

# The Story of AZT: Partnership and Conflict

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## A New Disease and a New Partnership

In April of 1982, California Congressman Henry Waxman held congressional hearings about a strange new disease that seemed to be affecting gay populations in New York and San Francisco. The disease, then referred to as gay-related immunodeficiency (GRID), afflicted at least 335 people, and had killed 136 of them. However, scientists from the Centers for Disease Control (CDC) and the National Cancer Institute (NCI) warned congress that potentially tens of thousands of people might unknowingly have the disease. Although the cause of the disorder was unknown, it seemed to be blood or sex-borne, and it gradually destroyed the immune system of patients, making them vulnerable to strange opportunistic infections, such as Kaposi's sarcoma and parasites never before seen in human subjects. Dr. James W. Curran, an expert on Kaposi's sarcoma, warned Congress that this new epidemic was of "urgent public health and scientific importance."<sup>1,2</sup> Waxman advocated increasing research spending on the disease, and later introduced a bill that appropriated 15 million dollars to study the disease at the CDC and at the NIH.<sup>3</sup>

The name "acquired immune deficiency syndrome" (AIDS) was later selected for the disease, as the number of cases grew to 593 cases in September of 1982 and 1641 cases in June of 1983. There was a sense of urgency within the scientific community as groups were established to study causes and treatments for the disease. Scientific journals including *The New England Journal of Medicine* and *Science* recognized the importance of rapid publication

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<sup>1</sup> Henry Waxman, Kaposi's Sarcoma and Related Opportunistic Infections [not yet recognized as AIDS]. *Subcommittee on Health and the Environment, Committee on Energy and Commerce, House of Representatives*, 100th congress, Los Angeles, CA. April 13, 1982.

<sup>2</sup> Altman, Lawrence K. New Homosexual Disorder Worries Health Officials. *New York Times*, 11 May, 1982. national edition.

<sup>3</sup> Rimmerman, Craig A., Kenneth D Wald and Clyde Wilcox. *The Politics of Gay Rights*. Chicago: The University of Chicago Press, 2000.

of AIDS research, and in an unusual move began expedited publication of articles relating to the disease.<sup>4</sup> In a big step toward uncloaking the disease, Dr. Robert Gallo and his colleagues at the National Cancer Institute (NCI) published a series of four papers in *Science* in May of 1984 demonstrating that a retrovirus – HTVL-II (now called HIV) – was the cause of AIDS.<sup>5</sup>

The co-discovery of the Human Immunodeficiency Virus (HIV) by Gallo and a separate team at the Pasteur Institute in Paris, France headed by Luc Montagnier was a mixed blessing for researchers interested in developing therapies for AIDS. While they now had a concrete target, retroviruses were known to be intrinsically challenging to treat.<sup>6</sup> Given the class of virus, it appeared unlikely to some pharmaceutical companies that an investment into AIDS research would ever bring high returns. Although the number of AIDS cases continued to double every six months, the total number of cases was still under 10,000 and many scientists including Dr. Norbert Rapoza of the American Medical Association suggested that the epidemic would soon begin to slow.<sup>7,8</sup> Some scientists who were well positioned to study the disease chose not to out of fear of contracting the deadly virus. Broder recalls that, “there [was] a potential lack of corporate memory. Some scientists and organizations that might have made a contribution did not respond to the AIDS emergency.”<sup>9</sup> Meanwhile, at the National

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<sup>4</sup> AIDS Articles to Be Speeded. *New York Times*, August 8, 1983. national edition.

<sup>5</sup> The discovery of HTVL-II (HIV) is a matter of great controversy, as both Dr. Luc Montagnier and Dr. Robert took credit for the discovery. The scientists continued to challenge each other's claims until 1987, when they agreed to share credit for the discovery of HIV. There are several books that address this controversy in great depth, including:

Crewdson, John. *Science Fictions: A Scientific Mystery, a Massive Cover-up, and the Dark Legacy of Robert Gallo*, Boston: Little, Brown, 2002.

<sup>6</sup> Goozner, Merrill. *The \$800 million pill: the truth behind the cost of new drugs*. Berkeley: University of California Press, 2004. p. 102-104

<sup>7</sup> Philip J. Hilts, *Protecting America's Health: The FDA, Business, and One Hundred Years of Regulation*. New York: Knopf, 2003. p. 242-243

<sup>8</sup> Testimony of T.E. Haigler, former president of Burroughs Wellcome, on the company's research of AZT. “AIDS Issues (Part I): Cost and Availability of AZT,” *Subcommittee on Health and the Environment, House committee on Energy and Commerce*. House of Representatives, 100<sup>th</sup> Congress. March 10<sup>th</sup>, 1987.

<sup>9</sup> Office of NIH History. *In their Own Words... NIH Researchers Recall the Early Years of AIDS*. Interview with Dr. Sam Broder. Page 2. Available from <http://history.nih.gov/NIHInOwnWords/index.html>

Cancer Institute (NCI), taxpayer money went toward establishing a Special Task Force on AIDS, with Gallo as the scientific director and Broder as the clinical director.

