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Biology in the Chemical Industry: Scientific Approaches to the Problem of Insecticide Resistance, 1920s –1960s

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This paper examines the intensification of research and development into organic and inorganic insecticidal compounds during the first half of the twentieth century, and the involvement of biologists within the insecticide industry. It attempts to trace the history of resistance research, while highlighting the role of the biologist within the chemical industry prior to the biotechnology era.

Specifically, this paper looks at the reaction of two private companies on the finding of resistance to insecticides: Geigy and Bayer. Geigy, who discovered the insecticidal properties of DDT, initially attributed resistance to ineffective application of insecticides or variable external factors. Only after doubling of the amount of DDT had failed to achieve the desired result, did the company undertake a biological research programme in an effort to understand resistance from a biological — as opposed to chemical — perspective.

Ultimately, scientists both inside and outside the industry accepted the biological fact of resistance and the realisation that chemical control by itself would not be able to circumvent an insect population's ability to tolerate lethal dosages of chemical insecticides. The shift in the insecticide industry's approach to biological research is instructive in understanding how industry can approach complex issues.

Introduction

Although manufactured chemicals have long been used to fight insect pests, research and development of inorganic and organic insecticidal compounds intensified during the first half of the twentieth century. It is self-evident that chemists were primarily responsible for the development of novel compounds and processes. What is less well understood is the involvement of biologists in the insecticide industry. When they are acknowledged at all, biologists are generally seen in subsidiary roles of testing chemical compounds and, indeed, biologists did largely fill such roles. But the widespread use of synthetic organic insecticides beginning in the 1940s brought biologists to a more prominent position within the chemical industry due to the emergence of insect resistance to common insecticides such as DDT in the field. Although initially sceptical, several leading insecticide manufacturers hired biologists in the 1950s and 1960s to investigate the biological basis for insecticide resistance and thereby enhanced their stature among the more dominant group of chemists.

The phenomenon of insect resistance to insecticides has been known to scientists since the beginning of the twentieth century.[1] The first cases were reported in the 1910s in the fruit growing regions of the western United States, which were among the first areas to be treated with heavy doses of chemical insecticides. By 1938, a total of five cases had been reported in which localised strains could no longer be controlled by standard chemical treatments and several resistant insect varieties had been created in laboratory studies.[2] By 1951, there were more than two dozen resistant species on at least four continents[3] and the numbers continued to climb. At present there are more than 500 documented cases of insects resistant to more than 300 chemical compounds around the globe.[4]

Research on insecticide resistant has primarily been the domain of economic entomologists working at state and federal agricultural research stations. Their general research approach was first to document reported cases of insect resistance in the field and second to conduct field and laboratory experiments to establish an explanation for resistance based on current biological ideas of genetics, physiology and biochemistry. The basic biological approach proceeded piecemeal until 1937, when noted evolutionary biologist Theodosius Dobzhansky cited the cases of insecticide resistance in southern California as "probably the best proof of the effectiveness of natural selection yet obtained."[5] Dobzhansky's influential work in combining experimental developments in genetics with Darwinian theory of natural selection is widely recognised as the beginning of the evolutionary synthesis.[6] In addition to its influence among evolutionary biologists and geneticists, Dobzhansky's theory also provided an explanatory framework for the cases of insecticide resistance that had to this point been lacking. Economic entomologists working on the question of resistance could now fit their individual cases into the comprehensive framework of genetic mutation, population dynamics and natural selection. In this population view of insecticide resistance, "[t]he insecticide serves to select out the individuals carrying the gene or genes" that confer resistance while those individuals that lack the resistance genes die off.[7]

Dobzhansky's work had a decided influence among resistance researchers at agricultural research stations and, increasingly, at universities, throughout the twentieth century. Researchers and managers with the insecticide industry also grew increasingly concerned

[1] For other discussions of the history of insecticide resistance see John S. Ceccatti, "Resisting insects: shifting strategies in chemical control," *Endeavour* 28 (2004):14–19; Christian W. Simon, *DDT: Kulturgeschichte einer Chemischen Verbindung* (Basel: Christoph Merian Verlag, 1999); John Perkins, *Insects, Experts, and the Insecticide Crisis: The Quest for New Pest Management Strategies* (New York: Plenum Press, 1982), 34–7; and Edmund Russell, *War and Nature: Fighting Humans and Insects with Chemicals from World War I to Silent Spring* (Cambridge: Cambridge University Press, 2001), 24–5, 197–203.

[2] Henry J. Quayle, "Development of Resistance to Hydrocyanic Acid in Certain Scale Insects," *Hilgardia* 11 (1938), 183–210.

[3] Frank H. Babers and John J. Pratt, "Development of Insect Resistance to Insecticides II," (USDA, Bureau of Entomology and Plant Quarantine, 1951, E-818).

