ously question a large set of conclusions, including clock inferences, "the mitochondrial Eve," and countless phylogenies.

Eyre-Walker *et al.*'s conclusion rests on one observation, that a "phylogenetic tree constructed using human mitochondrial sequences contains a large number of homoplasies." The paper concludes that this high number of homoplasies must be the result of recombination between maternal and paternal lineages.

However, a fundamental principle of their tree construction algorithm is that hypothetical ancestral types at nodes of the tree all are extinct. There is no reason to believe that this is a valid assumption for populations in general, and specifically in the case of humans, where the time since a common ancestor probably is only around 200,000 years. The likely presence of haplotypes ancestral to other recorded haplotypes in the analyzed population sample will automatically lower the number of inferred homoplasies and could even remove them all.

The high number of homoplasies claimed by the authors might well be an artifact of the analysis applied. An answer to the important question of mitochondrial recombination is likely to stem from the application of more appropriate analytical tools to the now very large database of human mitochondrial sequences.

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Are Centrosomes or Aneuploidy the Key to Cancer?

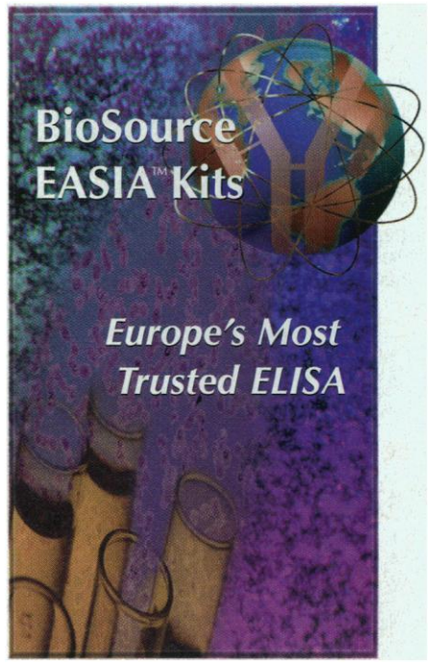
A News of the Week article by Elizabeth Pennisi about centrosome replication (5 Feb., p. 770) points out that centrosomes "might be a key to cancer." Indeed, abnormal structures and numbers, that is, more than two, of centrosomes have already been found in nearly all cancers tested (*1, 2*). The idea that centrosomes might be a key to cancer originated with Theodor Boveri, who proposed almost a century ago that multipolar mitosis causes aneuploidy, an abnormal balance of chromosomes, and that aneuploidy causes cancer (*3*).

However, as Pennisi says, Boveri's "idea got lost, as researchers concentrated on understanding the specific gene malfunctions that lead to cancer." Accordingly, gene mutations are now investigated to explain the abnormal centrosomes and the aneuploidy of cancer cells. For example, mutant p53 (*4*) and an overexpressed centrosome-associated kinase SKT15 (*5*) are thought to destabilize centrosome replication, and a defective mitotic checkpoint gene is thought to cause chromosome nondisjunction (*6*).

But these mutations are consistently found in only a minority of cancers. The p53 mutation is found in fewer than half of aneuploid and genetically unstable colon cancers (*7*); only 12% of primary breast cancers contained the mutant kinase (*5*); and only two of 19 aneuploid colon cancers contained the mutated, putative checkpoint gene (*6*). In contrast, nearly all cancers are aneuploid (*8*) and have abnormal centrosomes (*1, 2*). In addition, there is as yet no functional proof that the mutations cause aneuploidy.

I therefore suggest that both the abnormal structures and numbers of centrosomes in cancer cells are caused by aneuploidy (*9–11*). Because aneuploidy unbalances huge numbers of genes, it can readily explain, by abnormal dosages of normal genes and thus independent of gene mutation, not only abnormal centrosomes, but also the many other dominant, cancer-specific phenotypes, including dedifferentiation, neoantigens, metastasis, altered growth, morphology, and metabolism (*9, 11*). All these complex phenotypes are determined in vivo by assembly lines of many kinetically linked enzymes (*12*). It is for this reason that aneuploidy can change cellular phenotypes much better than gene mutation. Aneuploidy changes cellular phenotypes like a car factory changes its output, by altering the number of assembly lines. Balanced changes produce more or fewer normal cars, but random changes (aneuploidy) produce abnormal cars (cancer). By contrast, negative gene mutations are typically recessive; even rare positive mutations are buffered by up- and downstream enzymes of an assembly line (*12*) and thus are unlikely to generate the dominant phenotypes of cancer cells (*13*). In support of this view, some researchers interviewed by Pennisi propose that aneuploidy causes cancer by altering the dosage of apparently unmutated "oncogenes" and "tumor suppressor genes." But they do not suggest that changing the dosage of one gene by means of the chromosome number simultaneously changes that of thousands of others.

