THE CHALLENGE OF CHRONIC VIRUS INFECTIONS

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1. INTRODUCTION

The career and contributions of Prof. Piet De Somer have bridged the era between the solution of major problems concerning acute virus infections and the newly emerging problems concerning the control of chronic infections due to microorganisms and especially those caused by viruses. His work on the ribonucleic acid of poliovirus hallmarked the beginning of molecular virology, and helped related investigations to stay the fear of poliomyelitis epidemics. He then pursued investigations on antiviral drugs and interferon, work still of great interest and importance. His strong interest in cancer viruses at a time when it was widely believed that viruses played no role in human neoplastic disease, has been amply justified by the discovery of a class of retroviruses associated with human T-cell lymphomas (HTLV) and acquired immunodeficiency syndrome (AIDS) (1,2) which predispose individuals to a variety of malignancies. I have no doubt that were he still alive today, his research interest would focus on chronic virus infections and ways to control or prevent disease by these viruses.

Acute diseases due to viruses have been known for millenia. The early work of Jenner, which resulted in the development of a vaccine against smallpox, was followed by that of Pasteur and the production of an antirabies vaccine. These pioneering studies stimulated a variety of investigations demonstrating that various diseases of plants, animals, and man were due to "filterable agents", subsequently referred to as viruses. The famous observations of Ellermann and Bang (3) and of Rous (4) suggesting that chicken leukemia and chicken sarcomas, respectively, could be induced by viruses undoubtedly focussed attention on the possibility that malignancy might be caused by this class of microorganisms.

These observations, coupled with developments in cell culture and media to support these cultures, subsequently led to the large-scale introduction of a vaccine against yellow fever (5) and to vaccines against a number of acute virus infections (i.e., poliomyelitis, rubeola, rubella, and mumps). While some of these vaccines, including the more controversial influenza virus vaccine, have had variable success, those against poliomyelitis, measles (rubeola), and rubella have been especially successful (Table 1). The most successful has been the smallpox vaccine, which has effected the total eradication of this disease from the world population. The elimination of smallpox was aided by the absence of an animal reservoir for the virus and by judicious use of the vaccine by public health officers on a global scale. Nobel prizes were awarded to many of the key investigators for these studies concerning the properties of viruses and their control (Table 2).

The successful control of acute virus infections, reductions in bacterial diseases because of improvements in sanitary engineering, and the