[4] Mark A. Whalon, *Database of Arthropods Resistant to Pesticides*, Michigan State University, Center for Integrated Plant Systems, 2000 <http://www.cips.msu.edu/resistance/rmdb/index.html>.

[5] Theodosius Dobzhansky, *Genetics and the Origin of Species* (New York: Columbia University Press, 1937), 161.

[6] See *The Evolutionary Synthesis: Perspectives on the Unification of Biology*, eds. Ernst Mayr and William B. Provine (Cambridge: Harvard University Press, 1980) for more background.

[7] Henry J. Quayle, "The Increase in Resistance in Insects to Insecticides," *Journal of Economic Entomology* 36, no. 4 (1943): 493–500, on 498.

over the rise of resistance but their general approach to the problem was somewhat different, reflecting the concerns of a chemicals-based business. It is fair to say that the initial cases of resistance to inorganic compounds did not register significantly with the insecticide manufacturers and their distributors. During the 1920s and 1930s, a handful of scientists employed by industry addressed the issue but generally attributed the apparent loss of effectiveness of insecticidal compounds to ineffective application or variable external factors such as weather conditions. Beginning in the early 1940s, with the advent and widespread use of DDT and other synthetic organic insecticides, industry's approach to the phenomenon of resistance underwent a dramatic shift. The earliest reports of DDT resistance were believed by scientists and managers of the J. R. Geigy Company of Basle, Switzerland (hereafter Geigy), which developed and manufactured the product, to have resulted from faulty formulation or application errors, similar to the reaction in the previous period. However, after laboratory tests soon revealed these assumptions to be incorrect, Geigy took a decisive step of developing a biological research programme within the company in an effort to understand resistance from a biological perspective. Previously, biologists working within chemical companies focused their efforts on efficacy and toxicity testing. Geigy's biological research initiative, although still much smaller than its ongoing chemical research programs, was notable in its effort to employ biologists in fundamental research. In the late 1950s, the Bayer company also initiated a biological research programme aimed at understanding the underpinnings of resistance. Although the archival evidence is scant, it appears that most other major insecticide companies did not embark on similar programs until the late 1970s or early 1980s coincident with the rise of molecular biology and the subsequent incorporation of biotechnological techniques into some aspects of the chemical industry.

This paper attempts to trace the history of resistance research in the insecticide industry while highlighting the shifting role of the biologist within the chemical industry.

Industry's Initial Response to Resistance, 1920s–1930s

When insecticide resistance first emerged in the 1910s and 1920s, industrial research on the issue was relatively limited. The primary response of industry during this early period was to counter the genetic explanations of resistance offered by field entomologists with alternative scenarios based on external factors, such as weather, or on non-heritable changes within insect populations. Both of these strategies had the effect of negating the biological side of resistance and putting the emphasis on proper application of insecticides which had demonstrated reduced effectiveness. In 1929 and 1931, scientists from the Owl Fumigating Corporation of Arizona and the Pacific R&H Chemical Corporation of California, developed a theory called "protective stupefaction" to explain the apparent resistance of some insects to insecticides. In one study, the researchers found that an initial exposure to a sub-lethal concentration of insecticide caused a temporary increase in the insect's ability to withstand a subsequent treatment of lethal concentration. Such a condition could be created in the field by careless workers who sprayed fumigant in the wrong direction or when removing a fumigation tent under windy conditions. They concluded that "stupefaction may be partially prevented or overcome by mechanically accelerated gas diffusion, higher dosages than normal with proportionately shortened exposure and by pulling tents from tree to tree against the air movement."[8] Another study by the same group found that a "the black scale from the so-called resistant district are a hardy strain more difficult to kill than those in other districts [but] it was possible to kill them all by a high dosage of cyanide."[9] A subsequent report by a different group indicated that proper use of a vaporiser to circulate the fumigant quickly can prevent the stupefaction effect.[10] In the 1930s another researcher from the Owl Fumigating Corporation determined that factors such as temperature, humidity and time of exposure could influence the effectiveness of an insecticidal treatment and called into question the biological explanations by Henry J. Quayle and others.[11]