Indeed, aneuploidy can even explain the "genetic instability" of cancer independent of gene mutation, because aneuploidy generates nonparental karyotypes autocatalytically (*10, 11*). [This hypothesis does not exclude that mutation of mitosis genes also may cause aneuploidy as, for example, in Bloom's syndrome (*14*)]. My hypothesis further predicts that carcinogens function as aneuploidogens, which has been demon-



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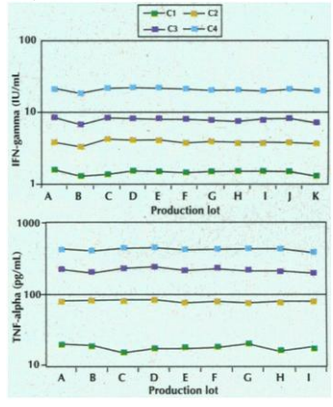

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strated by me and my colleagues (*9, 15*) and by others (*16*), and that cancer may be more effectively prevented by controlling aneuploidizing agents than by controlling conventional mutagens.

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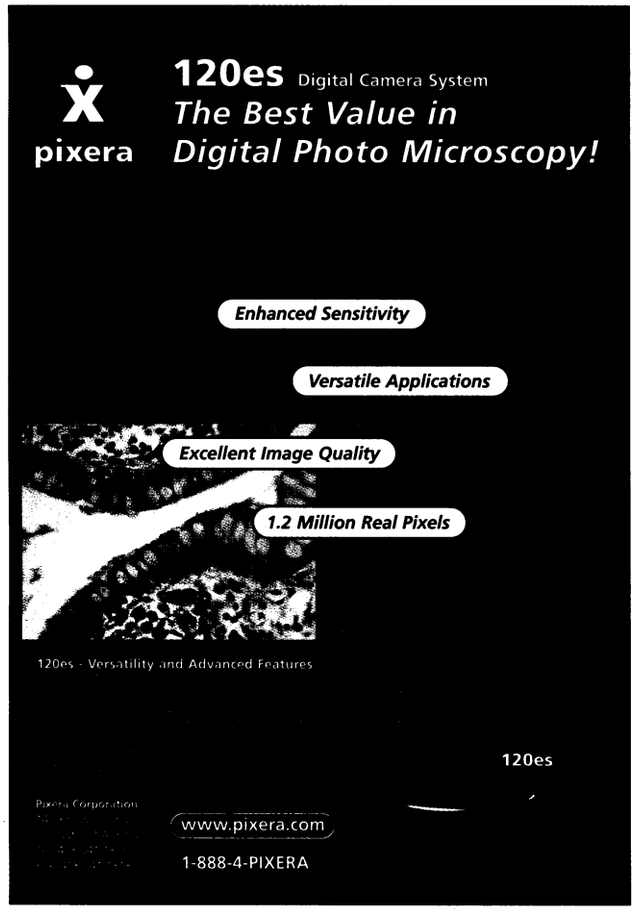
Eastern Europe's Research Gamble: The Czech Perspective

At the beginning of 1999, the new Framework 5 research program of the European Union was launched. Ten formerly socialist European countries have been admitted as associated participants. On this occasion, Robert Koenig published an article (News Focus, 1 Jan., p. 22) discussing the level and current problems of science in those countries.

We would like to point out some problems with the treatment of the data on citation statistics and offer a few additional comments on the subject. Having analyzed in detail the data provided by the Institute for Scientific Information (ISI), we conclude that the table on citation impacts in Koenig's article is based on an option that allows the user to extract the citation impact for a 5-year period, 1993 to 1997. This particular choice seems unfair, specifically for the Czech and Slovak republics. Czechoslovakia split into two states, the Czech Republic and the Slovak Republic, at the beginning of 1993. ISI provides independent statistics for the Czech and Slovak republics only from 1994 on. The split of the former Soviet Union and Yugoslavia occurred earlier. Therefore, the new states formed on these territories have had separate representations in the ISI database since 1993. Consequently, only the 4-year citation impact for the Czech and Slovak Republic was compared with the 5-year impact for the other countries in the table. We recalculated the citation impacts for all the countries listed in the table for the 4-year period 1994 to 1997 to make them directly comparable with the data available for the Czech and Slovak republics. After this recalculation, the Czech Republic becomes 22nd and the Slovak Republic 27th out of 33 European countries, instead of 29th and 33rd, as stated in Koenig's article.



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