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From Pioneering Invention to Sustained Innovation

HERBICIDES AT DUPONT

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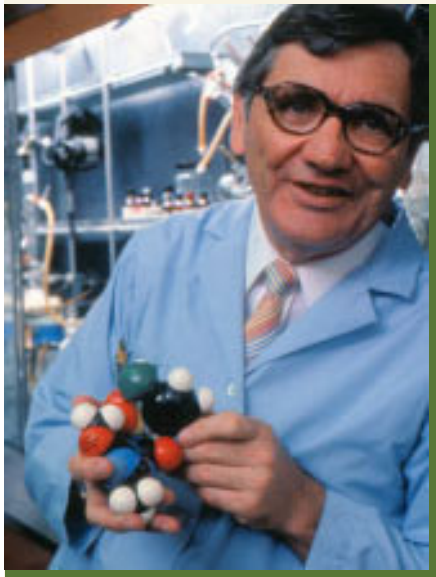


George Levitt with a model of Glean. Courtesy of the Hagley Museum and Library.

The oil shocks of the 1970s hit hard in the United States. Americans felt the effects in their daily lives as they formed lines at gas stations and feared for their jobs. While families struggled to adapt, chemical companies scrambled to find new niches that would allow them to retain their relevance in the new economy. Supply problems and high feedstock prices forced chemical industry leaders to dramatically cut costs and move into new product lines. At DuPont, one of the most venerable names in American chemistry, managers looked for ways to develop areas that required less dependence on oil. The company's new corporate plan emphasized the life sciences: agrochemicals, pharmaceuticals, and medical products. And with its executive committee averse to the idea of major acquisitions, DuPont turned to its own researchers for ideas.

Agriculture was not an entirely new direction for DuPont; the company had researched and produced herbicides, pesticides, and fungicides on a small scale for nearly 50 years. In 1975, however, one of their researchers, George Levitt, discovered sulfonylurea herbicides, a class of chemicals that would revolutionize the market and DuPont's place in it. By 2001 DuPont's crop protection division was producing 40 products and maintaining operations in 40 countries. But while sulfonylurea herbicides are now widely used in the global weed-control market, DuPont nearly canceled the research program in its infancy. The story of its survival offers a telling example of how one company turned a pioneering invention into a sustained program of innovation.

The Origins of an Herbicide

George Levitt joined agrochemicals research at DuPont in 1956. Early in his tenure there he synthesized several compounds derived from various arylsulfonyl isocyanates. (A sulfonyl group consists of a highly oxidized sulfur atom double bonded to two oxygen atoms and single bonded to two other organic groups.) These derivatives showed no biological activity in primary response screenings for plant growth regulators, insecticides, and fungicides, but they were nevertheless added to DuPont's chemical library. Levitt moved on to other projects. Almost 16 years later a DuPont entomologist working on a new screen for mite chemosterilants found some activity in one of these derivatives, a sulfonylurea. Intrigued, Levitt began making analogs of the sulfonylurea molecule and had them screened for various responses. Most of the analogs showed little promise, but one demonstrated a weak ability to slow plant growth at a rate of two kilograms per hectare. Levitt did not think this finding was particularly promising and did not bother to include it in a report to management on his activities, but it was of mild-enough interest that he mentioned it to his supervisor, Raymond W. Luckenbaugh, in August 1974.

Luckenbaugh agreed that it was a mere "wiggle of activity." But he too had been interested in sulfonylurea compounds and encouraged Levitt to continue his work. Luckenbaugh believed in having his chemists "scout around" and pursue any wiggles of activity they found. He gave Levitt a list of 90 sulfonylurea molecules in DuPont's chemicals library. Of these only 2 showed promise; coincidentally, Levitt had synthesized both of them in 1962.

Levitt noticed that these 2 molecules shared an interesting characteristic. Each had a heterocyclic group attached to the nitrogen end of the sulfonylurea chain; in fact, they were the only 2 among the 90 to have heterocyclic compounds in their structure. Remembering that many heterocyclic compounds are biologically active, he realized that this might be a fruitful area of research. A widely selling corn herbicide contained a heterocycle, as did some DuPont products. Heterocyclic derivatives were also found in some fungicides and pharmacological agents. Perhaps, thought Levitt, different heterocyclic compounds could lead to greater biological activity. This insight proved crucial.