Although AIDS did not fall directly under the title of cancer research, the NCI was uniquely outfitted among divisions of the NIH to do applied drug research. Since the passage of the National Cancer Act in 1971, scientists at the NCI screened thousands of compounds for anti-cancerous properties, and established clinical trials to test the compounds in patients. The process turned the NCI into an unprofitable pharmaceutical giant, well prepared to test potential anti-retroviral agents.<sup>10</sup> Even if the NCI had vast resources, Broder realized that the fastest way to develop a treatment for AIDS would be through a partnership with the pharmaceutical industry. Going against the wisdom of many of his colleagues who suggested conducting a “step by step... rational drug synthesis,” Broder sought a corporate collaboration. He envisioned that the pharmaceutical industry could provide potential drug candidates that they would otherwise be unwilling to invest in, and the NCI could test the drug candidates for anti-HIV activity. The drugs would be delivered to the NCI under code, such that the drug’s identity and thereby the company’s proprietary rights would be protected. In exchange for testing the coded drugs, the pharmaceutical companies provided a circumvention of federal bureaucracy, and a commitment to develop and commercialize promising drugs.<sup>11</sup>

Broder contacted drug officials all across the country, asking them to send compounds that might show anti-HIV activity for testing in his lab. While some companies were eager to cooperate, others showed no interest. Dr. Robert Yarchoan, working in Broder’s lab, met with officials at Pfizer to discuss a possible partnership and was quickly turned away. He

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<sup>10</sup> Goozner, p. 101-102

<sup>11</sup> Office of NIH History, Interview with Dr. Sam Broder p. 3

recalls that, “the scientists there shrugged their shoulders, and were uninterested in developing drugs for such a rare disease.”<sup>12</sup> One company that expressed immediate interest in cooperating with Broder was Burroughs Wellcome Co., located in Triangle Park, NC. Burroughs Wellcome, the U.S. unit of London’s Wellcome PLC, was home to some of the leading antiviral researchers in the country, including Gertrude Elion who discovered the company’s anti-Herpes drug *acyclovir*, for which she won the Noble Prize. Scientists working at the company viewed research into AIDS as a natural extension of their antiviral program, and had already begun an AIDS research program in June of 1984.<sup>13</sup> Dr. Dani Bolognesi, who worked at the nearby Duke University Medical Center and was familiar with Broder and many of the company’s top scientists, arranged a meeting for October 5<sup>th</sup> 1984 at the company’s headquarters.<sup>14</sup> At the meeting, Burroughs Wellcome made a commitment to try to develop a drug in partnership with the NCI researchers. Broder remembers that “...they were willing to do things, to develop products, and not just to talk.”<sup>15</sup> The arrangements were settled with a handshake. Burroughs Wellcome would become one of fifty companies to send compounds under code to Broder’s lab, although they were the first to make a serious commitment.<sup>16</sup>

### **The Story of AZT**

Ms. Martha St. Clair and other scientists at Burroughs Wellcome began screening house compounds for use in AIDS therapy. The scientists were reluctant to work with live and potentially fatal HIV, and instead used two murine retroviruses – the Friend Leukemia

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<sup>12</sup> Dr. Robert Yarchoan. Personal Communication. April 26, 2006.

<sup>13</sup> Opening statement of T.E. Haigler, former president of Burroughs Wellcome, on the company’s research of AZT. “AIDS Issues (Part I): Cost and Availability of AZT,” *Subcommittee on Health and the Environment, House committee on Energy and Commerce*. House of Representatives, 100<sup>th</sup> Congress. March 10<sup>th</sup>, 1987. p. 6-8

<sup>14</sup> Arno, p. 39

<sup>15</sup> In their own words. Broder interview. Page 3

<sup>16</sup> Arno, p. 40

virus (FLV), and the Harvey Sarcoma virus (HaSV) – to test the drug candidates. On October 29, 1984, Dr. Janet Rideout selected Burroughs Wellcome compound #509US1 off the shelves for testing by Ms. Clair. Ms Clair found that the compound showed significant activity against FLV and HaSV.<sup>17</sup>

Burroughs Wellcome compound #509US1 was azidothymidine (AZT). Although this was the first time that AZT was considered for the treatment for AIDS, the compound had been in the public eye for a long time. AZT was first synthesized in 1964 by Dr. Jerome P. Horwitz who was working at the Michigan Cancer Foundation in Detroit under an NCI grant.<sup>18</sup> At the time, Dr. Horwitz and his colleagues were tired of randomly testing drugs off the shelf against cancer, and they sought to design a novel compound that would inhibit the duplication of cancerous cells.<sup>19</sup> They designed a group of compounds called dideoxythymidines that would imitate DNA nucleosides, the raw material used to make DNA. When cancer cells divide, they must also duplicate their DNA, one base pair at a time. The dideoxythymidines were designed to be “fraudulent” base pairs that would be incorporated into the cancer cell DNA, but would prevent any base pairs from binding to them, thereby terminating the DNA strand and stopping the cancerous tumor from growing.<sup>20</sup> AZT was one of the dideoxythymidines that Dr. Horowitz and his colleagues produced, and it is a thymine analogue.<sup>21</sup> However, when AZT was tested in leukemic mice, it showed no positive effects.<sup>22</sup> The cell’s proteins rejected the fraudulent base pairs instead of incorporating them into the

