SENAGO, ITALY—Three centuries ago cardinals seeking refuge from a plague in nearby Milan stayed here at the Villa San Carlo Borromeo, a grand estate surveying the village from its highest hill. The villa and its inhabitants have fallen on harder times since. The cracked plaster and faded paint on its high walls are covered with modern art of dubious quality. Now it is the private museum of Armando Verdiglione, a once prominent psychoanalyst whose reputation was stained when he was convicted in 1986 of swindling wealthy patients. Today the villa is hosting refugees of a different sort: scientific dissidents flown in by Verdiglione from around the world to address an eclectic conference of 100-odd listeners.

At the other end of the dais from Verdiglione is Sam Mhlongo, a former guerrilla fighter and prison-mate of Nelson Mandela and now head of the department of family medicine and primary health care at the Medical University of Southern Africa near Pretoria. Mhlongo has urged President Thabo Mbeki to question the near universal belief that AIDS is epidemic in South Africa and that HIV is its cause.

Between them sits Peter H. Duesberg, an American virologist who has also challenged that belief. Duesberg is now tilting at a different windmill, however. In a reedy voice clipped by a German accent, he explains why he believes the scientific establishment has spent two decades perfecting an utterly incorrect theory of how cancer arises.

It is an odd speaking engagement for a scientist who isolated the first cancer-causing gene from a virus at age 33, earned tenure at the University of California at Berkeley at 36 and was invited into the exclusive National Academy of Sciences at 49. Today many of his colleagues from those early efforts to map the genetic structure of retroviruses occupy the top of the field. Robert A. Weinberg has a huge lab at the Whitehead Institute for Biology in Cambridge, Mass., with 20 research assistants, a multimillion-dollar budget and a National Medal of Science to hang in his office. David Baltimore got a Nobel Prize and now presides over the California Institute of Technology.

“I could have played the game and basked in the glory” of early success, Duesberg says, and he is probably right. But instead he broke ranks and bruised egos. And so, 10 days before attending this eccentric symposium, Duesberg had to dash off a desperate letter to

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**PETER H. DUESBERG: SHUNNED SCIENTIST**

- His theory that HIV does not cause AIDS, outlined at duesberg.com, is rebutted at www.niaid.nih.gov/spotlight/hiv00/
- Twice married, he has one five-year-old son and three grown daughters. When not in the lab, he likes to roller-skate.
- “Surely 5 percent of the funds for science could be set aside for work on fringe theories that could be revolutionary.”

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**Profile**

**Dissident or Don Quixote?**

Challenging the HIV theory got virologist Peter H. Duesberg all but excommunicated from the scientific orthodoxy. Now he claims that science has got cancer all wrong    By W. WAYT GIBBS
Abraham Katz, one of the handful of rich philanthropists who have been his sole source of funding since he was cut off from all the normal channels five years ago.

“We’re down to our last $45,000,” the 64-year-old Duesberg confides glumly as we stand in the dark courtyard of the villa. Katz, whose wife suffers from leukemia, is his final hope; if this grant doesn’t come through, Duesberg will have to cut loose his two assistants, close his lab at Berkeley and move to Germany. That is where he was born to two doctors, where he worked through a Ph.D. in chemistry and where he says he still has an open invitation to teach at the University of Heidelberg.

Leaving the U.S., if it comes to that, would thus close the loop on a roller coaster of a career. Although his ascendance is clear enough, it is hard to say exactly when his fall from grace began. Several weeks later as we talk in his small lab—one fifth the size of the facilities he once had—he hands me a paper he published in 1983. “This is the one that started it all,” he says.

The paper is not, as I expect, his now infamous 1988 article in *Science* provocatively entitled “HIV Is Not the Cause of AIDS.” Nor is it any of the several dozen articles and letters he published in peer-reviewed journals over the next 10 years arguing that the link between HIV and AIDS is a mirage, an artifact of sloppy epidemiology that has lumped together different diseases with disparate causes just because the sufferers have all been exposed to what he calls “a harmless passenger virus.”

Although these dissenting theories of AIDS did not originate with Duesberg, he soon became their champion—and thus the target of derision for those who feared that disagreement among scientists could confuse the public and endanger its health. When Mbeki, after consulting with Duesberg and other AIDS experts, told the International AIDS Conference last year that he felt “we could not blame everything on a single virus,” more than 5,000 scientists and physicians felt it necessary to sign the Durban Declaration, devoutly affirming their belief that HIV is the one true cause of AIDS.

Duesberg’s arguments ultimately converted no more than a tiny minority of scientists to his view that “the various AIDS diseases are brought on by the long-term consumption of recreational drugs and anti-HIV drugs, such as the DNA chain terminator AZT, which is prescribed to prevent or treat AIDS.” Or, as he puts it more bluntly in Milan, in rich countries it is the toxicity of the very drugs that are prescribed to save HIV-infected people that kills them.

The hypothesis has never been tested directly, although Duesberg claims it could be done ethically by comparing 3,000 HIV-positive army recruits with 3,000 HIV-negative recruits matched for disease and drug use. And so his idea has died as most failed theories do, never fully disproved but convincingly rebutted—in this case by a 40-page treatise from the National Institute for Allergic and Immune Disease—and ultimately ignored by nearly everyone working in the field.

But Duesberg didn’t even know AIDS existed in 1983, when he wrote the paper that he says first marked him as a troublemaker. The title seems innocuous: “Retroviral Transforming Genes in Normal Cells?” But in Duesberg papers the question mark often signals that he is about to yank on the loose threads of a popular theory. This time the theory concerned cancer.

