Inventing AZT

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Charles Mackay's 'catalogue of some of … mankind's … more *outré* enthusiasms', *Extraordinary Popular Delusions and the Madness of Crowds*, first published in 1841, tells how alchemy flourished for centuries, its eminent practitioners tapping sultans and princes for treasure with the promise that they could multiply it, for the pursuit of the philosopher's stone and for the *elixir vitae*. He describes an experiment of the famous Bernard of Treves and his disciples, who 'imagined that there was a marvellous virtue in all excretement, especially human' and who accordingly proceeded to put

> forty-two marks of gold … into a crucible, with a quantity of salt, copperas, aquafortis, egg-shells, mercury, lead, and dung. The alchymists watched this precious mess with intense interest, expecting that it would agglomerate into one lump of pure gold. At the end of three weeks they gave up on the trial, upon some excuse that the crucible was not strong enough, or that some necessary ingredient was wanting. Whether any thief had put his hands into the crucible is not known, but it is alleged that the gold found therein at the close of the experiment was worth only six-teen marks, instead of the forty-two which were put there in the beginning.

The great American war on cancer was just such an affair. In every respect. Biologist Linus Pauling, who notched up not one but two Nobel prizes in his lifetime, wrote it off as worse than folly; he thought it 'essentially a fraud'. Another Nobel laureate, James Watson, the double helix guy, called it, with ripe historical redolence, 'a lot of shit'. In was in this dead-end pursuit in the early sixties that cancer researcher Dr Richard Beltz, now a biochemistry professor emeritus at the Seventh

Day Adventists' Loma Linda University School of Medicine in California, was cooking up new poisons to kill cells with a view to finding that magic bullet to cure cancer that everyone was after. He related to me:

> I synthesized AZT in my laboratory as a NIH Senior Research Fellow (National Cancer Institute) in the autumn of 1961. The AZT was among a group of four new thymidine analogs that I prepared at that time. AZT proved to be the most biologically active of these compounds in preliminary tests. My biological tests showed (1) AZT inhibited the growth of E. coli and S. potsdam [*bacteria*] at very low concentrations, and (2) cultures of E. coli put on agar plates containing AZT showed AZT-resistant clones after a few days of incubation. Subcultures of these clones were entirely resistant to growth inhibition by AZT. Further work showed that AZT had no effect upon the DNA synthesis of T2 bacteriophage [*a virus*] propagated in E. coli cultures. Finally, I prepared 1 gram of crystalline AZT and sent it to a friend at Yale University, Dr. Allen Sartorelli, Professor of Pharmacology, who tested it for anticancer activity. The AZT proved to be inactive against two experimental animal tumors which he was using at that time for screening. This used up the 1 gram of AZT. In my laboratory I found AZT incapable of inhibiting the growth of Jensen sarcoma cells in vitro, at very high concentrations. Thus, AZT showed no activity as a potential anticancer drug when tested by the methods of that era. What I have written here summarizes my work with AZT. I did many other experiments within the framework of these findings, but that work consisted of filling in details.

In every account describing the invention of AZT that has been published to date, the credit gone to another cancer researcher, Jerome Horwitz. In *AIDS & HIV in Perspective* (Cambridge University Press, 1994) Professor Barry Schoub, Director of the National Institute of

Communicable Diseases in Johannesburg, claims, 'Zidovudine was first synthesised by Horwitz in 1964 together with other nucleoside analogues.' In his excellent examination (from a conventional, orthodox perspective) of the potent social forces that shaped the erection of the HIV-AIDS construct, *Impure Science: AIDS, Activism and the Politics of Knowledge* (University of California Press, 1996), assistant professor of sociology Steven Epstein at the University of California at San Diego, claims similarly:

> In the early 1960s, a researcher named Jerome Horwitz at the Michigan Cancer Institute decided to design a drug that would keep cancer cells from duplicating. With funding from the NCI, and working with such unlikely ingredients as herring sperm, Horwitz and his co-workers designed a group of compounds called dideoxythymidines that were designed to look like nucleosides, the building blocks of DNA. In theory, these nucleoside analogues would substitute themselves for real nucleosides, thereby interfering with formation of DNA molecules. Without more DNA, the cancer cells would simply stop duplicating. In practice the treatment was a complete failure.

Elinor Burkett's searchlight on the corrupt underbelly of AIDS, *The Gravest Show on Earth: America in the Age of AIDS* (Picador, 1996) states:

> Among Wellcome's compounds was a herring and salmon sperm extract developed by Detroit researcher, Jerome Horowitz [*sic*], as a possible cancer treatment. His concoction, AZT, had never made it into human testing. It had been so ineffective against cancer cells, and so toxic that Horowitz didn't even take out a patent.

In *Inventing the AIDS Virus* (Regnery, 1996), cell and molecular biology professor Peter Duesberg of the University of California at Berkeley repeats: 'AZT was invented … in 1964. Jerome Horwitz, heading a lab at the Detroit Cancer Foundation … created a chemically modified form of

a DNA building block.' In *Positively False* (IB Taurus, 1998), Joan Shenton says: 'AZT was first developed as a cancer chemotherapy drug in 1964 (to kill unwanted cells)' – tying the discovery of AZT to Horwitz by the year mentioned. In its press release on 20 March 1987, the day AZT was licensed as an AIDS drug, the FDA stated similarly: 'Retrovir was originally developed in 1964 by Dr. Jerome Horowitz [*sic*] of the Michigan Cancer Foundation as a possible treatment for cancer.'

