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Appraising Aneuploidy as a Cancer Cause

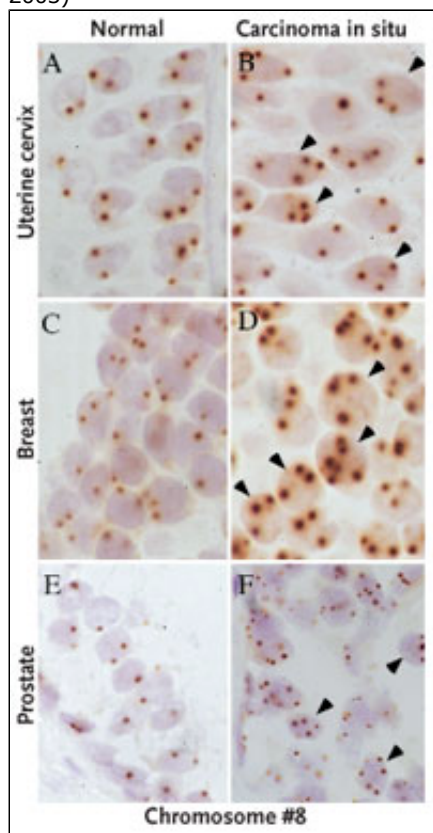
A conference considers a theory that blames tumorigenesis on chromosomal gains and losses | [By Douglas Steinberg](#)

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About 70 scientists recently attended an invitation-only California premiere tinged with controversy. But the event neither lit up a Hollywood theater nor unveiled an edgy new film. Billed as the "first conference on aneuploidy and cancer," it took place at Oakland's Waterfront Plaza Hotel in late January.

The conference explored whether aneuploidy, the cellular state of gained or lost chromosomes, is a driving force behind cancer. German biologist Theodor Boveri first floated that idea a century ago, and since then, cytologists have often observed aneuploid patterns in tumors. Colorectal cancer cells, for example, regularly gain a copy of chromosome 7, 8, 13, or 20, or lose chromosome 18.

Interest in aneuploidy declined over the past 30 years, as countless studies supported the theory that tumors arise from mutations, amplifications, and deletions of specific genes. Yet doubts have



THE TRIPLETS OF CELLVILLE: When stained with a biotinylated probe specific for the chromosome 8 centromere, diploid cells from normal human uterine cervix (A), breast (C), and prostate (E) tissue show two signals. Aneuploid cells from carcinoma tissues in situ (B, D,

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and F) each have three or more signals.

persisted about whether such discrete genetic changes occur at the murky onset of cancer, and

whether these changes are necessary or sufficient for the full-blown disease.¹

A few scientists have consequently revived the aneuploidy theory. In its extreme form, the theory excludes any causative role for mutations, amplifications, or deletions. But many of the Oakland conferees favored a less radical hypothesis: Aneuploidy can indeed result from discrete genetic changes and is only one cause among several in triggering tumorigenesis. "Mutations weren't dead" at the conference, concedes co-organizer Peter H. Duesberg, a controversial molecular and cell biology professor at the University of California at Berkeley. "That's definitely true. But they were certainly not the sole contenders."

DIPLOID VS. ANEUPLOID A pioneer in the field of retrovirus-mediated oncogenesis, Duesberg remembers concluding eventually that "it was not a good model for real cancer." Fifteen years ago, he began developing a theory positing that a cell becomes aneuploid either spontaneously or through the nonmutational effects of carcinogens. Aneuploidy creates protein imbalances that steadily increase chromosomal and genomic instability in the cell's progeny.²

"To various degrees, the majority of [aneuploid] cells are less viable, but some of them occasionally get a combination together that makes them more viable in the habitat of the organism than a normal cell would be," explains Duesberg. "Then you have selective advantages, and then you get the end product of such a process of somatic karyotype evolution," namely a tumor.

Duesberg's notoriety--he has long maintained that HIV does not cause AIDS--surely clouds appraisals of his aneuploidy theory. But some of the Oakland conferees credit his extremism with stimulating the reexamination of important issues pertaining to cancer's origins. "I think having someone who argues for aneuploidy alone makes a whole lot of people go out and test whether or not that's true," suggests Stephen J. Doxsey, an associate professor of molecular medicine at the University of Massachusetts Medical School in Worcester.