E. De Clercq (ed.), *Frontiers in Microbiology*

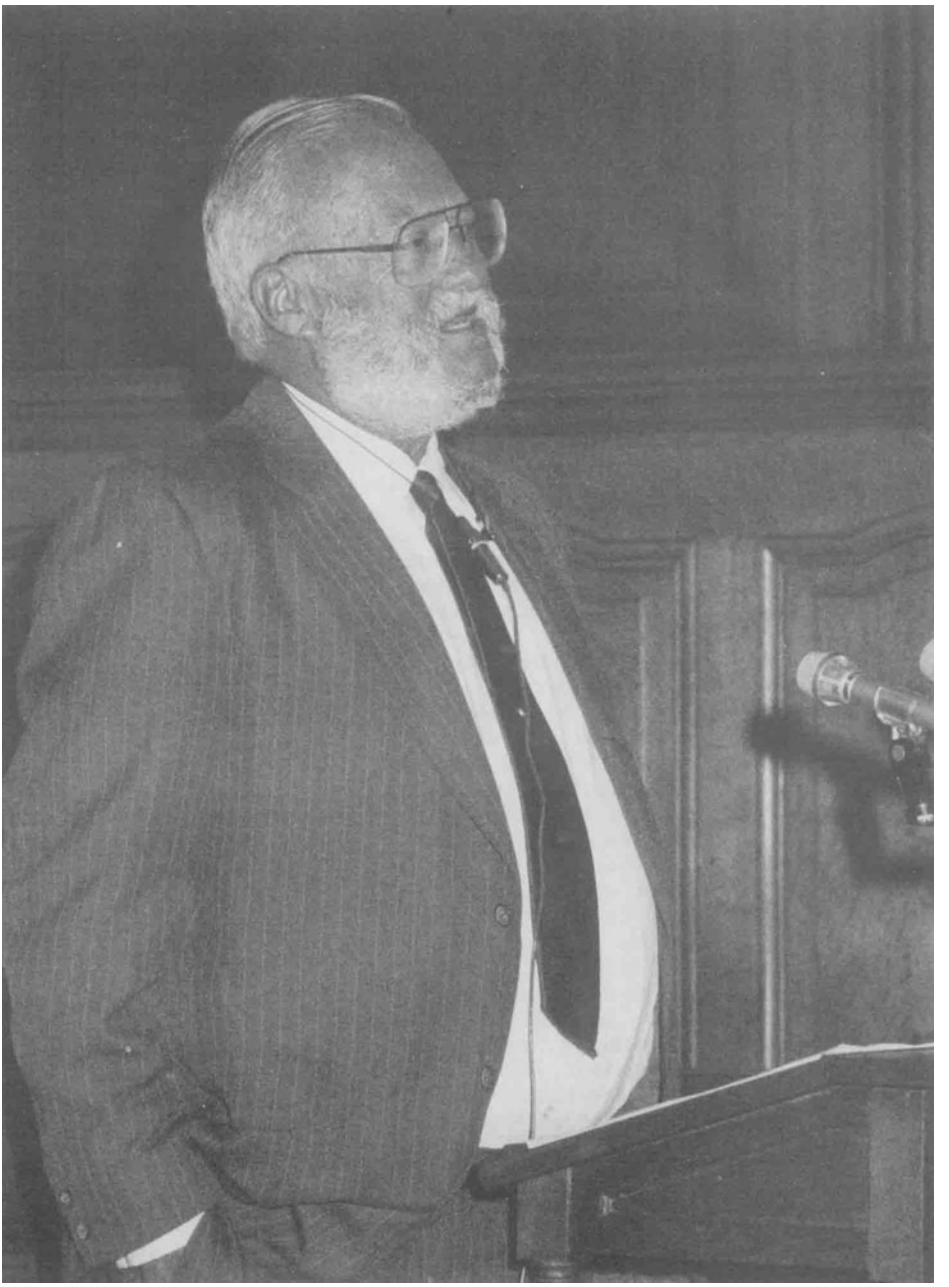

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TABLE 1. Development of successful virus vaccines for human use.

Virus	Year	Type of vaccine
Smallpox	1798	Attenuated
Rabies	1885	Inactivated
Yellow fever	1940	Attenuated
Polio	1953	Inactivated
	1955	Attenuated
Rubeola	1963	Attenuated
Rubella	1969	Attenuated
Mumps	1968	Attenuated
Hepatitis B	1981	Inactivated

widespread use of antibiotics suggested to many that chronic virus infections could be controlled in similar fashion. Far-reaching discoveries have prompted such hopes in every decade (Table 3). Regrettably, the poor record of medicine in controlling chronic infections due to any microbial organism, including malaria, tuberculosis, syphilis, gonorrhea, as well as many parasitic infections in Third World countries, was not taken into account in these calculations.

In the face of the first increase in the incidence of gonorrhea in the United States in ten years, with resistance of the disease to tetracycline and sulfonamide on the rise and because the organism poses a serious fertility problem in the Third World, the development of vaccines against N.gonorrhea have received a new impetus. Regrettably, protection by anti-pilus and anti-P-1 protein vaccines against N.gonorrhea has not been realized despite the induction of neutralizing antibody. Syphilis remains a public health problem and astonishingly, the role of the immune system in moderating or exacerbating the disease remains a mystery. Equally disappointing is the knowledge that systemic vaccination against chlamydial infection may cause tissue damage. Vaccines against these chronic infections were marginal at best and for many virus diseases, useful vaccines await the future (Tables 4 and 5). Chronic infections have posed far greater problems than envisioned and will continue to resist efforts for control despite the impact of molecular biology, biotechnology, and advances in immunology.

Chronic virus infections can be subdivided into those involving the central or peripheral nervous systems, the vascular system, and mucosal cells lining various body tissues. Of special interest are viruses affecting the vascular and nervous systems because they are generally more severe and have more far-reaching consequences to the patient. In addition, they flare up most readily in patients on immunosuppressive therapy to prevent transplant rejection or as part of chemotherapeutic regimens for the treatment of cancer. These patients, already at high risk, are further endangered by viruses activated by such treatment.

Diseases now known or thought to be associated with chronic virus infections include subacute sclerosing panencephalitis (SSPE, due to rubeola virus); neurologic symptoms due to human immunodeficiency virus (HIV); multiple sclerosis (perhaps due to an HTLV-like virus); Alzheimer's and Creutzfeldt-Jakob disease (unproven but suspected virus etiology). Viruses found in the vascular system include, among others, those associated with

TABLE 2. Nobel Prize research that impacted on virus discoveries.

