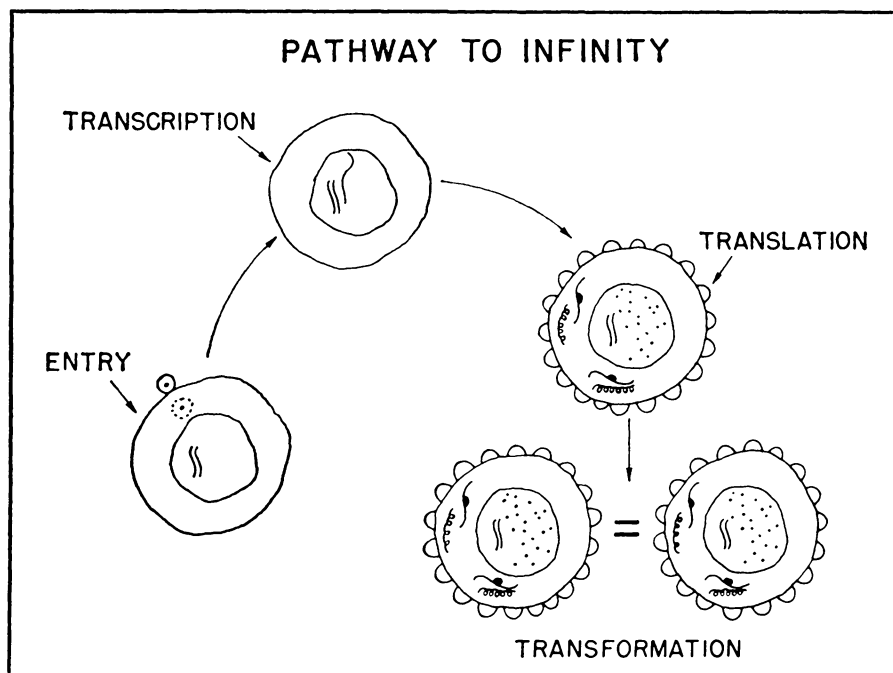


# Defective virus a key

Elusive virus bits and one virus type may be the starting point for all human cancers; research stimulates talk of vaccines



Dr. Rapp

by Barbara J. Culliton

*When a virus enters and transforms a cell, cancer cells replicate indefinitely.*

Viruses cause cancer.

Though there is no proof, there is little doubt.

The evidence is all circumstantial, but as it accumulates, it appears to point inevitably to a positive verdict. And scientific jurors are becoming more and more categorical in their indictment of viruses.

"I am convinced," declares Dr. Fred Rapp, chief of microbiology at the Milton S. Hershey Medical Center in Hershey, Pa., "that under the right conditions, in a susceptible cell, any virus can cause cancer."

**The keystone** to the logic of his conviction, widely shared, is the history of animal experiments, coupled with test-tube work, in inducing cancers with viruses. It may be a fact that researchers are increasingly leery of flat extrapolation from animal experiments and observations to man. But growing realization that the elemental biochemistry of the cells of animals and humans—if not plants as well—shows striking similarities, is overcoming that feeling.

"We know of about 80 viruses that definitely cause cancer in a host of animal species including monkeys," says Dr. Frank J. Rauscher, director of the virus program of the National Cancer Institute in Bethesda, Md. Man just cannot be that different when it comes

down to it, he argues. The odds are too high against it.

And while Dr. Rapp's indictment of all viruses is certainly speculative, the identification of single viruses has long seemed right around the corner.

From evidence to be published before the end of this year, Dr. Robert J. Huebner, also of the cancer institute, contends that a single virus may underlie all types of human cancer. An agent known as the C-type RNA virus, he suggests, is passed on from mother to offspring as if it were a gene (SN: 11/9, p. 463).

Now, he says, "the new hypothesis predicts that both spontaneous cancers and cancers induced by chemical and physical agents will be the result of expression of the oncogene (cancer-causing gene) of covert C-type RNA virus." Recovery of whole C-type RNA viruses from various animals and of viral segments from human tumors suggests to Dr. Huebner that these viruses may have some generalized role in the development of cancer.