Another approach within industry was to develop standardised methods for determining the extent of resistance in the field and for testing new chemical compounds in the laboratory. In 1928, A. F. Swain and Charles E. Duggan, field entomologists with the California Cyanide Company, discussed methods of determining the effectiveness of hydrocyanic acid (HCN) fumigation to control the black scale, a citrus pest in southern California. In an effort to sustain HCN sales in areas where resistant scales had appeared, the company launched a programme of "Guaranteed Pest Control" under which the company would provide additional treatments if the initial fumigation failed to kill a sufficient number of the insects. The problem for Swain and Duggan was to develop a method to determine whether the subsequent treatments were necessary. They based their approach on a method of "unit counts" employed by the California Fruit Grower's Exchange in which branches infested with the scale were collected in the field following treatment and the number of living scale insects counted. But whereas this method was typically used to determine the level of fumigation for the following season, Swain and Duggan proposed to use the test throughout the season to determine whether additional fumigations were necessary. Yet, despite developing a standard system of counting the scale that involved selecting trees along a diagonal through the orchard and sampling branches from the same position of each tree, the authors concluded that "the investigator can select satisfactory units only by carefully judging the placement of the scale before commencing his selection."[12] Hence, a large degree of individual knowledge of both the pest and host species, as well as considerable experience in making judgments about the level of infestation and the relative success of HCN treatments, made the tests highly variable.

A second attempt at standardisation within industry came from the Rohm and Haas company. Also in 1928, C. H. Peet, a chemist, and A. G. Grady, an entomologist, developed

[8] Geo P. Gray and A. F. Kirkpatrick, "The Protective Stupefaction of Certain Scale Insects by Hydrocyanic Acid Vapor," *Journal of Economic Entomology* 22 (1929): 878–892.

[9] Geo P. Gray and A. F. Kirkpatrick, "The Resistance of the Black Scale, Saissetia Oleae Bern., to Hydrocyanic Acid Fumigation," *Journal of Economic Entomology* 22 (1929): 893–7, on 893.

[10] F. S. Pratt, A. F. Swain and D. N. Eldred, "A Study of Fumigation Problems: Protective Stupefaction, Its Application and Limitations," *Journal of Economic Entomology* 24 (1931): 1041–1063.

[11] William Moore, "Difference between Resistant and Non-Resistant Red Scale in California," *Journal of Economic Entomology* 29 (1936): 65–78; William Moore, "Fumigation Experiments with the California Red Scale under Orchard Conditions," *Journal of Economic Entomology* 27 (1934): 1042–1055; William Moore, "Studies of the 'Resistant' California Red Scale Aonidiella Aurantii Mask. in California," *Journal of Economic Entomology* 26 (1933): 1140–1161.

[12] A. F. Swain, "Significance of Mid-Season Units Counts on Resistant Black Scale," *Journal of Economic Entomology* 21 (1928).

a standardised laboratory method for testing the effectiveness of new insecticidal compounds. The Peet–Grady method consisted of standardised apparatus, procedures, and even experimental insects so that "the superficial variables which have heretofore been ignored, or too little considered, can be so accurately controlled that only the biological variable remains to remove such tests from strict reproducibility and the average will be just as certain as life insurance mortality tables."[13] The apparatus consisted of a wooden chamber, six feet on each side to allow the insects to move about freely, which was coated with a non-absorbent material. The insecticidal compound was introduced through an atomiser that produced a fine spray, and an oscillating fan installed inside the chamber facilitated the rapid and even dispersal of the compound within the chamber. For the test, approximately one hundred house-flies were placed in the chamber and a predetermined amount of the compound sprayed in through the atomiser. After ten minutes, the flies that fell to the ground were collected and transferred to cages where, after 24 hours, the number of dead flies were recorded. "Tests conducted following this procedure," they concluded, "show a low average variation and it is entirely reasonable to presume that any investigator could obtain very uniform results following the method."[14] In a separate article published the same year, Grady established methods for rearing the "large culture of flies of high vitality" throughout the year as needed for these tests.[15]

While no record could be found of the use of the "unit count" test developed by Swain and Duggan, the Peet–Grady test did become an industry standard. And although it was not designed specifically to test for resistance, its usefulness in this area was quickly recognised within the insecticide industry. In 1936, the National Association of Insecticide and Disinfectant Manufacturers adopted the Peet–Grady method as the industry standard in testing liquid insecticides.[16] The following year, variation between insect populations in resistance was noted as a reason to modify the test to allow for statistical treatment of the data collected, rather than the raw numerical tabulation of the percentage of flies killed.[17]

Resistance in the Age of Synthetic Organic Insecticides, 1940s–1960s: The Case of Geigy

Prior to the 1930s, most chemical insecticides were either plant extracts (such as pyrethrum, rotenone and nicotine), petroleum products (such as kerosene and lubricating oil) or inorganic compounds (such as calcium arsenate, lead arsenate and copper sulfate).[18] This began to change in the early 1900s as the chloralkali industry developed novel organochlorine compounds to use up surplus chlorine. Some of these compounds were effective insecticides.

[13] C. H. Peet and A. G. Grady, "Studies in Insecticidal Activity. I. Testing Insecticides Against Flies," *Journal of Economic Entomology* 21 (1928): 612–17, on 613.