Year	Recipient(s)	Contribution
1946	Wendell Stanley	Crystallization of tobacco mosaic virus
1951	Max Theiler	Yellow fever and attenuated vaccine
1954	Thomas Weller, John Enders, Frederick Robbins	Cultivation of polioviruses in cell culture; advent of modern virology
1958	Joshua Lederberg, Edward Tatum, George Beadle	Discovery that genes act by regulating specific chemical processes; genetic recombination; bacterial genetics
1959	Arthur Kornberg	Mechanisms in biological synthesis of nucleic acids
1965	Jacques Monod, Francois Jacob, André Lwoff	Genetic regulation of enzyme synthesis and lysogeny
1966	Charles Huggins, Peyton Rous	Research on chemical and viral etiology and cancer
1969	Max Delbrück, Alfred Hershey, Salvador Luria	The role of genetic material in bacterial and viral replication
1975	David Baltimore, Howard Temin, Renato Dulbecco	Characterization of the interaction between tumor viruses and the genetic material of the cell
1976	Baruch Blumberg, D. Carleton Gajdusek	Delineation of long incubation diseases caused by viruses
1978	Daniel Nathans, Hamilton Smith, Werner Arber	Development of restriction endonuclease technology; basis of bacterial resistance to bacteriophages
1980	Paul Berg, Walter Gilbert, Frederick Sanger	Pioneering work in recombinant DNA technology; methodologies for DNA sequencing
1982	Aaron Klug	Development of crystallographic electron microscopy elucidating the structure of viruses
1983	Barbara McClintock	Discovery of transposable genetic elements
1984	Cesar Milstein, Georges Köhler, Niels Jerne	Development of technique of monoclonal antibody formation and immuno-plaque technique
1986	Rita Levi-Montalcini, Stanley Cohen	Discovery of factors controlling cell growth and development

TABLE 3. Some important milestones in the development of virology.

Date	Contributor(s)	Contribution(s)
1798	Jenner	Developed vaccine against smallpox
1885	Pasteur	Produced rabies vaccine
1892	Ivanowski	Recognized a "filterable agent" as responsible for tobacco mosaic disease
1898	Löeffler and Frosch	Reported that the causative agent of foot-and-mouth disease was a virus
1899	Beijerinck	Demonstrated multiplication of tobacco mosaic virus in infected plant tissues
1902	Reed and Carrol	Discovered yellow fever virus
1908	Ellermann and Bang	Demonstrated transfer of chicken leukemia with cell-free extracts
1911	Rous	First evidence of a virus producing a solid tumor in an animal (chicken)
1915, 1917	Twort and d'Herelle	Separately discovered bacteriophage: d'Herelle developed the plaque assay and introduced the term bacteriophage
1928	Elford	Developed ultrafiltration methods providing comparative data on virus size
1931	Woodruff and Goodpasture	Introduced the use of embryonated eggs to propagate viruses
1933	Shope	Produced papillomas in rabbits with a filterable agent
1933	Ruska	Built first electron microscope
1935	Stanley	Crystallized tobacco mosaic virus
1936	Bittner	Described mouse mammary tumor virus and its transmission by milk
1939	Delbrück	Began systematic studies of bacteriophage
1940	Theiler	Developed effective yellow fever vaccine
1941	Hirst	Demonstrated that influenza virus would agglutinate red blood cells
1946	Lederberg and Tatum	Reported genetic recombination
1949	Enders, Weller and Robbins	Developed human cell cultures for quantitating replication of poliovirus by cytopathology
1950	Coons	Developed immunofluorescence technique
1951	Gross	Induced lymphoid leukemia in mice with cell-free extracts of tumors from leukemic mice

TABLE 3. (continued).

1952	Dulbecco	Developed the plaque technique for assaying animal viruses
1952	Hershey and Chase	Showed that only the DNA of bacteriophage is required for replication
1952	Zinder and Lederberg	Discovered transduction
1953	Lwoff	Discovered lysogeny
1955	Salk; Sabin; Koprowski	Developed effective poliomyelitis vaccines
1957	Isaacs and Lindenmann	Described interferon as antiviral
1960	Sweet and Hilleman	Discovered simian virus 40 (SV40)
1964	Epstein, Achong and Barr	Described the presence of a herpes-type virus (EBV) associated with Burkitt lymphoma
1964	Temin	Postulated that viral RNA can direct the synthesis of DNA provirus
1965	Blumberg	Identified hepatitis B virus
1966	Benjamin	Identified virus nucleic acid in transformed cells
1970	Baltimore; Temin and Mizutani	Independently found evidence of RNA-directed DNA polymerase (reverse transcriptase) in virions of RNA tumor viruses
1971	Gajdusek	Established Kuru as a viral disease
1965-1972	Arber; Smith and Wilcox; Danna and Nathans	Developed restriction endonuclease technology
1975	Berg; Maxam and Gilbert; Sanger	Developed recombinant DNA technology and methodologies for DNA sequencing
1975	Milstein and Köhler	Monoclonal antibody production
1977	Brugge and Erikson	Identified *scr* gene of Rous sarcoma
1980	Gallo	Isolated first human retroviruses (HTLV-I and II)
1982	Weinberg; Cooper; Wigler	Oncogenes described and partially characterized
1983	Montagnier; Gallo	Separately isolated human immunodeficiency virus

TABLE 4. Marginally effective human virus vaccines.

