THE NEOPLASTIC phenotype usually persists in progeny of cancer cells. An understanding of the mechanism of this persistence appears necessary to understanding the etiology of the cancer. Theories of persistence include genetic theories such as those involving somatic mutations or viruses, and epigenetic theories such as those involving embryonic arrests and activation. The oncogene theory (1) appears to combine viral and epigenetic theories by postulating that neoplasia results from the activation of a vertically transmitted provirus. However, this oncogene theory is basically an epigenetic theory, since it postulates a stable change in phenotype due to a switch in a regulatory system.

Recently, I have suggested a new genetic hypothesis which combines elements of somatic mutation and viral theories (2, 3). This protovirus hypothesis proposes apparent vertical transmission of the information for cancer, even though the germ line does not contain this information on its chromosomes (proviruses or oncogenes) or off its chromosomes (virions). The germ line is postulated to contain in its chromosomes the potential for genetic evolution by the somatic cells that may lead to the de novo formation of the information for cancer. Changes leading to cancer are not the normal roles of this genetic system. Normally the protoviruses from the germ line evolve in the somatic cells to differentiate the genomes of these cells by the creation of new DNA.

This apparent vertical transmission of the information for cancer differs from classical vertical transmission which involves the whole virus as an infectious particle in, for example, the milk or egg. It also differs from transfer of the DNA provirus of an RNA tumor virus, since in the protovirus hypothesis only the potential for genetic evolution of the information for cancer is transmitted in the DNA.

The earlier DNA provirus hypothesis, from which the protovirus hypothesis was derived, stated that replication of RNA tumor viruses involved a DNA intermediate and that permanent establishment in a normal cell of the genetic information for cancer required information transfer from viral RNA to DNA (4). Once this information transfer from RNA to DNA had occurred, further transfer of information from RNA to DNA was not required for the maintenance or the expression of the neoplasia. The DNA provirus hypothesis did not elucidate how the establishment in a cell of this new genetic information led to the neoplastic state.

Editor's note: Periodically the Journal will publish solicited guest editorials as a means of transmitting to investigators in cancer research the essence of current work in a special field of study. The Board of Editors will welcome suggestions for future editorials that succinctly summarize current work toward a clearly defined hypothesis regarding the causes or cure of cancer.
Normal Development

In speculating about the origin of viruses with this special mode of information transfer, RNA→DNA, I felt that RNA→DNA information transfer might play a role in normal organisms. Such reverse transcription could provide a mechanism for variability in the genome of somatic cells without disrupting the stability of the germ line. In the germ line only the usual modes of information transfer occur, that is DNA→DNA, DNA→RNA, and RNA→protein. Variation of expression occurs by control of the rate of these reactions, but variation of the DNA is supposed to occur only by random mutation followed by selection. The protovirus hypothesis states that somatic cells, in addition, use the RNA→DNA mode of information transfer, and new DNA sequences are formed by this process during the lifetime of a single organism.¹

An organism needs to identify cells in a stable way, so that one cell is identified as a retinal cell at a particular position, and another cell is committed to make antibody to a particular antigen. The most stable storage place for such information appears to be the cellular DNA. RNA→DNA information transfer in somatic cells would provide a mechanism for stable differentiation of DNA. Other mechanisms are possible, that is stable cycles of the type discussed by Monod and Jacob (5) or classical DNA episomes. The protovirus mechanism might be preferred to cycles because it involves a structure rather than a dynamic process. The protovirus mechanism might be preferred to classical DNA episomes because it does not require excision of DNA for information transfer. However, it is possible that all of these mechanisms exist.

The process of protovirus transfer might work as follows (text-fig. 1). A region of DNA in cell A serves as template for synthesis of an RNA which is transferred to cell B. In cell B, a new DNA is made by an RNA-dependent DNA polymerase, using the transferred RNA as template. The new DNA then integrates into the DNA of cell B. This integration could be next to the homologous DNA or at a different place. In either case, cell B would differ from cell A, which remains unchanged. This process could be repeated. If the new DNA in cell B was integrated in some new place, it might act as a template for RNA from itself and from a neighboring region. This RNA in turn could be transferred to cell C, transcribed into DNA, and integrated into the genome of cell C. Cell C would then differ from cell B and from cell A. These processes could continue and could involve a cell more than once. They would lead to the formation of duplications, tandem or distant, and possibly replacements.

In addition, there might be times when the RNA→DNA information transfer takes place only in cell A, with or without concomitant integration, thereby leading to gene amplification (6). However, if, as I believe (3), there is great genetic instability in this type of information transfer, variants would appear and wholly new DNA sequences could be formed.

