

HEALTH IMPLICATIONS OF VIRUSES FROM SOUTH AMERICAN MONKEYS 18

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HERPES-LIKE SIMIAN VIRUSES: RETROSPECTIVE AND PROSPECTIVE CONSIDERATIONS¹

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The introduction of improved tissue culture techniques for the study of viral pathogens of man has resulted in an explosive growth of virologic knowledge. Progress in the past two decades has been characterized by successive episodes of intense scientific activity and intellectual excitement, each stemming from isolation of a new agent or from development of new methodologic approaches. As a consequence of the cumulative efforts of many scientists, we now possess effective vaccines for the control of poliomyelitis, measles, rubella, and mumps.

The studies on poliomyelitis, perhaps more than generally realized, established a basic pattern for applied virologic research that included the preferential use of Old World monkeys as experimental subjects. Paradoxically, the *in vitro* procedures that initially were heralded as emancipating the researcher from dependence on monkeys for the study of

polioviruses stimulated the importation of tens of thousands of Old World monkeys into the United States and Europe. Those engaged in vaccine production found that monkeys and monkey tissues were essential for viral propagation and for testing safety.

As a consequence of work based primarily on Old World monkeys, a considerable body of knowledge has accumulated regarding simian viruses. In a recent review, Hull recorded 57 serotypes of simian agents representing seven different virus families (*I*). During this period the occupational hazards of B virus (*Herpesvirus simiae*) were recognized, and the disconcerting discovery was made that some lots of polio vaccine contained potentially oncogenic SV40 virus.

That new problems due to simian viruses might arise at any time was dramatically illustrated in 1967 by the Marburg incident, in which seven human deaths followed exposure to a previously unrecognized agent infecting a shipment of African green monkeys. Yet, considering that tens of thousands of monkeys were utilized and that millions of doses of vaccine derived from monkey cells have been distributed, it is amazing that the iatrogenic exposure of man to these simian viruses has been relatively free of unforeseen consequences. The excellent record for containing

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the hazards of indigenous viruses of Old World monkeys reflects vigilance that is now based on an extensive body of knowledge accumulated over two decades.

Currently, scientists interested in a variety of infectious agents are again enjoying the excitement and accelerated progress associated with introduction of a new methodologic approach—in this instance based on the increasing availability for research purposes of several genera of New World monkeys. Brief reference to selected studies will document the rapid acceptance of this new research resource by workers outside the field of classical virology. In 1966, Young *et al.*, employing *Aotus*, reported the transmission of *Plasmodium vivax* to monkeys, and the following year Geiman and Meagher infected *Aotus* with *Plasmodium falciparum* (2). Other New World monkeys have more recently been infected with malaria parasites of man. Thus, for the first time the pressing problem of chloroquine-resistant malaria can be studied in a convenient primate model.

In the area of helminthology, *Aotus* has recently been shown to be susceptible to infection with the three species of human schistosomes (3).

Experimental trachoma in Old World monkeys is a relatively benign process. However, as recently reported by Bell and Fraser, inoculation of the eye of the owl monkey induces severe clinical and microbiological disease (4). The owl monkey therefore supplants other animal models for testing experimental trachoma vaccines.

These examples not only emphasize the new-found potential of New World monkeys as subjects for research in nonvirologic areas, but also indicate the rapidly expanding chances for human contact with a new and little understood spectrum of simian viruses.

With this prologue we approach the topic of our symposium, namely, the viruses of South American monkeys. This meeting is a consequence of the unexpected, important, and yet disturbing discovery by our chairman, Dr. Luis Meléndez, and his co-workers that a herpes virus (*Herpesvirus saimiri*) recovered from the

squirrel monkey has the capacity to induce lymphomas in other New World primates. The process is remarkably malignant, with owl monkeys and marmosets succumbing 13-28 days after inoculation (5). Further, *Herpesvirus saimiri* can induce a lymphomatous response in animals as taxonomically distant as rabbits. The obvious question is, What would it do in man?

These observations come at a time when the herpes-related viruses of man are the subjects of increasing interest in terms of their oncogenic potential and because of their unique host-parasite relationships. The capacity to establish a persistent latent infection, with or without episodes of renewed clinical activity, is a little understood characteristic of the herpes group of viruses. This attribute, *per se*, is a matter of primary concern in the development of attenuated live viral vaccines against members of the herpes group.

For example, although we isolated varicella virus in 1953 (6), chickenpox persists unaltered in our midst. But how, in view of the host specificity of varicella virus, would one safely test an attenuated varicella vaccine? Decades of observing the human experimental host would be mandatory to assure that the latent vaccine virus did not subsequently resurface in the form of a peculiarly virulent attack of herpes zoster.

Members of another highly host-specific family of the herpes group of viruses, the cytomegaloviruses of man, can produce congenital brain damage and a variety of clinical syndromes ranging from infectious hepatitis to an infectious mononucleosis-like febrile illness. Indeed, the number of infants damaged as a consequence of congenital cytomegaloviral infection probably greatly exceeds the number affected by rubella virus (7). As with varicella, in studying the human cytomegaloviruses we lack a susceptible experimental animal. Hopefully, systematic screening of the New World primates will reveal animals that are susceptible to varicella and the human cytomegaloviruses.

In these introductory remarks I have omitted reference to Epstein-Barr virus and to the significant data indicating an etiologic relation of this agent to infectious mononucleosis,

Burkitt's tumor, and nasopharyngeal carcinoma. Nor have I referred to still controversial data bearing on the causal or casual relationship of *Herpesvirus hominis* Type 2 and human cervical carcinoma, or to the herpesvirus responsible for Marek's disease of chickens, or that associated with Lucke tumor of frogs.

I have instead chosen to emphasize that we are entering an exciting new period of virologic investigation. For two decades, following a pattern established by research on poliomyelitis, we utilized, of necessity, *in vitro* techniques based on the availability of Old World monkeys. Currently, with the increasing introduction of New World primates as research tools, a new spectrum of challenging investigative opportunities—and of hazards to human health—is evolving. The demonstration that herpesviruses of New World monkeys will induce rapidly fatal malignant disease in primates as well as in unrelated mammals will add impetus to work on the viral etiology of cancer in general, and will provide important new approaches to the chemotherapy and immunologic control of malignant disease.

But until the hazards for man of the new oncogenic herpesviruses are defined, distribution of the new agents should be monitored and limited to investigators competent and equipped to deal with dangerous viruses. We are now forced to develop policies designed to protect the health of the public on the basis of an educated guess rather than on the rational evaluation of scientific facts. However, the hypothetical picture of an unknowingly infected scientist who is excreting an oncogenic agent at home and in his community compels vigilance.

SUMMARY

Rapid progress has been made in studying man's viral pathogens over the past two decades. This has been characterized by successive

episodes of intense scientific activity and intellectual excitement, resulting from isolation of some new agent or development of new methodologic approaches. Scientists interested in a variety of infectious agents are now taking advantage of another new approach—use of several genera of New World monkeys that have become available for research.

The demonstration that herpesviruses of some of these New World monkeys can induce rapidly fatal malignant disease in animals is adding impetus to work on viruses and cancer, and is providing important new approaches to chemotherapy and immunologic control of malignant disease. However, until the hazards of the new oncogenic herpesviruses are defined, distribution of the new agents should be monitored and limited to investigators competent and equipped to deal with dangerous viruses.

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