In use
Adenoviruses (military recruits)
Influenza virus (older population)
Experimental
Cytomegalovirus (transplant recipients)
Varicella-zoster virus (selected children)

TABLE 5. No vaccines available.

Virus	No. of types
Herpes simplex virus	2
Epstein-Barr virus	1
Papillomaviruses	> 45
Polyomaviruses (BK, JC)	2
Creutzfeldt-Jakob virus	1
Respiratory syncytial virus	1
Rhinoviruses	> 100
Coxsackie virus (A, B)	> 30
Hepatitis A virus	1
Coronaviruses	2
Human T-cell lymphoma virus	2
Human immunodeficiency virus	> 4

AIDS (now known to be caused by HIV); cytomegalovirus, which can multiply in many tissues but quite often is implicated in interstitial pneumonia; and hepatitis B virus. Of the many viruses affecting other tissues, their association with human cancers has still to be ruled out especially in light of the presence of virus genetic material in many cancer tissues. Most prominent are the papillomaviruses, which cause a variety of warts and are associated with genital neoplasia and neoplastic diseases of other organs.

A number of viruses are spread by sexual contact (Table 6) : hepatitis B virus, herpes simplex virus type 2, cytomegalovirus, HIV, and certain papillomaviruses. Diseases caused by these viruses are governed by social and demographic factors (Table 7) and often affect the relatively young.

TABLE 6. Sexually transmitted viruses.

Herpes simplex virus types 1 and 2
Cytomegalovirus
Papillomavirus types 6, 11, 16, 18, 31, 33, and 35
Hepatitis A and B
Human immunodeficiency virus

TABLE 7. Social and demographic factors influencing trends in STDs.

Age distribution of population
Use of contraceptives
Sexual behavior

2. PROBLEMS ASSOCIATED WITH HERPES SIMPLEX VIRUSES (HSVs) AND CYTOMEGALOVIRUS

The herpesvirus group comprises numerous structurally related and morphologically indistinguishable viruses that infect humans and probably all animal species. The members that infect humans include HSV types 1 and 2 (HSV-1 and HSV-2), varicella-zoster virus (VZV), human cytomegalovirus (HCMV), Epstein-Barr virus (EBV). All can be life-threatening, reside in the host for extended periods of time, and can cause continued recurrent disease long after initial infection of the human host.

The DNA of herpesviruses has a molecular weight ranging from 80 to 150 million, with HSV having a DNA of 95 million, and the largest, HCMV, having a DNA of 150 million. All have a capsid surrounded by a lipid envelope containing a large number of proteins, of which several are glycosylated. Although morphologically indistinguishable, the DNA of these viruses varies both in size as well in structure (Fig. 1). The DNA of HSV-1, HSV-2, and HCMV can exist in four isomeric forms (6). The long and short unique regions are covalently linked and the junction region contains reiterated inverted repeats that are reproduced at both ends of the genome. The long and short components can invert independently producing four isomeric structures. The unique DNA structure of these three herpesviruses is by no means a requirement, as many other herpesviruses have only one isomeric form and cannot invert either of the two components. It is not known why evolutionary forces have enabled HSV-1, HSV-2, and HCMV to produce these four forms when only one is needed for infectivity and the rest appears to be of little consequence for infection or for virus survival.

Herpesviruses have a similar method of replication involving coordinated temporal synthesis (7). The genes involved in replication are designated immediate early (α), early (β), and late (γ) genes (Fig. 2). As a rule, one class of genes needs to be transcribed and translated for the second class to begin synthesis; synthesis by the next class generally shuts off expression of the earlier genes. There are five immediate early genes, at least one of which is required to activate all subsequent transcription. The early and late genes are a far larger and heterogeneous