Even the researchers who dredged AZT from medicine's trash can, and whose crummy laboratory studies were the basis for clinical trials on human subjects (without the usual preceding animal efficacy studies), misattribute the invention of AZT to Horwitz. In their letter to the *New York Times* on 28 September 1989 Mitsuya, Weinhold, Yarchoan, Bolognesi, and Broder corrected several lies told by the president of Burroughs Wellcome (now GlaxoSmithKline), T E Haigler Jr, in his own letter twelve days earlier, stealing the thunder for the invention of AZT and the initial research into its use as an antiretroviral drug. They wrote:

> The company did not perform the first synthesis of AZT. This was done by Dr. Jerome Horowitz [*sic*] at the Michigan Cancer Foundation in 1964, using a Government grant.

Horwitz (not 'Horowitz') got the kudos because he was the first to publish a paper in 1964 in which he described a way of synthesizing AZT and another similar nucleoside analogue. 'However,' as Beltz pointed out to me, 'there was no mention at all in this paper of biological activity or even of potential biological activity'. The popular record has it that Horwitz thereafter tried the drug out on leukaemic mice, without any success, whereafter he just shelved it. That's not quite right, Beltz says:

> I am personally aware that Horwitz went down the same trail of research that I went down after synthesizing AZT. That is, he tested it against experimental animal tumors and found it to be an

essentially inactive drug. The results of my tests and of Alan Sartorelli's tests at Yale with AZT on experimental tumors were also uniformly negative. I was struck by the lack of toxicity of AZT toward Jensen tumor cells … the drug was not effective for blocking tumor growth, even at quite high doses.

Beltz explained to me the reason why Horwitz made it to print and not him:

Let me tell you what happened. I synthesized AZT in the period from June-October, 1961, looking for new potential anticancer nucleoside analogs. … I delayed publication because my main research focus was to investigate the mechanism of control of DNA synthesis in regenerating liver. I never got around to publishing that early work on AZT. Then in February 1964 my laboratory was destroyed in a fire that burned down the biochemistry department where I was working. I took a 1 year sabbatical leave. The paper by Horwitz describing AZT synthesis was published in the *Journal of Organic Chemistry* in 1964 – Horwitz, J.P., Chua, J. and Noel, M.J. *Organic Chemistry 29: 2076-2078 (1964) Nucleosides. The monomesylates of 1-(2'-Deoxy-beta-D-lyxofuranosyl)thymine*. This was the first published record of AZT synthesis. Accordingly, Dr. Horwitz was properly given credit for being the first to synthesize AZT. I have never disagreed with the historians about this, because it was simply my own fault that I didn't get a paper out on it in 1962 or 1963. By 1964 it was too late. In 1987 the Burroughs-Wellcome Company was making AZT and selling it at what people generally thought was too high a price. To justify the price, David Barry, a Director of Research for the B-W Company, said in a *Wall Street Journal* article that AZT was made by a 7-step synthesis. My synthesis was a 4-step synthesis, so I wrote to Dr. Barry pointing this out and offering my method. There ensued a transfer of information from me to the B-W

> company, where they proceeded to check out my method. The result was that they wrote back to me after several months and said some complimentary things about the method but decided they would not need to use it because they said they basically already knew most of what I had told them. At that point Dr. Barry asked me for historical information about my synthesis of AZT and I replied with a dated, detailed history of the synthesis and testing of AZT in my laboratory. That document is in the files at Burroughs-Wellcome (now Glaxo). I heard nothing more after that, and I have been content to let the matter rest.

I'm pleased to report that the toxicity literature canvassed in an early draft of *Debating AZT*, which I requested Beltz to review, changed his mind about the utility of the drug as a treatment for AIDS, and especially about the wisdom of giving it to pregnant women. On 14 April 1999 Beltz answered an enquiry by my associate David Crowe in Calgary, Canada, concluding that

> we must admit [that AZT] has at least some limited value as an anti-AIDS drug, especially for preventing newborn children from AIDS-infected mothers from acquiring the disease.

But after reading *AZT: A Medicine from Hell* in *Debating AZT* he ditched that opinion. Though understandably put out by my initial imprecision concerning the early history of AZT, gleaned from the texts I cited above, he was happy to disown his creation and lend me his full support, writing on 11 May 2000:

> you are justified in sounding a warning against the long-term therapeutic use of AZT, or its use in pregnant women, because of its demonstrated toxicity and side effects. Unfortunately, the devastating effects of AZT emerged only after the final level of experiments were well underway, that is, the experiments which consisted of giving AZT to large numbers of human patients over

> a long period of time. Your effort is a worthy one … I hope you succeed in convincing your government not to make AZT available.

Possibly embarrassed by GlaxoSmithKline's atrocious misapplication of the cell-poison he'd conceived, Beltz was shy about his paternity, and said he would prefer it kept under the hat. In my opinion, however, his is an important story to tell, because it starkly sets his purpose in making AZT, namely to kill cells, against GlaxoSmithKline's claim that it kills viruses. The record of his invention of the chemical had already been in the public domain since 1972 in any event, albeit hardly ventilated. A student of his, one R Walters, wrote it up in a thesis. It sits on the library shelves of Beltz's university for all to see.

I thank Stuart Thompson for forwarding an email from Beltz, amplifying the history I'd initially got from him. Beltz sent David Crowe the same account of his first synthesis of AZT that he later sent me, but in his correspondence to me Beltz went on to explain how it happened that Horwitz got the credit.