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<sup>17</sup> Burroughs Wellcome Co. v. Barr Laboratories, 32 USPQ2d 1913 (Fed. Cir. 1994). Statement of facts p. 1-5

<sup>18</sup> Arno, p. 40

<sup>19</sup> A Failure Led to Drug Against AIDS. *New York Times*, Sept. 19, 1986. national edition.

<sup>20</sup> Philip J. Hilts. Experimental Drug AZT Was Designed for Tumors; Skill, Luck Led to Promising Tests on AIDS. *Washington Post*, Sept. 19, 1986. national edition.

<sup>21</sup> Horwitz, J.P., Chua, J. and Noel, M. J. *The monomesylates of 1-2'-Deoxy-beta-D-lyxofuranosyl Thymine Nucleosides*. *Organic Chemistry* 29: 2076-2078 (1964)

<sup>22</sup> Sneader, Walter. *Drug Discovery: a History*. Chichester: John Wiley & Sons Ltd, 2005. p. 260

DNA. Several decades later, Dr. Horowitz remembered AZT as a drug that ““failed miserably.”” Horowitz did not seek a patent for the compound, and abandoned it entirely<sup>23</sup> He did not know it, but it was the right drug but the wrong disease.

The drug was revisited in 1974 by Wolfram Ostertag at the Max Planck Institute who was studying the Friend Leukemia virus (FLV). Ostertag found that the AZT could successfully inhibit replication of the virus in mouse cells while leaving the mouse DNA unaffected. However, the finding did not cause a great stir because the Friend leukemia virus is a retrovirus, a class of virus that at the time was not thought to be a source of significant disease in human subjects.<sup>24</sup> Burroughs Wellcome resynthesized AZT and tested it in animals, but ultimately decided that although it was active against some viruses, the drug’s activity was not broad enough to justify development for human use.<sup>25</sup> The drug was then shelved away as Burroughs Wellcome compound 509US1.<sup>26</sup>

After Ms Clair confirmed AZT’s activity against retroviruses in November of 1984, a Burroughs Wellcome committee prepared a patent for future filing that covered the use of AZT as a treatment for HIV/AIDS. Burroughs Wellcome then sent AZT under the code name “Compound S” to Broder’s lab at the NCI on February 4<sup>th</sup>, 1985 for screening against live HIV. It was the 11<sup>th</sup> drug Burroughs Wellcome submitted for testing at the NCI.<sup>27</sup> The compound was also sent to a research laboratory within the FDA, and to Dr. Bolognesi and his coworkers at Duke University.<sup>28</sup> In a letter accompanying the drug, Dr. Lehrman

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<sup>23</sup> Philip J. Hiltz. Experimental Drug AZT Was Designed for Tumors; Skill, Luck Led to Promising Tests on AIDS. *Washington Post*, Sept. 19, 1986. national edition.

<sup>24</sup> Sneader, p. 260 -61

<sup>25</sup> Linda J. Wastila and Louis Lasagna, “The history of zidovudine (AZT)”, *Journal of Clinical Research and Pharmacoepidemiology* 4 (1990): 25-37

<sup>26</sup> Burroughs Wellcome Co. v. Barr Laboratories, statement of facts p. 5-15

<sup>27</sup> Chase, Marilyn. In War Against AIDS, Samuel Broder Serves as General and Private. *Wall Street Journal*, Oct. 17 1986. eastern edition.

<sup>28</sup> Arno, p. 40

described the compound's activity against FLV and HaSV, and suggested appropriate dosages for testing the drug.<sup>29</sup>

In Broder's lab, a Japanese postdoc named Hiroaki "Mitch" Mitsuya had developed a unique cell line called *ATH8* that would die very quickly when exposed to HIV unless it was protected by an active compound. Mitsuya sent "Compound S" through his patented assay and found that it was very effective at protecting his cell line against HIV, even at low dosages.<sup>30</sup> After testing more than 180 compounds from 50 pharmaceutical companies, Mitsuya thought he may have found a magic bullet.<sup>31</sup> Broder phoned Lehrman with the exciting results of Mitsuya's tests. The compound was also tested at the FDA lab, but scientists there could not verify the compound's activity against live HIV virus. However, testing by Bolognesi and his colleagues at Duke, in consultation with Mitsuya, succeeded in confirming that "Compound S" was active against live HIV in vitro.<sup>32</sup>

