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MARKET STRUCTURE AND TECHNOLOGICAL PERFORMANCE IN THE FOOD MANUFACTURING INDUSTRIES

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PART III

CHAPTER 8. HIGH-FRUCTOSE CORN SYRUP: A CASE STUDY

INTRODUCTION

This chapter describes the evolution of the industrial arts relating to high-fructose (or isomerized) corn syrup and provides a record of industial inventions suitable for testing several theories regarding the sources and effects of technological change. The first section discusses the economic importance and chemical properties of this innovation. The next section is an account of the development of the first techniques for manufacturing these syrups. In the remaining sections the introduction of improvements on these early methods is recounted, and the full historical record is then used to evaluate the theories of Schmookler, Schumpeter, and others concerning the economic and legal conditions for rapid technological growth and the effects of such growth on market structure.

For several hundred years men have been trying to prepare sugars from products of the maize plant. Parmentier in eighteenth-century France, Kirchhoff in nineteenth-century Russia, and Newkirk in twentieth-century America all contributed to these efforts. However, important though their accomplishments were, these men failed to discover a way to make corn syrups or sugars as sweet as sucrose. As a result, sweeteners produced from corn remained imperfect substitutes for those produced from cane or beets.

This remained true even after the introduction in the 1940's of acid-enzyme and enzyme-enzyme corn syrups. These products, though sweeter than those made exclusively by the old acidic methods of starch conversion, could not rival the sweetness of cane and beet sugar syrups. Composed primarily of glucose (dextrose), a monosaccharide only about 70 percent to 75 percent as sweet as sucrose, they were easily distinguishable from cane or invert syrups of equivalent specific gravity. Starch hydrolysis, regardless of how far it was carried or how pure its products were made, could never yield corn sweetners identical to sucrose.

However, what the corn wet millers could never hope to accomplish by means of starch hydrolysis they have in the past 15 years or so accomplished by means of glucose isomerization. The achievement in this period of enzymatic methods for converting part of the glucose in corn syrups to fructose, another monosaccharide closely related to glucose but much sweeter, has brought about the innovation of a new corn sweetener that has dramatically altered competitive relationships between the wet millers and the cane and beet sugar interests. The development of this isomerized or high fructose corn syrup has given the corn-refining industry the capacity for the first time to produce a sweetener that is a very close substitute for sucrose or invert syrup and to invade markets that had been reserved for the cane and beet processors.

The success that the wet millers have enjoyed in these new competitive ventures can be gauged from the remarkable growth in the shipments of the new isomerized syrups. In the 10 years since 1968, the volume of these goods sold has increased thirtyfold and their consumption per capita has risen by a similar amount (Table 8.1). Over the same period, there has been corresponding growth in the proportion of the U.S. corn grind allocated to the manufacture of the new syrups; largely as a result of this growth, the share of the grind going to the production of all corn sweeteners has gone up by almost 10 percentage points since 1968. Coincident with these trends, growth within the markets for cane and beet sugar has halted. U.S. deliveries of these commodities to all industrial users totalled 14,117,000 short tons in the two years 1972 and 1973, but only 13,107,000 short tons for 1977 and 1978. Although sucrose shipments to dairies and soft drink bottlers changed very little during the 1970s, those to manufacturers of baked goods, cereal products, confectionery, and various processed foods declined.[1] As a consequence, per capita consumption of cane and beet sugars in the U.S. has dropped steadily since 1972.[2] In the trade journals there is abundant evidence that these trends have largely been the results of industrial substitutions of high fructose cornsyrups for invert and sucrose syrups.[3]

Table 8.1. High-Fructose Corn Syrup, U.S. Domestic Shipments, 1967-1978

Year	Shipments, Pounds Commercial Weight[1] (000)	Shipments, Pounds Dry Weight (000)	Per Capita Food Use Dry Weight Pounds
1967	46,800	33,200	.14
1968	109,000	77,400	.34
1969	171,200	121,600	.54
1970	233,600	165,800	.73
1971	296,000	210,200	.92
1972	347,000	246,400	1.26
1973	625,400	444,000	2.07
1974	842,200	598,000	2.99
1975	1,498,400	1,063,800	4.97
1976	2,187,400	1,553,000	7.39
1977[2]	2,973,000	2,127,400	9.57
1978	3.604,600	2,590,000	12.31
1979	4,852,600	3,500,000	15.42

[1] Commercial Weight (weight of the syrup in the liquid form in which it is shipped) can be converted to dry weight (weight of the dry solids in the liquid syrup) by multiplying by a factor of .71.

[2] Preliminary statistics of the 1977 census of manufacturers report 1977 production of high fructose corn syrups as 3,202,900,000 lbs commercial weight and 2,274,059,000 lbs dry weight. Preliminary Report MC77-1-200-4 (P), *1977 Census of Manufacturers,* Table 3.

Source: Calculated from data given at ESCS, AMS, FAS, USDA 5 *Sugar and Sweetener Report* 46 (May 1980).

Both the relative price and the functional properties of the new isomerized syrups have appealed to industrial customers. Relative to cane or beet sugars, this new product has equal or greater sweetness but generally lower production costs (Table 8.2).[4] As a consequence, corn refiners can afford to sell it at prices substantially below those of the other nutritive sweeteners. During 1974-1978, for example, the wholesale prices for high fructose (dry basis, tank cars, Decatur) averaged 68 percent of those for refined cane sugar in the northeast marketing territory.[5] In recent years, the new corn syrup has offered important economies to the manufacturers of ice cream, jams, preserves, candies, carbonated beverages, capacity for crystallization, high-fructose corn syrup offers additional advantages over sucrose in many kinds of food processing. Moreover, its low viscosity allows it to be handled, stored, and blended with ease.[6]

Table 8.2. Comparison of Production Costs per Hundredweight, Caloric Sweeteners, 1975

	Costs Per Hundredweight
High-Fructose Corn Syrup[1]	
Gross Corn Cost (wholesale, No. 2 yellow dent, Chicago, $/bu)	$ 2.91
Credits from Sales of Corn Wet Milling By-Products	1.39
Net Corn Cost	1.52
2.915 bu corn per cwt. HFCS (dry subst.)	
Raw Material Costs ($/cwt. d.s.)	4.43
Depreciation and Maintenance (lower in larger, newer plants)	1.50
Labor (lower in larger, newer plants)	1.50
Enzyme costs (upper bound)	1.00
Total Production Costs ($/cwt. d.s.)	$ 8.43
Louisiana Cane[2]	
Production Costs ($/cwt., raw value)	$ 9.47
Processing Costs	5.05
Refining Costs	3.72
Total Costs	$18.24
Florida Cane[2]	
Production Costs	$ 7.37
Processing Costs	4.35
Refining Costs	3.72
Total Costs	$15.44
Mainland Cane[2]	
Production Costs ($/cwt., raw value)	$ 8.164
Processing Costs	4.614
Refining Costs	3.723
Total Costs	$16.501
Domestic Sugar Beet[2]	
Production Costs ($/cwt., raw value)	
Direct Costs (labor, supplies, equipment, etc.)	$ 5.63
Administration, interest, indirect costs	1.93
Land rent	.89
Processing Costs	
Factory operation	3.49
Marketing	2.40
Beet acquisition	1.13
Other costs	.81
Total	$16.28

[1] Sources: Personal interviews with executives of corn refining firms; C.R. Keim, The U.S. Market for High-Fructose Corn Syrup, 72 *Sugar y Azucar* 59 (May 1977); Cal Andres, Sweeteners Outlook, *Food Processing,* November 1976, p. 46

[2] Source: Robert Bohall et al., *The Sugar Industry's Structure, Pricing, and Performance.* CED,ERS-U.S. Dept. of Agriculture. AER No. 363 (March 1977). Tables 37 and 38.

This new syrup with so many desirable properties is the product of an enzymatically catalyzed reaction by which glucose in ordinary corn syrup is converted into its sweeter isomer, fructose, yielding a saccharide mix similar to that in total invert syrup.[7] Because the equilibrium constant of this isomerization reaction is close to one at temperatures suitable for optimal enzyme activity, the proportion of fructose in the mix is constrained to a maximum of about 50 percent.[8] However, syrups of enhanced fructose content (the so-called "second generation" high fructose corn syrups) can be made by the use of fractionation methods which permit the separation of sugars in the mix produced by the isomerization reaction at equilibrium. The enzymes catalyzing this reaction are xylose isomerase (EC 5.3.1.5) and glucose isomerase (EC 5.3.1.18).[9] When, through the agency of metallic ions, the glucose substrate is attached to the active sites of these enzymes, deprotonation occurs at C-2 through loss of a hydrogen ion, and an enediol intermediate (i.e., and compound, usually optically inactive, with two hydroxyl groups adjacent to a double carbon bond) is formed. Completion of the enolization reaction (i.e., one transferring a hydrogen ion from the carbon adjacent to a carbonyl group to the oxygen of that group) is followed by eventual protonation of C-1 to give fructose, a monosaccharide with the same molecular weight and formula as glucose but different properties (e.g., a sweetness about 65 percent greater).[10]

A similar isomerization reaction, also involving the formation of an enediol intermediate, occurs when glucose is treated for several hours with a dilute alkaline solution. However, this Lobry de Bruyn-van Ekenstein reaction yields less fructose than enzymatically catalyzed isomerizations and more ash, colored bodies, acid, and other undesirable by-products, the removal of which entails substantial refining costs. Numerous attempts to overcome these problems have so far failed to provide a alkaline method of making high-fructose corn syrups that can be profitably operated on a commercial scale.[11] However, in April of 1943, Corn Products Refining did introduce to the market "Humectose" (TM 404,105), a syrup of 20 percent fructose content made by alkaline methods that for a time was used as a moisturizing agent in tobacco.[12]

DEVELOPMENT OF FRUCTOSE SYRUPS

Early Work at Argo

The innovation of high-fructose corn syrups resulted from the discovery of a microorganism with the capacity to generate the enzyme(s) that will catalyze the isomerization of glucose (dextrose) to fructose (levulose). This discovery, which was made in 1956 at the Argo laboratories of Corn Products Refining, resulted from prior basic research on the biochemistry of carbohydrate metabolism.

The particular research that led to the Argo work was directed at determining how enzymes facilitate the utilization of glucose in the glycolytic catabolism by which energy is produced for life processes and the utilization of xylose (a pentose) in the synthesis of nucleic acids.[13] By 1955 these investigations had pickles, salad dressings, baked goods, catsup, and other foods that require large quantities of sweeteners in their preparation. Furthermore, the syrup improves the quality of many of these foods: In jams and canned fruits it enhances natural flavors, and in sweet pickles it improves texture and color. Because it exhibits high degrees of fermentability, osmotic pressure, and hygroscopicity but a low disclosed enzymes able to isomerize monosaccharides not only in their phosphorylated form (to which they are converted during glycolysis) but also in their free, unreacted form. Furthermore, workers at the National Research Council in Canada, Western Reserve University, and the Medical Bacteriology Division of the U.S. Army had established the presence of an enzyme, obtainable from extracts of the cells of at least three microorganisms, able to isomerize D-xylose, a monosaccharide similar to glucose, to D-xylulose. However, all these studies seemed to indicate that glucose was not a substrate for the isomerase that had been found.

Despite this last finding, these studies suggested to Dr. Albert L. Elder, research director at Corn Products Refining, that enzymatic methods might yet be developed that would allow the production of a glucose-fructose corn syrup superior to that which had been achieved after many years of research at Argo on alkaline isomerization.[14] Accordingly, in the spring of 1955 he decided to assign work on such a problem to a young biochemist who was about to join his staff at the Argo laboratories.

The young biochemist was Richard O. Marshall who had just completed a doctoral dissertation at the University of Wisconsin-Madison on the mechanism of citrulline biosynthesis under the supervision of Professor Philip Cohen of the Department of Physiological Chemistry.[15] When he arrived at Argo in May of 1955, Marshall received instructions directly from Elder on the research that he was to pursue:

> As he eyed me and chomped on his cigar, he said, "We've been trying for 20 years to produce a levulose bearing syrup by chemical means. See what you can do with enzymes."[16]

Marshall set to work immediately to find an isomerase that in one step would give the desired aldose-ketose conversion. After thoroughly searching the literature, he noticed a "fragment of information" in a paper by two investigators at Western Reserve University that suggested to him that the xylose isomerase they had studied, that from *Lactobacillus pentosus,* might have an affinity for glucose as a substrate, and furthermore, that "conditions might be defined wherein xylose isomerase would act on glucose."[17]

To test this conjecture, he began studying the activity of enzymes prepared from a microorganism similar to *L. pentosus* but with less stringent growth requirements and began also to develop analytical methods for the detection of fructose more sensitive than those used by previous investigators. During the winter of 1955-1956, Marshall experimented with different methods for enzyme extraction and glucose incubation. Finally, sometime in May of 1956, he observed that when glucose was incubated for forty-eight hours at 40°C. with an arsenate buffer, magnesium chloride, and cells from *Aerobacter cloacae*[18] grown on xylose, substantial quantities of fructose were formed. An application for a patent on this glucose isomerization process, the first that had ever been achieved, was filed in late December of 1956, and about three weeks later Marshall, in collaboration with Dr. Earl Kooi, his immediate supervisor, submitted to *Science* a report of his discovery.[19] Shortly after this article appeared in print, Corn Products Refining further publicizzed Marshall's achievement, emphasizing its possible commercial importance, in an announcement placed in *Chemical and Engineering News.*[20]

However, the Corn Products management perceived the commercial opportunities of Marshall's findings as less promising than those offered by the glucoamylase systems then being developed at Argo and Krefeld, Germany, for the manufacture of crystalline dextrose. As a consequence, they decided that work on the new glucose-isomerization process should be suspended and that Marshall should be transferred to the glucoamylase project. Because of his disappointment with this and other actions of the Corn Products management, Marshall decided in August of 1957 to leave the Argo laboratory and take a position with Grain Processing Corporation.

Despite Marshall's departure and the suspension of isomerization work at Argo, a Corn Products attorney continued, despite several adverse office actions, to press the application for a patent on the new enzymatic process for making fructose. In March 1960 she finallly won allowance for a continuation-in-part application. This new specification did not, however, accurately report Marshall's invention and, in addition, contained a serious error which was not corrected by successful execution of a reissue application. As a result, the patent on the Marshall process, which issued in August 1960 (U.S. Pat. 2,950,228), was invalidated 14 years later by the U.S. District Court for Delaware.[21] Argo did not resume work on glucose isomerization even though the new glucoamylase system was nearly completed. Interviews with current and former Corn Products employees indicate that there were several reasons for this failure to exploit the Marshall discovery.

Support within the company for continued studies of the *A. cloacae* isomerase ebbed with the departure of the principal advocates of such research. After Marshall left, Argo had no biochemists or fermentologists experienced in working with enzymes of this type. Further, A.L. Elder, who as research director had initiated and supported Marshall's investigations, was elected president of the American Chemical Society for 1959-1960. The duties of this position and his deteriorating health reduced the time he could give to detailed management of affairs at the Argo laboratory. Early in 1961, he asked to be relieved of his duties as research director, and in March of that year, Corn Products made him head of its Institute of Nutrition, a position he held until his retirement in 1966.[22]

Corn Products' biochemists also note that the economic prospects of the isomerization process, at least in the form that Marshall left it, were not attractive. The *Aerobacter* microorganism, which provided only modest enzyme yields, needed to be grown on xylose, a very costly material. Moreover, the isomerase it produced had a relatively low affinity for glucose as substrate, its Michaelis-Menten constant for the glucose reaction being more than one hundred times greater than that for the xylose reaction.[23] Using it, Marshall could isomerize less than one-third of the glucose he had incubated for 48 hours with the *Aerobacter* cells. Furthermore, the enzyme, a glucose-6-phosphate isomerase, (as later studies revealed), would act on nonphosphorylated glucose only in the presence of arsenate, a substance that for obvious reasons could never be used in the manufacture of edible corn syrups.[24] The costs of the research that would be needed to solve these problems and to provide an economical enzymatic process were wholly unknown.

