Human Cancer Virus Vaccines

The editor interviews
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Editor: It is well established that many tumors in animals are caused by viruses; is the same true of humans?

Dr. Hilleman: Although many factors such as radiation, environmental carcinogens, aging, hormones and genetics undoubtedly play a part in the etiology of cancer, available data supports the concept that the primary element in human cancer might be a virus and that all other agents might play only a secondary role. This view is reinforced by the fact that cancer cells often appear to have a new genetic input that allows them to make new and unique viral-specified antigens that are present in the cells and on their surfaces; secondary factors do not provide such genetic input.

Editor: If viruses were found to cause cancer in man, could a vaccine eventually be developed to prevent it?

Dr. Hilleman: Yes, we think so. At the moment, a very great amount of research is being directed toward finding the elusive cancer viruses in man. Once identified, these viruses could be used in developing a vaccine to prevent or limit cancer virus infection in nature, thereby breaking an essential link in the neoplastic chain and preventing cancer. But first, we must know which viruses are responsible for cancer and their natural history.

Editor: Why is the natural history of these viruses so important?
Dr. Hilleman: Learning the method by which cancer agents are transmitted, either horizontally as in infectious disease, vertically as in chromosomal inheritance or by infection acquired in utero, is essential to deciding whether a vaccine could be developed to combat them. Cancer transmitted horizontally by viruses might be prevented by viral vaccines. Transmitted vertically, it would be unlikely, although vaccines could possibly limit or prevent its clinical expression. Fortunately, evidence points largely to horizontal transfer, despite the so-called viogene-oncogene theory.

Editor: Would you explain the viogene-oncogene theory?

Dr. Hilleman: The viogene-oncogene hypothesis holds that many, if not all, cells carry genetic DNA sequences called oncogenes and virogenes that code for malignant transformation of cells and for infectious oncornaviruses. Normally “switched off,” these cells may be activated by carcinogenic chemicals, radiation, aging, DNA viruses or perhaps by the effect of RNA-helper viruses. In effect, the concept holds that genes for RNA tumor viruses are part of the heritable genome of animal cells and that these genes play a role in normal embryogenesis.

Editor: What data lead to this hypothesis?

Dr. Hilleman: The oncogene concept is formulated on the basis of studies in animals, particularly in highly inbred, highly leukemic mice. In these animals, vertical transmission, probably genetic, seems to be a significant factor in the development of leukemia. But, vertical transmission of leukemia might not be important in the real world of mice outside the laboratory; horizontal virus transmission in nature has not been adequately studied.

Editor: Is there any evidence to dispute the viogene-oncogene theory?

Dr. Hilleman: The concept fails to explain several facts, such as the established high-level horizontal transmission of leukemia in chickens; the ready transmissibility of cancer in animals given the same or closely related oncogenic virus by syringe and needle; and the exclusively horizontal transmission of the herpesviruses that cause Marek’s disease in chickens and renal carcinoma in frogs. Further evidence of horizontal transmission is provided by the demonstrated excretion of a leukemia-causing virus by infected cats and its transmission by contact. Though there is undoubtedly genetic transmission of a feline oncornavirus, as exemplified by the now famous RD-114 virus, it is questionable whether this agent ever causes cancer. All evidence points to the horizontal transfer in nature of the particular viruses that cause leukemia in cats, and the far lesser, if any, role of the covert oncogene. A parallel situation may also exist in the Wild Red Jungle Fowl. Here evidence indicates widespread horizontal transmission of the highly oncogenic subtypes A and B, and endogenous transmission of the slightly onco-
genic or non-oncogenic type E chicken virus. These kinds of data raise the question of whether the genetically transmitted oncornaviruses are oncogenic at all.

Editor: Would you describe the findings of the Spiegelman study, which I’m told disputes a genetic theory of transference?

Dr. Hilleman: Spiegelman and his co-workers studied leukemia that occurred in one member of each of two pairs of homozygous twins. In each case the leukemic twin carried virus-related nucleotide sequences in his leukocytes, not found in his healthy identical sibling. This would indicate a factor acquired either postnatally or in utero by some infectious process.