One contentious issue at the meeting was whether many malignant cells are indeed aneuploid. Some participants pointed out that leukemias and lymphomas are generally diploid. But Frederic M. Waldman, a professor of laboratory medicine at the UC-San Francisco, presented a finding of unexpected aneuploidy. Using a new technique known as array comparative genomic hybridization (CGH), Waldman, postdoc

Kshama Mehta, and colleagues analyzed seven cases of sporadic colorectal cancer with microsatellite instability.

Methods that measure a cell's overall DNA content have long pegged these tumors as diploid. But such methods can fail to detect chromosomal gains balanced by losses. Array CGH, in contrast, allows high-resolution scrutiny of chromosomal alterations. Waldman reports that all seven tumors displayed "significant numbers of genomic alterations," including gains and losses of whole chromosomes.

CYCLIN E AS A KEY One poster at the conference described a study testing aneuploidy's effects on gene expression. Thomas Ried, chief of the cancer genomics section at the National Cancer Institute, and postdoc Madhvi B. Upender added an extra copy of chromosome 3, 7, or 13 to a diploid colorectal cancer cell line and an extra copy of chromosome 3 to immortalized, but nonmalignant, breast epithelial cells. Not only did the expression levels of genes on the trisomic chromosome increase, but a substantial number of genes on other chromosomes were also affected. (Similar results occur in a mouse model of Down syndrome, a trisomy disorder.) But no specific expression patterns were detectable, Ried says. "It looks as if everything goes up a little bit."

Ried has tried unsuccessfully to turn normal cells malignant by adding a chromosome. But his ability to engineer viable aneuploid cells is already an accomplishment. Ronald A. DePinho, a professor of medicine and genetics at Harvard Medical School, and colleagues recently made cells rampantly aneuploid by knocking out a particular gene, thereby disturbing chromosomal segregation; the cells died.³ "It is clear that whole chromosomal gains and losses are not a highly productive route towards reshuffling your genetic deck in such a way that it leads to a procancer genotype," DePinho asserts.

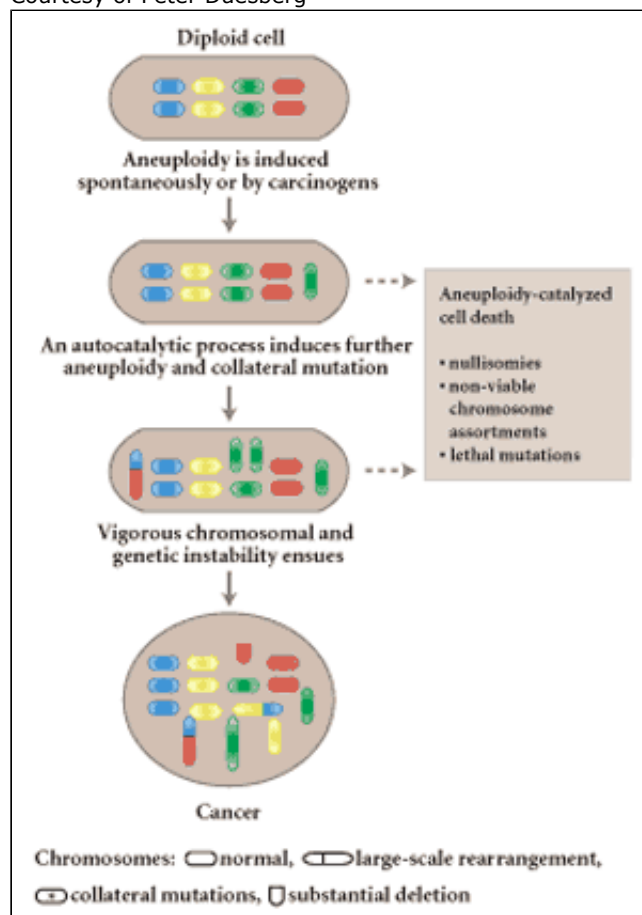
Gert Auer, an oncology and pathology professor at the Karolinska Institute and Hospital in Stockholm, disagrees. He deems aneuploidy an early, crucial condition underlying epithelial malignancies, which comprise the vast majority of solid tumors. In the 1990s, Auer and Ried together discovered that at later stages of colorectal cancer, amplifications often occurred on extra chromosomes that had been gained at earlier stages.

