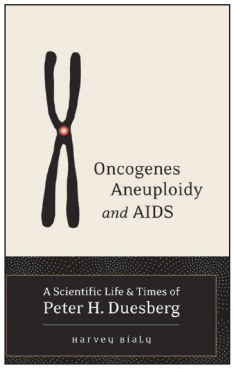
Iconoclast to the Max



Oncogenes, Aneuploidy and AIDS: A Scientific Life & Times of Peter H. Duesberg

by Harvey Bialy

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Reviewed by George L Gabor Miklos

In this authoritative and elegantly written book, Harvey Bialy exposes a microcosm of today's medical science in a blistering analysis of the history of modern cancer and AIDS research. An almost unique hybrid of scientific biography and autobiography, *Oncogenes, Aneuploidy and AIDS* is replete with Nobel laureates, editors of prestigious journals like *Nature* and *Science*, presidents of the US and South Africa and 'colorful' characters such as "Honest Dollar Bill" and the "OncoMouse." But the central figure of Bialy's book is Peter Duesberg, a classical, no-nonsense University of California, Berkeley, professor who has for more than 20 years presented data and interpretations to cancer and AIDS scientists that call into question the fundamental notions of causality they espouse and which represent the dominant, mainstream positions—that specific genes when mutated cause cancer, and HIV causes AIDS. The sadly predictable result of questioning these two sacred cows of modern biomedicine was the almost complete destruction of a once lofty professional standing. Of late, however, Duesberg's name has begun to undergo some significant reconstruction, as Bialy makes clear in telling the fascinating and instructive story of his banishment from the High Table and his recent partial return to favor.

To this reader, Duesberg's situation suggests parallels with that of another cell geneticist, the Nobel Prize winner Barbara McClintock. For decades her work was ignored by all except the very few who understood that the ideas and data were persuasive and worth serious consideration even though they did not fit the existing fashion—yet how right she turned out to be. The inescapable conclusion: clean data and perceptive, unbiased analyses win every time. Near the end of a chapter entitled "Good Mourning America," Bialy uses an analogy to an old television police series where the Los Angeles cop Joe Friday continually reiterates "Just the facts, ma'am," to emphatically make this point.

Oncogenes, Aneuploidy and AIDS has other global themes such as how science should be done, and the prominent role of metaphoric language in popular and professional scientific writing. Bialy's method is to examine the most important review articles and scientific papers in both cancer and AIDS that Duesberg published between 1983 and 2003, and the responses to them in the journals. He does this by weaving the hard science with historical and personal reflections to produce a contextual fabric that makes the book appealing and comprehensible to even a nonspecialist reader. As far as this reviewer is concerned, Duesberg gets the Big Picture correct on both cancer and AIDS because he demands the highest standards of data interpretation, something that is a common casualty in the cancer and AIDS fields where fame, stock options, potential blockbuster drugs, appearances on *Larry King Live* and the front cover of *Time* or *Newsweek*, often appear to take precedence. As the founding scientific editor of *Nature Biotechnology* and an early PhD from the first department of molecular biology in the country at UC Berkeley, Bialy has a privileged position, which he uses to impeccably demonstrate that Duesberg represents a golden era of molecular biology when there was no room for the shoddy overinterpretations and unimpressive correlations that pass for some of today's cancer and AIDS 'breakthroughs.'

Despite being the past recipient of an Outstanding Investigator Grant from the US National Institutes of Health, the Institutes' most competitive and highly regarded award, and a member of the US National Academy of Sciences since 1986, Duesberg became unfundable in parallel with his questioning of AIDS and cancer etiologies. But in testament to what makes the United States the epicenter of privately financed innovation, he succeeded in attracting support from a farsighted San Francisco philanthropist, and his ailing laboratory was rejuvenated. So real science continued, and together with Berkeley and University of Heidelberg collaborators, Duesberg produced a rigorous, quantitative genetic explanation of cancer that is based on massive chromosomal upheavals, a phenomenon called aneuploidy that for almost 100 years has been known to be the most consistent genetic alteration associated with solid tumors. In its modern metamorphosis at the hands of Duesberg and his colleagues, this explanation of cancer has begun to receive serious and well-deserved attention. The aneuploidy view is very different from the current mainstream one, which states that cancers arise because of the stepwise accumulation of mutations in oncogenes and tumor-suppressor genes, sometimes assisted by mutator genes in a chromosomally normal human cell. The implications for drug development are also very different for the two modes of cancer genesis, and herein lay the makings of an unavoidable clash that was almost as vicious as the more obvious one between viral and chemical causes of AIDS.