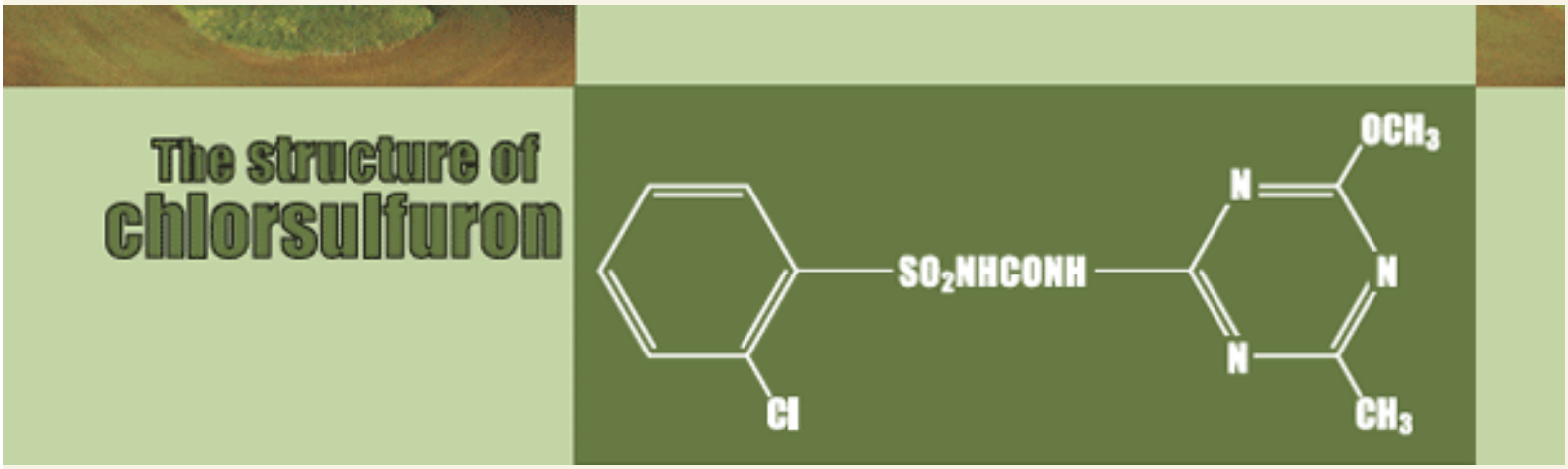
Levitt began making structural changes to the heterocyclic compound with the hope of developing molecules with greater herbicidal activity. One of these, named R4321, showed an astonishingly high level of plant-growth retardation when it was tested in July 1975. R4321 was so potent that minor residues remaining in the spray system damaged plants that were later being treated with other compounds. Levitt recalls, "I knew we were on to something with R4321, but I felt there was a lot more we had to do to upgrade that kind of activity. . . I didn't think that that was the end of the story . . . it was the beginning." The research program grew. In February 1976 Levitt created the molecule chlorsulfuron, whose field tests that summer surpassed even that of R4321.

When the early sulfonylurea compounds were first applied in field tests, DuPont's agents had never seen such high potency or low application rates. One field agent thought the manager prescribing the low rate was "nuts."

Others conducting early field tests at a university concluded that there was an error in the instructions; since herbicides were normally applied at rates of a few kilograms per hectare, not a few grams per hectare, they moved the decimal point by two places, effectively increasing the application rate 100-fold. Two years later weeds would still not grow in the test plot, despite the herbicide's half-life of about 6 to 8 weeks.

Chlorsulfuron was trademarked as Glean, and a new class of highly potent herbicides was born. In February 1978 Levitt created the molecules that would lead to two more herbicides, Oust and Ally. Glean and its chemical relatives kill weeds by inhibiting the enzyme acetolactate synthase, which is essential to their growth. They work on a wide range of grasses and broadleaf weeds but not on crops they are designed to protect. Crops like rice, wheat, barley, soybean, and maize are able to metabolize sulfonylurea compounds safely, and the herbicides are considered safe for humans and animals because they lack the enzyme that sulfonylurea molecules target.