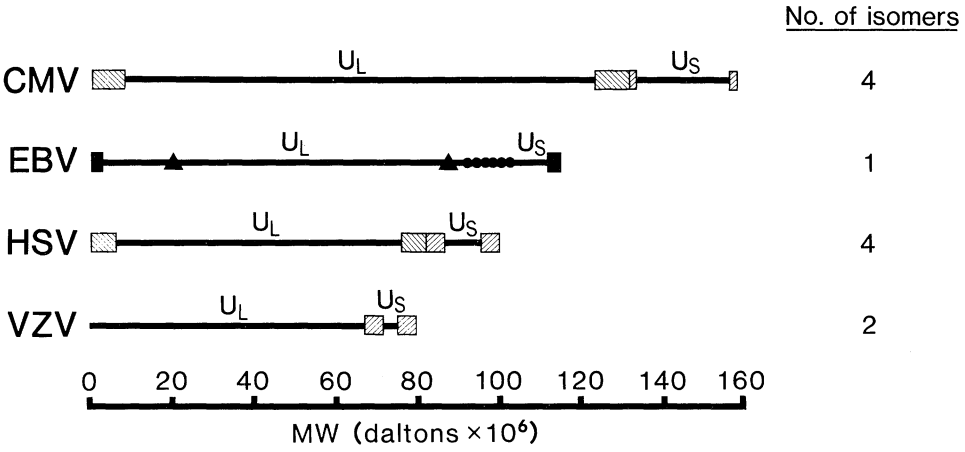

FIGURE 1. Comparative DNA structure of human herpesviruses.

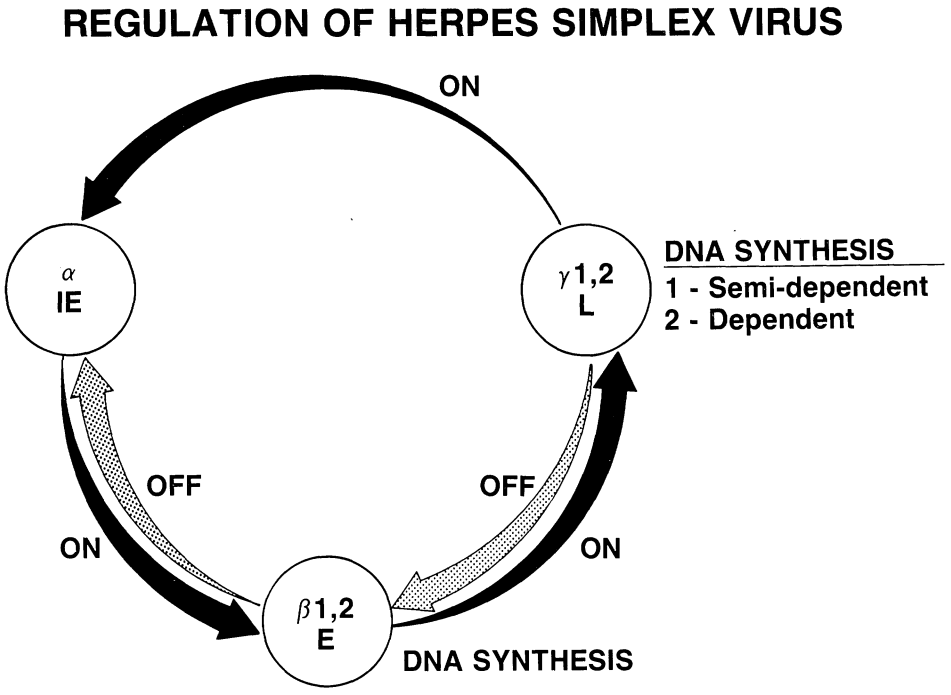

FIGURE 2. Regulation of replicative cycle of herpesviruses.

group; the early genes are primarily involved in the synthesis of virus DNA and include such well characterized virus genes as DNA polymerase, thymidine kinase, ribonucleotide reductase, as well as a number of major DNA binding proteins. The late genes generally specify capsid proteins including the glycoproteins found in the virion.

Of great importance is the fact that differences in the endonuclease digestion patterns of HSV-1, HSV-2, and HCMV DNA allow one to trace the virus during infection (8). This is mirrored by differences in polypeptide patterns. Whether such variations will ultimately confuse vaccine protocols and lower the efficacy of vaccines remains to be further investigated.

Genital herpes now has a reservoir of 40 to 60 million infected individuals in the United States. The disease has been spreading dramatically for ten years. There also is a major asymptomatic and undiagnosed reservoir, with an unknown percentage of these individuals shedding virus and therefore representing putative sources of infection. This has amplified the risk to newborns, resulting in an increase in neonatal infection from 4.8 to 14 cases per 100,000 live births during the last twenty years in the Seattle, Washington area (K. Holmes, personal communication).