Under these circumstances the expected rates of return on such a project fell below those of other research ventures available to the firm. During 1959-1963 work on isomerization was displaced not only by continuing efforts to improve enzymatic methods for making crystalline dextrose but also by studies directed at developing new consumer food products. William Brady, who had assumed the presidency of Corn Products in 1956, had come to believe that the firm's financial performance could best be improved by raising the proportion of its sales derived from shipments of branded consumer goods.[25] This policy of freeing the company from dependence on volatile commodity markets culminated in Brady's acquisition in 1958 of Best Foods, Inc., producer of such heavily advertised brands as "Hellmann's" mayonnaise and "Skippy" peanut butter.[26] Corn Products Company, the new corporation that resulted from this merger, invested heavily in research directed at improving such food products and, in particular, at developing a margarine which, made from polyunsaturated corn oil, could be advertised as an aid in reducing blood cholesterol levels.[27] Thirty-two (or almost 44 percent) of the 73 patents assigned to the firm with initial application dates in 1959-1963 disclosed inventions pertaining to food products (i.e., those assigned to the old Class .99), seven pertaining to margarines, four to peanut butters, and four to other oils and fats. Nine (or about 12 percent) of the inventions from this period related to the manufacture of dextrose, the field of art with the greatest number of patents.

Managerial reluctance to proceed with research on improving the Marshall process may also have arisen from an apprehension that a high-fructose syrup, even if it could be successfully developed and marketed, might only divert sales away from the company's other established products.[28] These potentially threatened products included not only crystalline dextrose and a wide variety of glucose syrups but also liquid and granulated cane sugars manufactured by Refined Syrups and Sugars, Inc., a firm acquired by Corn Products in the spring of 1957.[29]

Finally, its unhappy experience with zein and the other products of basic chemical research may have made Corn Products wary of undertaking other investments in entirely new, untested products and disposed to put money into research with less risk.[30]

For whatever reasons work on glucose isomerization was suspended at Argo the Corn Products management opened the door to others to take what benefit they could from exploiting the Marshall discovery.[31]

Japanese Contributions

Perhaps the first scientists to take advantage of these opportunities worked in the laboratories of the Japanese government. Marshall's research caught their attention because it raised the possibility that they might be able to utilize abundant domestic supplies of glucose, which was made by hydrolysis of starch from sweet potatoes, to reduce Japan's imports of cane sugar, which accounted for about 80 percent of the sweeteners consumed in that nation.[32]

In 1960, having studied the 1957 paper of Marshall and Kooi in *Science*,[33] Nobuzo Tsumura and Tomotaro Sato of the Food Research Institute in the Ministry of Agriculture and Forestry began experiments on an isomerase derived, like that of Marshall's, from *Aerobacter cloacae* bacteria. This work, which replicated Marshall's finding that enzymatic glucose isomerization was possible, resulted in several publications and a patent application.[34]

In the meantime, workers elsewhere in Japan were investigating the optimal conditions for the production and activity of isomerases generated by other microbial species. At the Fermentation Research Institute of the Agency of Industrial Science and Technology (part of the powerful Japanese Ministry of International Trade and Industry), Yoshiyuki Takasaki and Osamu Tanabe studied glucose isomerization induced by *Bacillus megaterium*, and at Kagawa University, Kei Yamanaka discovered that similar reactions could be catalyzed by enzymes released by *Lactobacillus* bacteria, especially *L. brevis.*[35]

This early Japanese work, which demonstrated that glucose isomerases were formed by a variety of microorganisms, was directed at finding enzymes of this class which, produced in good yields within inexpensive culture media, could catalyze under a wide pH and temperature range and without arsenate activators the isomerization of a higher proportion of glucose to fructose than had been achieved by Marshall. The first isomerases that were found to satisfy these conditions were those formed by microorganisms of the *Streptomyces* genus, a microbial group widely recognized as a good source of antibiotics and proteolytic enzymes.

Examinations of the metabolites of *Streptomyces* species for glucose-isomerizing activity were apparently begun about the same time in China and in Japan. In the first part of 1964, microbiologists in Shanghai at the Institute of Plant Physiology, Academia Sinica, investigated *S. griseus* and three other species but failed to find a xylose isomerase that would act on glucose.[36] However, Tsumura, Sato, and their colleagues at the Food Research in Tokyo reported in July of that year that they had isolated such enzymes in the culture filtrates of several *Streptomyces* species, especially *S. phaeochromogenes.*[37] More than a month earlier, Tsmura and Sato had filed an application for a patent covering their invention of means to obtain glucose isomerase by cultivating *S. phaeochromogenes* in either xylose or glycerol and means to use this enzyme to manufacture fructose.[38] The *Streptomyces* intracellular glucose isomerase, unlike that derived from *A. cloacae,* did not require an arsenate activator but did require cobalt and magnesium ions for heat stability and full efficiency.

Upon learning of the research at the Food Research Institute,[39] Takasaki and Tanabe of the Fermentation Research Institute at Chiba City also began studies on methods of producing fructose by the use of *Streptomyces* enzymes. During the winter of 1964-1965, they derived the desired isomerases from 32 species which had not been discussed in any of the reports of Sato and Tsumura and filed applications for patents to protect their discovery.[40] That spring they made the important discovery that *S. flavovirens* and a few other species secreted an enzyme (xylanase) which allowed them to grow and form glucose isomerase within nutrient media in which xylan, easily obtained from wheat bran or straw, had been substituted for the far more expensive xylose (wood sugar). Moreover, the intracellular isomerase, which was produced in satisfactory quantities, gave significantly higher yields of fructose than Marshall had been able to achieve with his *Aerobacter* enzyme. Immediately, patents on these inventions, which promised to provide an economical process for manufacturing high-fructose syrups, were sought.[41] The Ministry of International Trade and Industry, recognizing the potential commercial importance of this new technology it now held, secured patent protection for it in most of the nations of the industrialized world.[42] In contrast, the Marshall technology, in which Corn Products saw very little prospect of future profit, was patented only in the United States.

The *Streptomyces* microorganisms isolated by Takasaki and Tanabe were sufficiently productive and their isomerases sufficiently active and thermo-stable so that for the first time commercial manufacture of syrups containing 40-percent to 50 percent fructose appeared to be feasible. The syrups, however, that were produced in the laboratories of the Fermentation Research Institute in 1965 were quite dark and bitter and, therefore, required considerable refining in order to be acceptable for use in most foods. By 1967 these and other problems had been sufficiently resolved so that Sanmatsu Kogyo, licensee of the Ministry of International Trade and Industry, was able to begin the first commercial production of high-fructose syrup in the world.[43]

In the meantime, news of the Japanese progress in glucose isomerization was reaching American corn refiners. Corn Products and Clinton were perhaps the first firms to learn of the results of the work going on at the Food Research Institute and the Fermentation Research Institute. Through the staff of its Nakatani Memorial Laboratory in Tokyo, Corn Products probably heard about the performance of the new *Streptomyces* microorganisms well before the Takasaki-Tanabe patent applications were published in the spring of 1966. Clinton Corn Processing Company, which had no offices or laboratories in the Orient, apparently received early notice of the discoveries in Japan through informal and indirect communications with a Japanese company with which it had a special relationship.[44]

Which firm, Corn Products or Clinton, was the first to act on its advance intelligence is unclear, although sources in each seem ready to accord priority to the other. What is fairly clear is that during the fall and winter of 1965, representatives of these and of at least two other American wet-milling companies, Staley and Union Starch, traveled to Japan to investigate the isomerization technologies being developed and to find out the terms on which they might be licensed.

A delegation from Clinton/Standard Brands arrived in Tokyo sometime in the late summer of 1965.[45] Shortly after their arrival, the team of Dr. Lawrence Atkin, research director for Standard Brands; Dr. Robert V. MacAllister, research director for Clinton, and Dr. Robert G. Dworschack, Clinton's senior microbiologist, began negotiations with representatives of the Ministry of International Trade and Industry.[46]

During the first day of discussions, the Japanese officials requested the Americans to put forward a specific licensing proposal. By the next morning the delegation had a draft of such a contract. Extolling Standard Brands as a large, reputable business organization and emphasizing that it was in a most advantageous position to manage the American innovation of the new fructose syrups because of its substantial interests in the candy and baked-goods industries, the proposal, nonetheless, was unsatisfactory to the Japanese. Inconclusive discussions extending over several days led the Clinton/Standard Brands representatives to suspect that Corn Products and perhaps some other U.S. wet-milling companies might also be negotiating with the Ministry for licenses to the new *Streptomyces* enzymes.[47] Accordingly, in an effort to expedite the bargaining, Atkin and his colleagues engaged the services of a Japanese lawyer who, raised in New Jersey, had an excellent command of English and was able to speed up negotiations.

After almost a month of discussions, the Ministry of International Trade and Industry accepted terms of a contract under which it granted Standard Brands exclusive U.S. rights to the Takasaki-Tanabe process (including the right to sublicense) during a trial period in which the economic feasibility of the new technology could be evaluated at Clinton. Standard Brands agreed in return to provide the government with, in addition to other compensation, assistance in obtaining U.S. patent protection for its new syrup technology.

Some executives at the main offices of Standard Brands in New York at first were dubious about the proposed agreement that Atkin and his associates had negotiated and wished to see it amended substantially. However, enough support for the high-fructose-syrup venture existed among the company's leadership[48] that the Tokyo contract was given final approval. Standard Brands became the exclusive U.S. licensee to the enzyme technology developed at the Fermentation Research Institute, including the specific Takasaki-Tanabe invention claimed in a U.S. patent application filed in October 1965, which led to the issuance of U.S. Pat. 3,616,221 on October 26, 1971.

The Resumption of American Research

With the closing of this contract, Clinton/Standard Brands had preempted American access to the Japanese glucose-isomerization technology of greatest commercial value. The Japanese patent of Sato and Tsumura (assigned to the Ministry of Agriculture and Forestry), although it contains broad claims embracing the use of all *Streptomyces* microbes and thus arguably dominates the Japanese patent of Takasaki and Tanabe,[49] does not specifically lay claim to the use of xylanase-producing strains of the genus. In addition, the Sato-Tsumara patent was never extended through the acquisition of foreign counterpart patents, possibly as a result of political pressures from the Ministry of International Trade and Industry. Thus, when representatives of Corn Products, Staley, and Union Starch visited Japan in 1965 and failed to secure legal access to the Takasaki-Tanabe technology,[50] they left their companies with the alternatives of either developing their own distinctive isomerization process or trying to obtain from Standard Brands a U.S. sublicense to the Japanese enzymatic system.

The latter alternative was an anathema to Corn Products. It was not about to beg for any favors from Standard Brands, a company with which it was then engaged in an expensive legal and economic struggle for control of the market for margarines made largely from polyunsaturated vegetable oils,[51] or from Clinton Corn Processing, a company that in the 1930s had successfully circumvented the Newkirk patents for crystalline dextrose. Accordingly, to preserve its future access to any market for high-fructose syrups that might develop, Corn Products ordered its Tokyo laboratories to begin work on finding an isomerization process that would fall outside the claims of the Takasaki-Tanabe patents. After several years of work, the scientists at the Nakatani Laboratory found two species of *Streptomyces* microorgranisms able to grow on xylan sources such as straw and to produce extracellular glucose isomerase. These two enzyme sources, *S. olivochromogenes* (ATCC 32,114) and *S. venezuelae* (ATCC 21,113), have been utilized by Corn Products in most of its subsequent work on glucose isomerization.[52] Although any process in which they are used would seem to fall squarely within the broad first claim of the Takasaki-Tanabe patent,[53] the U.S. patent authorities, nevertheless, granted Corn Products a patent (U.S. pat. 3,622,463) in November 1971 on the inventions arising from its early Tokyo research. Neither Standard Brands nor the Japanese government challenged this action. Both perhaps realized that because of the publications and patents of Sato and Tsumura at the Food Research Institute, the validity of the Takasaki-Tanabe patent was itself open to question.

Staley received news of the Japanese discoveries quite late, and when it found that it could not do business with the Ministry of International Trade and Industry, it organized a research group at Decatur with the objective of finding a glucose isomerase not covered by the Takasaki-Tanabe patents.[54] Although its scientists had experience in studying alkaline isomerization (see U.S. Pat. 2,746,889) and knew a great deal about industrial enzymology, they were hindered in their search for such a novel catalyst by inadequate supplies of equipment for fermentation, a consequence of the firm's decision to satisfy all of its enzymic requirements by purchases from external suppliers such as Miles, Corn Product, or Wallerstein. Thus hampered, the Staley scientists were unable to make rapid progress in their microbiological investigations. Concerned that any long delays in developing isomerase technology might prevent their firm from sharing in the profits anticipated from the new fructose syrups, Staley executives elected to begin negotiations with Clinton/Standard Brands to secure a sublicense to the Japanese technology.

These discussions progressed quite smoothly because Clinton/Standard Brands had already offered such sublicenses to Staley and several other corn refiners.[55] Its willingness to do this resulted from its appreciation of the possible commercial and antitrust problems it might face in trying to develop a market for a new product of which it was the sole supplier. Believing that demand for the new fructose syrups could be augmented by multiplying the sources of their supply and confident that sublicensing would not jeopardize the advantages it had won through priority of innovation, Clinton/Standard Brands welcomed Staley's participation in the U.S. commercialization of the Takasaki-Tanabe process.[56] A sublicensing agreement between the two companies was quickly concluded in 1968, and Staley then made plans in the spring of 1969 to install the Japanese technology in a new $23,000,000 plant north of Philadelphia.[57] In 1974, two years after the Philadelphia plant began operating, Staley installed in its Decatur refinery the isomerization technology devised by its own research staff. This technology, so far as can be determined, is unprotected by patents.

Penick and Ford, not long after it was acquired by R.J. Reynolds Tobacco Company in 1965, also became interested in enzymatic methods for glucose isomerization. In 1967, its research director visited Japan to confer with scientists who were working on the development of such techniques. In the following year his staff at Cedar Rapids, Iowa, assisted by researchers of the parent company,[58] began intensive studies of both chemical and enzymic means of making fructose syrups from starch. These investigations first bore fruit in 1969 when micro-biologists isolated strains of bacteria of the genus *Arthrobacter* under a floor board in P & F-owned potato-starch plant in Idaho. These strains, able to grow on glucose in the absence of xylan, generated an isomerase that showed exceptional thermostability[59] and did not require arsenate activators. The determination of P & F/Reynolds to circumvent the broad claims of the Takasaki-Tanabe patent and therefore to investigate microbes belonging to genera other than *Streptomyces* was rewarded with the discovery of an important new source of the isomerizing enzyme. By November 1969, the process invention had developed to the point that Reynolds felt ready to specify it in applications for U.S. and foreign patents.[60]

In contrast to the research strategy followed by P & F/Reynolds in seeking new isomerases, yet another wet-milling company, Miles Laboratories, Inc., emphasized the screening of *Streptomyces* microorganisms for the desired enzymic activity. Miles, which had come into the enzyme industry in March 1956 with the purchase of Takamine Laboratory, Inc., entered the corn-refining industry 10 years later with the purchase of Union Starch and Refining Company, a privately held firm.[61] During the next several years, Miles applied its considerable resources in enzymology to the search for a *Streptomyces* isomerase more potent than those found by Takasaki and Tanabe. Such an enzyme, that from *S. olivaceus,* was eventually found during the winter of 1969 and subsequently given patent protection in the United States and several foreign countries.[62]

The only other technology for the manufacture of high-fructose syrups developed during the 1960s came from Baxter Laboratories, Inc. About 1966 Baxter, which had entered the enzyme business in 1958 with the acquisition of Wallerstein Company, Inc., decided that Japanese progress on the problems of glucose isomerization made it advisable to pursue a similar research program in its laboratories. Dr. Tibor Sipos, Baxter's principal investigator on this project, realized that the conventional batch processes used in enzymic conversions of glucose to fuctose were uneconomical because of the short life of the very expensive intracellular isomerases used. Accordingly, during 1968 and 1969 he looked for ways to attach (or immobilize) a *Streptomyces* isomerase to an inert, water-insoluble carrier material so that the isomerase might be used repeatedly within a continuous process of syrup manufacture and so that substantial economies might be realized relative to batch processes in which enzymes could not be recovered after use. The technique Sipos discovered in 1969 for adsorbing isomerase on DEAE cellulose, which was later patented by Baxter (U.S. Pat. 3,708,397), appears to be the first American invention to deal with the problems of immobilizing glucose isomerase.[63] Despite this distinction, the Sipos technology was too expensive for commercial application.[64] Baxter, which by the early 1970s had decided to sell the Wallerstein Company and leave the enzyme business, decided against investing the resources needed to improve the technology.

