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A report on research in progress at Caltech on the viruses that —instead of killing cells—cause them to multiply at a much faster rate.

by HARRY RUBIN

VIRUSES AND CANCER

POLIOMYELITIS AND INFLUENZA are two of the most familiar virus diseases. In both these cases, the virus produces disease symptoms by damaging or killing cells. It seems strange then that there are other viruses which not only fail to kill cells, but actually cause them to multiply at a much faster rate. This multiplication occurs in a very disorganized manner, and the result is a cancer which ultimately kills the host.

Most of these cancer-causing viruses have been found in chickens. The common leukemia of chickens is due to a virus; that is, we can make a cell-free extract from the tumor tissue which will cause a similar growth when inoculated into another chicken. This was discovered almost half a century ago. Similarly, many other chicken cancers, particularly those of connective tissue origin, are caused by viruses. One of these that has received a good deal of attention is the Rous sarcoma virus. This was discovered by Dr. Peyton Rous in 1910 at the Rockefeller Institute. He observed a large tumor in the breast muscles of a laboratory hen, and found that this could be very easily transplanted to other chickens by transferring intact cells. Then he found that cell-free extracts of the tumor, which were passed through filters of small-enough porosity to hold back the smallest bacteria, were just as efficient in transmitting the growth. More recently, it has been found that the same virus can also cause a completely different type of cancer, a carcinoma or epithelial cancer, if inoculated into the proper tissue of the chick embryo.

What distinguishes cancer viruses from ordinary viruses? In size and gross chemical composition there are no distinguishing characteristics. Yet one group causes cells to multiply malignantly, and the other group causes cells to die. This problem has been investigated in the Biology Division at Caltech. Rous sarcoma cells were removed from afflicted chickens and grown in tissue culture. In this way, the number of cells was always known, and the rate of virus production could be studied.

These cells were found to produce virus at a very slow but constant rate—approximately one virus particle per cell every day or two. Compare this with a poliomyelitis-infected cell which may produce 1000 virus particles within a few hours. This simple quantitative

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finding may indicate why such differences in pathological manifestation of the two groups of viruses are found.

A cell which only has to produce a single virus particle every day may have its normal metabolism upset somewhat—perhaps to the extent of being liberated from the normal regulating mechanisms of the animal and thereby becoming cancerous—but it will not be destroyed. A cell which has to produce a thousand virus particles in several hours has to divert all its metabolic machinery to this function. Not being able to carry on its own essential functions, it soon dies. Thus we have the first hint of an explanation for the distinctive pathologies.

Speculations on structure

It was once thought that cancer viruses contained normal unaltered host protein as an integral and functional part of their structure. This seemed to be a very important and exciting thing, since it suggested that these cancer viruses were very closely related to the cells which they parasitized, in contrast to the ordinary cell-killing viruses, such as polio, which have no such relation to the cells in which they multiply.

It seemed reasonable to speculate that cancer viruses originated in their host cells while the cell-killing viruses were of foreign origin. Some recent work at Caltech has indicated that, although the growth of Rous sarcoma cells is very strongly inhibited by antiserum to normal cells, there is no evidence for a relationship between cancer virus and normal cell protein of the sort that was once supposed.

Mammalian cancer viruses

Perhaps the most perplexing aspect of this problem is the ease of finding cancer viruses in chickens, contrasted with the great difficulty in demonstrating them in mammals. The first mammalian cancer virus was not isolated until 1936. In that year, John J. Bittner found that the common breast cancer of mice was ordinarily transmitted by a virus found in the milk of nursing mothers from a strain of inbred mice which had a very high incidence of breast cancer. However, to demonstrate the agent, Bittner had to infect mice within a few days after birth. Then he had to wait until these mice became mature nursing mothers themselves —a matter of almost a year—before the cancer appeared. Compare this with the Rous sarcoma virus of chickens, which can be inoculated at any age and will produce cancer in less than a week. In addition, Bittner had to have another inbred strain of mice which had a very low incidence of cancer, in order to convincingly demonstrate the effect of the virus. With chicken cancer viruses such complications did not exist.

Since 1936, only two more mammalian cancers have been shown to be of viral origin. In one of these, mouse leukemia, the difficulties in demonstrating the virus encountered with the breast cancer were multiplied. This suggests that the failure to isolate causative viruses from mammalian cancers may arise from such complications rather than from the absence of a virus. There is no evidence to suggest that causative viruses in any of the mammalian cancers are contagious in the way that polio or influenza is contagious.

Therefore the critical question—are all cancers, and particularly human cancers, caused by viruses?—must remain unanswered for the present. Certain aspects of the origin of even such thoroughly-studied viruses as those which infect bacteria are quite obscure.

Even in such well-defined systems the line between viruses as foreign invaders and as altered cell components is not clearly drawn. Speculation about the origin of human cancer, which is considerably more refractory to precise study, would therefore not be fruitful at this stage.

Viruses and human cancer

Two crowning difficulties in the study of the relation of viruses to human cancer must be kept in mind. The first is that most of the known cancer viruses are usually produced in such small quantities that they cannot be readily demonstrated by physical methods such as electron microscopy. The second is that they can generally cause cancer only in animals of the same species, and frequently, as in the case of the mouse tumors, only in very closely related strains of the same species.

To carry this to perhaps a not too absurd extreme, demonstration of a tumor virus in humans by the methods now known could involve inoculating newborn babies with tumor extracts and waiting 30 or 40 years until maturity was reached to see if cancer developed. Even then, a large enough group would have to be included to make the results significant when compared with the normal incidence of cancer in a control group, since we have no genetically pure strains to work with.

The promise of future research

This perhaps dramatizes the difficulties. There are some bright spots on the horizon of basic research. Perhaps the most promising is the great flowering of tissue culture work—growing cells, human as well as animal, outside the body—within the last few years. An outstanding example is Dr. Renato Dulbecco's work at Caltech. The information that is bound to arise from such work will profoundly influence our understanding of this problem.