A major problem associated with HSVs is the fact that they are introduced into the population at a fairly young age: HSV-1 generally infects children before they reach the age of 6 and HSV-2 often is introduced shortly after the onset of sexual activity. Following such introduction, both viruses can remain latent in the peripheral neurons, thus escaping elimination by both antibody and specific T-cell responses. An important fact is that there is 50 % base sequence homology between the nucleic acids of HSV-1 and HSV-2 (9), which is reflected in antigenic similarities in a number of HSV proteins, including some of the glycoproteins. This leaves some doubt as to the efficacy of vaccination. An individual infected with HSV-1 earlier in life and carrying antibodies capable of neutralizing both type 1 and 2 viruses is still susceptible to infection of the genital tract by HSV-2. Thus, natural immunity does not prevent reinfection by a virus that can be neutralized by circulating antibody and against which a T-cell-mediated response is present. This suggests that an innovative approach to vaccination against HSV is needed if the related diseases are to be prevented. Of further concern is the fact that the latent virus can travel down the anoxal pathway and cause recurrent disease in the face of an active immune response. Thus, any vaccine that fails to prevent the establishment of latency will not fulfill the purpose of preventing either virus infection or virus activation. Therefore, it becomes important to study how viruses remain latent and what causes activation.

In studying problems concerned with virus latency, we have chosen to establish in vitro cell culture systems to investigate the molecular events connected with virus latency. The problems posed include a better definition of the state of the viral genome during latency, the molecular steps required to activate the virus, and hopefully some way to prevent activation or to eradicate the virus in latently infected cells.

With the help of Professor Erik De Clercq, systems have been established in human embryo fibroblasts and in human neurons obtained from aborted fetuses (10,11). These studies have revealed that it is possible to establish virus latency [i.e., no virus can be detected (12,13)], that the latent virus is present as DNA and does not appear to be integrated in the host cell chromosomes (10), and that it is possible to activate the virus by a variety of techniques including superinfection with genetically unrelated but morphologically related HCMV (14). These studies established

that the superinfecting virus can induce HSV to replicate in latently infected cells and that the portion of the HCMV genome involved is a region of at least 22 kilobases (unpublished data). The task now will be to further narrow that portion of genome involved and to determine the functions associated with the HCMV genome that activate HSV.

In accompanying experiments, attempts to eradicate the virus in cell culture generally have proven unsuccessful. Nevertheless, there are imaginative ways to approach this problem using newer methods in biotechnology and we hope to carry out such experiments in the future.

Latency studies have been carried out with HCMV with similar results. However, it is noteworthy that it is more difficult to establish latent HCMV infection, perhaps because the replication cycle of this virus is so much longer than that of HSV. This is mirrored in the human body where HCMV tends to persist with a small amount of virus being released over long periods of time and where true virus latency has not been firmly established. That the immune system helps to check the spread of HCMV as well as HSV-1 and HSV-2 has been clearly established by the fact that immunosuppressive therapy causes massive infection of many organs by HCMV and may be life-threatening to those being treated with such drugs. This resulted in attempts to produce an attenuated live virus vaccine (15). However, the use of an HCMV vaccine in the general population is contraindicated because of the transforming properties of HCMV (16) and the failure to establish a good animal model enabling safety testing in non-human hosts. It is pertinent to note that very similar problems are involved with VZV vaccines; experimental VZV vaccines already undergoing extensive clinical trials worldwide (17) suffer from the same deficiencies that the HCMV vaccine has associated with it.

Such studies are especially important because HCMV infections are common worldwide, and result in numerous clinical syndromes. However, of special concern is the ability of HCMV to cross the human placenta; fully 1 % of all live births are congenitally infected by this virus, with 5 to 10 % of these infants suffering clinically manifest disease and an additional 10 to 30 % eventually demonstrating developmental or physical handicaps. The virus also has emerged as a major pathogen in immunosuppressed patients and in those suffering from AIDS. Thus, attempts to control this pathogen should receive high priority.

3. PROBLEMS ASSOCIATED WITH PAPILLOMAVIRUSES

Papillomaviruses have long resisted cultivation in cell culture systems, thus thwarting investigations into the properties of these viruses. Reports on papillomaviruses reach back as far as 1907. Ciuffo (18) observed that human warts could be induced by filterable agents (now known as papillomaviruses) and the pioneering work of Shope and his colleagues (19) on cottontail rabbit papillomavirus provided the first model of a naturally occurring virus-induced neoplasm. The number of papillomaviruses associated with human diseases has been open to question. However, recent advances in biotechnology have greatly catalyzed progress in this field.