As field tests continued, Levitt kept asking that the compounds be taken to their "breaking point." The idea was to keep reducing application rates until there was no activity, thereby indicating the herbicides' limits of potency. By 1978 the breaking point had not been found, but the number of chemists assigned to the sulfonylurea program began to be reduced. Glean's development was well along, and other herbicides were being tested. The company's leadership had anticipated the emergence of only two or three products from this particular vein of research. Senior management felt that sulfonylurea chemistry had yielded all that it could and that it was time to invest in other projects. Although such ideas were reasonable for some areas of chemistry, Levitt was convinced that sulfonylurea compounds had more to offer. Fortunately for DuPont, he found a sympathetic ear in Russell F. Bellina, a long-time employee who had recently become the company's synthesis manager for insecticides, fungicides, and herbicides.



Building a Research Program

Upon taking up his new position Bellina requested reviews of the various lines of research being pursued by his group members. When Levitt and his colleagues presented their work in 1978, Bellina was surprised. His understanding had been that the company would be scaling back its support for sulfonylurea compounds, yet all he could see was potential. "I thought this was the most exciting thing I had ever seen," Bellina recalls. He also realized that DuPont needed to act quickly. With ongoing patent activity and product launches, competitors would soon begin to move in. Bellina knew that DuPont had failed to ward off competition when it launched substituted urea herbicides, and he was worried that the company was doomed to let another opportunity slip away. "Russ Bellina really put the fire under the program," recalls Levitt. Keenly aware of the threat of competition and the vast possibilities yet to be explored, Bellina moved researchers from other projects and expanded the sulfonylurea innovation program from fewer than 3 full-time chemists to 12.

As DuPont reassigned its focus it began to develop a keener understanding of the tremendous potential of

cutting-edge laboratory research. In order to get the most out of the opportunity presented by Levitt's lab discovery, Bellina complemented his reallocation of resources with innovative laboratory practices. DuPont's chemical research strategy had mainly been to synthesize molecules and screen them for activity. If any molecule showed promising activity, researchers investigated its analogs. Chemists called this the "spray and pray" approach. Traditionally, the agrochemicals group did not do any basic research on the biological mechanisms of herbicides, fungicides, and insecticides. The new research strategy, in contrast, urged researchers to consider the basic biological mechanisms of agricultural chemicals and design molecules accordingly. About half a dozen scientists from DuPont's central R&D laboratories were immediately moved to the agrochemicals business; more were hired in the early 1980s to complement the growing synthesis group. As the sulfonyl-urea group benefited from more resources and science-based molecular design, their productivity increased.

Over the years thousands of molecules were synthesized; billions were possible. The innovation program at DuPont yielded dozens of sulfonylurea herbicides for use on a variety of crops. Until his retirement in 1986 Levitt continued synthesizing sulfonylurea compounds, eventually receiving 90 patents as inventor or co-inventor. Of all the molecules he created, four led directly to the herbicides Glean, Oust, Ally, and Harmony; his work indirectly contributed to dozens of others. DuPont named a new research building after him in 1988, and the following year the American Chemical Society presented him with its Award for Creative Invention. In 1993 he won the National Medal of Technology for his contribution to the discovery and commercialization of environmentally friendly herbicides to help ensure an abundant food supply for a growing world population. In 1999 George Levitt was among the scientists named a Hero of Chemistry by the American Chemical Society for innovative applications in food and agriculture.

The Benefits of Risk

The invention of sulfonylurea herbicides in 1975 was a catalyst for DuPont's transformation into a leader in the agrochemicals industry. Had Bellina failed to recognize the importance of Levitt's research, the company could very well have let an opportunity for success slip through its fingers.

Giving chemists the freedom to explore makes it more difficult to decide when to terminate a research program. Sulfonylurea compounds proved to be a vast and rich area of chemistry, but that knowledge emerged only from perseverance and creative exploration. Balancing the pursuit of new areas with the possibility of dead ends requires taking risks. Reflecting on this issue, Bellina says, "If you're not an optimist you shouldn't be in research. But I try not to carry that level of optimism to the point of absurdity, because sometimes you have to face [the reality that] your project's a failure, and the sooner you make the decision [to terminate it], the better off you are." Successful chemical companies can benefit from insights that come from combining molecular design with studies of mechanisms of action. But true innovation also requires a research environment where creative chemists are allowed to take risks on less obvious leads in hopes of discovering diamonds in the rough.