### **From Test Tube to Patient**

By the middle of 1985 there were over 10,000 AIDS patients anxiously awaiting a first treatment for their disease.<sup>33</sup> The extreme patient need for a drug sped up the process from test tube to patient tremendously. After filing 6 patents on the preparation and use of AZT, and racing through necessary animal tests in partnership with the NCI, Burroughs Wellcome submitted an application to the FDA for an Investigational New Drug (IND). In a miracle of bureaucracy, the FDA approved of the first AZT trial in only seven days.<sup>34</sup>

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<sup>29</sup> Burroughs Wellcome Co. v. Barr Laboratories, statement of facts p. 3-7

<sup>30</sup> Mitsuya H, Weinhold KJ, Furman PA, et al. 3'-azido-3'-deoxythymidine (BWA509U): An Antiviral agent that inhibits the infectivity and cytopathology-associated virus in vitro *Proc Natl Acad Sci USA* 1985; 82: 7096-100

<sup>31</sup> Philip J. Hilts. Experimental Drug AZT Was Designed for Tumors; Skill, Luck Led to Promising Tests on AIDS. *Washington Post*, Sept. 19, 1986. national edition.

<sup>32</sup> Arno, p. 40

<sup>33</sup> Office of NIH History, Timeline 1981-1988.

<sup>34</sup> Linda J. Wastila and Louis Lasagna, "The history of zidovudine (AZT)", *Journal of Clinical Research and Pharmacoepidemiology* 4 (1990): 25-37

Several hurdles emerged before the phase I trial. The first problem was that Burroughs Wellcome didn't have enough thymidine, an extract of herring sperm and the raw material needed for producing AZT, to make the drugs for the first clinical trial. But the NCI had some thymidine available, and to avoid delaying the trial, Broder arranged for a shipment of 50 kilos of thymidine to the pharmaceutical company. Broder recalls that, "there were going to be dramatic delays. And then, voilà, a shipment of thymidine arrived in the company loading dock."<sup>35</sup> Another problem was that at the last moment Burroughs Wellcome declared that they did not want to analyze samples containing live HIV from patients in the Phase I study.<sup>36</sup> Although typically the pharmaceutical partner is responsible for the analysis of the first drug trial, Burroughs Wellcome did not have any "P-3" highest level of biosafety labs available to analyze HIV positive samples, and the researchers at the company feared catching the fatal virus. Although Broder, Mitsuya, and other NCI researchers also did not have P-3 labs during the initial years of HIV research, they were willing to front the risk. Instead of delaying the drug trial, Broder arranged for all of the collecting and analyzing of samples to occur at the NCI or with his colleagues at Duke Medical Center.<sup>37</sup>

On July 3<sup>rd</sup>, 1985 at the NCI, a furniture salesman from Massachusetts named Joseph Rafuse became the first person to take AZT. Dr. Robert Yarchoan, who helped run the clinical trial at the NCI, administered the drug intravenously and then held his breath. He remembers that "the first hour was critical... we were worried he might go into a sort of biochemical shock and die."<sup>38</sup> Hours ticked by with no harmful effects. A total of 35 patients were eventually administered to the study at the NCI and at Duke, and many of the patients

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<sup>35</sup> Office of NIH History, Interview with Dr. Sam Broder p. 3

<sup>36</sup> Chase, Marilyn. In War Against AIDS, Samuel Broder Serves as General and Private. *Wall Street Journal*, Oct. 17 1986. eastern edition.

<sup>37</sup> Arno, p. 38-40

<sup>38</sup> Dr. Robert Yarchoan. Interview. April 26, 2006.

started showing signs of clinical improvements. After 6 weeks of drug administration, a battery of tests revealed that AZT raised the patients' T-lymphocyte counts and could infiltrate many parts of the body including the brain. The adverse effects of the drug were tolerable, consisting of headaches and bone marrow suppression in some patients.<sup>39</sup> The study continued for several more months until Yarchoan, Broder and their colleagues at Duke University felt confident that the drug was safe, and appropriate dosages for the drug were established.

The phase I trial did not have a control arm; the purpose of the trial was not to establish efficacy (although several positive gains were noted), but instead to determine the drug's safety profile, and to establish appropriate dosages. Throughout the phase I study, researchers at Burroughs Wellcome collaborated extensively with Broder and other NCI and Duke scientists. Upon hearing the initial promising results from the phase I study, approximately 30 Burroughs Wellcome investigators convened to devise a phase II double-blind, placebo controlled study that would demonstrate the drug's effectiveness. The trial would be financed solely by Burroughs Wellcome and would take place at 12 medical centers throughout the country. A total of 282 patients with AIDS or advanced symptoms of HIV infection participated in the study; half of the patients would receive AZT, and the other half would receive a placebo.<sup>40</sup>

By the time the phase II trial began, word of AZT's potential for treating AIDS spread to the general public. All aspects of the trial were closely followed by the media, and the trial soon became engulfed in various controversies. Some critics believed that AZT was too toxic

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<sup>39</sup> R Yarchoan, K.J. Weinhold, H.K. Lyerly, et al., Administration of 3'-azido-2'-deoxythymidine, an inhibitor of HTLV-II/LAV replication, to patients with AIDS or AIDS-related complex. *Lancet*, 1986: 1: 575-80