[14] Ibid., 617.

[15] A. G. Grady, "Studies in Breeding Insects Throughout the Year for Insecticide Tests. I. Houseflies (Musca domestic)," *Journal of Economic Entomology* 21 (1928): 598–604, on 598.

[16] Alfred Weed, "Official (Standard Fly Spray) Control Insecticide," *Soap* (Sanitary Products Sect.) 12, no. 7 (1936): 103.

[17] Jared H. Ford, "A Method for Standardizing Peet–Grady Results," *Soap* (Sanitary Products Sect.) 13, no. 6 (1937): 116–17, 120.

[18] Williams Haynes, *American Chemical Industry*, vol. 1, *Backgrounds and Beginnings* (New York: Nostrand, 1954), 362–5.

According to historian Williams Haynes, chloropicrin gas was the first example of this new class of insecticides (it was introduced in 1908), though its use for this purpose was restricted due to its obvious effects on humans. Another early organochlorine insecticide was *para*-dichlorobenzene (introduced in 1913), which was obtained as an by-product in the production of synthetic phenol by the Raschig process.[19] Several other synthetic organic insecticides were also produced in the 1920s and 1930s such as the thiocyanate ethers and esters, for instance, Lethane 384 introduced by Rohm & Haas in 1932.[20]

Beginning in the late 1930s, the insecticide industry entered a new phase in pest control with the strong push to develop synthetic organic chemical compounds as pest control agents. During this period, many chemical companies diversified their product lines to bolster sales in response to the difficulties posed by economic depression and the international effects of World War I. One company that achieved relatively rapid success by diversifying into pesticides was Geigy. Geigy was not alone in pursuing this strategy but the discovery of the insecticidal properties of DDT in the late 1930s placed Geigy ahead of its competition.

The pre-eminent example of a synthetic organic insecticide is DDT (dichlorodiphenyltrichloroethane). Although the compound was known since the nineteenth century, its insecticidal properties were discovered in 1939 by Paul Müller, a chemist working for Geigy in Basle.[21] Müller received a Nobel Prize for his work in 1948 but there was substantial controversy within the company over priority and ownership of this scientific achievement within the corporate context.[22]

The history of DDT is, of course, inextricably linked to environmental concerns that arose in the late 1950s and early 1960s, especially as they were presented in Rachel Carson's *Silent Spring*. But DDT is also a central character in the story of insect resistance research. In fact, it is due to its overwhelming success as an insecticide (resulting from its broad spectrum activity and long persistence) that brought the phenomenon of insect resistance to insecticides to the attention of corporate scientists and managers as well as to such diverse groups as the US Army and the World Health Organization.

Geigy was one of the 'big three' chemical manufacturers in Basle. Founded in the late eighteenth century, Geigy was primarily a manufacturer of synthetic and natural chemical dyes throughout the nineteenth and into the twentieth centuries. Geigy had a close, though competitive, relationship with both Ciba and Sandoz, the other main chemical companies in Basle. In 1918, the three companies formed an industry cartel called the Basler Interessengemeinschaft (the Basle or Swiss IG) to rival the combined German firms. Under the agreement, the companies shared technical information and exchanged materials with one another at cost. They also distributed their profits under a system in which Ciba received

[19] Dates of introduction taken from *Pesticide Manual*, ed. Hubert Martin (Droitwich: British Crop Protection Council, 1968), 93 and 140. This appears to contradict Haynes, *American Chemical Industry*, vol. 1, 365, and Russell, *War and Nature*, 49, both of whom claim chloropicrin insecticide was a spin-off from chemical warfare research in World War I.

[20] Perkins, *Insects, Experts, and the Insecticide Crisis*, 4–5.

[21] Simon, *DDT: Kulturgeschichte einer chemischen Verbindung*.

[22] See Christian Simon, "Belohnte Industrieforschung. Der Nobelpreis für Physiologie/Medizin 1948," in *Mitteilungen der Fachgruppe Geschichte der Chemie der Gesellschaft Deutscher* Chemiker 16 (2002): 134–150 for a discussion of these issues.

