Viruses and Cancer: Update

The Editor interviews:
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Editor: What is the newest development in virus research that is related to cancer?

Dr. Rapp: The most important recent discovery is the identification of viral gene products that may be responsible for cancer. Specifically, the virus that causes sarcoma in chickens elaborates a product that has been identified and isolated. Now the task is to determine how that product, when it's manufactured, can convert a normal cell to a cancer cell. That problem is currently being investigated.

Editor: What is the product?

Dr. Rapp: It's an enzyme, a protein kinase. It's not clear, at this time, exactly what this enzyme does in the cell. But if it can transform normal cells, that information may have far-reaching implications. All we are certain of at the moment is that the enzyme is coded by the virus gene and produced by the host cell.

Editor: Is just one virus gene involved?

Dr. Rapp: Yes. It is now believed that in leukemias and sarcomas, just one gene of the virus participates in the induction of cancer. In fact, with all oncogenic viruses, there are probably no more than a few genes involved in the malignant transformation of cells. The problem remains of identifying these genes, and
their range and mechanism of action. The sarcoma-inducing virus has only about four genes, so finding the single gene that's responsible was easier than it will be in the case of herpesviruses, which have about 80 genes.

Editor: 
*Do these cancer-inducing genes exert their effects in the course of viral replication in the host cell?*

Dr. Rapp: 
Not exactly. Herpesviruses, for instance, are cytopathic when intact. What occurs is that only a piece of the original DNA is inside the host cell—probably less than five percent of the genetic information of the virus. Therefore, the whole virus cannot be replicated. It may be that the whole virus is incorporated into the cell and is then fragmented by the host cell's enzymes. Or a viral unit that has only a piece of its DNA to begin with may get into the cell. A cell will naturally try to destroy any invading virus, but sometimes it fails to accomplish that. Although this is speculation, it's theoretically possible that if the host cell has a small break in its DNA, the piece of viral DNA could incorporate itself into the host’s genome.

This situation is enhanced experimentally, by the way, with the use of chemicals. If one damages a cell a little bit by introducing chemicals, the probability that a carcinogenic virus will convert the cell to cancer is increased.

Editor: 
*Do you subscribe, then, to a general hypothesis of co-carcinogenesis in the etiology of cancer?*

Dr. Rapp: 
My personal viewpoint is that cancer occurs as a result of a number of factors acting in concert; in that sense, it's really an accident. We all carry almost the same viruses, and we're all exposed, more or less, to the same environment. I look at it as an opportunistic event, where a number of factors—and you can assign any number you want here—occur at one place at one time, and a normal cell converts to a tumor cell and starts to grow. Even then, in most instances the body gets rid of the tumor cells. But when all the events are just right, the body's defenses fail for one reason or another. If we could somehow break the chain we could probably reduce the incidence of cancer.

Editor: 
*Are all cancers related to viruses?*

Dr. Rapp: 
I doubt it. There are so many different kinds of human cancer involving different organs and different populations, that a single, or consistent, etiologic agent seems highly unlikely. For instance, even in Burkitt's lymphoma, where the African type has been strongly associated with Epstein-Barr virus (EBV), there may be different causes in different populations. However, there are certain kinds of tumors that appear rather routinely in certain populations—the Chinese nasopharyngeal carcinoma, for example—and some of these may have a single cause or group of causes.

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Editor: Are there any newly-discovered viruses that have been implicated in the development of cancer?

Dr. Rapp: Yes. Research hepatitis B virus has been associated with liver cancer. Of other viruses, the oncornaviruses and herpesviruses are still the main "culprits." What's happened in research concerning these types of viruses is that with the increasing sensitivity of our technology, we are now confirming what used to be largely speculation about their association with certain tumors. A good example of this is found in the suspected relationship between herpes simplex type 2 virus (HSV-2) and human cervical cancer: with new techniques some investigators have found HSV-2 nucleic acids—that is, HSV-2 genetic information—in cervical cancer cells. What was once theoretical is now becoming more concrete. In determining risk factors associated with genetic deficiencies, on the other hand, we still are a long way from identifying the specific loci, or genes, that are involved. Human genetic techniques are not sensitive enough to detect the minor chromosomal changes or aberrations that in some cases may be responsible for the development of cancer.

Editor: In humans, evidence of viral oncogenicity is necessarily indirect. What is it that implies a causal rather than a coexistent relationship in certain cancers, since we know that intercurrent virus infections are fairly common in cancer patients?

Dr. Rapp: First of all, we have studies which show almost invariably that the virus infection preceded the cancer. One of the largest studies is taking place in Africa, where some 100,000 children have been followed to see when they were first exposed to Epstein-Barr herpesvirus and whether any of them develop the African (Burkitt's) lymphoma. I believe there are 14 or 15 cases by now and each child had been previously exposed to the virus.

Secondly, experimental work using normal human leukocytes has unequivocally demonstrated the oncogenic potential of these viruses in vitro.

Despite the strong evidence for a viral etiology in certain cancers, and there's more evidence today than ever before, absolute proof is still lacking. However, I believe we are getting closer to an answer.

Editor: What do you need to prove it?

Dr. Rapp: Right now the most conclusive evidence would be the development of a vaccine that would prevent virus-associated cancers. In cats we have done this—we know that cat leukemia is caused by a virus and we have an effective vaccine against that virus. The obstacle to developing an analogous vaccine for humans is of course the safety factor; human experimentation is out of the question.