Unfortunately for the establishment position, it has so far proven experimentally impossible to produce cancer in normal, diploid cells by multiple mutational routes. To use a phrase repeated to devastating effect in the book—to what should be the shame of numerous and very public defenders of both oncogenes and HIV—while specific mutated genes have "told us many things that we did not know, they have thus far not provided the answer to the all-important question of how." The mutation-cancer field is so befuddled, it will come as no surprise when the reader learns that the "guardian of the genome," the current *capo di tutti capi* of tumor suppressors, p53, was reclassified as

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a tumor suppressor after being a bona fide dominant oncogene for over a decade. As Bialy writes in one of the must-read, 'grace note' annotations, mutated oncogenes and tumor suppressors are about processes and have almost no individual value except in defined genetic backgrounds. They contribute to phenotypic endpoints that are only applicable in the context of a network perturbation. Thus, as is well known, but nevertheless conveniently ignored, a mutation in a tumor-suppressor gene may be associated with a high frequency of colorectal carcinomas in one genetic background, but the same mutation in a different genetic background yields a perfectly normal colon totally free of carcinomas.

For this reviewer, steeped in chromosomal mechanics, segmental aneuploidy and mutational profiles of eukaryotic genomes in different genetic backgrounds, the severe limitations of what individual mutations can and cannot do is based on rigorous and well-tested experimental foundations. The mutational underpinnings of cancer, by contrast, as currently set out by mainstream cancer researchers, simply don't cut the mustard in either predictive value or clinical usefulness. Trying to prolong the lives of cancer patients based on research emanating from the academic and pharmaceutical sectors has made it clear that something is seriously amiss with current approaches. For example, after three decades of research, there has been no reduction whatsoever in the incidence of the major solid tumors of the breast, lung, prostate and colon. All we have to show for the effort is a massive clinical black hole into which hundreds of billions of dollars of public and pharmaceutical money continues to be poured. This situation has been extensively (and exquisitely) documented by a devastating recent article in *Fortune* magazine by Clifton Leaf, entitled, "Why we are losing the war on cancer". As Andy Grove, the chairman of Intel pointed out to the magazine's editor, "It's like a Greek tragedy. Everybody plays his part, everybody does what's right by his own life, and the total just doesn't work." In this context, Duesberg's work on the importance of gross upheavals in the human genome in the etiology of cancers is of enormous significance, as the real clinical issue concerns the series of unstable network problems leading to metastasis. This metastatic dot is slowly assuming more prominence on the cancer radar screen, as the technology to examine the transcriptional outputs of single cancerous cells is being improved.

It cannot be overemphasized that cancer is not really a disease of uncontrolled growth. Cancer cells often divide more slowly than their progenitors and metastatic cells often become arrested at ectopic sites in the body. Henry Harris, a distinguished early pioneer of the tumor suppression field at the University of Oxford, made this same point when he wrote in the pages of *Nature* recently, "It would reduce confusion considerably, if it could be agreed that cancer, in the first instance, is not a disease of cell multiplication, but a disease of differentiation" (as quoted in the book). The triumvirate of Bialy, Leaf and Harris is a lethal cocktail for conventional theories of cancer. Either you are blasted from a cocooned world, or one of the great paradigm shifts in medicine has just passed you by.

There comes a time when throwing money at a problem is counterproductive and what is required is more cortical horsepower. It is a corollary of what the Nobel laureate Sydney Brenner has been saying for decades and which he put in prose in a favorite essay, "Sillycon Valley Fever." Brenner's point is brutal in its simplicity. How can you perform academic or commercially relevant biology if you don't think deeply? If you don't have a coherent theory and if you are dependent upon sophisticated technologies and bioinformatic protocols that you don't understand, then your data interpretations are in the realm of voodoo science. It is painfully obvious by now that this is where many cancer and AIDS researchers have located themselves—a conclusion attested to by the unchanged mortality rates of breast, lung, prostate and colorectal cancers and the mountain of contradictions in the scientific literature concerning presumed HIV pathogenesis, AIDS morbidity, mortality, epidemiology and demography. Having got it so wrong, they can't buy their way out of their self generated cul-de-sacs. The almost pathological obsession with gene-based solutions (cellular or viral), neat gene-based circuit diagrams, mutator genes and 'Molecular Portraits' of cancers has led to a medical science that has wasted a massive amount of resources and spawned a plethora of failed drugs.

Oncogenes, Aneuploidy and AIDS should be compulsory reading for those concerned with what the US (and other Western) governments are buying when they spend public money on cancer and AIDS research. It should also be compulsory for pharmaceutical and biotech executives, since most of their potential targets for solid tumors are irrelevant entities that continue to clog drug development pipelines. Finally, it should be read by anyone who is interested in the way scientific theories develop and are shaped by historical circumstances.

In his detailing of the academic trials, tribulations and recent emerging triumphs of professor Duesberg, Bialy provides a number of salient lessons. One of them is that something precious has been lost in our love affair with the technological marvels that permeate today's biomedical science. It is, after all, the human cortex that sets the standards of excellence. If those standards are compromised, we are on the inexorably downward slope of shallow thought and mindless turning of the millstone. The proposition is indeed a stark one, and it is a measure of Bialy's skill and artistry that he makes it thinkable.