While the invention market was growing through the R & D rivalry of Baxter, Miles, P & F/Reynolds, Staley, and Corn Products, scientists at Clinton were busy making improvements in the Takasaki-Tanabe process licensed from the Japanese government. They realized that this process in its original form could not be used to manufacture fructose syrups which could successfully compete with invert syrups made from sucrose. The process would be commercially feasible only if its efficiency could be raised by increasing the yield and useful life of the *Streptomyces* isomerase; moreover, the formation of colored bodies by the enzyme would have to be inhibited in order to lower refining costs. Clinton's technical staff, drawing on three decades of experience in working with fermentation problems,[65] significantly boosted isomerase yields by changes in culture media (U.S. Pats. 3,666,628 and 3,736,232) and by microbial mutation (U.S. Pat. 3,654,080), the same technique used by Armbruster several years before at Argo to raise yields of glucoamylase from *A. niger.* Furthermore, the great expansion of knowledge concerning enzymes and their immobilization that was then taking place allowed the Clinton scientists, as it allowed Sipos, to extend the effective life of their enzymes and achieve dramatic decreases in their costs of production.[66] Clinton's first continuous system for glucose isomeriztion, which was reduced to practice during 1970, provided for the steady flow of refined 93 percent glucose d.s. substrate liquor through a stationary bed of *Streptomyces* cells in which the isomerase had been entrapped through the action of heat (U.S. Pat. 3,694,314). The adoption of this new system brought large economic benefits in the form of reduced unit labor, capital, and enzyme costs; in addition, it also permitted substantial increases in product quality.[67]

As pilot-plant experiments demonstrated the commercial feasibility of Clinton's modifications of the basic Takasaki-Tanabe process, the New York management of Standard Brands gradually committed more resources to the project. This financial support enabled Clinton to become the first American company to produce high-fructose corn syrup on a commercial scale. On February 15, 1967, the company made its first shipment of "Isomerose 30" (TM 848,278), a corn syrup of 14 percent to 16 percent fructose content made by a batch process.[68] In the following year Clinton began distributing "Isomerose 100," which had a fructose content of 42 percent and was the first corn syrup to be as sweet as sucrose in solutions of comparable levels of solids. Although this new product was initially manufactured by a batch process, after the fall of 1972 it was made by Clinton's automated, continuous process using immobilized enzymes in fixed bed reactors.[69]

Staley, Clinton's licensee, was the second U.S. company to operate a commercial process for the isomerization of glucose. On February 1, 1971, it began shipping limited quantities of its "Isosweet" (TM 931,909) high-fructose corn syrup; commercial-scale production of the new syrup began in the following year at the company's new plant in Morrisville, Pennsylvania.

ECONOMIC AND TECHNOLOGICAL GROWTH

The history of high fructose corn syrups can be used to test theories regarding the relationship between economic and technological growth. One of the more influential of these theories is that of the late Jacob Schmookler. In his *Invention and Economic Growth* (1966), Schmookler argued that the supply of invention is perfectly elastic in all fields of art and that technological growth always results solely from changes in the demand for invention, as these are reflected in changing expectations of the profits to be realized from research investments in various fields. These expectations, according to Schmookler, are formed from perceptions of the sizes of the markets for the goods to which the various classes of invention are relevant. This theory implies a high and positive correlation between the economic growth of an industry and the rate at which its technology is being improved and expanded.[70] For purposes of the present discussion, this implication can be interpreted to require that the volume of invention relevant to isomerized corn syrups must vary directly with the volume of sales of corn syrups and, as the innovation matures, with that of the isomerized syrups themselves.

The object of this section is to determine the extent to which this requirement can be met and, therefore, the extent to which the Schmookler theory can provide a satisfactory explanation of the history of high-fructose corn syrups. In addition, attention will be given to testing the theory, which is closely related to Schmookler's, that the expectations of the profits to be realized from inventions of a certain class depend not on the sales volume but rather on the profit rates of the industry to which those inventions pertain. This theory implies a positive relationship between the volume of invention relevant to isomerized corn syrups and the profit rates from the manufacture of corn syrups and, later, those from the manufacture of those isomerized syrups themselves. That is, technological growth should vary directly with the general level of prosperity within the industry using the inventions.

The previous section described the growth during the late 1960s in the market for inventions relating to glucose isomerization. This development occurred when returns from manufacturing conventional corn syrups were depressed by excess supply and severe price competition. Sometime in 1967, Cargill, Inc., the giant Minneapolis commodities firm, acquired Corn Starch and Syrup Company, an enterprise organized a few years earlier by a group of Iowa businessmen for the purpose of building and operating a small wet-milling plant in Cedar Rapids. The output from this new plant aggravated a condition of excess supply that had arisen during that year as a result of a decline in demand for glucose syrups. Cargill, having the advantage of an efficient new plant, began discounting its syrup prices to maintain its sales volume and to allow operation of its plant at as close to full capacity as possible. Its competitors, also burdened with heavy fixed costs and therefore by an urgent need to avoid operation at suboptimal volumes,[71] responded by discounting their prices too. The resulting price cutting reduced revenues at the very time that raw-material costs were rising on corn markets. In 1967, glucose syrups prices were driven to their lowest level in 17 years. During the second quarter they recovered somewhat as demand from the ice cream and canning industries rose, but toward the end of November, they were cut again by 60¢/cwt. This vigorous price competition continued until the middle of 1969 when Corn Products initiated a price increase of 25¢/cwt., which other producers followed.[72]

This price competition, which recurred in an even more intense form a few years later when Grain Processing Corporation began producing corn-syrup, had at least three important effects. For one, it allowed Cargill, equipped with very modern capacity, to gain market share at the expense of the older companies in the corn syrup industry.[73] For another, it ground down profit margins in such companies as Corn Products and Staley which depended heavily on corn-syrup sales. From 1966 to 1968 the return on stockholders' equity achieved by Staley fell from 12.44 to 6.98 percent, and that for Corn Products went down from 15.4 percent to 13.3 percent during the same period.[74] However, although rates of return on corn syrups were depressed, aggregate sales of these products did not fall and actually increased by about 11 percent from 1966 to 1969. Finally, the market conflict incited by Cargill's entry into the industry persuaded many corporate managers that sales of corn syrups could not materially contribute to and might well detract from the growth of sales and profits. In particular, marketing executives began to look with little favor on these product lines, and they were not much more sanguine about the commercial prospects of the new isomerized corn syrups being developed at Clinton.[75] Thus, the innovation of high fructose syrups in the 1960s, like that of enzymically converted glucose syrups in the 1950s, followed administrative conflicts within corporations in which research directors and their allies, who were confident about the ultimate success of the new product, prevailed against marketing managers and their allies, who were not.

Prosperity in the corn syrup industry was not, therefore, a stimulus to the development of the technology that changed that industry so dramatically in the 1970s. On the contrary, the research leading to the high fructose corn syrups may well have been a defensive reaction against the excess capacity and low, unstable margins suffered by manufacturers of corn sweeteners during the last half of the 1960s.[76] At least one industry executive, on returning in 1965 from discussions in Japan with Takasaki, was hopeful and confident that the new isomerized syrups "could 'revolutionize' the corn syrup business in the U.S., which at the time was in a pitiful condition of overcapacity and underpricing."[77] The technology relating to glucose isomerization grew, therefore, as a result of autonomous increases in the supply of invention arising from basic research on enzyme immobilization during the 1960s and as a result of increases in the demand for invention that may have been induced by economic stagnation and declining profits within the corn syrup industry. High fructose corn syrup, contrary to the implications of one of the theories under discussion, appears to have been developed not because of high profits but in order to bring them about.

During the early stages of its development, however, the new syrup was not strikingly effective at doing this. Well before the extraordinary increases in sugar prices of 1974, food processors often were reluctant to accept the new sweetener despite its cheapness relative to sucrose. Clinton and Staley had to build the market for high fructose corn syrup by providing technical service to a wide range of potential industrial customers. Their representatives had to demonstrate to soft drink manufacturers, bakers, canners, and others that incorporation of the new syrup in their products would both reduce their ingredient costs and preserve, if not increase, product quality. There was, as Staley's president has emphasized, no great surge in demand for the new sweetener when it was first brought to market in 1968-1972:

> Despite what one reads in the press today, sweetener users did not and do not rush to accept high fructose corn syrup. It did not sell itself in the early 1970s any more than it sells itself today. High fructose syrup was an unknown, and food and beverage processors do not readily change formulas to accomodate an unproven ingredient.[78]

The tepid reception given high-fructose corn syrup during its first years on the market did not, however, dampen research on the enzymatic processes used in its manufacture. About a quarter of the U.S. patents issued within this field of art so far have initial application dates in the three years after 1969 (Table 8.3).[79] During this period several companies vied with each other to increase the efficiency with which they could produce and, by means of immobilization techniques, the efficiency with which they could use glucose isomerases. Scientists in the laboratories of Corn Products (now CPC International, Inc.), in addition to experimenting with isomerases derived from microorganisms of the *Bacillus* genus (U.S. Pat. 3,826,714), worked to increase both the yields of isomerase from *S. olivochromogenes* (U.S. Pats. 3,770,589 and 3,813,318) and the useful life of those enzymes by conjugating them to particulate magnesium carbonate on which they could be used repeatedly while retaining 80 percent of their native activity (U.S. Pats. 3,847,740 and 3,941,655).[80] As researchers at Miles were devising immobilization systems for their enzymes from *S. olivaceus* (U.S. Pat. 3,779,869), those at Penick & Ford/Reynolds were engaged in similar work with their *Arthrobacter* enzymes (U.S. Pat. 3,821,086). In the meantime, Anheuser-Busch entered the R & D competition by discovering isomerases in the culture filtrates of species of the *Aerobacter* (U.S. Pat. 3,813,320) and *Actinoplanes* genera (U.S. Pat. 3,832,988). Clinton, the indirect cause of much of this research, was itself investing resources in the improvement of its continuous process for the manufacture of high fructose corn syrup (U.S. Pats. 3,788,945; 3,829,362; 3,834,940; and 3,909,354).

Table 8.3 Patents Relating to High-Fructose Corn Syrup, Distribution by Initial Application Dates, 1956-1978.[1]

Application Year	Primary Patent Groups[2]	Secondary Patent Group[3]
1956	1	1
1957	0	0
1958	0	0
1959	0	0
1960	0	0
1961	0	0
1962	0	0
1963	0	0
1964	0	0
1965	1	1
1966	0	0
1967	1	1
1968	5	5
1969	5	5
1970	6	9
1971	8	15
1972	7	12
1973	15	18
1974	10	12
1975	13	13
1976	13	14
1977	4	4
1978	2	2

[1] As of May 1980.

[2] Primary Patent Group: U.S. patents (most of which are originally or cross classifed into unofficial subclass 195-31F) with claims *exclusively* directed toward processes of glucose isomerization.

[3] Secondary Patent Group: The Primary Patent Group and U.S. patents (most of which are in C1.195) with claims directed toward the immobilization of glucose isomerase as well as other enzymes.

During the latter half of 1973, this research and the programs of technical service that accompanied it finally began to yield good returns as the rate of growth in shipments of high fructose syrup increased. As food processors learned to substitute the new corn sweetener for sucrose in their products, sales of Clinton's "Isomerose" and Staley's "Isosweet" expanded. The volume of shipments of these products grew by about 17 percent during 1972 and by 80 percent during 1973 (Table 8.1). The acceleration in growth, as Table 8.3 shows, was associated with a sharp increase in the number of successful patent applications for inventions relating to glucose isomerization. This correlation suggests, but does not and cannot demonstrate,[81] that the growing acceptance of high fructose corn syrup within the food industry led to a quckening of research on the enzymic processes by which it is produced.

A similar conjunction of economic and technological growth appears in the records for 1974-1976. During this period, a marked drop in world sugar stocks following the poor harvests of 1973-1974 and 1974-1975 collided with steadily rising world demand to drive sucrose prices to extraordinary heights.[82] As wholesale prices of refined sugar quadrupled between the third quarter of 1973 and the third quarter of 1974, food manufacturers increased their consumption of high-fructose corn syrup.[83] Because this swelling demand could not be satisfied from existing capacity, prices of the new corn sweeteners were forced up, and despite concurrent rises in the price of corn, Clinton and Staley were able to realize unusually large profits. Indeed, so abundant were Staley's profits that they provoked an attempt by H.J. Heinz company, a heavy user of sugar and corn syrups, to acquire the company through an exchange of stock.[84] Even after sucrose (and high fructose) prices had fallen from their 1974 levels, the boom continued. Having learned to use high-fructose corn syrup when refined sugar cost $40/cwt., many food manufacturers used it in even larger quantities when refined sugar cost $20/cwt. in 1975. In the three years after 1973 the industry achieved a 250 percent increase in the volume of shipments of high-fructose corn syrup.

Coincident with the boom in high fructose during these three years, basic research on glucose isomerization apparently intensified. During 1974-1976, there was a pronounced increase in the number of scientific publications pertaining to the enzymic production of fructose from glucose as well as an increase in the number of nations contributing to this literature (Table 8.4). Moreover, the volume of patented invention ralating to glucose isomerization technology remained large relative to pre-1973 levels. Thus, the commercial growth of high fructose after the second quarter of 1973 does approximately coincide with an apparent growth in its technology. However, this relationship does not hold when data on the secondary rather than the primary patent group are used to measure technological growth (Table 8.3).

Neither set of data is satisfactory for such a purpose. Because they do not record all patent applications relevant to glucose isomerization but only those that were successful, they fail to measure the growth of technology that, though valuable, could not be patented because of administrative negligence or error or deliberately was not patented in order to avoid public disclosure. Unfortunately, data on all patent applications are available only from those countries such as West Germany, Belgium, and Japan (but not the United States) that publish the full text of applications (usually about eighteen months after the filing date) to allow public participation in their novelty examination.

Table 8.5 shows the distribution, by filing date, of all (or at least almost all) Japanese patent applications, unexamined and examined, pertinent to high fructose corn syrup. In recent years, Mitsubishi Chemical Industries, Denki Kagaku Kogko K.K., and Kyowa Hakko Kogyo have been manufacturing for Japanese food processors ever increasing volumes of this new sweetener. In 1973 they made from tuberous starches about 30,000 tons of syrups high in fructose; two years later their aggregate output had more than doubled to approximately 75,000 tons, and in 1976 was estimated to be 130,000 tons.[85] The data on Table 8.5 clearly show that growth in the volume of patent applications, successful and unsuccessful, relevant to glucose isomerization accompanied this remarkable commercial growth.