There would be regions in the genome predetermined for this type of transfer. The specificities of the appropriate polymerase and integration systems would select these regions on the basis of their base sequences. The time and extent of protovirus transfer would be controlled by the availability of the polymerase and integration systems, and the absence of possible inhibitory systems, especially nucleases. Selection of randomly appearing variants could also be through the properties of the polymerase, integration, and, possibly, inhibitory systems. This selection would involve selection of cells altered by the presence of new protovirus DNA. These selection processes would allow random variations to persist and to become amplified. Together these processes could lead to differentiation among the genomes of the somatic cells in an organism.²

In the development of an organism, information transfer from DNA→RNA→DNA would allow variability and

¹ Information transfer from RNA to DNA could occur in the germ line without affecting progeny individuals if this DNA was not integrated. Strictly speaking, only integration of such DNA would usually be forbidden in the germ line.
² The successful experiments on nuclear transplantation from somatic cells to eggs (7) do not invalidate the protovirus hypothesis. There are two aspects of this hypothesis which can lead to reversibility. One is crossing-over to remove a duplication, as seen in the bar region of Drosophila (8). The other is epigenetic controls, which could inactivate regions of new genetic information in embryonic cells. These hypotheses might also encompass the cases of reversibility of the malignant phenotype (9).
amplification; information transfer from DNA→DNA would allow stability and storage.

The normal physiological evolution of the protovirus-derived DNA's would fall within a pattern predetermined by the rest of the cell genome and by the state of the cell and of the developing organism. Integration of protovirus-derived DNA, specifying some polymerases, for example, next to a region controlling membranes or other aspects of the cell surface could affect surface specificities of the cell. Integration next to a region controlling cell multiplication could affect multiplication control of the cell. Continued evolution along these lines could put together in a contiguous region of the chromosomes the information necessary for formation of an enveloped virion.

Abnormal Development (Carcinogenesis)

In the normal physiological evolution of the protovirus DNA, information from the environment would be effective only as it affected the general state and differentiation of the organism. However, protovirus evolution could by some random events give rise to a virus which could enter an organism from the outside. Because the virus has the ability to insert information into the cell, it could short-circuit the requirement for protovirus evolution. For example, once RNA sarcoma viruses were formed, they would upon infection make new DNA which would contain all of the information necessary to bring about neoplastic transformation. No multiple cycles of DNA→RNA→DNA information transfer need occur.
However, apart from laboratory conditions, such single-step transfer processes might never lead to cancer.

In normal development, this DNA→RNA→DNA information transfer could be used to identify cells as being of a particular type and to recruit other cells into a related or identical form. A cell's particular differentiated state could be partially specified by the types of new protovirus-derived DNA it contained. RNA transcribed from this new protovirus-derived DNA could be transferred to other cells and thus induce an orderly conversion of the other cells into the same or a related differentiated state. Examples of such differentiation might be the secondary antibody response (10) and embryonic induction.

The usual process leading to cancer could be a variation in the normal physiological evolution of the protovirus DNA, so that variants which contain information for the cancer appeared either by mutation of the base sequences or by integration in incorrect places or both. Since DNA→RNA→DNA information transfer involves DNA, RNA, and enzymes (protein), the formation of variants may result from the response of any of these molecules to irradiation or chemicals. This oncogenic process would not require the formation of an RNA tumor virus. It would require only alteration of the information in cells, so that there was the information which was necessary for cancer. This information for cancer may or may not be homologous to the information in RNA tumor viruses. The nature of this information is not considered here (see 2, 11).

In extreme cases, one could imagine that a product of protovirus evolution would infect the germ line, become integrated there, and thus also affect progeny organisms. Such a process could provide part of a mechanism for inheritance of some acquired characters. Selection at the level of the germ cells and at the level of the organism would also be involved.

This protovirus theory was derived a priori from consideration of the origin of RNA sarcoma viruses. It also explained the presence in uninfected cells of DNA homologous to a portion of the RNA of RNA tumor viruses (12, 13), and the apparent vertical transmission of the information for RNA tumor viruses (1, 14).

Since the protovirus theory was derived, several new experimental findings have been made which are relevant to it. An RNA-directed DNA polymerase has been found in virions of visna virus and simian foamy virus (15, 16). Neither of these viruses has so far been associated with neoplasia. Preliminary evidence suggests that RNA-directed DNA polymerase may also be involved in gene amplification in oocytes of Xenopus (9). Uninfected chicken cells may contain an element which is inherited as a single Mendelian dominant gene and can become infectious after phenotypic mixing with an RNA tumor virus (17). This element could be a protovirus-derived element that was not yet a complete virus genome. It also could be a defective provirus. Antigens related to RNA tumor viruses are found in normal mouse embryos (18). These antigens could represent the RNA-directed DNA polymerase and other proteins of the protoviruses.

Finding an RNA-directed DNA polymerase in uninfected tissues of normal organisms may be the first direct evidence bearing on this hypothesis. Knowledge of the specificities and time of occurrence of such a polymerase would aim in demonstrating the type of information transfer postulated here.

However, even if this protovirus theory is correct in its essentials, it raises the question of how carcinogens cause the misevolution of protoviruses to give rise to information for the neoplastic phenotype and how such information in protovirus-derived DNA actually causes the neoplastic phenotype.

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