**Demonstrating clearly** that viruses do in fact cause human cancer is something scientists have felt themselves on the verge of doing for years. However, it is something they will never be able to do directly, simply because they cannot inject a suspect cancer virus into a healthy human being. Extensive efforts

have been made to isolate viruses from human tumors with hope of establishing the connection between specific viruses and certain cancers, but these, too, have met with failure.

The failure could be because whole, recognizable viruses are not involved.

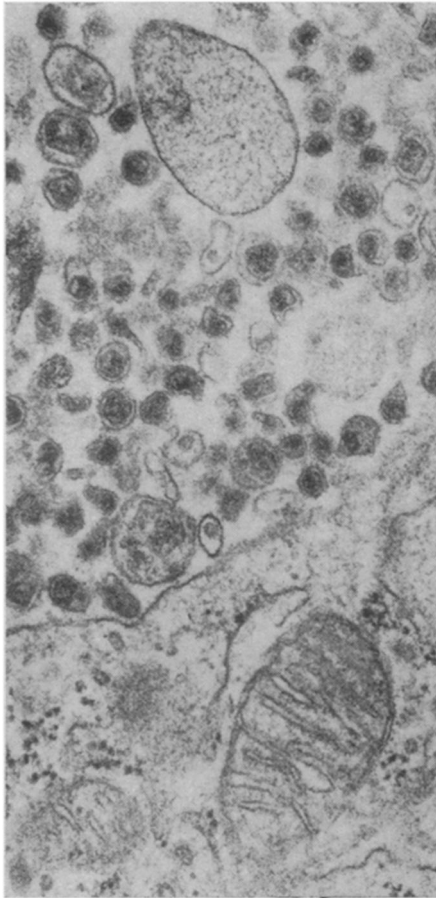
"It is quite likely," Dr. Rapp told a recent Hershey seminar sponsored by the American Cancer Society, "that defective viruses are what we're after."

According to Dr. Rapp, it is logical to assume that a whole virus, after entering a cell, would replicate and kill its host as it split that host cell to spew forth new viruses. A defective virus, on the other hand, might lack the genetic information it needs to replicate while still possessing the ability to transform a cell, thus changing it from a normal to a malignant cell without actually destroying it.

"The real challenge," Dr. Rapp asserts, "is to learn how a virus particle might do this. What appears clear is that the key to neoplasia is the regulatory mechanism at work in the host cell and the effect of a cancer virus gene on that mechanism."

In some still unknown step, a gene in the host cell is either switched on or off in a biochemical event that results in loss of cell control and therefore in unchecked growth.

Dr. Rapp suggests focusing research



Dr. Huebner

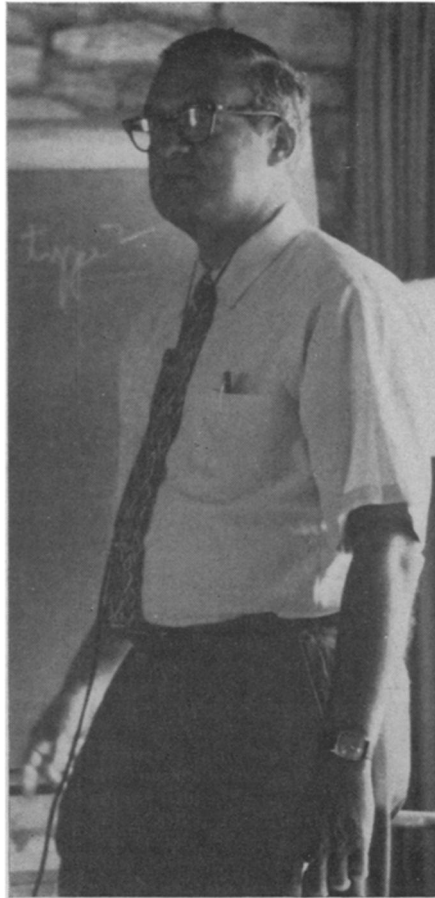
*C-type RNA viruses may be key.*

on the simian papovavirus 40 (SV40), a DNA virus known to cause animal tumors. "It is an ideal model for studying the process of cell transformation," he says, "because it contains only limited genetic information. This viral genome codes for about 10 average-sized proteins, that's all. Therefore, if these few viral genes were to be characterized, it should be possible to determine what is necessary to effect the transformation of a normal cell into a cancer cell." Conceivably, that process, if understood, could be blocked or reversed.