There is another way, and the population is, in fact, doing
it: there is a tremendous increase in venereally-transmitted HSV-2 in many parts of the world, including the United States. Humans are, in effect, injecting themselves. If that virus is associated with cervical cancer, 15 to 20 years from now we should see an increase in cervical cancer, or at least in cervical dysplasia as evidenced by Pap screening. There are increases here and there in certain kinds of cancer—pancreatic cancer, for example—and we cannot explain them. Now we have a clear and early warning concerning a possible increase in male and female genital cancer. If it comes to pass, it will be a strong argument for a viral etiology.

Editor: We've seen much in the press and elsewhere in the past few years, attacking virus research programs in cancer. How enthusiastic is the support—and the funding—at the present time?

Dr. Rapp: The level of funding has remained stable; there has been no increase or decrease in available money. But inflation has taken its toll and decreased purchasing power, and that is a serious problem. But interest in viral research in general is very high because it's known that viruses are related to quite a few diseases. Cancer is the attention-getter, of course, and receives most of the media coverage. As a result, the public has been waiting for a major breakthrough—a vaccine, for example, or a cure. And that hasn't been forthcoming. Cancer is a chronic disease, no doubt having multiple and complex etiologies. Historically, chronic diseases have been very difficult to prevent by vaccination.

Although disappointment is seen in some sectors, there's been no flagging of interest or reduction of funds for research in oncogenic viruses. Right now, of course, everybody's focusing on environment and lifestyle, and a great deal of effort and money are being expended to evaluate the role of environment in cancer and other diseases. In cancer research we must avoid faddism—whether it concerns etiology, treatment or pathogenesis. Until all the facts are in, one can go very badly astray. Certainly lifestyle and environment play some role in the development of cancer; for instance, the incidence of lung cancer is increased in cigarette smokers. But the majority of smokers never develop lung cancer, and this tells us plainly that there's more to it than simply habit or environment. Though environmentalists may argue otherwise, the research that is going forward in virology is probably the most critical in our efforts to discover what converts normal cells to cancer cells.

Editor: What is your feeling about the potential of interferon as an anticancer agent?

Dr. Rapp: I think some scientists may be prematurely optimistic about interferon. It has been purified to an acceptable point, and there are plans to use it in very large quantities, amounts which
appear to have anticancer activity. I think it's certainly worth testing, to see whether there is significant objective reduction of deaths. The most troublesome problem is that we have no idea, over the long term, just what the administration of such large amounts of interferon—these are nonphysiologic doses—will do. Also, the evidence to date is somewhat controversial. Nevertheless, I think we should proceed with interferon research, but I would guard against overoptimism. The early studies with BCG were highly optimistic, and that optimism has dwindled somewhat.

Editor:  

Hasn't there been a great deal of controversy about the treatment of herpes simplex with ultraviolet light?

Dr. Rapp:  

Yes, there was heated debate, but I think that's been resolved; that treatment is no longer advocated. Our original reasons for questioning it centered on our belief that the procedure itself—which involves the breaking of the viral DNA—is potentially carcinogenic. We showed that to be the case, and others corroborated our findings. And studies at Harvard, as well as elsewhere, indicated that the UV treatment is no better than a placebo. So here is a treatment that is probably hazardous and also doesn't work. It should not be used by the practicing clinician.

Editor:  

Is there general acceptance of the idea of a viral etiology for certain cancers?

Dr. Rapp:  

Yes, I think so. Yet, there are some who don't accept the viral theory. Epidemiologists in particular do not like to consider a viral etiology, using the argument that viruses are infectious agents and therefore cancer should behave like other infectious diseases. We should see clustering, for instance. But this is a misinterpretation of the facts. Acute infectious diseases, like measles or polio, are spread in a certain way. Chronic diseases—and cancer is a chronic process—are not transmitted the same way. They do not tend to cluster, and there's simply no merit to the often-used argument that a cluster must appear for the disease to be caused by a virus.

Editor:  

What about the recent reports of a leukemia cluster among children in New Jersey?

Dr. Rapp:  

There are four billion people in the world and statistically this could have occurred by chance alone. On the other hand, there's a distinct possibility that it wasn't merely chance. Either way, these anecdotal reports of clustering are not really significant in proving or disproving a viral etiology.

Also, up until a few years ago we thought that viruses infect people and then disappear. We now know that those viruses persist; most of us are infected for life by large numbers of viruses.
In what form do they exist in the body?

We have an answer for only one or two viruses. The herpes simplex virus is the most extensively studied and it is clearly associated with certain kinds of nerve cells. It's under tight control by those cells and does not multiply in them. It multiplies when it gets into epithelial cells, though how it travels from nerve to epithelial cells is unknown.

This, in fact, is that “black hole” of cancer research, possibly the most baffling aspect of all. It may take anywhere from a few to as many as 50 years for cancer to become clinically evident, and we simply don’t know what happens during that time interval. Take DES: the daughters whose mothers took DES during pregnancy developed vaginal adenosis or clear cell carcinoma eight to 20 years after birth. There’s a huge gap between exposure to the agent and detectable tumor. What happened in the interim? That’s the “black hole” in our research, and no one quite knows how to get into it. This is an area that needs considerable research urgently.

Thank you, Dr. Rapp.

THE LANGUAGE OF MEDICINE

Though there are only a few remnants of humoral pathophysiology in the modern language of medicine, the vernacular retains quite a number of allusions to this old theory; we still hear references to sanguine, phlegmatic and choleric temperaments, and often speak of being in a good (or bad) humor. Little if anything of the astrological side of ancient medicine survives in modern language besides the lay term lunatic.

From: The Language of Medicine: Its Evolution, Structure and Dynamics, by John H. Dirckx, M.D., published by Harper and Row, Inc., 1976. Page 67.