Table 8.4. Scientific Publications Pertaining to Glucose Isomerization and Resulting Syrups, 1957-1979.

Year	Scientific Publications	Year	Scientific Publications
1957	1	1969	7
1958	0	1970	5
1959	0	1971	9
1960	2	1972	9
1961	3	1973	9
1962	7	1974	26
1963	8	1975	33
1964	9	1976	26
1965	5	1977	24
1966	5	1978	27
1967	7	1979	25
1968	4		

Publications by Country of Origin

	1957-1968	1969-1979
United States	2	74
Japan	48	46
Denmark	0	12
United Kingdom	0	6
Netherlands	0	7
Finland	0	6
U.S.S.R.	0	7
Brazil	0	4
India	0	5
Poland	0	4
France	0	3
Republic of China	0	4
Hungary	0	3
Italy	0	2
West Germany	0	2
Mexico	0	2
Yugoslavia	0	2
Others	1	7

Source: *Chemical Abstracts.* Data were compiled by examining all abstracts cited under the following headings in the Fifth, Sixth, and Seventh Collective Indexes: Glucose Isomerase, Formation of Fructose, and Xylose Isomerase; by examining all abstracts cited under those and the following additional headings in the Ninth Collective Index: Glucose Reactions, Glucose Syrup, Isomeration; by examining all abstracts cited under the following headings in the Chemical Substance Index, Ninth Collective Index: Glucose Isomerase, Xylose Isomerase, Fructose; by examining all abstracts cited under the above headings in the keyword indexes of individual *CA* volumes, 1977-1979II.

Table 8.5. Japanese Published Patent Applications and Publications Relating to High-Fructose Corn Syrup, Distribution by Initial Application Dates, 1960-1978[a]

Application Year	Number of Published, Examined and Unexamined Applications
1960	0
1961	1
1962	1
1963	0
1964	2
1965	7
1966	1
1967	1
1968	2
1969	4
1970	6
1971	6
1972	8
1973	13
1974	18
1975	19
1976	34
1977	13
1978	2

[a]As of February 1980.
Source: Abstracts of published unexamined (Kokai Tokkyo koho) and examined (Tokko koho) patent applications to the Japanese Patent Office, appearing in *Chemical Abstracts,* vols. 63-90. Also included in the totals are Japanese patent applications indicated in Convention priority data given in published West German patent applications (Offenlegungsschriften).

The expansion of technological knowledge represented by these and the previously referenced patent statistics had by the end of 1976 led to the discovery of commercially important sources of glucose isomerases in at least 11 *Streptomyces* species, the three *Bacillus* species, and in microorganisms belonging to 11 other genera.[86] The enzymes from these several organisms exhibit dissimilar affinities for glucose (i.e., Michaelis constants), optimal reaction conditions, and glucose-isomerizing activities.[87] The enzymes isolated most recently are not mere duplicates of those isolated in the early research in Japan; rather, they are novel and distinctive industrial catalysts. Among those of the most commercial importance there are the isomerases developed from *Actinoplanes missouriensis* NRRL B-3342 by Anheuser-Busch, Inc. (U.S. Pat. 3,834,988); from *Streptomyces olivaceus* NRRL 3583 by Miles Laboratories, Inc. (U.S. Pat. 3,779,869); from *Arthrobacter nov. sp.* NRRL B-3724-28 by Penick & Ford/Reynolds Tobacco (U.S. Pat. 3,645,848); and from *Bacillus coagulans* NRRL B-5656 by Novo Industri A/S, a Danish enzyme house (U.S. Pat. 3,979,261).

The expansion of knowledge was also manifested in the variety of immobilization techniques that were available for licensing by the end of 1976. There was a Clinton/Standard Brands system in which the *Streptomyces* isomerase was coupled to CEAE-Cellulose by means of electrostatic (ionic) absorption (U.S. Pat. 3,788,945). Scientists at Reynolds and Penick & Ford had developed an alternative system in which enzyme-bearing *Arthrobacter* cells were coagulated into a pasty mass and thereby insolubilized (U.S. Pat. 3,821,086) ; in November 1976, Penick & Ford sold its rights to this process to Imperial Chemical Industries, Ltd.[88] Novo Industri offered a system in which partially ruptured *Bacillus* cells were reacted with glutaraldehyde to form a gel that could be dried into solid particles (U.S. Pat. 3,980,521) . Patents assigned to Corning Glass Works disclosed a technique for immobilizing isomerases by adsorption on porous alumina bodies (U.S. Pat. 3,868,304, et al.) ; access to this technology was, however, preempted very early by Corn Products through the purchase of an exclusive license.[89] In addition, there was also a system developed by Miles Laboratories which employed glutaraldehyde to agglomerate *Streptomyces* cells into granules (U.S. Pat. 3,779, 869) and one developed by Gist-Brocades N.V., a Dutch firm, which also used glutaraldehyde to entrap an isomerase from *Actinoplanes* organisms, within the matrix of a gel (U.S. Pat 3,838,007) .[90] The later system was produced under a license from Anheuser-Busch. Plug-flow (i.e., packed bed) columnar reactors are used in all these systems except Clinton's, which operates with a shallow-bed reactor.

This variety of immobilization systems is no more a mark of wasteful, duplicative research than is the variety of isomerase sources that resulted from competition on the invention market. Each technique for insolubilizing enzymes provides a distinctive mix of benefits and costs to the industrial user. Coupling the isomerase to the carrier by physical adsorption (Corning) or by ionic bonding (Clinton/SB) requires no harsh chemical reaction that might disturb the steric structure of the enzyme and thus lower its activity; however, the resultant is weak relative to the covalent bonds used in other systems (Novo) . Again, systems involving the immobilization of whole cells (Reynolds/P & F, Novo) avoid the costs of enzymic extraction but their reactions are slower as a consequence of the interposition of the cellular wall between enzyme and substrate.[91]

Rivalry on the invention market, by expanding the technological options open to corn refiners, and by driving down the price of such options, has probably lowered barriers to entry into the business of making high-fructose syrups. These barriers are imposing: The capital costs of erecting a wet-milling plant of minimum optimal scale (about 30,000 bu/day grind capacity) are about $60 million.[92] However, they become even more formidable if the potential entrant must also face the highly uncertain costs of developing its own isomerization technology or licensing such technology. Analogous barriers very possibly protected Corn Products for many years against the competition of new producers of crystalline dextrose monohydrate, allowing it as late as 1964 to control almost 90 percent of the national output of this commodity.

However, the contrast between the history of the market for crystalline dextrose and that of the market for high-fructose corn syrup is striking. Clinton, which at one time dominated the high-fructose market as Corn Products did the market for crystalline dextrose, has in recent years been producing a steadily declining proportion of the national output of high-fructose corn syrup. The entry barriers that once protected Clinton seem to have been considerably more superable than those that for so long helped to maintain Corn Product's tight control over the dextrose business.[93] Despite the great capital costs of new plants, the number of producers of high fructose has been increasing year after year. With competition on the invention market resulting in an abundance of alternative isomerization technologies available for licensing, several companies, with only negligible investments in research and technical service, have been able to take advantage of the early marketing work of Clinton and Staley and to follow them into the manufacture of the new corn sweetener. As a consequence, concentration in the industry has fallen dramatically. Clinton, which in 1975 controlled almost two-thirds of the national output of high fructose, today must share such a two-thirds portion, as shown in Table 8.6, with two manufacturers, Staley and ADM Corn Sweeteners.[94]

Table 8.6. Product Market High Fructose Corn Syrup, 1979.

Firm	Approx. Capacity Millions of Pounds/yr. (dry wt.)	Product Trade Name	First Use of Trade Name in Interstate Commerce
A.E. Staley Mfg. Co.	1,420	"Isosweet"	February 1, 1971
ADM Corn Sweeteners[1]	1,340	"CornSweet"	November 21, 1974
Clinton Corn Proc. Co.[2]	1,050	"Isomerose"	February 15, 1967
Amstar, Inc.	340	"Amerose"	July 2, 1975
Hubinger Company[3]	300-350	"Hi-Sweet"	not available
Car-mi, Inc.[4]	280	"Isoclear"	February 10, 1977
Amalgamaize, Inc.[5]	250	"Tru-Sweet"	February 17, 1976
CPC International, Inc.	200	"Invertose"	February 27, 1975
Holly Sugar Corporation	100	not available	Summer 1980
Great Western Sugar Company	100	"GW HFCS-42, -55"	Late Summer 1980

[1] Division of Archer-Daniels-Midland Company.

[2] Subsidiary of Standard Brands, Inc., since 1956.

[3] Subsidiary of H.J. Heinz Company since 1975.

[4] Joint venture of Cargill, Inc. and Miles Laboratories, Inc./Bayer, A.G.

[5] Joint venture of Amalgamated Sugar Corp. and American-Maize Products Company.

Sources: Company reports; *Chemical Engineering,* Sept. 27, 1976, at 54; *Wall Street Journal* May 17, 1979, at 12, Jan. 31, 1980, at 2, and June 27, 1980, at 31; data from the First Manhattan Company and Lamborn & Company reported at W.J. Johnson, Economic Factors that Affect New Product Substitution: A Case History 8 *Ind. Marketing Mgt.* 145, 149 (1979); U.S. Patent & Trademark Office, *Official Gazette* (Trademarks); trade sources.

Amstar Corporation, the nation's largest sugar refiner, was the third firm to enter the industry after Staley. In 1973 it leased a small (14,000 bu/day) wet-milling plant at Dimmit, Texas, that had been sold in February of that year by Dimmit Agri-Industries, Inc., an agricultural cooperative.[95] Using under license Novo Industri's "Sweetzyme" (TM 997,829) isomerase, Amstar began production of high fructose at Dimmit in the summer of 1974 and announced its intention to spend more than $20 million to double the plant's capacity.[96] By the start of 1975, trade sources credited it with a 5 percent share of the market for the new syrups.

Novo's enzyme technology also facilitated the entry of Archer-Daniels-Midland Company into the industry. In 1968, the Iowa businessmen who in the previous year had sold to Cargill the Cedar Rapids plant of their Corn Starch & Syrup Company, used the proceeds from that sale, supplemented by a $3 million bank loan, to put up yet another wet-milling factory in the same city. This small (8,000 bu/day) plant became the nucleus of Corn Sweeteners, Inc., which was organized in February 1970.[97] In April 1977, Archer-Daniels-Midland Company purchased a controlling interest in the fledgling corporation and announced plans to expand its Cedar Rapids plant.[98] Shortly after this expanded plant began making regular-conversion corn syrup, ADM set up in 1974 a pilot plant for the production of high fructose. Initially, ADM used enzymes supplied by Miles Laboratories, the company from which ADM two years before had purchased what was left of Union Starch and Refining Company. Wanting to shift to Clinton and Staley the full burden of providing the technical/customer service required to develop a wide market for high fructose, ADM delayed its entry into that market until the fall of 1975. At that time, it began production at Cedar Rapids using enzyme technology licensed from Novo Industri.[99] Once it had entered the industry, ADM competed vigorously. Convinced that existing plants in the industry were for the most part too small to realize all available economies of scale, ADM during the fall of 1975 and the winter of 1976 expanded the capacity of its Cedar Rapids plant to 165,000 bu/day, thereby making it the largest manufacturing establishment of its kind in the world.[100] Benefiting from the efficiencies of this huge plant and from an intimate knowledge of the sweetener industry gained through ownership of a sugar refining company in Louisiana, ADM very quickly became the second or third largest supplier of high fructose syrups.

Although Miles failed to win the enzyme business of ADM Corn Sweeteners, it did win that of another large commodity house and corn wet miller. In 1975, Cargill, Inc. entered into an agreement with Miles by which the two companies formed a joint venture, Car-Mi, Inc., for the purpose of building and operating a syrup refinery in Dayton, Ohio, adjacent to Cargill's wet milling plant and to the site of Miles' proposed citric-acid plant. By April 1977, this refinery was producing tanker loads of high fructose from starch slurry supplied by Cargill and from hydrolases and isomerases supplied by Miles.[101]

In August of the same year that Car-Mi, Inc. was organized, the American Maize-Products Company and the Amalgamated Sugar Company formed a similar joint venture, the Amalgamaize Company. In March 1977 Amalgamaize began producing high-fructose syrups at a new plant in Decatur, Alabama. Amalgamaize uses enzymes and immobilization systems supplied by Novo Industri A/S.

Although Corn Products, using its own enzymes, had produced limited quantities of a 45 percent fructose syrup from a pilot plant at Pekin as early as the fall of 1972,[102] it did not begin manufacture of the commodity on a commercial scale until February 1976. In the interim it acquired, as noted previously, an exclusive worldwide license to the immobilization system developed by Corning Glass Works that, in conjunction with its own *Streptomyces* enzyme preparations, it now uses at its Argo refinery and will presumably use at its proposed refineries in Stockton and Winston-Salem.

In recent years two more companies have licensed the technology necessary to enter the high fructose industry. In 1975, H.J. Heinz Company acquired the Hubinger Company and about four months later announced that it would spend $30 million to put its new subsidiary into the business of supplying a full line of the new syrups.[103] This money went primarily for the construction of a 100,000 sq. ft. refinery adjacent to Hubinger's existing mill at Keokuk, Iowa. Operations at this new facility began in early 1978, and, according to some trade reports, are probably based on technology licensed from Novo. In the summer of 1977, Holly

Sugar Corporation announced that it too would be joining the high fructose industry through the construction of a corn wet-milling plant and refinery next to its beet sugar factory in Tracy, California; the technology to be used at this plant has not been disclosed.[104]

As ADM and the other new producers were installing high fructose capacity amounting in the aggregate to well over one billion lbs/yr (w.b.), Clinton and Staley were also expanding their plants. By the second quarter of 1976 Clinton had increased its capacity 32 percent; during its 1975 fiscal year Staley doubled the volume of high fructose that it could manufacture from its Decatur and Morrisville plants. In August 1977 Staley's capacity increased to almost two billion pounds per year with the initiation of operations at its highly automated plant at Lafayette, Indiana.[105]

The output from this new capacity came on the market as falling sucrose prices were slowing growth of demand for high-fructose corn syrup. Under the pressures of the excess supply thus created, prices of the new sweetener, which had been very stable during the first four months of 1976, broke sharply in September and followed the downward trend of wholesale sugar prices. During January, the Decatur tank-car quotations averaged $15.14/cwt. (d.b.), but during the following November, they averaged only $11.30/cwt.[106] Prices recovered only slightly during 1977 and remained well below the $13 level. Competition intensified in the spring of 1978 as Car-Mi and Amalgamaize cut their quotations in order to gain greater market shares and thereby touched off a price war in the industry. Decatur tank-car quotations, which had averaged $11.97/cwt (d.b.) in the first quarter of 1978, fell to an average of $11.26/cwt in the following quarter.

This sustained depression of high fructose prices caused profit margins in the industry to collapse.[107] Largely because of falling prices for its "Isosweet" syrups, Staley's net earnings slipped from $50,362,000 (6.5 percent of sales and $4.73/common) in FY1975 to $24,480,000 (2.2 percent of sales and $2.70/common) in FY1977.[108] During approximately the same period and for much the same reason the gross earnings of Standard Brands' food-ingredient divisions, which include Clinton Corn Processing Company, dropped from $75,007,000 to $26,416,000.[109]

The marked decline in prices and profits within the high-fructose industry caused several firms to alter their plans. As early as May 1976, Anheuser-Busch decided to postpone indefinitely adapting its Lafayette plant to the manufacture of the new sweetener and to concentrate its energies instead on licensing its isomerase technology.[110] The following September, Amstar similarly curtailed its investments in the industry by dropping its plans to construct a second high-fructose refinery.[111] Clinton, having built such a refinery at Montezuma, New York, delayed putting it into operation until December 1978. Great Western Sugar and General Foods, which at one time or another had considered coming into the industry, decided to stay out.