52%, while Geigy and Sandoz each received 24% of the annual total. This arrangement persisted until 1951. In 1970, Ciba and Geigy merged to form Ciba–Geigy, which then merged with Sandoz in 1996 to form Novartis. Most recently, Novartis separated its agribusiness unit from its other operations and merged it with agricultural chemicals division of Zeneca, the British chemical company that itself was 'de-merged' from ICI in 1993. This new concern is now called Syngenta.[23]

In the early 1930s, Geigy management embarked on a course of diversification from dyes into pesticides and pharmaceuticals to compete more effectively with its international rivals in the wake of declines in the textile and dyestuffs business (arguably, this was not a decline, but a change from a high-tech product to a low-tech one, with increased competition from American and other European companies). The new research and development costs were expected to be expensive, but it was argued that the expense was necessary to stay competitive in the future by acquiring scientific knowledge owned exclusively by the company. The 1936 Annual Technical Report, for example, stated that "research is the basis of our [Geigy's] development and in our opinion is the best investment of capital for the long run. . .for without scientific work today, little scientific and commercial success can be expected in the future."[24]

Beginning in 1936, the Geigy Board of Directors appointed Paul Läuger, a dyestuff chemist, to lead the new R&D effort. Läuger followed two related paths in the new pesticide research. First, he directed the research chemists already working for Geigy to test systematically a large array of chemical compounds for their toxic effects on insects and other pests. To this end, the chemists had to "become their own biologists."[25] Läuger already had an interest in biological research since about 1930 and taught himself how to rear moth larvae that he used in testing potential moth-proofing agents. Other chemists, such as Paul Müller, also learned to breed insects and conduct their own tests, often with input from entomologists at the Swiss agricultural research stations.

The second prong of Geigy's new R&D strategy was to hire additional researchers with experience in zoology, physiology and entomology. Läuger envisioned the revamped research department as a quasi-academic institution, complete with regular colloquia to encourage interdisciplinary interactions. In 1934, Läuger hired Henri Martin, a recent Ph.D. in organic chemistry from the University of Basle. But what made Martin especially appealing to Läuger was that he also had extensive training in physiology, pharmacology and other fields at the intersection of chemistry, biology and medicine. In 1937, Geigy hired an outside consultant in biology named Wille (no first name is given) who had previous experience in field-testing insecticides, to take Geigy's "great chemical achievements and apply them for the control of various types of plant pests."[26]

One practical result of the new research effort was an increase in the number of compounds that were available for biological testing. In 1937, Geigy's biological laboratory

[23] Christian Simon, "The Rise of the Swiss Chemical Industry Reconsidered," in *The Chemical Industry in Europe, 1850–1914: Industrial Growth, Pollution, and Professionalization*, eds. Ernst Homburg, Anthony S. Travis and Harm Schröter (Dordrecht: Kluwer Academic Publishers, 1998), 9–27. Additional company information from Gale Business Resources online database and company websites.

[24] Technischer Jahresbericht 1936, Geigy Archives GB21. (Author is not noted, probably Läuger.)

[25] Simon, *DDT: Kulturgeschichte einer chemischen Verbindung*.

[26] Technischer Jahresbericht 1937, Geigy Archives GB21.

tested 1531 new products for insecticidal activity against moths — more than double the previous year's number. They also tested 621 potential fungicides and 543 bactericides among other types of compounds. In 1938, the total number of tests grew to more than 45,000 from almost 6500 the year before. To handle this increase, Läuger hired another biologist, Robert Zinkernagel, to provide the "specialist knowledge" these tests required, while Wille continued to develop long-term field tests for new pest control products.

The first commercial product to emerge from this research was a moth-proofing agent called Mitin that combined the 'colourfastness' of a dye (this property allowed it to bond with the fabric although it was transparent) with the toxic properties required of a pesticide. The success of Mitin encouraged the board of directors to broaden the company's research and development efforts towards other kinds of synthetic pesticides for agricultural and household markets. The company's first plant protection product was a seed disinfectant called Graminon, which resulted from the collaborative research efforts of Müller and the biologist Wille.[27]

In 1939, Läuger noted that an all-out effort was being made to bring Mitin into commercial production and that work on other products was continuing "full-throttle ahead." Läuger noted that, in addition to the moth-proofing agent, "there are also some other substances that are highly effective against flies" but warned that further research was needed to determine their effectiveness.[28]

One of these promising compounds was DDT. Under Läuger's leadership, Müller had been conducting laboratory tests of various synthetic compounds on aphids and mosquitoes using the botanical insecticides pyrethrum and rotenone as controls. In the fall of 1939, Müller identified one of these more promising compounds, known as P1139, and in the spring of 1941 it was field tested at the Swiss Federal Research Station at Wädenswil, located just outside of Zurich. After successful field tests and government approval (both of which took place at the field station), Geigy marketed DDT under the trade name Gesarol beginning in 1942.[29]

Other researchers at Geigy had also developed some new pharmaceutical products by this time but Läuger indicated his research bias by noting that "from a purely scientific perspective, pest control is among the most interesting areas since it combines the experience and expertise of many different areas such as dye synthesis, bacteriology, pharmacology, and toxicology that offer new perspectives and new working hypotheses." As for DDT, Läuger explained to the board that "now that encouraging results are at hand, we plan to build up this area [of research] vigorously, since we have reason to believe that we possess a great advantage over all of our competitors in the Swiss chemical industry."[30]

Since DDT first went on the market during the war, its effectiveness in killing insects was quickly recognised as armies on both sides of the conflict employed it to combat disease-causing insects among troops in battle zones and among civilians in occupied territories. But after only a few years, reports came from the field indicating that DDT had lost its effectiveness, first in neutral countries such as Sweden and Switzerland, where it had been used for agricultural purposes, and later in the United States and Italy, where it had been applied by the US military.