**In spite** of the fact that progress is being made, researchers in the field of viruses are still looking for a real breakthrough to stimulate more investigation (viruses have somewhat fallen behind immunology as a focal point) and draw young workers into the field. The last burst of enthusiasm came in the early 1960's when Dr. Huebner identified information about viruses in animal cancers.

Dr. Huebner now has put all his efforts on the one virus on which he is about to publish: the C-type RNA. He is expanding his theory that latent, covert viruses in the body are cancer-causers.

Some recently completed studies show that C-type RNA viruses clearly cause cancer in mice, chickens, cats and



Alan Davis

*Dr. Rapp: All viruses implicated.*

probably hamsters. Identification of particles or defective C-type RNA viruses in tumors in guinea pigs, rats, swine, snakes and human beings tie these RNA viruses to cancer in these species. The unique quality of these viruses, Dr. Huebner believes, is that they are transmitted through normal hereditary mechanisms, behaving more like repressed or switched-off genes than like infectious agents.

In some unidentified way, carcinogenic agents including irradiation, chemicals and even other viruses activate these viral genes lying dormant within a cell and trigger the transformation to malignancy.

Within the bounds of this theory then, all viruses may indeed cause cancer, but only because they, like other carcinogens, awaken C-type RNA genes and not because of any direct effect upon a cell. This, of course, remains to be proved, depending ultimately on an explanation of the transformation process and mechanisms of gene control.

**If the virus-cancer** proposition were proven to everyone's satisfaction, what then? Vaccines, virologists traditionally say, are the first line of attack. On this point there is a certain amount of disagreement. On the one hand, some scientists charge, there are too many viruses involved to make vaccines practical, and others consider vaccines a

much too risky approach at this time. Yet, in a view widely held, however, vaccines theoretically offer one of the most rational ways of dealing with cancer.

Says Dr. James T. Grace, director of the Roswell Park Memorial Institute in Buffalo, N.Y., "If we had the money, we could develop a vaccine against the EB virus within a year."

**But proving** its effectiveness in preventing Burkitt's lymphoma and other lymph cancers would be a long and difficult challenge, requiring years of study of large numbers of individuals. Vaccine critics claim this route is a dead end. Says one, "Sure, he could make a vaccine in a year but, how would he test it? No one would agree to a live vaccine for safety's sake. A dead one might be short-acting. And how could you measure its effect? Actually, lymphomas do not occur frequently among the population."

And though the EB or Epstein-Barr virus has been recovered from cells of 100 percent of patients with lymphoma, and from a majority of persons with mononucleosis and from healthy volunteers, it is impossible to link it firmly to cancer. "The mere fact that it is so easy to recover whole viruses is itself suspicious," observes Dr. Rapp. "Why should one be so much simpler to find than all others?"

But vaccine advocates persist. In fact, the cancer institute last March opened a hot virus laboratory in a \$3.5 million building similar to the Lunar Receiving Laboratory in its designated purpose: to keep the scores of tumor viruses inside and the rest of the world out. There a \$10 million leukemia vaccine program is among high priority projects, though there is little to report as yet.

**Since 1962** researchers have been trying to induce leukemia in newborn monkeys with the intention of using such animals as a model of the human disease and a possible source of material for vaccine production. "Up to now, however, none of the 10 species has developed this blood cancer," Dr. Rauscher observes, "though the project is not old enough yet to rule any animals out. The onset of leukemia may take 7 to 10 years."

Whether the NCI investigators will get their 10 years is, at this time, questionable. In the face of stringent budget cuts, recently announced by the Department of Health, Education and Welfare, the cancer institute announced it would have to sacrifice hundreds of these expensive animals because it could no longer afford to pay to maintain them. This statement, however, has been interpreted by many as a desperate plea to Congress for funds rather than a real threat to the animals. ◇