The prolonged slump in high-fructose prices may have affected research as well as capital investments. A material decline in invention relating to glucose isomerization is consistent with the data of Tables 8.3 and 8.5, which show large decreases after 1976 in the numerical measures of such innovative activity for both the United States and Japan. These data must, however, be interpreted with caution. The apparent drop in patent applications shown in the data for 1977 and 1978 may simply be an artifact of administrative and publication lags or the result of a decrease in the supply of invention, which could be caused by a falling off in the rate of growth of scientific knowledge pertaining to glucose isomerization. Some applications dating from 1977-1978 may still be pending before the patent authorities (as of June 1979) or may not yet have appeared in *Chemical Abstracts*. It is doubtful, though, that this will turn out to be the total explanation for the sharp drop in U.S. patents for 1977 indicated by Table 8.3. As of April 21, 1979, the filing date of the oldest application pending at the U.S. Patent and Trademark Office before Examining Group 170, within whose purview all high fructose applications would likely fall, was December 1, 1977.[112] This suggests that most (but certainly not all) of the 1977 applications that ever will be patented have already appeared in the *Official Gazette*. That the apparent drop in patent applications may alternatively be the consequence of a decrease in the supply of invention seems improbable in view of the data of Table 8.4, which show no substantial decline in the rate of output of relevant scientific publications after 1976. There is, therefore, some reason to believe that declining profits in the contemporary high-fructose industry have, by decreasing the demand for invention, depressed the rate of growth of its technology. Such a sequence of events is of course consistent with the theories under review.

It appears, however, that these theories cannot satisfactorily explain the history of high fructose corn syrups; the constant relationship between economic and technological growth that they require has not been observed. After 1972, as the discussion in this section has indicated, technological growth seems to have coincided with economic growth in the high-fructose industry. As the price and sales of the new corn sweetener rose rapidly during 1973-1975 and as manufacurers' profits increased, there was a corresponding expansion of the flow of invention directed at improving this product or the processes used in its manufacture. And as profit margins in the industry contracted in recent years, the flow of invention seems also to have contracted. However, before 1973 and the great explosion of sugar prices, economic and technological growth appear to have been related somewhat differently. In the early period of the evolution of high fructose technology, the correlation between invention flows and profits in the corn-sweetener industry is either zero or negative. These early discoveries were not called forth by changes in the demand for invention induced by concurrent economic growth and prosperity in the industry to which they were most relevant. On the contrary, industrial researchers put down the technological foundations of the high fructose industry during 1967-1972 when corn-syrup markets were yielding only disappointing profits as a result of overcapacity and price wars. In doing so, they were certainly influenced by changes in the supply conditions of invention brought about by progress in the life sciences, especially increases in the stock of knowledge relating to enzymes and their immobilization that were achieved in the 1960s. In addition, they may also have been influenced by increases in the demand for invention that were a defensive reaction against adverse market conditions.

The failure of the Schmookler theory is illustrated by the low and negative correlations between high fructose sales and primary patents for 1967-1978. The contemporaneous correlation coefficient for this period and these variables is but -.1223; the coefficient for primary patents and high fructose shipments of the previous year is -.3757. These results, incidentally, are fairly consistent with the finding that the correlation between the total patent volume of all corn-refining firms and the total corn grind of the industry two years earlier is but .1966.

The history of the evolution of first-generation high-fructose corn syrup discredits therefore the theories that flows of invention within an industry must be positively related to either its sales or its profits. Schmookler cannot be correct that economic growth is a prerequisite for technological growth. And because flows of invention do not appear to vary directly with the prosperity and growth of the industry using those inventions, it cannot be true, contrary to Schmookler, that the supply of invention is always perfectly elastic and/or that the demand function for invention has the form which he specified. The conjunction of these assumptions was required to generate the empirical implications of the Schmookler theory. Since these implications conflict with the observations reported here, one or both of these assumptions must be wrong. Perhaps there is no invariant relationship between the demand for invention and the sales or profits of the firms likely to use that invention. Perhaps the supply of invention is less than perfectly elastic and subject to periodic changes. Both of these possibilities are consistent with the data assembled here.[113]

THE STRUCTURE OF THE INVENTION MARKET

Tables 8.7, 8.8, and 8.9 present data on the structure of the market for inventions pertaining to high-fructose corn syrup: the distribution of patent ownership and some of the characteristics of suppliers of technology.

It is apparent that by the late 1970s, several firms controlled the techological resources needed for the manufacture of high-fructose corn syrup. This low degree of market concentration, as previously noted, has been reflected in the rivalry of Clinton, Novo, ICI, Gist-Brocades, and Miles to sell enzyme systems to corn refiners such as American Maize and ADM Corn Sweeteners. Clinton's monopoly of the technology for glucose isomerization proved to be very brief. In all segments of the current invention market (see Table 8.8), that firm, despite its early leadership, must now compete with several other sellers of technology. In this sense, the market for high-fructose invention can be said to be competitive and certainly more so than the corresponding market for crystalline dextrose monohydrate which the Corn Products Refining Company dominated for so many years.

This competitive invention market has generated a correspondingly competitive product market. As indicated in Table 8.6, the number of sellers of high-fructose corn syrup has steadily increased since 1971 when Clinton and Staley were the only sources of this product. This entry into the market has had significant effects on the structure of the entire corn refining industry. As ADM, Heinz, Amalgamated Sugar, Cargill, and Amstar have invested large sums in the construction of high-fructose syrup refineries, the position of the previously dominant firm in the industry (CPC International) has been weakened (at least temporarily); the position of at least one previously weak firm (Hubinger) has probably been strengthened, and several new refiners with substantial resources have emerged as rivals to the firms that have been leaders in the industry for decades.[114] It seems, therefore, that the history of high fructose corn syrup so far is not consistent with the views of those who, like Phillips, hold that important innovations must increase the degree of concentration in industrial markets.[115]

Table 8.7 High-Fructose Corn Syrup: Distribution of Patents Among Assignees, June 5, 1980.

Assignee	Primary Patent Group[1] No. of Patents Assigned	Avg. Corp. Sales,[2] 1972-74 ($ millions)
Clinton Corn Proc. Co./St. Brds.	17	150-200 (est.)
CPC International Inc.	16	1,998
Corning Glass Works	7	904
Novo Industri A/S (Denmark)	6	3,585
R.J. Reynolds Tobacco Co.	6	—
Agency Ind. Sci. & Tech., Japan	5	1,167
Mitsubishi Chemical Ind., Ltd.	4-½	54 (1974)
Anheuser-Busch, Inc.	4	351
Miles Laboratories, Inc.	3	5,452
Imperial Chemical Industries, Ltd.	3	2,055
Baxter Laboratories, Inc.	2	367
A.E. Staley Mfg. Co.	2	473
Penick & Form, Ltd., Inc./Univar	2	56
Private Inventors	2	
Seikagaku Kogyo Co., Ltd.	1-½	
Tanabe Seiyaku Co., Ltd.	1	
Nippon Oil Co., Ltd.	1	
Givaudan Corporation	1	
Nat. Food Res. Instit., Japan	1	
Phone-Poulenc S.A. (France)	1	2,661 (1974)
Redpath Industries, Ltd.	1	
Mitsui Sugar Co., Ltd.	1	
	Secondary Patent Group[1]	
American Cyanamid Company	6	1,204
Research Corp.	3	—
Corning Glass Works	3	904
Monsanto Co.	1	2,790
Ranks Hovis McDougall Ltd. (U.K.)	1	—
Denki Kagaku Kogyo Kabushiki Kaisha	1	—
W.R. Grace & Company	1	2,892
Agency Ind. Sci. & Tech., Japan	1	—
Pfizer, Inc.	1	1,307
Nat. Food Res. Instit., Japan	1	—
Pfeiffer und Langen, A.G. (FRG)	1	167 (1974)
Purdue Research Foundation	1	

[1] See Table 8.3 for definitions of these terms.

[2] Source: *Moody's Industrial Manual;* corporate reports; R.R. Bowker Co., Gower Press Ltd., A.S. Okonomisk Literature, *Europe's 5000 Largest Companies 1975* (1975).

+ One patent is jointly assigned to Mitsubishi and to Seikagaku.

Table 8.8 Patents Relating to High-Fructose Corn Syrup (Primary & Secondary Groups), Distribution Among Classes of Invention, May 31, 1979.

Patent Assignees	Number of Patents in Invention Class	Earliest Application Date of Patents in Class
Fermentation Efficiency		
CPC International, Inc.*	5	1959
Anheuser-Busch, Inc.	4	1972
Clinton Corn Proc. Co.	3	1970
Imperial Chemical Ind., Ltd.	2	1974
Novo Industri A/S	2	1973
R.J. Reynolds Tobacco Co.	2	1969
Miles Laboratories, Inc.	1	1969
Givaudan Corporation	1	1975
Japan, Min. Int. Trade & Ind.	1	1965
Nippon Oil Co., Ltd.	1	1976
Pfeiffer und Langen A.G.	1	1974
Isomerization Efficiency: Miscellaneous		
CPC International, Inc.*	3	1971
A.E. Staley Mfg. Co.	3	1973
Imperial Chemical Ind., Ltd.	1	1975
Japan, Min. Int. Trade Ind.	1	1969
Private Inventor	2	1976
Mitsubishi Chemical Ind., Ltd.	1	1976
Clinton Corn Proc. Co.	1	1976
Isomerization Efficiency: Immobilization of Isomerases		
CPC International, Inc.*	4	1972
Mitsubishi Chemical Ind., Ltd.	3	1975
Corning Glass Works	5	1973
Clinton Corn Proc. Co.	6	1970
Japan, Min. Int. Trade Ind.	2	1968
Baxter Laboratories, Inc.	1	1969
R.J. Reynolds Tobacco Co.	2	1971
Penick & Ford, Ltd., Inc.	2	1976
Miles Laboratories, Inc.	1	1971
Denki Kagaku Kogyo K.K.	1	1973
Novo Industri A/S	2	1974
Tanabe Seiyaku Co., Ltd.	1	1973
Showa Sangyo Co., Ltd.	1	1976
W.R. Grace & Company	1	1972
Rhone-Poulenc, S.A.	1	1973
Purdue Research Foundation	1	1976
Japan, Min. Agric. & Forestry	1	1975
Refining Efficiency		
Clinton Corn Proc. Co.	3	1968
CPC International, Inc.*	2	1970
Novo Industri A/S	1	1975
Mitsubishi Chemical Ind., Ltd.	1	1974
Reactor Efficiency		
Clinton Corn Proc. Co.	1	1975
R.J. Reynolds Tobacco Co.	2	1973
CPC International, Inc.*	1	1973

*Before April 1969, Corn Products Company; before September 1958, Corn Products Refining Company

Note: During 1965-1971 most patents in these groups taught methods for raising the productivity either of the microorganisms that synthesized isomerase (fermentation efficiency) or of the enzymes themselves (isomerization efficiency). Through microbial mutation, alteration of growth media, and substitution of species, yields of glucose isomerase/xylose isomerase per fermenter volume were materially increased.

Other patents were concerned with lowering refining costs by inhibiting the formation of colored bodies and other impurities during syrup manufacture or with improving the processes for removing those materials once they were formed (refining efficiency).

By the late 1960s it was apparent that the greatest gains in productivity were to be realized through immobilization of enzymes and continuous processing. Enzymes fixed to an insoluble carrier such as DEAE cellulose or porous alumina bodies could be used and reused for hundreds of hours as part of a continuous process that permitted, as discussed in the text, substantial increases in both efficiency and product quality. Since 1973 inventions of this class have predominated in the market.

In the process of applying these new immobilization technologies certain problems were encountered in column reactor design and operation, and by 1973 patent applications dealing with these difficulties began to appear (reactor efficiency).

The gains in efficiency brought about through all this activity on the invention market are well reflected in the steady decline in manufacturers' average enzyme costs. Prior to the introduction of feasible immobilization methods these costs were, in the words of one industry scientist, "just tremendous" and amounted to perhaps as much as $2.50-$2.75/cwt. (d.b.) of high-fructose syrup produced. Continuous processes such as Clinton's (now obsolete) pressure leaf filter immobilization system permitted these costs to fall into the range of $.80-$.90/wt. (d.b.). With the current technologies manufacturers can attain unit enzyme costs as low as $.30/cwt. (d.b.).

Note: Inventions relating to the manufacture of so-called "second-generation" glucose-fructose syrups (i.e., those with fructose contents higher than 42%) by means of ion exchange fractionation or other methods fall outside the scope of the present work and are not therefore considered here.

Table 8.9. Important Primary Patents Relating to High-Fructose Corn Syrups Issued Prior to 1979, Distribution by Assignees and Field of Art.

Patent Assignees	Number of Patents in Invention Class	Earliest Application Date of Patents in Class
Fermentation Efficiency		
Clinton Corn Proc. Co.	4	1968
CPC International, Inc.	3	1967
Novo Industri A/S	2	1973
R.J. Reynolds Tobacco Co.	2	1969
Imperial Chemical Ind., Ltc.	2	1974
Japan, Min. Int. Trade & Ind.	1	1965
Miles Laboratories, Inc.	1	1969
Anheuser-Busch, Inc.	1	1972
Nippon Oil Co., Ltd.	1	1976
Isomerization Efficiency: Miscellaneous		
Japan, Min. Int. Trade & Ind.	1	1969
Imperial Chemical Ind., Ltd.	1	1975
Isomerization Efficiency: Immobilization of Enzymes		
Clinton Corn Proc. Co.	4	1970
Corning Glass Works	3	1973
R.J. Reynolds Tobacco Co.	2	1971
Baxter Laboratories, Inc.	2	1969
Miles Laboratories, Inc.	2	1971
CPC International, Inc.	2	1972
Novo Industri A/S	1	1974
Rhone-Poulenc, S.A.	1	1973
Tanabe Seiyaku Co., Ltd.	1	1973
Independent Inventor	1	1976
Refining Efficiency		
Clinton Corn Proc. Co.	2	1968
CPC Internatonal, Inc.	1	1970
Novo Industri A/S	1	1975
Mitsubishi Chemical Ind., Ltd.	1	1974
Reactor Efficiency		
Clinton Corn Proc. Co.	1	1973
Mitsubishi Chemical Ind., Ltd.	1	1976

Note: Important primary patents are defined to be those in the primary patent group that have foreign counterpart patents in at least three of the following countries: United Kingdom, France, Belgium, Netherlands, Japan, South Africa, and Canada.

Developments within the corn-refining industry may also conflict with the view, often associated with Schumpeter, that only firms large enough to have substantial market power are capable of making important contributions to the advance of the industrial arts. Although several such firms (CPC, Reynolds, Anheuser-Busch) have indeed generated significant patented inventions relating to high-fructose corn syrup, they have not been the sole source of such technological improvements. Clinton, which in the middle 1960s was only the fourth largest producer of corn syrups in the U.S. with a market share less than half that of CPC, nevertheless was the firm that did the most to create a high-fructose industry. Novo Industri and Miles Laboratories, two firms of modest size, have provided enzyme systems that have been adopted by high-fructose producers throughout the world. The probative value of these apparent exceptions to the Schumpeterian theory may, however, be questioned, for Clinton has enjoyed the financial backing of Standard Brands, a large food processor, and Novo and Miles do occupy important positions in the world enzyme industry.