[27] A. Buxtorf and M. Spindler, *15 Years of Geigy Pest Control* (Basel: J. R. Geigy, 1954).

[28] Technischer Jahresbericht 1939, Geigy Archives GB21.

[29] Buxtorf and Spindler, *15 Years of Geigy Pest Control.*

[30] Technischer Jahresbericht 1941, Geigy Archives GB22.

The first reports of the apparent ineffectiveness of DDT in the field came from Sweden where it had been used against stable flies. The response of the Geigy DDT committee was to halt production and investigate what was believed to be a formulation problem. When the product was shown to be correct, they decided to simply increase the concentration of DDT in their Gesarol products from 5 to 10%.[31] The following year, stable flies in Sweden were still surviving the increased levels of DDT. Subsequent discussions on the "DDT problem" at Geigy ranged from errors in application to external conditions such as high humidity — resistance, however, was not initially cited.[32]

The first mention of insect resistance as a problem with DDT in the Geigy annual technical reports came in 1947 in a report titled "Methods to Combat the DDT-Resistant Flies in Sweden." The report's author, Robert Wiesmann, stated that "the solution to the problem with the Swedish flies [*Schwedenfliegenproblem*] is an urgent matter for us" and noted the intensified search for other products that were still effective against the resistant flies. Several promising candidates had already been identified, leading Wiesmann to conclude that "it is hoped that this problem will be met with a solution in the foreseeable future."[33]

Geigy hired Wiesmann in 1944 along with four other Ph.D. biologists — including its first two women Ph.D.s — to work in Wiesmann's group.[34] Previously, Wiesmann worked as an entomologist at the Swiss agricultural research station in Wädenswil, and collaborated with Müller in the initial field testing of DDT in 1941.[35] Although Geigy biologists continued in the role of testing new chemical compounds for their effectiveness as insecticides, Wiesmann himself was given considerable latitude to pursue lines of research more consistent with that of the experimental field biologist, especially in the area of insecticide resistance. In one such study, he found that houseflies in the area around Basle differed greatly in their reaction to DDT exposure from those collected in Sweden where DDT resistance had already emerged.[36]

This line of research continued into the 1950s, but as reports of problems with DDT in the field continued to mount, the biological laboratory was reorganised by bringing in two new directors to lead sections on applied biology and applications. Wiesmann's group, now known as 'Entomology,' was freed from the routine tasks of biological screening and could focus on more 'fundamental' questions, primarily concerning the physiological nature of resistance.[37] Still Wiesmann's perspective on resistance was clearly that of an industry scientist and not that of the agricultural field station scientist focusing on the practical problems of the farmer. In a 1954 review, Wiesmann noted that the early cases of resistance to inorganic compounds did not rise to the level of "practical significance" since they could

30 Technischer Jahresbericht 1941, Geigy Archives GB22.

31 Jahresbericht Schädlingsbekämpfung 1945, Geigy Archives PA30.

32 Protokoll betreffend Fabrikationsprogramm der DDT-Produkte 1946 vom 7. Dezember 1945, Geigy Archives PA78 and Dr. R. Wiesmann, Das DDT-Problem vom wissenschaftlich-biologischen Standpunkt aus gesehen, 12. März 1946, manuscript, Geigy Archives PA78.

33 Technischer Jahresbericht 1947, Geigy Archives GB23.

34 Technischer Jahresbericht 1946, Geigy Archives GB23.

35 See for example, Robert Wiesmann, "Neue Versuche mit Arsenersatzstoffen im Obstbau," *Schweizerische Zeitschrift für Obst- und Weinbau* 51 (1942): 155–165.

36 Robert Wiesmann, "Untersuchungen ueber das physiologische Verhalten von Musca domestica L. verschiedener Provenienzen," *Mitteilungen der schweizerischen entomologischen Gesellschaft* 20 (1947): 484–504.

37 Technischer Jahresbericht 1953, Geigy Archives GB25.

typically be solved by the use of a new compound, rather "the resistance phenomenon was considered more as a scientifically interesting problem" but "with the appearance of highly effective synthetic contact insecticides, this perspective had to undergo a fundamental revision."[38] In other words, from the industry perspective, insecticide resistance became a practical problem only with the advent of wide-spectrum synthetic organic insecticides, such as DDT, that were employed on a broad and massive scale.