He and others had shown that when certain retroviruses inanimate their genes into the cells of mice, the cells turn malignant. Weinberg, Baltimore and others in the field speculated that perhaps similar genes, which they called “proto-oncogenes,” lie dormant in the human genome, like time bombs that turn on only if a random mutation flips some sort of genetic switch. This hypothesis spawned a cottage industry to search for oncogenes, so-called tumor suppressor genes and, most recently, cancer “predisposition” genes.

As two decades passed, human genes with sequences similar to the viral oncogenes were found, and support for this story of cancer’s origin solidified. “If you were to poll researchers, I’d guess 95 percent would say that the accumulation of mutations [to key genes] causes cancer,” says Cristoph Lengauer, an oncologist at Johns Hopkins University.

But the story also grew steadily more complicated—and, to Duesberg, less convincing. Scientists expected to find some combination of oncogenes and tumor suppressor genes that are always mutated, at least in certain forms of cancer. They did not. Instead the number of putative cancer genes has leaped into the dozens, experiments have shown that different cells in the same
malignancy often contain different mutations, and no clear pattern perfectly matches the supposed cause to actual human disease. Cells taken from patients’ tumors typically translate their mutant genes into a mere trickle of protein, in contrast to the flood of mutated protein churning in cells transformed by a virus.

Beginning with his 1983 paper, Duesberg has also picked at theoretical weak spots in the orthodox view. Some tumors are caused by asbestos and other carcinogens that are chemically incapable of mutating specific genes, he points out. Mice genetically engineered to lack tumor suppressor genes and to overexpress oncogenes should all develop cancer in infancy—but they don’t. Given the measured rate of spontaneous mutations and the number of cells in the human body, the average person should harbor 100,000 cancer cells if even one dominant oncogene existed in the genome, Duesberg calculated in a paper last year. But if simultaneous mutations to three genes were required, then only one in 100 billion people would ever acquire cancer.

In 1997 Duesberg published what he thought was a better hypothesis. There is one characteristic common to almost every malignant tumor ever studied: nearly all the cancerous cells in it have abnormal chromosomes. In advanced cancers the cells often have two or three times the normal complement of 46 chromosomes. In new tumors the gross number may be normal, but closer examination usually reveals that parts of the chromosomes are duplicated and misplaced.

German biologist Theodor Boveri noted this so-called aneuploidy of tumor cells almost a century ago and suggested that it could be the cause of cancer. But that idea lost traction when no one could find a particular pattern of aneuploidy that correlated with malignancy, except in chronic myelogenous leukemia, which is not a true cancer because it doesn’t spread from the blood to other parts of the body.

Recently, however, Duesberg and a few other scientists analyzed aneuploidy more closely and argued that it can explain many of the mysteries of cancer better than the current dogma can. Their alternative story begins when a carcinogen interferes with a dividing cell, causing it to produce daughter cells with unbalanced chromosomes. These aneuploid cells usually die of their deformities. If the damage is minor, however, they may survive yet become genetically unstable, so that the chromosomes are altered further in the next cell division. The cells in tumors thus show a variety of mutations to the genes and the chromosomes.

Because each chromosome hosts thousands of genes, aneuploidy creates massive genetic chaos inside the cell. “The cell becomes essentially a whole new species unto itself,” Duesberg says. Any new “species” of cell is extremely unlikely to do better in the body than a native human cell—and that may explain why tumors take so long to develop even after intense exposure to a carcinogen, he argues. The aneuploid cells must go through many divisions, evolving at each one, before they hit on a combination that can grow more or less uncontrollably anywhere in the body.

So far Duesberg has only a scattering of experimental evidence to support his hypothesis. In 1998 he showed that there is a roughly 50-50 chance that a highly aneuploid human cancer cell will gain or lose a chromosome each time it divides. Last December he reported that aneuploid hamster cells quickly developed resistance to multiple drugs—a hallmark of cancer—whereas normal cells from the same culture did not.

But it isn’t easy to do experiments when every one of his last 22 grant proposals to nonprivate funding agencies was rejected, he says. Although Duesberg maintained a facade of defiance in Milan, he acknowledged in a moment of fatigue that “it is depressing that even private foundations are unwilling to fund research that has high risk but high potential payoff.”

His mood had lifted somewhat by May, when I visited his lab. A letter from Abraham Katz tacked to the door stated that his request was approved: he would be getting $100,000, enough to keep the lab running for another nine months.

It seems unlikely that nine months will be enough to persuade other researchers to take his aneuploidy hypothesis seriously. But it is possible. Numerous papers in major journals this year have pointed out the importance of “chromosome instability,” a synonymous phrase, in cancer formation. Lengauer and Bert Vogelstein, also at Johns Hopkins, have been particularly active in promoting the idea that aneuploidy—which Lengauer insists must be a consequence of gene mutations—may be a necessary step for any tumor to progress.

Is Duesberg now willing to lay down his lance and play within the rules of polite scientific society? He recognizes that his combative stance in the HIV debate came across as arrogant. “With AIDS, I was asking for it a bit,” he concedes. “At the time, I thought I was invulnerable.” The experience may have tempered his ego, although he still mentions the Nobel Prize four times in a three-hour interview. Duesberg himself is pessimistic that he will ever be welcomed back into the club. “When you are out of the orthodoxy,” he says softly, “they don’t recall you.”