SCIENTIFIC LITERATURE AND GOVERNMENTAL REGULATIONS

The scientific literature, as well as patent literature, has influenced the evolution of high-fructose technology. Table 8.10 indicates that the publications that have had the greatest influence, as measured by the frequency of their citation, have originated primarily with Japanese scientists working in the public sector. These data provide additional evidence of the large importance of the seminal work of Marshall at Argo which directly influenced Takasaki and the other early Japanese investigators. Marshall's role in the development of high fructose could be considered analogous to that of Schoch, another scientist employed by Corn Products, in the development of derivatized starches. Given the freedom to pursue basic research, both men provided pivotal discoveries that enabled other scientists to make rapid progress toward the realization of important technological goals.

The actions of U.S. regulatory agencies apparently have not had a material effect on either the technological or commercial development of high-fructose corn syrup. There is, for example, no evidence that officials of the U.S. Food and Drug Administration, an agency often accused of inhibiting or slowing the innovation of new food technologies, have ever challenged the safety of this product or sought to delay its distribution.[116] Indeed, by liberalizing the standards of identity for fruit jams and preserves in 1974, they very possibly aided the innovation of the new corn sweetener by expanding the markets open to it.[117] Perhaps the only adverse impact of regulation on the development of high fructose may have originated with the Department of Justice, which challenged the acquisition of Penick & Ford by R.J. Reynolds Tobacco Company in 1965.[118] According to some reports the lengthy litigation and the uncertainty created by this action stopped Reynolds from making the capital investments that would have allowed Penick & Ford to enter the high-fructose business in the early 1970s. Univar Corporation, to which Reynolds sold P & F under terms of a 1969 consent decree,[119] did not have the financial resources to make such investments or, for that matter, the investments necessary to modernize P & F's existing plant and equipment.[120] As a consequence, the company had to give up its plans to manufacture "Pensweet" syrups using the *Arthrobacter* isomerase that it had developed in conjunction with Reynolds.[121] In November 1976, P & F sold all rights to its glucose-isomerization technology to ICI United States, Inc., a subsidiary of Imperial Chemical Industries, Ltd., which is presently working it in an enzyme plant that it has constructed at Atlas Point, Delaware. Having discovered that it did not have the resources to compete in the high-fructose industry, Penick & Ford soon also discovered that it no longer had the resources to compete even in the glucose-syrup industry. In February 1977, burdened with a hopelessly obsolete plant that did not permit it to meet the challenges posed by low sugar prices, the company was forced to end all wet-milling operations at Cedar Rapids.[122] At present it is producing only specialty starches from raw materials provided by ADM Corn Sweeteners under a long-term supply contract.

Table 8.10 The Most Frequently Cited Publications Relating to Glucose Isomerization, 1957-1975.

Article	Author's Affiliation	Total Citations	Net Citations	Net Cit./Yr.
Marshall; Kooi, 125 *Science* 648 (1957)	Corn Prod. Ref. Company	28	28	2.00
Yamanaka, 151 *Biochim. Biophys. Acta* 670 (1968)	Kagawa University	24	22	2.44
Takasaki, *Fermentation Advances* 561 (1969)	Min. Int. Trade. Ind., Japan	23	21	2.63
Takasaki, 30 *Agr. Biol. Chem.* 1247 (1966)	do.	25	19	1.73
Tsumura; Satco, 29 *Agr. Biol. Chem.* 1129 (1965)	Min. Agric. & Forestry, Japan	20	19	1.58
Takasaki, 33 *Agr. Biol. Chem.* 1527 (1969)	as above	20	17	2.13
Strandberg, 14 *Biotech. Bioengin.* 509 (1972)	NRRL, U.S. Dept. Agric.	17	17	3.20
Strandberg, 21 *Appl. Microbiol.* 588 (1971)	do.	17	16	2.67
Vieth, 15 *Biotech. Bioeng.* 565 (1973)	Rutgers Univ.	18	15	3.75
Wang, 15 *Biotech. Bioeng.* 93 (1973)	do.	14	12	3.00
Yamanaka, 27 *Agric. Biol. Chem.* 265 (1963)	as above	11	11	.85
Yamanaka, 27 *Agric. Biol. Chem.* 271 (1963)	as above	11	10	.77
Tsumura, 25 *Agric. Biol. Chem.* 616 (1961)	as above	12	10	.72
Takasaki, 31 *Agric. Biol. Chem.* 309 (1967)	as above	10	8	.80
Giovenoco, 36 *FEBS Letters* 57 (1973)	SNAM Progetti, S.p.A.	8	8	2.00

Definitions:

Total Citations: all citations to the article within subsequent articles appearing in *SCI* source journals, 1961-1976

Net Citations: total citations less those citations to the article made by its author in subsequent publications

Net Citations/Year: net citations divided by the number of years between 1960 and 1976 that the article was available for citation

Source: Institute for Scientific Information, *Science Citation Index*, 1961-1976

The high-fructose industry of Western Europe, in contrast to that of the United States, has suffered from the actions of regulatory authorities. In order to protect the sugar-beet industries of France and Germany, European Economic Community officials on July 1, 1977 imposed a production tax on the five manufacturers of high fructose within their jurisdiction (Graanderivaten Raffenaderijen Amylum N.V. of Belgium; Tunnel Refineries, Ltd., of London; Roquette Frere, S.A. of France; Doninklijke Schoten Honig, N.V., of the Netherlands; and Maizena G.m.b.H., the CPC German subsidiary).[123] Trade sources report that during the late 1970s this special tax, which raised the costs of these five firms by about $70 per ton, substantially restrained the growth of the high-fructose industry of Western Europe.

INFLUENCE OF THE PATENT SYSTEM

Patent laws can affect the rate of techological progress within an industry by influencing the managerial demand for invention and the supply of invention. Within the high-fructose industry they have apparently influenced both.

Interviews with trade sources indicate that the patent laws probably increased business managers' demand for invention by reducing the risks of investment in research on glucose isomerization. Patenting of the inventions produced by such research apparently allowed firms to reduce the hazards of loss or depreciation of intellectual assets because of piracy of trade secrets, independent discovery, or rapid imitation. Sources at Clinton and at Standard Brands, for example, were doubtful that their managers could have been persuaded to commit substantial resources to the high-fructose program without the prospect of patent protection of resulting inventions. The expected returns from such investments would have been much lower, they felt, if managers had had to rely exclusively upon the laws of trade secrecy to secure intellectual property created by corporate laboratories. They and other sources in the industry were skeptical that any company could have kept secret for very long the methods of enzymic glucose isomerization, and therefore, could have realized more than a fleeting competitive advantage because of superior technology.

Trade sources acknowledged, of course, the costs of patent protection: the necessary disclosures that invited efforts by competitors to circumvent one's claims and the expenses of obtaining and enforcing patents. However, managers apparently perceived the benefits of patent protection as outweighing these costs, since there were no reports from any sources of unpatented technology relating to corn-syrup manufacture.[124]

The industrial chemists and fermentologists responsible for developing the processes used to make corn sweeteners emphasized that the patent laws increased the supply of invention by inducing the diffusion of valuable technical information and thereby reducing the costs of research. Many felt that the disclosure of the results of industrial research in the patent literature provided information that had stimulated and aided further investigations. In the absence of the patent laws, such communication among industrial scientists and the associated benefits would, it was believed, have been greatly diminished. The objection can, of course, be made that such communication imposes serious social costs, for it encourages wasteful, duplicative research.[125] However, in the case of high-fructose corn syrup, this objection does not seem to have much force. As previously discussed, the rivalry among Clinton, Miles, Novo, Reynolds, and the other firms within the invention market produced a diversity of enzyme-immobilization systems that represented genuine technological progress.

CONCLUSION

This chapter must report a failure to find theories capable of explaining the technological history of first-generation high-fructose corn syrup.

The record assembled here is not consistent with theories implying a close and positive correlation between either the economic growth or the profits of an industry and the growth of the technology which it uses. These findings imply that, contrary to Schmookler's assumption, the supply of invention is not perfectly elastic and/or that the demand for invention is not a positive function of the sales or profits of the firms likely to use that invention.

The record here also contradicts the theory of Phillips that major innovations must increase levels of concentration in the industries adopting them. It may also conflict with the Schumpeterian view that market power is a necessary condition for sponsorship of important inventions.

There is little evidence that the actions of American regulatory authorities, especially those of FDA officials, have inhibited the development of glucose-isomerization technology. However, there is satisfactory evidence, most of which has been gathered from interviews with research directors in wet-milling firms, that the patent laws have favored such development by increasing both the managerial demand for invention and the supply of invention.

FOOTNOTES

[1] *4 Sugar and Sweetener Report* 31 (May 1979), Table S-7.

[2] *Id.*, at 36, Table S-11.

[3] "Sweet Competition," *Wall Street J.*, Nov. 2, 1976, at 1; "Atlanta Dairies Uses High Fructose Syrup," *Dairy and Ice Cream Field*, Nov. 1975, at 28; Corn Sweetener Market, *Chemical Week*, Oct. 29, 1975, at 31; Cal Andres, "Improved Food Quality with Lower Costs," 40 *Food Processing* 46 (May 1979); Cal Andres, "HFCS Improves Flavor Retention of Jellies, Jams, Preserves," 39 *Food Processing* 64 (Nov. 1978); J.N. Major, Jr., "High Fructose Corn Syrup in Preserves," 99 *Food Production Management* 10 (July 1976).

[4] Table 8.2 is by no means a definitive statement of the relative costs of production of sucrose and high-fructose corn syrup in 1975. Although sugar refiners have for some time disclosed their costs to the U.S. Department of Agriculture, corn refiners have generally been secretive about the economics of their operations. As a result, the costs of high-fructose production can only be estimated by consultants and industry observers who, though knowledgeable, cannot have access to the accounting records that they would need to arrive at accurate measurements.

Such estimation is made difficult not only by the constant change in production techniques but also by the problems encountered in determining capital and processing costs for several firms. Joint production at a refinery of high fructose and other sweeteners makes uncertain the best way to distribute overhead costs among the several outputs. The capital costs of high fructose manufactured from a totally new plant usually exceed by some degree those of high fructose manufactured from a refinery added to an existing plant. Processing costs are affected not only by the cost of corn and the price received for wet-milling by-products, data that are generally within the public domain, but also by the size, location, and age of the plant and by the state of enzyme technology.

For other attempts to estimate the relative production costs of sucrose and high fructose, both of which yield conclusions consistent with the statement in the text, see Cal Andres, "Sweeteners Outlook," 37 *Food Processing* 46, 47 (Nov. 1976); Ezriel M. Brook, *High Fructose Corn Syrup: Its Significance as a Sugar Substitute and Its Impact on the Sugar Outlook,* World Bank Commodity Paper (No. 25, (April 1977), reprinted at 109 *F.O. Licht's International Sugar Report,* (No. 8, March 14, 1977).

[5] 4 *Sugar and Sweetener Report* 53 (May 1979), Table 11.

[6] J.M. Newton and E.K. Wardrip, "High-Fructose Corn Syrup," in *Symposium: Sweeteners* 87, 93-94 (George Inglett ed., 1974).

[7] Total invert, however, has less dextrose, more polysaccharides, and some residual sucrose.

[8] Y.Y. Lee, A.R. Fratzke, K. Wun, and G.T. Tsao, "Glucose Isomerase Immobilized on Porous Glass," 18 *Biotech. Bioengin.* 389, 404 (1976); R.V. MacAllister, E.K. Wardrip, and B.J. Schnyder, "Modified Starches, Corn Syrups Containing Glucose and Maltose, Corn Syrups Containing Glucose and Fructose, and Crystalline Dextrose," in *Enzymes in Food Processing* 331, 354 (Gerald Reed, ed., 1975).

The fructose content of "first-generation" high-fructose corn syrups has been 42 percent.

[9] In its 1964 recommendations, the Commission on Biochemical Nomenclature of the International Union of Pure and Applied Chemistry and the International Union of Biochemistry recognized only the first enzyme, giving it the systematic name of D-xylose ketol-isomerase. In its 1972 recommendations, published in 1973 as *Enzyme Nomenclature,* the Commission recognized the second enzyme, giving it the systematic name of D-Glucose ketol-isomerase; however, some biochemists do not believe that any such distinct enzyme exists.

[10] The best discussion of these matters is perhaps R.V. MacAllister's "Nutritive Sweeteners Made from Starch," 36 *Advances in Carbohydrate Chemistry and Biochemistry* 15, 49 (1979).

[11] M. Seidman, "New Technological Development in D-Fructose Production," in *Developments in Food Carbohydrates* 19, 20-21 (G.G. Birch and R.S. Schallenberger eds., 1977).

[12] The alkaline methods used are disclosed in U.S. Pat. 2,354,664 (1944) /Fr. Pat. 882,693; Brit. Pat. 549,143; and Can. Pat. 425,431.

[13] This literature is reviewed in J.P. Casey, "High Fructose Corn Syrup: A Case History of Innovation," 29 *Die Starke* 196 (1977); same article reprinted at 19 *Research Management* 27 (Sept. 1976); 22 *Cereal Foods World* 48 (Feb. 1977); and at 6 *Industrial Marketing Management* 23 (Jan. 1977).

[14] *Ibid.*, at 199.

[15] Richard O. Marshall, *The Nature of the Intermediates in Enzymatic Citrulline Synthesis,* unpublished Ph.D. Disseration, University of Wisconsin-Madison (1955).

[16] Letter from Dr. Richard O. Marshall to the author, September 30, 1977.

[17] *Ibid.*

[18] The microorganism was at the time believed to be *Pseudomonas hydrophila*, NRC 491 and 492. This misidentification was not revealed until late 1960, a delay which was to have consequences for Corn Products.

[19] R.O. Marshall and E.R. Kooi, "Enzymatic Conversion of D-Glucose to D-Fructose," 125 *Science* 648 (April 5, 1957).

[20] 35 *Chem. Engin. News* 7 (April 15, 1957).

[21] *CPC International, Inc. v. Standard Brands, Inc.*, 385 Supp. 1057 (D. Del. 1974). The patent was held unenforceable because of misrepresentations to the U.S. Patent Office in the CIP application and because its claims misidentified *Pseudomonas hydrophila* as the source of the isomerizing enzyme. See note 18, *supra.*

[22] 38 *Chem. Engin. News* 37 (March 20, 1961). Elder (1902-76) was a professor of chemistry at Syracuse University before joining the War Production Board in 1941. From 1944 to 1961 he served as director of research for Corn Products Refining Company, the corporate predecessor of CPC International. Obituary, 21 *Cereal Foods World* 461 (Aug. 1976).

[23] The M-M constant (i.e., the substrate concentration at which the reaction velocity is one half the maximum velocity at saturating substrate concentration) for glucose was .5 moles/liter and that for xylose was .0037 moles/liter.

The corresponding kinetic parameters for glucose isomerization in modern commercialized systems appear to be less than half as large as Marshall observed for his reactions. See, for example, Norman Lloyd and K. Khalleluddin, "A Kinetic Comparison of *Streptomyces* Glucose Isomerase in Free Solution and Adsorbed on DEAE-Cellulose," 53 *Cereal Chemistry* 270, 279 (March-April 1976).

[24] Poul Poulsen and Lena Zittan, "Continuous Production of High Fructose Syrup by Cross-Linked Cell Homogenates Containing Glucose Isomerase," *Methods in Enzymology* 809, 811 (1976).