Insecticide Resistance Research at Bayer

Although Geigy was the first insecticide company to engage in basic research on the problem of resistance, some other companies followed suit as resistance appeared to their products. One of the first was the Bayer company, which developed its first synthetic insecticide, antinonnin, at the end of the nineteenth century and established a crop protection laboratory and an associated technical service department in the 1920s.[39] Beginning in the 1930s and continuing through the 1940s, Bayer chemist Gerhard Schrader developed two innovative lines of insecticides that would prove profitable to the company. The first line was based on organophosphate compounds, such as tetraethyl pyrophosphate that was marketed under the brand name Bladan beginning in 1942. These compounds were of the same class of highly toxic substances used as nerve gases on which Schrader conducted early phases of research and development. Related compounds such as paraoxon, parathion and guthion were developed in subsequent years. The second line of insecticidal products developed by Schrader was based on a novel mode of action. These so-called systemic insecticides were absorbed directly into the plant tissue making them toxic to insect pests. This latter group included the brand name Systox and other compounds. Bayer also developed carbamate-based insecticides for use in agricultural as well as public health.

Chemical research for plant protection was based at Bayer's original Elberfeld site which was founded in the 1860s for aniline dyestuffs production. Biological testing of potential insecticidal compounds were conducted at Bayer's Biological Institute, which was established in Leverkusen in 1924 along with several experimental fields on the outskirts of the property. A larger agricultural research station known as Höfchen was purchased in 1940.[40] Following the war and the dissolution of IG Farben, Bayer reorganised its plant protection department bringing the scientific and sales areas under single leadership and expanded its pesticide research into ten separate areas of insecticide, fungicide and a new direction in herbicide research. Among the changes, a new insecticide research laboratory was set up at the Höfchen research station along with the original laboratory at the biological institute. The new insecticide research laboratory at Höfchen was directed by Dr. Günther Unterstenhöfer.[41]

[38] Robert Wiesmann, "Der heutige Stand des Insektizid-Resistenzproblems," *Mitteilungen aus der Biologischen Bundesanstalt für Land- und Forstwirtschaft* 83 (1955): 17.

[39] See also, Erik Verg et al., *Meilensteine: 125 Jahre Bayer, 1863–1988* (Leverkusen: Bayer AG, 1988), 103, 226–9, 404–7, and "Bayer. . .A Global Pesticide Company," *Farm Chemicals*, September 1967.

[40] Verkauf Pflanzenschutz, Wissenschaftliche Abteilung Pflanzenschutz 1949/1956, Bayer Archives, BAL 1.6.6, 4, 92, 94–105.

[41] Verkauf Pflanzenschutz, Wissenschaftliche Abteilung Pflanzenschutz 1949/1956, Bayer Archives, BAL 1.6.6, 101.

As with Geigy and within the chemical industry in general, the approach to pest control at Bayer emphasised the production of chemical compounds with the biologist placed in a subsidiary role of testing compounds for their pesticidal properties and toxicological effects. Schrader himself noted that "plant protection research today means cooperative research among chemists, biologists, and toxicologists. The chemist synthesises the active compound; the biologist tests it for its effectiveness against pests and diseases and for its tolerance in plants, first in the laboratory, then in the greenhouse, and finally in the open field; the toxicologist investigates the multifaceted questions that arise in connection with human exposure to this new substance."[42]

But the appearance of insect resistance to chemical insecticides posed a unique challenge to this central dogma of the chemical insecticide industry. At Bayer, knowledge of insecticide resistance can be traced to a scientific meeting among Bayer's chemists and biologists engaged in plant protection in November 1950.[43] The report noted that "the search for a non-toxic and persistent fly substance remains thus far without success. DDT and Gix [a Bayer trade name for a DDT-based compound] are not completely satisfactory since they have already resulted in resistant fly strains."[44] The primary response was continued research into systemic insecticides and organophosphorus compounds. In 1954, Unterstenhöfer reported an increase in insect species resistant not only to DDT but many other commercial preparations and noted that often alternative compounds were often less effective and more toxic.[45]

Bayer's strategy towards the resistance problem differed from that of Geigy. Whereas Wiesmann's research centred on understanding the complex physiological, morphological and even behavioural aspects of insect control, Unterstenhöfer simply stressed that the "continuing lesson of cases of resistance among insects and spider mites requires the development and testing of new insecticidal and acaricidal compounds." Bayer had some success in this endeavour with several organophosphorus and chlorinated hydrocarbon compounds, but these newer alternative soon developed their own resistance problems. As early as 1957, for example, Gerhard Schrader made a patent application for a class of compounds including dodecyl xanthate that was "very effective against spiders which are resistant to halogenated hydrocarbons."[46]

By 1960, Unterstenhöfer was able to give his own assessment of the resistance problem, aided in part by Bayer's collaboration with Robert Metcalf, an American economic entomologist from the Citrus Experiment Station in California, one of the original sites of insecticide resistance research in the 1910s.[47] In a manner similar to Wiesmann,

[42] Gerhard Schrader, "Der Weg zu neuen Pflanzenschutzmitteln", in *Beiträge zur hundertjährigen Firmengeschichte, 1863–1963* (Leverkusen: Farbenfabriken Bayer, 1963), 128.

