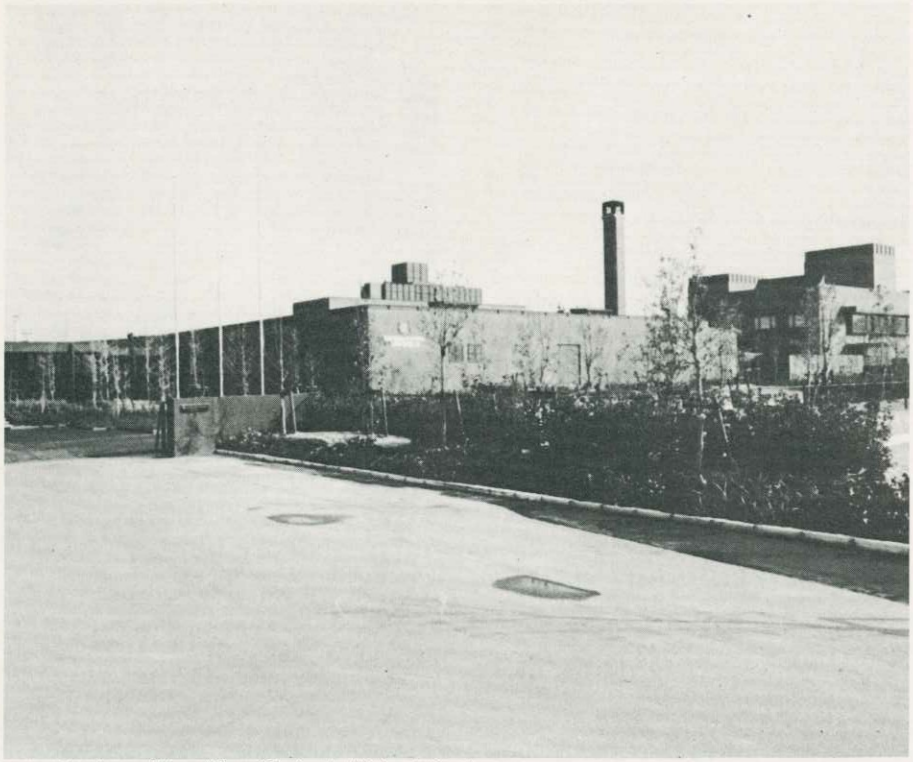


Fujisaki Institute of Hayashibara Biochemical Laboratories, Inc.

as well as into the development of the leisure industry to satisfy the Japanese people's desire for a higher quality of life.

For instance, Hayashibara owns islands in the scenic Seto Inland Sea National Park and an entire cape. He plans to develop these into a grand resort area. In Kyoto, he built a first-class international hotel which opened three years ago. He is now planning to tear down the 50-year-old Kyoto Station Hotel, which stands on a choice plot of land in front of Kyoto Station. Explains Ken: "The area fronting Kyoto Station is a dreary sight and is unbecoming to the image of Japan's ancient capital. I want to re-develop the area into something which will become one of Kyoto's major attractions."

Ken's business strategy as a venture capitalist is clearly defined: first, to invest in biotechnology the profits from the company's carefully-planned real estate business and its traditional manufacturing division. And second, to earn royalties from its biotechnology patents and re-invest the proceeds in further R&D.

Asked when and how he expects to profit from these investments, Ken replies: "I am not thinking in terms of profit. We can earn short-term profit anytime we want. Presently, I see no need for it."

Ken does not like to commit his company deeply to unnecessary plant and equipment investment or to the consumer goods market, which would disperse its resources. He wants to stay uncommitted and unburdened. He has, for example, resolved never to increase the number of employees beyond 300.

Starch production based on petrochemical technology

Ken sometimes seems like a ballplayer who either blasts a home run or goes out swinging. His first home run was the "starch chemistry industry."

The price of starch, the raw material of starch syrup, had been artificially fixed at a high level to protect domestic potato farmers. Shortly after Ken became president, Japan liberalized its sugar imports, but the price of starch remained high. Naturally, cheap sugar flooded the market and starch syrup became uncompetitive. Hundreds of farmers growing potatoes for starch syrup went bankrupt. Hayashibara, too, slid into the red.

Desperately searching for a remedy, Ken hit on the idea of applying petrochemical technology to starch production. Petroleum and starch both contain carbon and hydrogen. The petrochemical plants dissolve or compound the basic elements of petroleum to produce a great variety of petrochemical products. Ken thought the same formula could be applied to the starch industry with similar results. The basic idea was to decompose starch into glucose and to compound the glucose with something else to produce new products. Fortunately, Ken's father Ichiro had discovered that starch production efficiency can be improved when an enzyme is used to decompose the starch, and had built a plant to manufacture glucose by this method.