[25] Discussions of Brady and his corporate policies can be found in George Bookman, "The Uncommon Market of Corn Products," 65 *Fortune* 99 (March 1962); "The Voracious Appetite of Corn Products Co.," 86 *Forbes* 15 (July 1, 1960); "Brady of Corn Products Refining," 55 *Fortune* 136 (Feb. 1957); and "Corn on the Cob," 78 *Forbes* 22 (Nov. 15, 1956).

[26] Preliminary agreement on the merger was announced by officers of the two companies on July 16, 1958. 188 *Comm. Finan. Chron.* 245 (July 21, 1958). Corn Products Company, the product of the merger, came into being on September 30, 1958. 188 *Comm. Finan. Chron.* 1394 (Oct. 6, 1958).

Earlier Brady had also acquired Laurel Products of Harshaw Chemical, manufacturer of "NuSoft" fabric rinse, C.H. Knorr Co. in Germany, manufacturer of dehydrated soups; and firms producing branded milk additives and dog foods. 33 *Chem. Engin. News* 1288 (March 28, 1955); 187 *Comm. Finan. Chron.* 2000 (May 5, 1958).

[27] This work eventuated in the issue of a patent, U.S. Pat. 2,995,039 (1969) /W. Ger. Pat. 1.157,065; Can. Pat. 677,443; Brit. Pat. 932,994; and Indian Pat. 70.603, and in the introduction in late September of 1960 of "Mazola" (TM 721,414) margarine which was much touted in the company's annual report for that year (at 5).

The Corn Products patent on the process for making the new margarine was, however, later invalidated. *Corn Products Company v. Standard Brands, Inc.*, 359 F. 2d 739 (7th Cir. 1966).

[28] Managerial reluctance to invest in high-fructose corn syrups once they had already been innovated by Clinton was explained in just such a fashion by a Corn Products marketing executive. "How Sweet It Is," 55 *Barron's* 11, 70 (Dec. 1, 1975).

[29] 185 *Comm. Finan. Chron.* 1152 (March 11, 1957).

[30] In the late 1950's there appeared in the business press several reports suggesting disenchantment at Corn Products with the returns from its Chemical Division: "Brady has continued but not stepped up the research program, and has switched the direction to quick-pay-out products." "Brady of Corn Products Refining," 55 *Fortune* 136, (Feb. 1957). See also the complaints against industrial products reported in "Corn Products Finds Other Fields Are Green," *Business Week*, July 5, 1958, at 76, 78.

A chemist who worked at Argo during this period has confirmed Brady's unhappiness with the performance of the Chemical Division and misgivings about basic research.

[31] Some, such as the technical staff at Anheuser-Busch, Inc. and Union Starch and Refining Company, decided that the only benefit they could derive from Marshall's research was a demonstration that enzymatic isomerization could not be made an economical process. Accordingly, they intensified their efforts, all of which were unavailing, to find a practical process of alkaline isomerization. See, for Anheuser-Busch, Inc., U.S. Pats. 3,305,305 (1967); 3,383,245 (1968); 3,690,940 (1972); and 3,684,574 (1972); for Union Starch, U.S. Pat. 3,432,345 (1969).

Similar work was also pursued at the laboratory of one of Corn Products Company's European subsidiaries. See U.S. Pat. 3,475,216 (1969).

32 Y. Takasaki, Y. Kosugi, and A. Kanbayashi, "*Streptomyces* Glucose Isomerase," in *Fermentation Advances* 561 (D. Perlman ed. 1969).

33 "In 1956, Marshall, et al. observed the formation of glucose isomerase . . . It was the only previous paper available when we initiated the study in 1960. Acting on their work as only clue, we had undertaken this study." T. Sato and N. Tsumura, "Enzymatic Conversion of D-Glucose to D-Fructose," 67 *Kogyo Kagku Zasshi (J. Ind. Chem., Japan)* 683 (1964).

All other Japanese workers on glucose isomerization make similar acknowledgements of Marshall's priority and the importance of his work in the evolution of research in this area. See, for example, the literature review of S. Suzuki, "Starch Hydrolyzing Industry in Japan: The Progress of the Past Decade and Future Prospects," 17 *J. Jap. Soc'y. Starch Sci.* 155, 171 (1969).

34 N. Tsumura and T. Sato, "Conversion of D-glucose to D-fructose by a Strain of Soil Bacteria," 24 *Bull. Agric. Chem. Soc'y. Japan* 326 (1960); "Enzymatic Conversion of D-glucose to D-fructose: Identification of Active Bacterial Strain and Confirmation of D-fructose Formation," 25 *Agric. Biol. Chem.* 616 (1961); "Fructose Accumulation Activity of Aerobacter cloacae, Strain KN-69," *ibid.*, at 620.

Jap. Tokkyo koho (Publ. Pats) S37-9964 (August 1, 1962), to T. Sato and N. Tsumura.

35 Y. Takasaki and O. Tanabe, "Formation of Fructose from Glucose by Bacteria: Properties of Glucose Isomerase," 20 *Hakko Kyokaishi* 449 (1962), 60 *Chem. Abstr.* 806; Y. Takasaki and O. Tanabe, "Studies on the Isomerization of Sugar by Bacteria (Two Parts)," 36 *Nippon Nogeikagaku Kaishi (J. Agric. Chem. Soc'y., Jap.)* 231 (1963); "Sugar Isomerases," 27 *Agric. Biol. Chem.* 265 (1963).

36 Tzu-Yuan Hsu and Shen-Chiung Shen, "D-Xylose Isomerase of Streptomyces griseus," 4 *Sheng Wu Hua Hsueh Yu Sheng Wu Wu Li Hueh Pao (Acta Biochemica* et *Biophysica Sinica)* 342 (1964); 62 *Chem. Abstr.* 6728.

37 S. Tsumura, E. Itakura, and T. Sato, "A Study on Isomerization of Dextrose by a Streptomyces Strain, paper, presented at the annual meeting of the Agricultural Chemical Society of Japan, Sapporo, July 20, 1964. Information on this paper has been supplied by a very reliable industry source.

38 Jap. Tokkyo Koho 66 17, 640 (Oct. 7, 1966, appl., June 12, 1964), to T. Sato and N. Tsumura. This became Jap. Pat. 489,867. 68 *Chem. Abstr.* 86143.

Jap. Tokkyo Koho 69 28,473 (Nov. 22, 1969, appl., June 12, 1964), to T. Sato and N. Tsumura. This was a division of the first application and covered techniques for producing the isomerizing enzyme. 72 *Chem. Abstr.* 107407.

Both applications disclosed inventions relating to *S. phaeochromogenes* and six other species within the same genus.

The inventions were later discussed in the following papers: N. Tsumura and T. Sato," Enzymic Conversion of D-glucose to D-fructose," 29 *Agric. Biol. Chem.* 1129 (1965); N. Tsumura, E. Sakakura, M. Ishikawa, and T. Sato, "Enzymic Conversion of D-glucose to D-fructose," 23 *Hakko Kyokaishi* 516 (1965); N. Tsumura and M. Hagi and T. Sato, "Propagation of Streptomyces phaeochromogenes in Presence of Cobaltous Ion," 31 *Agric. Biol. Chem.* 902 (1967).

39 Takasaki and Tanabe, in two of the patent applications discussed at note 40, *infra*, explicitly acknowledge the priority of Sato and Tsumura in exploring *Streptomyces* isomerases. See also on this same matter Suzuki, Starch, *supra* note 33, at 171.

40 Jap. Tokkyo koho 66 7428 (April 22, 1966, appl., Jan. 30, 1965), 66 7430 (April 22, 1966; appl., Feb. 18, 1965), and 66 7832 (April 22, 1965; appl., Jan. 30, 1965), all to Y. Takasaki and O. Tanabe; 65 *Chem. Abstr.* 9700, 11311, and 11310 (respectively).

41 Jap. Tokkyo koho 66 7431 (April 22, 1966; appl., May 11, 1965), to Y. Takasaki and O. Tanabe (later, Jap. Pat. 484,472); Jap. Tokkyo koho 69 16,352 (July 19, 1969; appl., May 11, 1965), to Y. Takasaki and O. Tanabe, with K. Yoritomi (Sammatsu Kogyo Co., Ltd.).

These inventions were later discussed in the following publications: Y. Takasaki, "Sugar-Isomerizzing Enzyme," 30 *Agric. Biol. Chem.* 1247 (1966); Y. Takasaki, "Kinetic and Equilibrium Studies on D-glucose-D-fructose Isomerization," 30 *Agric. Biol. Chem.* 309 (1967).

42 All of the Takasaki-Tanabe applications in Japan were consolidated for the purpose of obtaining foreign counterpart patents. The foreign applications eventuated in the issuance of the following patents: U.S. Pat. 3,616,221 (1971); Can. Pat. 873,851; Brit. Pat. 1,103,394; Fr. Pat. 1,471,775; W. Ger. Pats. 1,792,748 and 1,567,323; and patents, the numbers of which are unavailable, in the Netherlands, Belgium, Portugal, Switzerland, and Spain.

43 H. Ishikawa, et al., "Production of High Fructose Corn Syrup by an Immobilized Glucose Isomerase," 74 *Am. Inst. Chem. Engin., Symp. Series* 36 (No. 172, 1978).

[44] Trade sources indicate that Clinton's special relationship with the Japanese firm began in the early 1960s when a delegation from this company visited the United States and found that Clinton was the only wet miller willing to open its plant for inspection tours. During the following summer an employee of the Japanese firm was sent to Clinton to study corn-refining technology in the company's laboratories. Communications he received during that period from his superiors in Japan contained information on the work of Takasaki and Tanabe, news which he then relayed to Clinton scientists.

[45] Mermelstein, in his "Immobilized Enzymes Produce High Fructose Corn Syrup," 29 *Food Technology* 20 (June 1975), states that the trip to Japan occurred in October of 1965, which accords with an account given by a very reliable trade source. However, according to this and another such source, the Clinton/SB delegation experienced a large earthquake toward the end of its stay in Tokyo. Such tremors occurred in that city on August 29 and September 2, but none took place during October. *New York Times,* August 30, 1965, at 2:3; September 3, 1965, at 18:2. This suggests that the trip probably was in the month of August.

[46] The account which follows of the Tokyo negotiations has been constructed from information provided by very reliable industry sources.

[47] This worry was apparently unfounded. So far as can be determined, Clinton was the only company at the time seeking a license agreement from the Japanese government.

[48] This support appears to have been led by O. Lester Applegate, a senior vice president, to whom Standard Brands gives much credit for the innovation of its high-fructose corn syrup. See B. Abrams, "Standard Brands President, Gutoff, Quits After 17 Months; Applegate is Successor," *Wall Street Journal,* October 2, 1978, at 22:1. It is also significant that when the Institute of Food Technologists gave its 1975 Food Technology Industrial Achievement Award to Clinton for its high-fructose syrups, Applegate accepted the award on behalf of the company. See Mermelstein, *supra,* note 45 at 20.

[49] The conflict between the Sato-Tsumura patents and those of Takasaki-Tanabe resulted in an opposition proceeding before the Japanese Patent Office in the spring of 1971. *Nikkan Kogyo Shinbun,* April 9, 1971.

[50] The reasons for the success of Standard Brands and the failure of the other companies are not altogether clear. Sources at Corn Products and Staley insist that by the time their representatives talked to the Japanese government, the Clinton/Standard Brands delegation had already won agreement to an exclusive U.S. license, and as a consequence they found officials unwilling to deal with them. On the other hand, reliable sources at Clinton report that other U.S. corn refiners had preceded them in negotiations with the ministry and had left Japan without a contract either because they had found the ministry's terms unacceptable or because they had been rebuffed in their attempts to purchase the Takasaki-Tanabe patents.

[51] See the case cited at note 27, *supra.*

[52] See. E.R. Kooi and R.J. Smith, "Dextrose-Levulose Syrup from Dextrose," 26 *Food Technology* 57 (Sept. 1972); U.S. Pats. 3,813,318 (1974); 3,847,740 (1974); and 4,956,065 (1976).

[53] Claim No. 1 of U.S. Pat. 3,616,221 (1971) embraces any iosomerization process using enzymes from "a microorganism which is a member of the *Streptomyces* genus and which is characterized as having the ability to assimilate xylan and D-xylose to produce the glucose isomerizing enzyme."

[54] Information in this paragraph has been supplied by a very reliable trade source.

[55] However, it did not offer such licenses to all corn refiners. After an unavailing trip to Japan in 1965 to seek a license from the government to the Takasaki-Tanabe technology, an official of Union Starch experienced a similar lack of success in obtaining a sublicense from Clinton. Letter from James P. Casey (formerly, Vice President of Research, Union Starch and Refining Co.) to the author, September 13, 1977.

[56] It will be recalled that Corn Products Refining licensed American Maize under the Newkirk patents, thereby providing an alternative source of supply for crystaline dextrose.

[57] *New York Times,* May 16, 1969, at 64:7.

[58] All chemical and enzymological research was carried out at the Reynolds laboratories in North Carolina, but all pilot-plant testing took place at the Penick & Ford plant in Cedar Rapids.

The information in this paragraph has been supplied by very reliable trade sources.

[59] Enzymic thermostability is of economic importance because the equilibrium constant of the isomerization reaction, which is slightly endothermic, increases with temperature, thereby permitting production of syrups of higher fructose contents.

[60] These applications led to the issuance of the following patents: U.S. Pat. 3,645,848 (1972) /Can. Pats. 984,775-776 (1976); Brit. Pat. 1,328,970; Fr. Pat. 2,069,558; West German Pat. 2,055,515; and others.

[61] 44 *Chem. Engin. News* 34 (Oct. 31, 1966). Miles left the industry six years later when in March of 1972 it discontinued operations at the obsolete wet-milling plant at Granite City, Illinois, which it had inherited from Union Starch. *Wall Street Journal* Feb. 22, 1972, at 15:4. On April 1, 1972, it sold all its distribution facilities for syrups and starch to Archer-Daniels-Midland Co. for $739,937, and on February 15 of the next year, it sold the plant itself to the same company for $576,000.

[62] U.S. Pat. 3,625,828 (1971) /Can. Pat. 920,077; Brit. Pat. 1,280,396; Fr. Pat. 2,043,399; and W. Ger. Pat. 2,018,058.

[63] The Sipos patent has the earliest application data (Dec. 22, 1969) of all patents of U.S. origin dealing with immobilization of glucose isomerase and arguably anticipates a later Clinton/Standard Brands patent (U.S. Pat. 3,788,945) which also discloses a process for immobilizing a *Streptomyces* isomerase on DEAE cellulose.

However, before Sipos had reduced his invention to practice Takasaki and his colleagues at the Fermentation Research Institute had invented a means of fixing isomerase within the bacterial cells through heat treatments and thus permitting its continuous use. See U.S. Pat. 3,753,858 (1973; Japanese appli., Jan. 20, 1968).

[64] It was, however, evaluated by Staley as a possible alternative to the Clinton/Standard Brands technology.

[65] It will be recalled that Clinton had started the enzymic manufacture of lactic acid prior to World War II and that during the 1960s, it had done a good deal of work on glucoamylase.

[66] See Thomas Richardson, "Introduction, Symposium: Immobilized Enzymes in Food Systems," 39 *J. Food Sci.* 645 (1974).

[67] B.J. Schnyder, "Continuous Isomerization of Glucose to Fructose on a Commercial Basis," 26 *Die Starke* 409 (Dec. 1974).

[68] "Isomerose 30" was also sold to the baking industry under the name "Lev-U-Dex." 10 *Cereal Sci. Today* 217 (May 1968).

Although limited shipments of this first high-fructose syrup began, as the text indicates, in the early part of 1967, it was not until the spring of 1968 that Clinton began advertising it to the trade. The first publicity on the product appeared in the January 1968 issues of trade journals, and the first formal advertisements followed in May. See, for example, 40 *Food Engin.* 80 (May 1968).

