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Sailor-Shooting

Interview: US molecular biologist and cancer expert Peter Duesberg on anti-smoking campaigns, gene mutations, aneuploidy, and the failure of established cancer research

By Torsten Engelbrecht

***FREITAG**: Renate Künast, Germany's federal minister for consumer protection, nutrition, and agriculture, has announced that she will take increased action against additives in cigarettes. As well, the pop icon Kylie Minogue, ill with breast cancer, is asking her fans to donate to cancer research instead of sending her flowers. Experts note, however, that the rate of illness from the various types of non-smoking-related cancers has risen noticeably since the beginning of the 1970s, when US president Nixon proclaimed the "war on cancer" – a rate parallel to the increased research expenditure. Meanwhile, 220,000 people die from cancer every year in Germany – while in the USA only 550,000 die each year. What is going wrong?*

PETER DUESBERG: The main problem lies in the entirely one-sided devotion of research to the so-called gene mutation theory. Mutations in so-called oncogenes are said to stimulate tumor growth, while tumor suppressor genes slow the growth of tumors. Hundreds of billions of dollars have already been pumped into the search for oncogenes and tumor suppressor genes. But as George Miklos, one of the major players in gene research, phrased correctly in the professional journal *Nature Biotechnology*: The gene mutation hypothesis about cancer is "fundamentally incorrect" and amounts to "Voodoo science".

Where do you see the most crucial contradictions?

Practically all oncogenes have been tested in mice without causing cancer. And in a majority of "solid cancers" – i.e. the types of cancer that tend to metastasize and show resistance to chemotherapy – no cancer genes, including in this case oncogenes, has been found at all. According to the gene mutation theory, cancer-causing matter – carcinogens – functions mutagenically, i.e. is gene-changing. However, approximately half of these carcinogens are not mutagens, such as asbestos, hormones, nickel, or mineral oil. A further basic assumption of the gene mutation theory is that cancers are diploid, that is, they have a normal set of 23 chromosome pairs, each of which has thousands of genes. However, the solid cancers are aneuploid, i.e., the chromosomes are damaged or in incorrect number.

But would it not be at least theoretically conceivable that genes produce cancer?

It takes a very long time until breast cancer develops, for example, usually decades. This phenomenon completely contradicts genetics. If one mutates a gene, then one sees the new appearance – the phenotype – immediately in the next cell generation. Cancer, however, is a lengthy process. One can expose mice to a controlled quantity of a carcinogenic X-ray just for an instant, whereupon the mice continue to live as before for at least six months to one year – until finally the cancer emerges. Now four to seven gene mutations are required for the development of an advanced cancer cell – a procedure that in reality takes a very long time and is supposed to account for the span of time until the outbreak of the cancer. In order to prove this, gene mutations would have to be inserted in a test tube into a normal, thus diploid, cell until a cancer cell is produced. This has been attempted for many years, but it never worked.

Your counter-theory for gene-mutation is called aneuploidy...

We will stay with the mouse example: The X-ray triggers a chromosome revolt, which only many cell generations later produces a cancer cell with its own chromosome set. Either certain chromosomes are missing or extra ones are present. Such chromosomally destabilized cells proceed step-by-step, from a tolerable hyperplasia or benign tumor to full metastatic malignancy without the need of any special mutations in any special genes. This process usually lasts for a long time and offers an explanation for the decades that are needed on average before cancer "breaks out". In these cells certain chromosomes are missing and others may be duplicated.

Do you have an example?

In the typical human intestine, lung, or prostate cancer – which rank among the most frequent kinds of cancer – there are 30 to 40 pairs of chromosomes instead of the normal 23. Cancer is thus a new species, far more removed from we humans than a gorilla. It is not a "plain" gene mutation that cannot mutate the species. The German biologist Theodor Boveri described the aneuploidy theory in 1914, at a time, when gene fixation was not yet mainstream practice. At that time, it was still assumed that with certain cancers, such as lung or intestine, constant abnormal chromosome numbers would have to be present, but this assumption could not be proven. Therefore the theory was not accepted. Today we recognize that no one cancer of the large intestine has the same chromosome damage as another cancer of the large intestine. But one parallel always appears: The more aggressive the cancer, the more heavy the chromosome damage.

Prominent established cancer researchers such as Bert Vogelstein or Christoph Lengauer confirm that aneuploidy can be observed in practically all cancers. But they maintain that a gene mutation precedes the chromosome damage.

For the time being, this is just another hypothesis. In individual cases it may be coincidentally true. But the probability that one – for example through radiation – mutates a gene, which then causes the damage to the chromosome, is extremely small. It is like a person who wants to sink a battle ship. Either one shoots at a sailor – the gene – or at the

hull – the chromosome set. The probability that one would hit the ship – the chromosome set – is a-hundred-thousand-fold higher. Along with that, all gene functions in the cell are recessive, meaning that even if a gene is affected and mutates, the cell machinery continues to run, because the second gene of the pair continues to work unchanged.