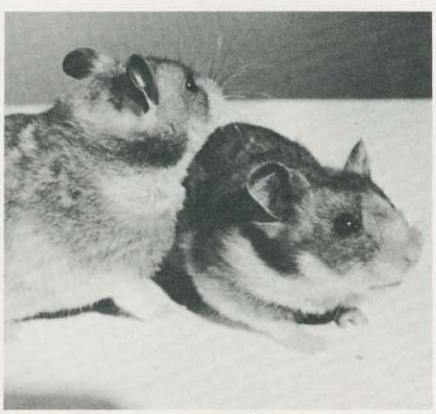
Applying this basic technology but using a special enzyme as a catalyst, Ken succeeded in developing high-purity maltose composed of two glucose molecules. The special enzyme was found in soil obtained in, of all places, a city in Osaka Prefecture, and was produced by a rare bacteria. Today high-purity maltose is used all over the world as an intravenous solution in place of glucose, and 95% of the solution used is produced by Hayashibara. Because maltose is composed of two glucose molecules, it can supply twice as many calories as an equivalent amount of glucose, thus cutting by half the time required for an intravenous drip.

Following the development of high-purity maltose, Hayashibara succeeded in using its starch chemistry expertise to create completely new products, such as "pullulan," a starch-based edible plastic "coupling sugar," a low calorigenic sweetener that helps prevent tooth decay, and "maltitol," a low calorie sweetener.

Hamster-produced interferon

Nine years ago, Ken visited Dr. Tsunataro Kishida, an interferon researcher at Kyoto Prefectural University of Medicine, through the introduction of a mutual acquaintance. In those days, interferon was attracting worldwide attention as a miracle drug, and a handful of doctors were experimentally administering interferon to cancer patients. However, research was impeded by a shortage of interferon and its high price. Listening to Kishida's appeal, Ken replied, "I'll take care of it."

Interferon was not being mass-produced anywhere in the world because the technology was still immature. Interferon is a high polymer glico protein produced in the human body, and at the time it was manufactured either from huge quantities of white blood corpuscles or by tank-culturing fibroblast. Hayashibara's research team concluded there could be no break-



Hamsters play a central role in Hayashibara Corp.'s interferon production.

through technology for mass-producing interferon using these methods.

The team then hit on the idea of implanting human cells into animals. But while it was clear that this was the most efficient approach, the research team was concerned over possible impurities. Nevertheless, Ken resolved to try.

Hamsters were finally selected from among the many species of animals used in the company's experiments. Human lymphoblastoid cells implanted with cancerous cells were injected into the backs of newborn hamsters. In four weeks, a lump of lymphoblastoid cells formed. This lump was surgically removed and an inducer applied to produce interferon.

As much interferon can be produced from one hamster as from blood donated by 200 people. The amount is equivalent to 10 doses of interferon for a cancer patient. One hamster gives birth to 10 babies at a time, which mature in only four weeks. Cancerous lymphoblastoid cells can be cultured and bred literally in geometrical progression. The cost is only one-several-thousandths of traditional methods, while impurities can be removed almost completely by screening.

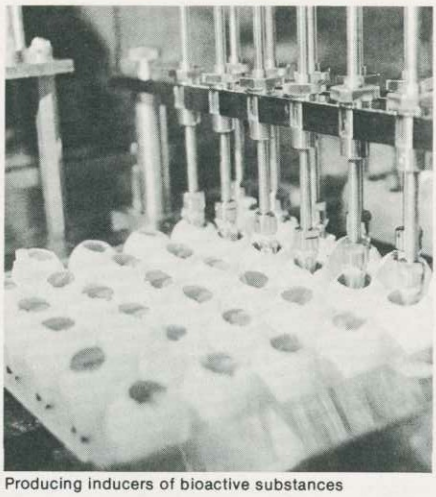
Hayashibara at present breeds 50,000 hamsters at the Hayashibara Biochemical Laboratories, which were completed in 1981. The interferon produced here accounts for about 50% of the world's total production.

While this production method is simplicity itself, Hayashibara was the first in the world to apply it, and also holds the patents. The company supplies interferon to domestic pharmaceutical makers, which produce and market interferon as medicine. Clinical tests were started 18 months ago and are scheduled to be completed by the end of this year.

Today, attention is centered on interferon's effectiveness against viruses, rather than cancer. But this does not disappoint Ken, because interferon is just one of the many biologically active substances that can be produced through cell culture using hamsters. The Hayashibara research team knew this from the beginning.