[69] Mermelstein, *supra* note 45, at 22, 24.

[70] In his book, Schmookler stated his argument in greater detail and with greater rigor than is suggested in the text. He assumes (1) that at any time the stock of knowledge is large enough so that it does not constrain the inventive potential of a field; (2) that inventors allocate their research resources so as to maximize their expected profits; (3) that, if a new capital-good invention will capture a constant share of the market for inventions of that type, then the expected profit from such an invention will vary directly with the expected size of the relevant market for the capital good; (4) that the present size of such a market correlates well with its expected size when returns from a prospective invention accrues; (5) that the probability that an invention will be made is proportional to its expected profitability; (6) and that the cost of making an invention is independent of the size of the expected market for the capital good. It then follows, argues Schmookler that the larger the expected size of the market for the capital good affected by the invention, the larger the yield from the invention and the larger the chance it will be made. Moreover, it also follows that the larger the present size of the goods market, the larger is the chance that the invention will be made. Hence, ". . . the number of inventions in the field will be highly correlated with its present sales volume" (given the expected cost of invention and the share of the invention market that it is expected to achieve). *Invention and Economic Growth* 113 (1966).

[71] This economic constraint was concisely described by O.L. Applegate, a Standard Brands vice president, in explaining why his firm delayed starting up a new plant it had constructed at Montezuma, New York: "We either run full tilt or we stop." "Darkness Before Dawn," 121 *Forbes* 67 (June 26, 1978), at 68.

[72] "Corn Syrup Price Hike Expected to Stick as All Firms Go Along," 195 *Oil, Paint and Drug Reporter* 32 (June 9, 1969). See also on the corn syrup price war the following: F.W. Campanella, "Husky Corn Products," 48 *Barron's* 9 (July 22, 1968); "Mother Corn Tries Harder," 102 *Forbes* 59 (Oct. 15, 1968).

[73] By 1974, after building another modern plant in Dayton, Ohio, Cargill had captured about 16 percent of the corn-syrup market and thus had become the third largest producer. At this time, Staley and Corn Products, the leading firms, had about 18 percent shares. Trade sources.

[74] This performance led the new president of Corn Products, Howard Harder, to declare in the fall of 1968 that "we had a hell of a time with this corn-syrup price war last year." "Mother Corn," *supra,* note 72, at 59.

For a discussion of the similar effects of the 1972 price war among corn syrup producers, see "Corn—An Editorial," 68 *Sugar y Azucar* 15 (Oct. 1973).

[75] J.P. Casey, *supra* note 13, at 201.

[76] This interpretation seems most evident in the discussion given at Corn Syrup Hike, *supra* note 72.

[77] Letter from James P. Casey to the author, September 13, 1977.

[78] Donald E. Nordlund, "Catalyst in the Sweetener World," 9 *Agri-Industry News* (Corn Refiners Assn., Inc.,) 1, 2 (April 1977), Same paper appears at 39 *Amer. Dairy Rev.* 368 (July 1977).

[79] If patents in the secondary group (see Table 8.3) are considered, the proportion falling within this period increases to 35 percent.

[80] Immobilization, though it increases the useful life of enzyme preparations, usually causes a material reduction in their catalytic activity. The coupling of the enzyme to the carrier may reduce the number of active sites available for substrate contact or perturb the enzyme's steric structure. Some hydrolases (i,e., enzymes catalyzing hydrolysis) show a 60 percent to 95 percent drop in activity when bound to an inert carrier; the objective of research on their immobilization must therefore be to find carriers that allow this loss to be minimized. H. Orth and W. Brummer, "Carrier-Bound Biological Active Substances and their Applications," 11 *Angew. Chem. Int. Ed.* 249 (April 1972).

[81] One reason this is so is that the number of *successful* patent applications does not measure the volume of research. There may be a divergence between such volume and even the number of *all* patent applications, successful or not.

[82] Robert Bohall, et. al., *The Sugar Industry's Structure, Pricing and Performance* 56-68 (CED-ERS, U.S. Dept. of Agri., Agri. Econ. Rept. No. 363, March 1977).

[83] See the references cited at note 3, *supra.*

[84] Staley: "Sweet Profits from a Sugar Substitute," *Business Week.* August 4, 1975, at 76.

[85] Kenicki Okada, Immobilized Enzyme, 10 *Chemical Economy and Engineering Review* 20, 21 (December 1978).

[86] Seidman, note 11, *supra. at 22-23.*

[87] M. Vaheri and V. Kauppinen, "Improved Microbial Glucose Isomerase Production," 12 *Process Biochemistry* 5 (July/August 1977). The activity, for example, of the isomerase from *S. olivaceus* (used by Miles) is but 38 percent that of *S. flavovirens,* IFO 3197.

[88] Penick & Ford, under the terms of its sale by Reynolds to Univar Corp. in 1971, held rights in North and South America under the patents assigned to its former parent. On November 15, 1976, Imperial, through its subsidiary ICI U.S., Inc., purchased these rights and announced that it would begin commercial production of glucose isomerase using this and its own technology at a plant being built at Atlas Point, Delaware. This plant began operations during the spring of 1977. *Wall Street Journal,* Nov. 18, 1976, at 21:3; *Chem. Market Report,* Nov. 22, 1976, at 1; *Chem. Engin. News,* Dec. 6, 1976, at 13.

[89] "A Sweet Future Buoys High-Fructose Corn Syrup," *Chemical Engineering,* September 27, 1976, at 54, 56.

[90] In addition, immobilization systems for glucose isomerase were available about this time from Mitsubishi Chemical Industries/Seikagaku Kogyo, Denki Kagaku Kogyo, Kyowa Hakko Kogyo, and SNAM Progetti, S.p.A. However, these systems have yet to be marketed in the United States.

[91] The advantages and disadvantages of the different techniques for immobilization are discussed at Hachiro Ishikawa, "Isomerization of Glucose with Immobilized Enzyme," 9 *Chemical Economy & Engineering Review* 33 (May 1977). See also Jan Konecny, "Enzymes as Industrial Catalysts," 29 *Chimia* 95 (March 1975).

[92] Discussions by the author with an experienced engineer and inventor employed by a large company supplying equipment to corn refiners have disclosed that the minimum optimal scale for wet-milling plants is primarily determined by the capital costs of the primary starch-gluten separators, which increase in proportion to the .6 power of the capacity of those centrifuges. The author's source estimated that minimum optimal scale was probably about 20,000 bu/day in 1957 and about 35,000 bu/day at present, an estimate that agrees with those made by other trade sources. Industry executives

indicate that capital costs for new plants rise by about $2,000,000 for each additional thousand bushels of grind capacity installed; thus, a new plant of about minimum optimal scale should cost about $60,000,000 or perhaps a bit more.

These estimates appear to be confirmed by the data being made available on new plants for the manufacture of high fructose. John Labatt, Ltd. and Redpath Industries, Ltd., for example, formed a joint venture in 1977 to put up such a plant in southwestern Ontario which, with a planned capacity of about 25,000 bu/day, was expected to cost $60,000,000 to build. *Wall Street Journal,* Dec. 20, 1977, at 2. Recently, CPC International, Inc., announced that it would be constructing a 32,000 bu/day wet-milling plant in California for the manufacture of high fructose at a cost of $60,000,000. *Wall Street Journal,* May 17, 1969, at 12.

[93] This is explained, of course, not only by the higher degree of competition on the market for inventions relating to high-fructose corn syrup but also by the higher rate of growth of the industry using those inventions.

[94] The estimate of the 1975 share is taken from an unpublished market study prepared for a large food processor and supplied by an industry source. The estimate of the present share is taken from Bill Abrams, "CPC to Decide on High-Fructose Facility," *Wall Street Journal,* May 15, 1979, at 30:1.

[95] In November 1974 Dimmit Agri-Industries filed a civil antitrust suit against members of the corn-refining industry, charging them with a conspiracy to depress prices of corn products in order to drive it out of business. *Dimmitt Agri-Industries, Inc. v. CPC International, Inc.,* Dkt. No. CA 2-74-144, U.S. District Court, N.D. Texas Wall Street Journal, April 10, 1975, at 29:1. This case is currently (1981) on appeal to the U.S. Court of Appeals, Fifth Circuit (Dkt. No. 80-2065, filed Sept. 24, 1980).

[96] New York Times, August 20, 1974, at 54:6; also, 69 *Sugar y Azucar* 8 (September 1974).

[97] *Wall Street Journal,* April 29, 1970, at 31:2.

[98] *Wall Street Journal,* April 8, 1971, at 34:5.

[99] Production of the firm's "Corn Sweet" product (TM 1,070,709) had begun in semi-commercial quantities from the pilot plant in November 1974.

For a statement of ADM's strategy concerning entry into the high-fructose business, see "When Competition Against Sugar Turned Sour," *Business Week,* November 15, 1976, at 136.

[100] J.R. Russo, "High Fructose Corn Syrup at 4-Million Pounds/Day," 48 *Food Engineering* 61 (May 1976).

[101] Cargill and Miles also formed another joint venture, Mi-Car International, Inc., for the purpose of licensing high-fructose technology to foreign companies. At present, Mi-Car has contracted to supply such technology to AIPK Poljoprivreda Bosanska Dubica, a Yugoslavian food processor, and to KOMPLEX, the Hungarian state agency for plant purchasing. *Wall Street Journal,* Dec. 8, 1977, at 27; April 17, 1978, at 21; also, *Chem. Mark. Rptr.,* April 24, 1978 at 7:1.

These projects in the Eastern Bloc countries also involve Miles Kali-Chemie GmbH & Co., a joint venture formed in 1972 between Miles and Kali-Chemie A.G. of Hanover, West Germany that maintains enzyme manufacturing facilities at Nienburg, West Germany from which it has supplied isomerases to some European high-fructose producers. 13 *Process Biochemistry* 39 (May 1978).

[102] 44 *Food Engineering* 45 (Dec. 1972); see also the firm's annual report for 1972, at 4.

[103] *New York Times,* March 26, 1976, at 55:3; 21 *Cereal Foods World* 228 (June 1976).

[104] *Wall Street Journal,* August 29, 1977, at 17.

[105] Corporate annual reports. Staley's new plant is discussed at W.H. Lemaire, "Remarkable Advances in Process Control," 50 *Food Engineering* 55 (July 1978).

[106] 3 *Sugar and Sweetener Report* 38 (February 1978).

[107] For discussions of the slump in the high-fructose industry see references cited notes 71 and 99 *supra.*

[108] See Staley's *Annual Report, 1977,* at 1, 5 and 27; A.E. Staley Mfg. Co., Form 10-K Annual Report, FY 1977, at 8. The decline was moderated by a steady drop in corn prices during 1976 and 1977.

[109] E. Ross Johnson, Chief Executive Officer of Standard Brands, in his letter to stockholders in the firm's *1978 Annual Report* stated in part: "A key factor in keeping our 1978 earnings from rising even higher has been the low level of profitability at our Clinton Corn Processing Company, a situation that has been present for the past 2-½ years. This industry which is highly capital intensive, has been plagued by low sugar prices and tremendous over-capacity. This has led to depressed selling prices . . . for our ISOMEROSE High Fructose Corn Syrup."

See also the FY 1977 annual report of Archer-Daniels-Midland Co., at 9.

[110] *Wall Street Journal,* May 27, 1976, at 10:5. A-B licensed its *Actinoplanes* technology to Gist-Brocades, N.V. of Delft, Netherlands. About the same time Gist-Brocades also purchased the Waller-

stein Division of Baxter-Travenol Laboratories, Inc. and set up a U.S. subsidiary, GB Fermentation Industries, Inc., to manufacture glucose isomerase and other enzymes. *Wall Street Journal,* July 14, 1977, at 25:5.

[111] *Chemical Marketing Reporter,* September 20, 1976, at 4.

[112] 982 *Official Gazette,* 41 (May 29, 1979).

[113] In June of 1978, Great Western Sugar Company began construction in Johnstown, Colorado, of a high-fructose syrup refinery and an associated corn wet-milling plant with a capacity of 8,000 bu/day. These facilities, which will use an enzyme system supplies by Novo Industri, are to be in operation in the summer of 1980.

[114] CPC's share of the total industry corn grind has fallen from about 40.5 percent in 1956 to about 20 percent at the present time. Whether this trend will be reversed by the firm's recently announced investments in new plants at Stockton and Winston-Salem and in expanded capacity at Argo is, of course, uncertain.

[115] Almarin Phillips, *Technology and Market Structure* (1971).

[116] Having subjected their isomerase-producing microorganisms to extensive toxicological testing, Clinton, Novo, Corn Products, Anheuser-Busch, and ICI United States have filed with the Food and Drug Administration petitions requesting that their enzymes be affirmed GRAS (Generally Recognized As Safe) and hence suitable for use in the manufacture of foods. GRAS Pat. 4G0042, Standard Brands, Inc., 41 *Fed. Reg.* 28310 (1974); GRAS Pat. 6G0060, Anheuser-Busch, Inc., 41 *Fed. Reg.* 17953 (1976); GRAS Pat. 7G0086, Novo Laboratories, Inc./Novo Industri A/S, 42 *Fed. Reg.* 27298 (1977); GRAS Pat. 7G0084, CPC International, Inc., 42 *Fed. Reg.* 28601 (1977); and GRAS Pat 7G0078, ICI United States, Inc./ICI Ltd., 42 *Fed. Reg.* 43668 (1977). In response to these petitions, FDA officials have not raised any objection to the use of these several enzymes in the preparation of high-fructose corn syrups.

[117] In November 1973, the National Preservers Association, specifically calling attention to the introduction of high-fructose corn syrup, petitioned the FDA to change the standards of identity, first promulgated in 1940, for fruit jelly and preserves (codified then at 21 C.F.R. § 29.2 and 29.3). In particular, it proposed that the FDA should rescind the requirement that corn sweeteners be no more than 25 percent by weight of all sweeteners used in the manufacture of such food products. 38 *Fed. Reg.* 31450 (1973).

On August 22, 1974, the FDA issued the final order amending the standards of identity for fruit jelly and preserves so as to permit manufacturers to use corn sweeteners in unlimited amounts in the preparation of these products. 39 *Fed. Reg.* 31304 (1974). The new standards are currently codified at 21 C.F.R. § 150.140 and 150.160. 42 *Fed. Reg.* 14302 (1977).

[118] See *U.S. v. Penick & Ford, Ltd.,* 242 F. Supp. 518 (D.N.J. 1965) (denying motion for preliminary injunction against the merger).

[119] *Wall Street Journal,* August 22, 1969, at 5:1. The sale was consummated on June 1, 1971.

[120] During 1974-75 Univar did, however, provide assistance with a limited modernization of the Cedar Rapids refinery.

[121] Univar Corporation, *Annual Report 1975,* at 11.

[122] *Wall Street Journal,* February 14, 1977, at 16:5; Univar Corporation, *1976 Annual Report,* at 5.

Some idea of the very high labor costs burdening P & F can be gained from a comparison of its operations with those of its Cedar Rapids neighbor, ADM Corn Sweeteners. With a work force of 675, P & F's aged plant had a grind capacity of about 60,000 bu/day; ADM, with a work force of less than 200, could daily grind 165,000 bu/day at its huge new plant.

[123] *Chemical Age,* July 8, 1977, p. 4.

[124] However, the optimum conditions and equipment for operating a patented process in a plant, often called "know-how," are frequently kept as trade secrets.

[125] See, for example, Sir Arnold Plant, "The Economic Theory Concerning Patents for Invention," 1 *Economica* 2d 30, 46 (Feb. 1934).