There are approximately 45 human papillomaviruses (HPVs), based on characterization by DNA homology; if an HPV shows less than 50 % homology with existing types, the HPV is classified as a new type. Many HPV DNAs have been reproduced in vitro and their genes have been translated. Thus, the genome of papillomaviruses follows a closed circle of double-stranded DNA and is well characterized (Fig. 3). Also well established are the tissue locations of some of the papillomaviruses. For example, it is now known that HPV types 6, 11, 16, 18, 31, 33 and 35 are involved in the

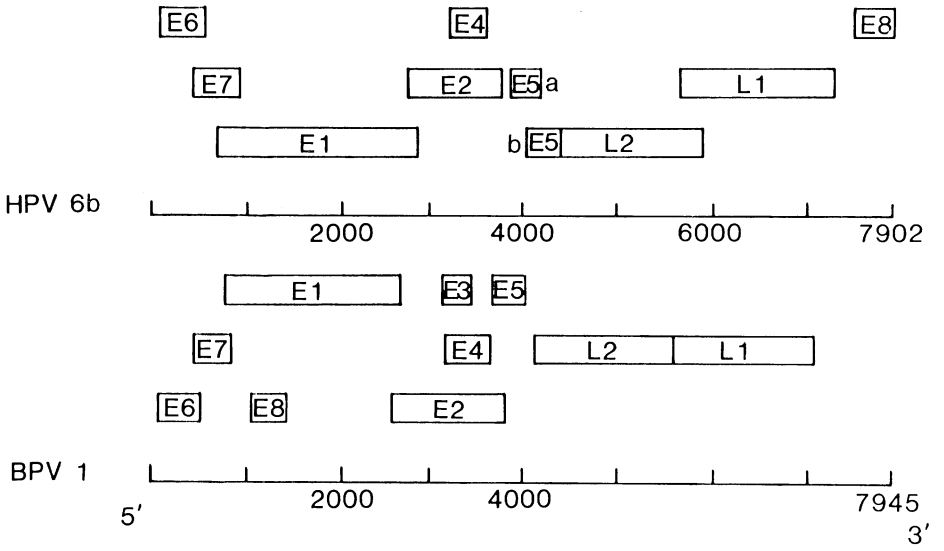

FIGURE 3. Genome organization of papillomavirus DNAs; human papillomavirus type 6b (HPV 6b) and bovine papillomavirus (BPV 1).

etiology of genital warts and that HPV types 6 and 11 are associated with respiratory papillomas which are often acquired at birth. Other HPV types are the causative agents of warts at other sites (Tables 8 and 9). The DNA of these viruses is known to persist and the virus is produced only in the keratinizing layers of the wart. However, the underlying squamous cells appear to contain the virus genome, which appears to be under the control of the cell as no virus particles are produced even though small amounts

TABLE 8. HPVs associated with benign warts.

HPV type	Lesions
1a, b, c	Plantar warts
2a-e	Common hand warts
3a, b	Flat warts/juvenile warts
4	Plantar warts
7	Butchers warts
10a, b	Flat warts
13	Oral focal hyperplasia (Heck lesions)
34	Bowenoid papulosis
36	Actinic keratosis
37	Keratoachanthoma
39	Cutaneous lesions
41	Flat warts

TABLE 9. HPVs associated with epidermodysplasia verruciformis.

HPV type	Lesions
5a, b	Macules
8	Macules
9	Warts and macules
12	Warts and macules
14a, b	Skin lesions
15	Skin lesions
17a, b	Skin lesions
19-29	Warts and hyperplastic lesions

of viral DNA are retained. On occasion, some benign warts progress to carcinomas (20). It is now known that some HPV DNA types are consistently associated with specific carcinomas (Table 10). Thus, there is strong evidence that the etiology of certain cancers involves particular HPV types, but more evidence is required to make such an association more than casual and raise it to the level of causation (Table 11). In this regard, the problems associating HPVs with cancer are not different from those associating the herpesviruses with cancer or hepatitis B virus with primary hepatocellular carcinoma.

TABLE 10. HPVs associated with cancer in situ or invasive carcinoma.

HPV type	Lesions
6a-f	Condylomata acuminata; cervical intraepithelial neoplasia I, II, III; vulvar intraepithelial neoplasia I, II, III; laryngeal papillomas
11a,b	Condylomata acuminata; cervical intraepithelial neoplasia I, II, III; laryngeal papillomas
16	Condylomata acuminata; cervical intraepithelial neoplasia I, II, III; vulvar intraepithelial neoplasia I, II, III; Bowenoid papulosis; malignant carcinoma, cervix and penis
18	Malignant carcinoma, cervix and penis
30	Laryngeal carcinoma (rare)
31	Cervical intraepithelial neoplasia; malignant carcinoma, cervix
33	Bowenoid papulosis; cervical intraepithelial neoplasia; malignant carcinoma, cervix
35	Cervical intraepithelial neoplasia; malignant carcinoma, cervix
38	Melanoma
40	Laryngeal carcinoma

TABLE 11. Association of human papillomaviruses with genital cancer.