<sup>40</sup> Burroughs Wellcome Company: the Retrovir Story by b.W. Co. People. Winston-Salem, North Carolina: Hunter Publishing Co. 5, 1987

for weak AIDS patients, while others accused Burroughs Wellcome and the FDA with hindering the drug's availability. Many critics felt that the placebo arm of the arm was unethical, and called for all patients to have access to the drug. Burroughs Wellcome's spokespersons vigorously defended the trial, but the company recognized the high stakes of the trial and, in collaboration with the NCI and the National Institute of Allergy and Infectious Diseases (NIAID), they established an independent Data and Safety Monitoring Board (DSMB) consisting of various AIDS experts that were removed from the trial.<sup>41</sup>

In September of 1986, only 7 months after the trial was started, the board concluded that there was a significantly lower mortality rate in patients randomly assigned to receive AZT than the placebo. Only one of the 145 patients receiving AZT had died, compared with 16 patient deaths from the 137-patient placebo group. The trial was halted, and the patients who had received placebos were given the opportunity to take AZT.<sup>42</sup>

Burroughs Wellcome quickly prepared a New Drug Application for the FDA for the use of AZT, to be marketed as Retrovir by the company, in the treatment of AIDS or advanced symptoms of HIV infection. To speed up the process of approval, Burroughs Wellcome submitted their drug application in separate parts, the last of which was completed and submitted in December of 1986. In the meantime, the company made Retrovir available for free to many AIDS patients. By March of 1987, 4500 AIDS patients, or one third of all Americans living with AIDS, had received free Retrovir handouts from the company. The company estimated that the handouts cost the company over \$10 million.<sup>43</sup>

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<sup>41</sup> Wastila p, 25-37

<sup>42</sup> Testimony of T.E. Haigler, former president of Burroughs Wellcome, on the company's research of AZT. "AIDS Issues (Part I): Cost and Availability of AZT," Subcommittee on Health and the Environment, House committee on Energy and Commerce, 100th Congress. March 10th, 1987.

<sup>43</sup> Burroughs Wellcome Company: the Retrovir Story by b.W. Co. People. Winston-Salem, North Carolina: Hunter Publishing Co. 5, 1987

Although the drug was not yet approved, Burroughs Wellcome diverted more than one fifth of its research and development spending to the drug, and poured in an additional \$80 million in capital and raw materials specific to the drug. The company succeeded in increasing production of AZT 1000-fold through various refinements in the efficiency of the six chemical reactions needed to produce the drug, accomplishing a perfection of drug synthesis that would normally take several years. Although supply of the drug was initially limited due to exhausted worldwide supplies of thymidine, the raw material needed for the production of AZT, Pfizer inc. developed a 10-step synthesis of thymidine that promised to increase supply of the compound. Burroughs Wellcome projected that by the end of 1987, Retrovir would be available for over 30,000 patients.<sup>44</sup>

In January of 1986, an FDA committee voted 10-1 to recommend the approval of Retrovir for the treatment of AIDS, and two months later the FDA accepted the committee's decision and the drug was approved.<sup>45</sup> Any physician could now write a prescription for Retrovir, the first approved treatment for AIDS. In less than 3 years, AZT had progressed from the obscure shelves of Burroughs Wellcome to pharmacies all across the country, providing for patients a measure of hope at a time when there was none. For the development of a drug, in the words of Dr. Broder, this was "the speed of light."<sup>46</sup>

Part of the reason for the rapid development of the drug must be attributed to the intense patient demand, allowing circumvention of many timely steps and a length FDA approval. However, the incredible rate of development would not have been possible without

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<sup>44</sup> Testimony of T.E. Haigler, former president of Burroughs Wellcome, on the company's research of AZT. "AIDS Issues (Part I): Cost and Availability of AZT," Subcommittee on Health and the Environment, House committee on Energy and Commerce, 100th Congress. March 10th, 1987.

<sup>45</sup> Testimony of Dr. David Barry. "AIDS Issues (Part I): Cost and Availability of AZT," *Subcommittee on Health and the Environment, House Committee on Energy and Commerce*, 100th Congress. March 10th, 1987.

<sup>46</sup> Office of NIH History, Interview with Sam Broder p.4

the efficient partnership that emerged between the scientists at the NCI and Duke and the investigators at Burroughs Wellcome. For Broder, the success of the partnership was a relief. “I felt very confident... that there would be all sorts of people... who would have found thousands of reasons why what we were doing was not appropriate, and required a lot more paperwork. And those forces tend to become very quiet after a project seems to have worked.” The collaboration between the NCI and Burroughs Wellcome in the development of AZT laid the foundation for future government-private partnerships. The National Institute of Allergy and Infectious Diseases (NIAID), which adopted from the NCI the responsibility of leading AIDS research soon after the approval of Retrovir, established a network of physicians to test drugs from other pharmaceutical companies just as Broder had done with his tiny laboratory three years earlier.<sup>47</sup> Broder’s previously doubted and criticized collaboration was now a model for government research.