Thomas Ried, head of the department of Cancer Genomics at the US National Cancer Institute, has been quoted in 2003 in "Scientific American" with the words: "So I actually think Duesberg is right that aneuploidy can be the first genetic aberration in cancer cells. But he also argues that no gene mutations are required. This is simply not true."

For 80 years, scientists have believed in the gene mutation theory as an explanation for cancer – nevertheless, where is the mutation that causes cancer? If someone could describe this, then we could have a scientific discussion. Instead, we can just talk about questions of faith. Aneuploidy is absolutely sufficient as explanation. In order to explain Down's Syndrome, where three instead of the normal two 21st chromosomes are present, there is no requirement for a gene mutation.

In the April issue of "Nature Medicine" a trial vaccine is described that for the first time ever is supposed to be able to extend the life expectancy of patients with prostate cancer. How do you classify such success stories?

The idea of immune therapy for cancer is 100 years old. Paul Ehrlich already postulated that one can use immunity to fight against cancer. But it has been a hopeless venture. The cancer cell does not contain new genetic material – but the immune system still only recognizes foreign material. If mutated genes could activate the immune system, then we all would be long dead, because the immune system would kill cells daily en masse. In actuality, ordinary gene mutations are channeled through the body under the "radar screen" of the immune system. The topic is often revived, but always it turns out to be a false alarm. Take the example of the initial clinical successes of the substance *Imatinib* in relation to chronic myeloid leukaemia – these results could not be repeated later on. In addition, in many cases a resistant form of the cancer emerged again later. There are no real long-term studies at all. That makes it practically impossible to make statements about "life-prolonging effects". The heralded improvement that occurs refers to periods of perhaps several weeks – for which one pays US$ 50,000 or US$ 100,000. For businesses that is marvelous, but what does do for the patient? If the gene mutation thesis were correct, then it would be theoretically possible to achieve success by blocking the gene-changing effects. But the nature of the cancer cell just simply is the instability of the chromosome set (aneuploidy). Therefore the drugs are not effective.

What would be the consequences if the aneuploidy theory were to be generally accepted?

Diagnostic capabilities would be strongly improved through analysis during the early stages for aneuploidy instead of gene mutation, either of tumor growth or through pap-smear tests of suspected malignant uterine-tissue– this analysis already done in Sweden, for instance. This can mean that one does not operate on a prostate, because it is not yet aneuploid. One would continue to hold it under observation and would switch, for example, to a diet that is "cancer-friendlier". Also one could determine, on the basis of a chromosome analysis, to which chemotherapy the cancer is already resistant. Vogelstein already recommended this one year ago.

Women are sometimes told, they have a genetic predisposition for breast cancer – and then "preventively" have their breasts removed. Or the thyroids of healthy infants are cut out "as a precaution". How does this fit the aneuploidy theory?

Such a procedure would be at best legitimate if one knew what causes cancer. But since even the proponents of the gene mutation hypothesis say that they have "no proof of any mechanisms of the origin of cancer", one can only designate such interferences as catastrophic. An organ is removed because of an alleged certainty, a position that cannot be held scientifically. And nobody can shut out the possibility that "non-inherited" habits like smoking or eating habits play an important role or even the crucial role in the emergence of cancer.

Tumor tissue is by far the most acidic type of body tissue. Despite this, the role that acid-forming nutritional habits play in the development of cancer has not been investigated. In this regard, there has been much more headway made in the field of osteoporosis. Even in the brochures from osteoporosis pill manufacturers it says: "Avoid acid-generating foods such as meat or sweets."

The over-acidification of the body as a basis for the emergence of cancer has already been investigated by the Noble Prize winner Otto Warburg. Healthy body cells burn sugars to carbon dioxide, the cancer cells ferment sugars to lactic acid, thus creating the typical overly acidic environment. With genes, one knows that in the case of cell multiplication the probability that a mutation results is one in a million. Accordingly, one would have to compute how large the normal occurrence of aneuploidy is in normal cells. Subsequently, one can measure the rate of aneuploidy in the blood and compare these results to those of people who eat a lot of acid-forming foods such as meat, rice, fish, eggs, or sweets as well as to those of vegetarians of all kinds.

In which direction will the international cancer medicine research be heading next?

If we are lucky the aneuploidy theory will find favor within the cancer establishment. Miklos brings up a good point. He says that the many billions that are allocated to gene mutation research would be much better spent if research priorities were first re-evaluated. One would have to first dismiss the fallacious notion that individual gene mutations in a tumor are the optimal starting point for research toward the causes of cancer. The opposing clinical reality holds that it is not single changes in genes, but rather chromosomal damage that leads to the fact that metastatic malignancy, accounting for 90 percent of all deaths due to cancer, causes cancer cells to explore new niches and become resistant to medication-based therapies.

Peter Duesberg is professor at the University of California in Berkeley, member of the renowned American National Academy of Sciences, and co-discoverer of the first known so-called oncogene "src"