[43] Protokoll zur wissenschaftlichen Konferenz über Neuentwicklung von Pflanzenschutzmitteln am 15. November 1950, Bayer Archives, BAL 329/1514.

[44] Ibid., 2.

[45] Protokoll der wissenschaftlich technischen Pflanzenschutz-Besprechung vom 11. Februar 1954, Bayer Archives BAL 329/1514.

[46] Gerhard Schrader, Insecticide, 1957, Patent No. DE 1021626.

[47] Metcalf and colleagues were involved in the testing of several of Bayer's insecticides including Gusathion since the 1950s. See, for example, H. Tietz, R. L. Metcalf and T. R. Fukuto, "Das Verhalten des Insektizids 'Gusathion' auf Baumwollpflanzen und das Rückstandsproblem im Baumwollsamen," *Höfchen Briefe* 5 (1957): 273–284. Although this report deals with the issue of insecticide residues in the plant, in other articles Unterstenhöfer cites articles by Metcalf and colleagues during the same time period that discuss the resistance question.

Unterstenhöfer describes resistance as a complex biological phenomenon that results in physiological, biochemical and genetic changes in pest insect populations. Although Unterstenhöfer stressed that "these cases [of resistance] should indeed be taken quite seriously, they need not trigger an atmosphere of panic." As a counterbalance, he cited Metcalf's claim that only a small percentage of pest insect species had demonstrated resistance to date. He also advanced two related strategies to deal with the resistance problem. First, as noted above, the chemical industry should continue the development of new insecticidal compounds to replace those to which resistance had been shown. Second, resistance could be prevented by alternating the application of different compounds, as had been shown with antibiotic resistance.[48]

Geigy, Bayer and the other major insecticide companies continued biological (and chemical) research throughout the 1960s and indeed to the present but their approach gradually shifted from one of control to management as scientists both inside and outside of industry accepted the biological fact of resistance and the realisation that chemical control by itself would not be able to circumvent an insect population's ability to tolerate lethal dosages of chemical insecticides. To be sure, industry (as well as many within the entomology community) continued to search for new chemical compounds that displayed novel modes of action that might provide an answer to the problem of resistance. But in general, industry expressed its growing realisation that the chemical approach to pest control needed to be modified with a more 'biological' understanding of the phenomenon of insecticide resistance.

Conclusions

The history of industrial research on insecticide resistance during the twentieth century sheds light on the relatively unexplored role of biological research within the chemical industry prior to the biotechnology era. It is perhaps worth noting in passing that even the newer approaches to insect control based on biotechnology can also result in resistance.[49] In 1984, the leading insecticide manufacturers formed an industry group designed to coordinate research efforts both within industry and in academia, to document the growing number of cases of resistance worldwide, and to inform farmers about strategies to minimise the emergence of resistance in the field.[50] The insecticide industry is, of course, not monolithic and approaches can vary from company to company and over time. It should also be stated that the agricultural chemical industry has maintained its core focus of developing

[48] Günther Unterstenhöfer, "Über den gegenwärtigen Stand der Insektizid- und Akarizid-Resistenz," *Höfchen-Briefe* 13 (1960): 141–150.

[49] Bruce E. Tabashnik, "Evolution of Resistance to Bacillus Thuringiensis," *Annual Review of Entomology* 39 (1994).

[50] See, for example, Guenther Voss, "Insecticide/Acaracide Resistance: Industry's Efforts and Plans to Cope," *Pesticide Science* 23, 2 (1988): 149–156; Gary D. Thompson and Paul K. Leonard, "The Insecticide Resistance Action Committee: A Continuing Industry Initiative," in *ACS Symposium* Series (1996), 645 (*Molecular Genetics and Evolution of Pesticide Resistance*): 187–195; and Paul K. Leonard, "There Has Never Been a Better Time or a Greater Need for Resistance Management," *Pesticide Science* 51, 3 (1997): 387–390.

new chemical compounds (whether by traditional synthesis or by incorporating biotechnology) in the on-going battle against insects and other pests (and also to succeed vis-à-vis their competitors). But the insecticide industry has undergone changes in regard to its approach to biological research on the resistance question that can be instructive in understanding how industry can approach complex issues.

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