Editor: Is it known which viruses are responsible for cancer in man?

Dr. Hilleman: No. Explorations are being made to determine whether cancer in man is caused by RNA oncornaviruses or DNA viruses, such as the herpesvirus, alone or in conjunction with an accompanying oncornavirus. The DNA viruses of humans, especially the herpesviruses, stand in better stead than the oncornaviruses in at least two respects. One is their undisputed horizontal transmission, and the other is their ability to be grown in the laboratory. Although it has long been known that cancer in animals is caused by oncornaviruses, more than six decades of research have failed to establish their role in human cancer.

Editor: What particular herpesviruses are suspect?

Dr. Hilleman: The Epstein-Barr (E-B) virus is the prime suspect of the herpesviruses for several reasons: its ubiquitous presence in Burkitt’s lymphoma and nasopharyngeal carcinoma; its role in causing lymphoblasts to replicate indefinitely in vitro; the observed time-space clustering of cases in epidemic Burkitt’s lymphoma belts; and the inordinately high E-B antiviral antibody levels in patients with Burkitt’s lymphoma. For the present, however, E-B virus is impractical to study from the vaccine standpoint because of its very limited proliferation in vitro.

Similarly, herpesvirus hominis types 1 (oral) and 2 (genital) might play a role in a variety of human cancers of the nasal-oral-pharyngeal region, the genitourinary tract, and the lower intestine. Strong supporting evidence is provided by: (1) the demonstration of non-virion herpesvirus antibody in persons with such diseases; (2) the occurrence of inordinately high levels of herpesvirus type 2 neutralizing antibody in persons with cervical carcinoma (suggesting periodic productive replication of the virus); (3) the finding of herpesvirus antigens in exfoliating squamous carci-
noma cells of the uterus; (4) the isolation of herpesvirus 2 from cervical carcinoma on cultivation at high pH; (5) the reported finding of herpesvirus genetic material in cells from cervical carcinoma; and (6) the neoplastic transformation of hamster cells infected with herpesvirus and rendered genetically defective by treatment with ultraviolet light or white light with neutral red.

Editor: Would you describe the form that a vaccine could take regardless of whether the cancer agent is RNA or DNA?

Dr. Hilleman: The vaccine could be composed of live, attenuated or killed viruses. The killed vaccines could be made up of either whole virus particles or antigenic subunits alone, and the vaccine could be aqueous in form or given in an adjuvant, such as the emulsified peanut oil adjuvant 65 recently licensed for general use in the United Kingdom.

Editor: What are the relative merits of each?

Dr. Hilleman: Attenuated, live virus vaccines, presently being used to prevent acute illnesses, generally afford a higher level and longer lasting immunity than do killed vaccines. In addition, they require only a small amount of virus for immunization, which is often a practical necessity. However, live, attenuated vaccines need markers of viral attenuation to establish safety with some degree of reliability, even before initiating clinical trials in man. The present lack of such markers will be a real deterrent to development of live cancer virus vaccines in man. It may be important to note, however, that in domestic animals, experience with live herpesvirus vaccines has been excellent in terms of safety and efficacy as, for example, swine pseudorabies vaccine, infectious bovine rhinotracheitis vaccine, and the vaccine for Marek’s disease in chickens. Since killed virus vaccines do not require markers of viral attenuation, they might be preferred in some cases. Furthermore, the poorer immunologic performance of killed virus vaccines may be overcome in large measure by use of an emulsified peanut oil adjuvant to induce a higher level and longer lasting immunity while requiring a smaller antigenic mass than the ordinary aqueous vaccines.

Editor: Would either a killed virus vaccine or an attenuated, live virus vaccine be able to provide total protection against cancer?

Dr. Hilleman: No vaccine can afford total protection against reinfection with the same virus, whether the disease is poliomyelitis, smallpox or rubella. The important fact is that vaccination limits the degree of replication of the subsequent virus infections and inhibits the extent of viral spread in which the critical damage is expressed, whether it be by cell lysis or neoplastic proliferation. In the case of cancer,
an attenuated, live virus vaccine would not be expected to prevent reinfection with cancer virus, but it could prevent the infection from being expressed as clinical cancer.