Mass-production of bioactive substances

In fact, by using hamsters, Hayashibara jointly with Mochida Pharmaceutical Co., Ltd. discovered CBF (Carcino Breaking Factor), a glico protein effective in containing cancer. CBF was accidentally discovered in the autumn of 1981 from among what were regarded as impurities in interferon. Animal tests have established that CBF has the outstanding characteristic of destroying cancerous cells without damaging normal cells. Clinical tests have already been started,



Producing inducers of bioactive substances

and there are great expectations that CBF may yet be made into a cancer-killing drug without side effects.

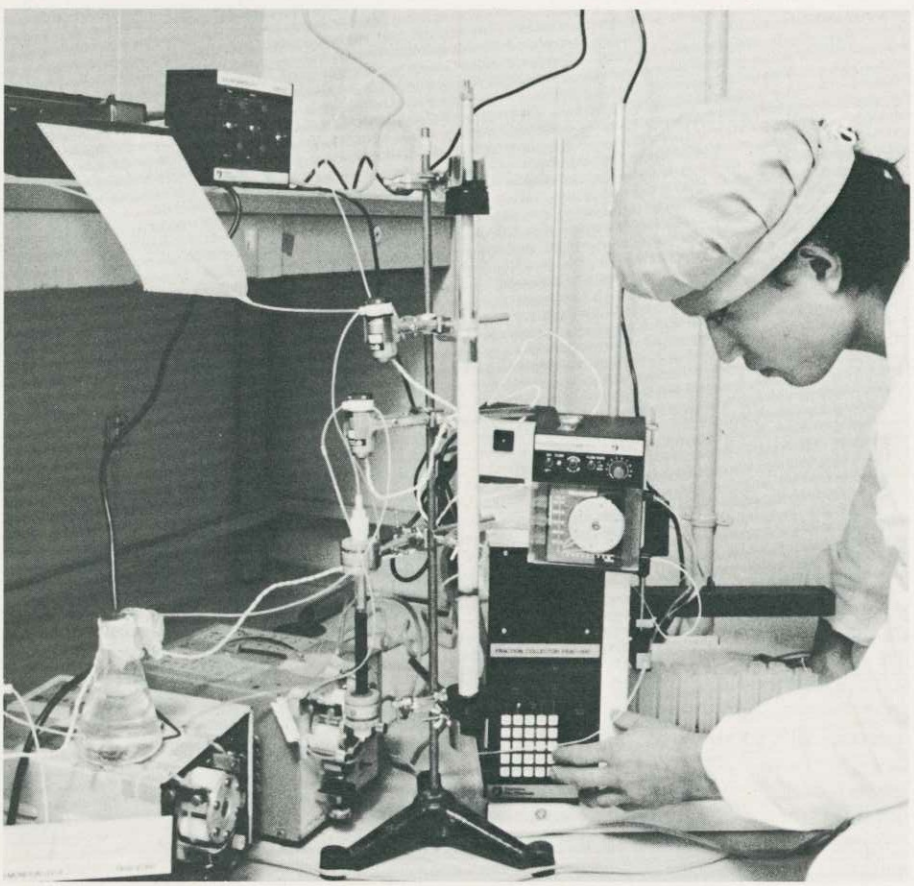
Another factor with the same characteristic is TNE (Tumor Necrosis Factor). TNF has been known of for a century, but it is extremely difficult to make into medicine. Animal blood must be used, meaning there is a great danger of causing allergic or shock reactions in patients. But this disadvantage can be eliminated if human lymphoblastoid cells are multiplied in hamsters and TNF screened from the multiplied cells.

Using the same method, Hayashibara succeeded in extracting Interleukin 2 (IL2), another bioactive substance which multiplies the "T cells" that help the immune reaction in human bodies.

The most promising field in biotechnology is gene recombination. This method, however, cannot create substances identical to human bioactive substances, which have a glico protein structure in which glucose and protein interlock in a highly complex way, although it can produce bioactive substances consisting entirely of protein. The United States monopolizes almost all the patents concerning gene recombination technology, and newcomers are naturally at a disadvantage. But the hamster multiplication method developed by Hayashibara is most effective in mass-producing these substances, because various kinds of valuable substances can be generated simultaneously.

"Genetic engineering is typically American, but the method of producing unlimited quantities of bioactive substances vital to human subsistence via animal bodies is typically Oriental," Ken says.

A monument stands in the compound of the Hayashibara Biochemical Laboratories. It is dedicated to the souls of the hamsters which were sacrificed to save human lives. Ken and the research staff gather around this monument once a year to offer prayers for the peaceful repose of their small helpers. ●



Purification of bioactive substances