At the Oakland conference, Auer presented a study of 104 breast tumors in which he and colleagues differentiated between genomically stable and unstable cases of aneuploidy.⁴ The hallmark of instability, the far more deadly condition, was a heterogeneous cell population exhibiting varying degrees of aneuploidy. Stable aneuploid tumors, on

the other hand, contained cells that were all, for example, triploid or tetraploid.

Ulrike Kronenwett, a graduate student in Auer's lab, found more mRNA transcripts for cyclin E, the cell-cycle protein, in the genomically unstable tumors. A new paper might explain why cyclin E protein levels also increase in cancer. Christoph Lengauer, an associate professor of oncology at Johns Hopkins University School of Medicine, and MD-PhD student Harith Rajagopalan detected a mutant hCDC4 gene in 22 of 190 colorectal tumors and in 4 of 58 adenomas, a lesion that can precede colorectal cancer by as much as 30 years.⁵ Calling the adenoma result "amazing," Lengauer points out, "It's extremely rare to find mutations in early adenomas because they are so early in tumorigenesis."

Courtesy of Peter Duesberg



CARCINOGENESIS VIA ANEUPLOIDY: According to some biologists, cancer arises from a cell that has survived the gain or loss of a chromosome. This state of aneuploidy unbalances the teams of proteins that synthesize, repair, and maintain DNA, and that ensure proper chromosomal segregation during mitosis. The resulting genetic and chromosomal instability causes a chain reaction of aneuploidization and mutation. Some of the cell's

progeny eventually turn malignant.

The protein encoded by hCDC4 helps to ubiquitinate cyclin E, and ubiquitination leads to cyclin E's proteolysis. Experimenting on cells manipulated to lack hCDC4, Rajagopalan observed that they had higher cyclin E levels, as expected, but also exhibited mitotic abnormalities and aneuploidy. The mechanism by which higher cyclin E levels create chromosomal instability remains "unsolved," says Lengauer.

THERAPEUTIC OPTIONS In a pilot study, Auer's team also saw more aberrant centrosomes in genomically unstable aneuploid cells compared to other cell types.⁴ Centrosomes are the microtubule-containing organelles that organize the spindle fibers along which the chromosomes move during mitosis. These organelles help maintain genomic stability and are abnormal in nearly all carcinomas, Doxsey notes. "We think that as soon as you have an extra copy of a centrosome, in the next [cell] division you're going to have aneuploidy," he adds.

Last year, Doxsey, pathologist German A. Pihan, and colleagues reported that centrosomal abnormalities and chromosomal instability occur together in pre-invasive carcinomas. But Doxsey stresses that such correlative data alone cannot prove that centrosomal defects contribute to cancer. "We're trying to make cells with centrosome defects and ask whether that alone can drive tumor-like features," he says.

Doxsey and Pihan demonstrated in 2001 that prostate cell lines that ectopically express the centrosomal protein pericentrin develop centrosomal abnormalities, aneuploidy, and a tumor-like phenotype. In Oakland, he showed pictures of a cell his lab had engineered that contained three centrosomes (instead of the normal two) and formed a tripolar spindle, leading to chromosomal missegregation.

Centrosomal defects and aneuploidy should become routine diagnostic and prognostic markers, researchers say. Auer notes that Swedish clinicians already consider aneuploidy in determining treatments for various tumors. Nevertheless, aneuploidy's other therapeutic implications are mixed. On the positive side, precancerous aneuploid cells could be vulnerable to lifestyle changes, such as quitting a smoking habit. In studies on beagles 20 years ago, Auer learned that before aneuploid bronchial cells turn malignant, they can be induced to die if the aneuploidy-inducing carcinogen is removed.

But Auer and Duesberg doubt whether transformed aneuploid cells can similarly be forced into apoptosis. Another pessimistic prediction of aneuploidy theory, Duesberg argues, is that targeting mutations, as many new drugs do, "is probably useless." Lengauer, however, suggests

an intriguing approach to treating chromosomal instability in early adenomas: "Perhaps we can increase that instability so that the cells die. As long as there are little tumors, that might work."

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