### **The Price of AZT (Retrovir)**

After an FDA committee recommended the approval of Retrovir, Burroughs Wellcome made a shocking announcement: the drug would retail for \$188 per bottle of 100, 100 mg capsules, or approximately \$7,000-\$10,000 per patient per year.<sup>48</sup> This announcement marked the beginning of a long conflict between the government and the Burroughs Wellcome over the cost of AZT that would forever taint the successful partnership that had emerged between the two parties.

In March of 1987, almost immediately after the announcement, Congressman Waxman held hearings in front of the Subcommittee on Health and the Environment about the development and distribution of AZT. Since 1982 when Waxman held his first hearing about

<sup>47</sup> Goozner , p. 104

<sup>48</sup> Testimony of T.E. Haigler, former president of Burroughs Wellcome, on the company’s research of AZT. “AIDS Issues (Part I): Cost and Availability of AZT,” Subcommittee on Health and the Environment, House committee on Energy and Commerce, 100th Congress. March 10th, 1987.

the disease, the number of AIDS patients had increased from under 500 to about 25,000 people in the U.S. alone. Since AZT was proven to extend the lives of AIDS patients, Waxman argued that it would be unethical to deny a patient access to the drug's because of its high cost. In his opening remarks Waxman explained that, "giving patients sugar pills because they are part of a study can be justified as an effort to learn about a disease and its cure. Giving patients nothing [when a treatment is available but is too expensive]... can be rationalized only as a part of a system that provides health miracles to the wealthy and health neglect to the poor." Waxman's goal for the hearings was to ensure that AZT would be available for all AIDS patients.<sup>49</sup>

Waxman's hearings addressed two primary questions: is the price of AZT fair, and who is responsible for paying for the drug if it is too expensive for an AIDS patient? To address the concerns over the high cost of the drug, T.E. Haigler Jr., the president of Burroughs Wellcome, was called to testify about the company's justification for the high price of AZT. Haigler described the numerous considerations in determining the drug's price, including the costs of developing, producing, and marketing the drug. He also suggested that the market for Retrovir was uncertain, because other AIDS therapies might soon replace AZT. Despite the high price tag, Haigler demonstrated that Retrovir was cost-effective. Several studies estimated that the cost of treating an AIDS patient was in the range of \$43,500-\$150,000 per year, due to the high number of opportunistic infections and hospitalizations that are associated with AIDS. Because AZT could improve the health of patients, it was estimated that the drug could reduce the cost of treating AIDS patients by 60%, passing on a savings of \$386 million for the 20,000 AIDS patients who would be treated with the drug.

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<sup>49</sup> Senator Waxman opening remarks. "AIDS Issues (Part I): Cost and Availability of AZT," Subcommittee on Health and the Environment, House committee on Energy and Commerce, 100th Congress. March 10th, 1987.

Given these factors, Haigler argued that the price was “reasonable.” The company would also continue its limited indigent care program, offering free AZT to patients on a case by case basis, although Haigler suggested that the magnitude of potential need was beyond the scope of his company and should be addressed by the government, employers, and the health insurance industry.<sup>50</sup>

Waxman scrutinized every aspect of the company’s AZT price calculations. He argued before the subcommittee that Burrough’s Wellcome’s contributions in the development of AZT were modest, as most of the key work was performed by the government. Waxman also pointed out that at the time of the phase II trial, AZT was considered an Orphan Drug because of the modest number of people with AIDS, and therefore the company received a 72% subsidy of the clinical costs as mandated by the Orphan Drug Act. This subsidy was on top of the existing 25% tax credit for increased research and development. Waxman pressed Haigler for an approximation of total research and development costs after the tax credits, but Haigler argued that the costs were hard to identify, and argued instead that there were many other factors considered in the drug’s market price.

The hearings were only the beginning of a firestorm of criticism the company would receive about the cost of AZT. Physicians such as Richard Hersey wrote letters to various newspapers and to congress stating that “profit beyond reasonable cost should play no role in life and death decisions.”<sup>51</sup> Many state agencies such as the New York State Consumer Protection Board criticized the company, and AIDS activist groups such as AIDS Coalition to

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<sup>50</sup> Testimony of T.E. Haigler, former president of Burroughs Wellcome, on the company’s research of AZT. “AIDS Issues (Part I): Cost and Availability of AZT,” Subcommittee on Health and the Environment, House committee on Energy and Commerce, 100th Congress. March 10th, 1987.

<sup>51</sup> Richard Hersey. Offer AZT at Cost. New York Times Editorial Desk. April 25, 1987. Late City Final Edition.