Viral DNA in dysplasia, cancer in situ, carcinoma
Viral DNA in metastatic cells
Viral DNA; episomal in condyloma, integrated in carcinoma
Virus and DNA can transform cells
Transformed cells cause tumors

What would make such associations convincing would be the use of a vaccine to prevent virus infection and a subsequent reduction in the number of cancers associated with that particular virus. This may well be accomplished with hepatitis B virus and primary hepatocellular carcinoma since the hepatitis B vaccine is being administered in countries with a high incidence of liver cancer where hepatitis B is a major public health problem.

The certainty and the assurance that a vaccine against HPVs might be developed and prove to be efficacious are very low at the moment. Nevertheless, it is worth pursuing. However, better ways must be found to grow large quantities of papillomaviruses to better characterize the proteins and their functions. At the moment, only DNA homology studies separate these viruses and very little is known about their antigenic differences so that seroepidemiology is not feasible. This in turn means that the level of HPV infection in the general population remains unknown and the transmission of many HPVs is poorly understood.

4. PROBLEMS ASSOCIATED WITH HIV

The problems associated with this virus are immediate and serious and Dr. R.C. Gallo will confront these issues in great detail in the subsequent paper. HIV is generally introduced by sexual transmission or introduction of infected blood products, resists eradication, infects a number of cell types, which certainly include T4 helper cells or their precursors, and causes widespread damage to the immune system as well as to cells of the central nervous system.

Associated with AIDS are opportunistic infections by a great variety of organisms and neoplastic disease, which usually are controlled by the immune system but which flourish when that mechanism is impaired. Since HIV integrates its genome, after it has been transcribed to DNA by reverse transcriptase, into the host chromosomes, eradication will not be simple, and prevention of disease will rest on the ability to block the virus at the portal of entry or the reverse transcription step. In addition, the role of this and related viruses (many are yet to be isolated) in central nervous system disorders and other tumors or disease syndromes remains to be studied. Since it is now known that HIV undergoes antigenic changes, successful vaccine therapy will face the same handicaps that have prevented effective influenza virus vaccines. An animal model for testing safety using human viruses is not in sight, although there are animal models for related animal retroviruses. Whether these are relevant to human disease remains open to question.

5. THE CHALLENGE OF THE ETIOLOGY OF DISEASES NOW LINKED TO VIRUSES

The initial association of microorganisms, including viruses, with acute infections was fairly simple and direct. Following establishment of Koch's postulates linking microorganisms to disease, a large number of disease syndromes were attributed to bacteria, a few to viruses, and subsequent investigations have not changed many of these assignments. Unfortunately, Koch's postulates are difficult to apply directly to viruses, since viruses often do not cross species barriers and replication in another cell type (i.e. an animal host) is not always possible. Thus, Koch's postulates cannot be fulfilled for many of the diseases associated with viruses. The same problems that have haunted viral oncologists over the past 70 years in establishing a connection between viruses and cancer continue to plague those working on diseases with as yet unknown etiologies. Recent studies on multiple sclerosis by Prof. Hilary Koprowski and colleagues (21) suggest that an HTLV-like virus may be involved; however, this remains to be confirmed by other investigators. In addition, diseases of the central nervous system with suspected viral etiology, such as Alzheimer's, Creutzfeldt-Jakob, and other autoimmune disease complexes require further investigation. The mere presence of a virus or its nucleic acid in tissue is not enough to establish etiology, as such materials often represent "passenger" information that does not involve causation. This is akin to the problem with AIDS, which renders the patient susceptible to a variety of microorganisms that produce disease syndromes that are not caused directly by HIV. The challenge of virologists, molecular biologists, and investigators examining epidemiology and pathogenesis will be to try creative ideas to better understand the causation of these chronic infections. The ultimate hope is that such understanding will lead to therapy or preventive measures that will reduce the incidence of these diseases and the attendent physical, mental, and financial hardships.

6. CONCLUSIONS

Virologists and scientists in other disciplines have been instrumental in reducing the effects of acute infections on the health of the population. Especially impressive is the near eradication of infections that used to produce high morbidity and mortality in children. Many of these illnesses have now been relegated to rate events in advanced countries and incidences certainly will decline in the Third World. Better understanding chronic virus infections coupled with attempts to treat and prevent those infections will be the focus of investigations during the next decade. It is hoped that the massive effort now aimed at the AIDS virus (one of those establishing chronic infection) will spill over into research on other virus infections and so that at the end this century may be heralded by major health advances against chronic infections.

ACKNOWLEDGEMENTS

The authors thanks M.K. Howett for critical review of the manuscript and M. Clement for editorial assistance. New observations cited in this paper were supported in part by grants CA 27503, CA 34479 and CA 09124 awarded by the National Cancer Institute, and by BRSG grant S07 RR05680-18 awarded by the Biomedical Research Support Grant Program, Division of Research Resources, National Institutes of Health.

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