A good example is the highly effective vaccine against Marek's disease in chickens. The attenuated, live virus vaccine does not prevent reinfection or persistence of the virulent virus, but it does prevent its clinical expression as cancer.

Editor: *What research approach is your laboratory pursuing at this time?*

Dr. Hilleman: Our program is fixed on both RNA and DNA viruses. However, we are concentrating primarily on two viral groups, DNA herpesvirus hominis types 1 and 2, which cause labial and genital herpes in man, and the RNA feline leukemia-sarcoma virus complex, for which no human leukemia virus counterpart has been isolated as yet.

Editor: *Would you describe your work on herpesvirus hominis types 1 and 2 vaccines?*

Dr. Hilleman: Yes. Herpesvirus hominis vaccines have no reliable marker for oncogenicity that might apply to man and, therefore, a live virus vaccine is not receiving primary emphasis in development. Even a killed whole virus vaccine raises doubts as to safety, based on data that show neoplastic transformation in vitro by viruses inactivated by ultraviolet light or by photodynamic effect, and induction of lymphoma in owl monkeys by heat-inactivated herpesvirus saimiri virus. Therefore, there is current preference for subunit vaccines that contain the immunologic determinants of the herpesviruses but are free of all viral nucleic acid.

Editor: *How then would a subunit vaccine be produced?*

Dr. Hilleman: Herpesvirus hominis strains derived from cells of chick embryos from special leukemia-free flocks appear to produce sufficient amounts of glycoproteins (which are probably the predominant determinants for immunity), to be economically practical for vaccines. Further, their immunogenicity can probably be enhanced by coupling with larger molecules such as polypeptides or by formulation in adjuvant 65. These, I emphasize, are approaches and not realized accomplishments.

Editor: *What work is being done in your laboratory on the feline leukemia-sarcoma complex?*

Dr. Hilleman: Cats, like humans, are highly outbred and are subject to many of the same environmental conditions as man. Considering the dif-
ference in life span, they develop leukemia and sarcoma at roughly the same rates as man. Furthermore, evidence points to the horizontal transfer in nature of the particular viruses that cause leukemia in cats.

Since the feline leukemia vaccine development is being used as a model for an eventual human vaccine, work is being directed toward developing a technology for making a killed virus vaccine that would be safe and hopefully practical for man. Significantly, there is no indication to date of immunologic tolerance to any of the feline leukemia-sarcoma virion or virus-associated cell membrane antigens in cats.

Studies in the mouse and avian leukemia-sarcoma systems have provided data that should help researchers to predict what may be discovered in the feline studies. Neutralizing antibody, induced by killed or live virus, limits infection and prevents disease.

Editor: What problems have you encountered or might expect to encounter in your work on cancer virus vaccines?

Dr. Hilleman: First, the causal agent must be reliably propagated in the laboratory in sufficient quantity in some cell or tissue that is considered acceptable for human use. Then, there must be sensitive and adequate means for detecting and quantifying the virus, and adequate procedures must be at hand for assessing its safety and efficacy.

Editor: The evaluation of safety and efficacy would be a major hurdle to overcome in developing a vaccine. How could they be assessed?

Dr. Hilleman: Because of the long incubation period for cancer in man, it might be a long time before the efficacy of vaccines to prevent cancer could be measured. However, an estimate of likely efficacy might be obtained from studies on the prevention of the acute lytic forms of the disease, viz., herpesvirus labialis and genitalis. In this instance, limitation of viral events causing acute illness might be expected to indicate a reduced probability for neoplasia also. Another estimate of probable efficacy might be obtained from studying marmosets and other primates. They develop lymphomas and leukemia after inoculation with herpesvirus saimiri derived from squirrel monkeys. Herpesvirus saimiri vaccines prepared by the same procedure as a herpesvirus hominis vaccine and tested in the marmoset system might be expected to yield significant data that reasonably could be extrapolated to man. Long-term tests for safety would, of course, have to be carried out, but the use of killed vaccines, especially subunit vaccines, should provide, a priori, a large amount of confidence for safety.

Editor: Thank you, Dr. Hilleman.