Unleash Power staged protests urging the company to reduce the drugs cost.<sup>52</sup> To quell these criticisms, Burroughs Wellcome announced a 20% price cut in December of 1987, and another 20% price cut in September of 1989 in response to intense pressure from Congress and from AIDS activists.<sup>53</sup> Even as the price of AZT dropped, the world wide sales for the drug continued to soar to \$225 million as AIDS epidemic continued to spread.<sup>54</sup>

### **A Conflict about Inventorship**

The price cuts did not hush Burroughs Wellcome's opposition. Instead, the company's critics used the price cuts to demonstrate that the price of AZT was inflated all along.<sup>55</sup> Burroughs Wellcome's argument that it had to recoup its investment in AZT was no longer sustainable as it continued to post enormous yearly profits to its stock investors. To defend the incredible profits from AZT, the company promoted their final line of defense. The message was simple: we deserve to earn a fair profit because we developed the drug. To emphasize Burroughs Wellcome's roll in the development of AZT, the company pursued a strategy of downplaying the contribution of the Duke and NCI scientists. Consistent with this strategy, Haigler wrote an editorial to the New York Times emphasizing the contributions of his company:

Late in 1984, our scientists discovered that AZT showed potential in fighting the AIDS virus. We sent the compound, with others, as coded samples to Samuel Broder's laboratory at the National Cancer Institute. Dr. Broder, unaware of the identity of the samples, confirmed to us that AZT was active against the AIDS virus. Burroughs Wellcome was thereupon granted patents for the use of Retrovir for the AIDS virus. There was no race to the patent office...<sup>56</sup>

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<sup>52</sup> Arno, p. 71-82

<sup>53</sup> Specter, Michael. Price of AZT to be Cut 20 Percent; Manufacturer Acts After Heavy Pressure. Washington Post. Sept. 19, 1989. final edition

<sup>54</sup> Hilts, Philip J. AIDS Drug's Maker Cuts Price by 20%. New York Times. Sept. 18, 1989. late edition

<sup>55</sup> Hilts, Sept. 18, 1989

<sup>56</sup> Haigler, T.E. Jr. Reduced Dosage Cuts Cost of AIDS Drug. New York Times, Editorial Desk. September 16, 1989. late edition.

Burroughs Wellcome echoed this message in newspaper interviews and in its annual report, systematically understating the contribution of government scientists.<sup>57</sup>

Burroughs Wellcome's efforts to justify the high cost of AZT permanently damaged the amiable relationship that had developed between the researchers at the company and the scientists at the NCI and Duke. In a private letter to the company, Broder warned that if they did not give the government appropriate credit for the development of AZT, future partnerships with the NCI could be jeopardized. But Burroughs Wellcome did not back down from its interpretation of AZT's development, aware that the already strong resistance to AZT's price would get even stronger if they did.<sup>58</sup>

The NCI and Duke scientists involved in the development of AZT were enraged. In their opinion, Dr. Broder's lab hadn't "confirmed" the activity of AZT against the AIDS virus as Haigler suggested in his letter, but had instead discovered it. And there was no mention in Haigler's letter of the contribution of Horowitz who first synthesized AZT on an NCI grant, or of Ostertag who first tested AZT against a retrovirus. Without public relations spokespersons to defend their contributions, NCI's Broder, Mitsuya, and Yarchoan, and Duke's Bolognesi and Weinhold fired back with a letter to the editor of the *New York Times*. In this letter they pointed out that, "Indeed, one of the key obstacles to the development of AZT was that Burroughs Wellcome did not work with live AIDS virus nor wish to receive samples from AIDS patients." The scientists argued that the rapid development of AZT would have been impossible without the "sizeable contributions" of government-sponsored research.<sup>59</sup>

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<sup>57</sup> Arno p. 138

<sup>58</sup> Arno p. 58

<sup>59</sup> Credit Government Scientists With Developing Anti-AIDS Drug. *New York Times*, Editorial Desk. September 28, 1989. late edition.

The fight between the government scientists and Burroughs Wellcome erupted into a much larger conflict as groups concerned about the price of AZT sided with the government scientists and pressed their case. Convinced that the government scientists played a key roll in the development of the drug, some these groups contemplated the possibility of challenging Burroughs Wellcome's AZT patent rights. If it could be proven that the government scientists had inventorship rights to AZT, Burroughs Wellcome would lose its exclusive rights to produce, distribute and sell AZT. This would open the door for many different pharmaceutical companies to produce the drug, thereby lowering its market price. At Broder's request, the NIH hired an outside counsel to investigate the AZT patents, and the council concluded that the government's contributions in the development of AZT were substantial enough to warrant a legal challenge over the rights to the AZT patents.<sup>60</sup>

The Commercial Litigation Branch of the Justice Department ultimately did not file a lawsuit against Burroughs Wellcome over the AZT patent, but the counsel opened the doors for other groups to become involved. In Canada, where AZT was similarly priced, two generic drug manufactures, hoping to undercut Retrovir's sales, challenged the Burroughs Wellcome patents by arguing that the company did not invent the drug but rather performed "workshop improvement."<sup>61</sup> In the U.S., Public Citizen, a nonprofit public interest litigation group founded by Ralph Nader, sued Burroughs Wellcome, accusing the company of "fail[ing] to disclose to the Patent Office relevant and material facts in the original AZT patent application."<sup>62</sup> The group hoped to prove that the AZT patent was invalid, allowing for the generic manufacture of AZT.<sup>63</sup>

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<sup>60</sup> Arm p. 139

<sup>61</sup> Arm p. 139-141

<sup>62</sup> People With AIDS Health Group v. Burroughs Wellcome Co. *District Court for the District of Columbia*. 1991

<sup>63</sup> Public Citizen News Release. Suit Seeks to Strip Burroughs Wellcome of Patent on AZT. Mar. 19, 1991.

Soon after the Public Citizen lawsuit was filed, Barr Laboratories, an American generic drug manufacturer, became interested in selling a generic version of AZT. By this point worldwide sales of AZT topped \$1 billion, and so the potential market for a generic drug was enormous. On March 19, 1991 the company filed an Abbreviated New drug Application to market a generic version of AZT. Burroughs Wellcome filed suit against Barr for patent infringement, and Barr filed a counter claim, seeking corrections to list Broder, Mitsuya, and Yarchoan as coinventors of AZT. Although Barr's generic version of AZT would infringe on the patents, it had obtained a license from the government to manufacture and sell AZT, and the government would be deemed the owner of the patent if the government's scientists were coinventors. Another generic maker, Novopharm Inc. followed Barr's example in attempting to market a generic version of AZT; this spawned another set of suits and countersuits that was soon consolidated with the Barr lawsuit. The NIH, which had long considered challenging the Burroughs Wellcome patent, supported Barr and Novopharm in the patent case, and contributed two of its own lawyers to the fight.<sup>64,65</sup>

The lawsuits progressed slowly through the courts. Each lawsuit brought with it front page newspaper articles describing the contentions of the government and corporate scientists, permanently damaging the public's perception of the partnership behind the creation of AZT. The various court cases may also have caused books about the development of AZT—written while the lawsuits proceeded through the courts—to view the NCI and Burroughs Wellcome partnership especially harshly. Each of the lawsuits was eventually dropped or won by Burroughs Wellcome, the last case ending in 1994 after a set of appeals.<sup>66</sup>

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<sup>64</sup> Gladwell, Michael. NIH May Seek To Void Firm's Patent on AZT; Success Could Cut AIDS Drug's Price. *Washington Post*. March 29, 1991. Final Edition

<sup>65</sup> Burroughs Wellcome Co. v. Barr Labs Inc., 40 F.3d 1223, 1228 *Fed. Cir.* 1994

<sup>66</sup> Riordan, Teresa. A Court Ruling Extends Burroughs-Wellcome's Monopoly on the AIDS drug AZT. *New York Times*. Nov. 28, 1994. Late Edition – Final

## After AZT

Although Broder and his colleagues spent countless hours testifying against Burroughs Wellcome in court, they remained firm believers in government-private partnerships. Even after the court cases ended, denying him the status of coinventorship of AZT, Broder still viewed the Burroughs Wellcome partnership as a success. “AIDS was a public health emergency, and it was essential to get things started. AZT is out there. It is an approved product. I view that as successful example of a public-private collaboration.”<sup>67</sup> However, Broder and his colleagues would also concede that they had been naïve in their initial dealings with the company.<sup>68</sup> In the development of AZT, they had not focused on issues of pricing or patenting, but were oriented only towards getting an approved product as quickly as possible. After AZT, government researchers would be more careful.

Broder became the head of the NCI shortly after the development of AZT, and although he encouraged researchers in the institute to engage in collaborations with the pharmaceutical industry, he insisted that reasonable price clauses be inserted into all development agreements between the NCI and industry. Broder was concerned that the reasonable price clause might discourage innovation and collaboration with the NIH, but his experience with AZT convinced him that the clause was necessary.<sup>69</sup> Similarly, when another nucleotide analogue, Didanosine (DDI), showed promise against HIV in his own lab, Broder, Mitsuya, and Yarchoan all put their names on a government patent for the drug before seeking collaborations with pharmaceutical companies. The NCI then chose to work with Bristol-Myers to test and develop the drug, and inserted a reasonable price clause into the agreement, thereby lowering the market price of the drug.<sup>70</sup>

<sup>67</sup> Office of NIH History, Interview with Sam Broder p. 4

<sup>68</sup> Arno, p. 139

<sup>69</sup> Office of NIH History, Interview with Dr. Sam Broder p. 4

<sup>70</sup> For a more extended description of the development of DDI, see Arno, p. 178

The efficient NCI and Duke University collaboration with Burroughs Wellcome in the development of AZT demonstrate that at a fundamental level, partnerships between pharmaceutical companies and the government can succeed. Although it is easy to criticize the high price of AZT and the partnership that allowed it, it is important to remember that the drug arrived at a time when there was no other treatment for AIDS, and it prolonged the life of thousands of patients. The remarkable development of AZT may never have been possible if not for the agreeable collaboration between the government and Burroughs Wellcome to find a treatment for AIDS. The high price of AZT and the resulting contentions that emerged because of its price, taught the government important lessons about improving partnership, paving the way for even more successful partnerships with the pharmaceutical industry in the future.