CHAPTER 4

Patterns of Some Viral Diseases of Humans

We have seen that the process of infection and consequent disease is controlled by a number of factors ranging from the effect of specific genes controlling aspects of pathogenesis to more subjective factors that can be classified as important in overall virulence of the disease. Viral diseases and infections can be categorized generally according to fate of the host and the virus itself. A very simple classification is based on the following criteria:

1 Does the infected individual usually recover or die?
2 If the victim recovers, is this recovery a full one or are there lasting sequelae?
3 Does the virus stay associated with the victim following apparent recovery?
4 If the association is lasting, is the virus maintained in an infectious form either sporadically or constantly?

These criteria are useful to organize detailed knowledge of the results of specific virus diseases within the context of possible courses and outcomes. A number of specific examples are outlined in this chapter.

Some viral diseases associated with acute infection followed by virus clearing from the host

An acute infection is essentially one in which the disease caused by the pathogen occurs suddenly;

its symptoms appear rapidly and follow a specific and relatively short time course. Many acute virus infections follow a rather simple and uncomplicated route of infection and recovery. It is important to keep in mind, however, that just because the pattern of infection and disease by a particular virus is simple, there is no a priori reason why serious or fatal consequences of the infection cannot ensue.

Colds and respiratory infections

Cold viruses (rhinoviruses and coronaviruses) are spread as aerosols. Infection is localized within the nasopharynx, and recovery involves immunity against that specific virus serotype. The vast array of different cold viruses and serotypes ensures that there will always be another one to infect individuals. Although generally these types of respiratory diseases are mild, infection of an immune-compromised host or a person having complications due to another disease or advanced age can lead to major problems.

Influenza

The epidemiology of **influenza** is an excellent model for the study of virus spread within a population. While symptoms can be severe, in part due to host factors, the virus infection is localized, and the virus is efficiently cleared from the host. Flu viruses have evolved unique mechanisms to ensure constant generation of genetic variants, and the constant appearance of new influenza virus serotypes leads to periodic epidemics of the disease. Some of these mechanisms are described in detail in Chapter 16. The respiratory distress caused by most strains of flu virus is not particularly life threatening for healthy individuals, but poses a serious problem for older people and individuals with immune system or respiratory deficiencies. Some strains of the virus cause more severe symptoms with accompanying complications than others. At least one strain, the Spanish strain, caused a worldwide epidemic with extremely high mortality rates in the years immediately following World War I.

Variola

The disease caused by infection with **smallpox** (**variola**) virus is an example of a much more severe disease than flu, with correspondingly higher mortality rates. There are (or were) two forms of the disease: *variola major* and *variola minor*. These differed in severity of symptoms and death rates. Death rates for variola major approached 20%, and during the Middle Ages in Europe, reached levels of 80% or higher in isolated communities. Virus spread was generally by inhalation of virus aerosols formed from drying exudate from infected individuals. The virus is unusually resistant to inactivation by desiccation and examples of transmission from contaminated material as long as several years after active infection were common.

The disease involves dissemination of virus throughout the host and infection of the skin. Indeed the pathogenesis of mouse pox described in the last chapter provides a fairly accurate model of smallpox pathogenesis. The virus encodes **growth factors** that were originally derived from cellular genes. These growth factors induce localized proliferation at sites of infection in the skin, which results in development of the characteristic pox.

Infection of an "accidental" target tissue leading to permanent damage despite efficient clearing

Some viruses can target and damage an organ or organ system in such a way that recovery from infection does not lead to the infected individual's regaining full health despite generation of good

immunity. A very well understood example is paralytic poliomyelitis. Poliovirus is a small enteric virus with an RNA genome (a **picornavirus**), and most infections (caused by ingestion of fecal contamination from an infected individual) are localized to the small intestine. Infections are often asymptomatic, but can lead to mild enteritis and diarrhea. The virus is introduced into the immune system by interaction with lymphatic tissue in the gut, and an effective immune response is mounted, leading to protection against reinfection.

Infection with poliovirus can lead to paralytic polio. The cellular surface protein to which the virus must bind for cellular entry (the receptor) is found only on cells of the small intestine and on motor neurons. In rare instances, infection with a specific genotype that displays marked tropism for (propensity to infect) neurons (a neurovirulent strain) leads to a situation where virus infects motor neurons and destroys them. In such a situation, destruction of the neurons leads to paralysis.

It should be noted that paralysis resulting from neuronal infection does not aid the virus's spread among individuals; this paralytic outcome is a "dead end." Perhaps ironically, the paralytic complications of poliovirus infections have had negative selective advantages, since if such a dramatic outcome did not occur, there would have been no interest in developing a vaccine against poliovirus infection!

A variation on the theme of accidental destruction of neuronal targets by an otherwise relatively benign course of acute virus infection can be seen in **rubella**. This disease (**German measles**), which is caused by an RNA virus, is a mild (often asymptomatic) infection resulting in a slight rash. Although infection is mild in an immunocompetent individual, the virus has a strong tropism for replicating and differentiating neural tissue. Therefore, women in the first trimester of pregnancy who are infected with rubella have a very high probability of having an infant with severe neurological damage. Vaccination of women who are planning to become pregnant is an effective method of preventing such damage during a localized rubella epidemic.

Persistent viral infections

Viruses that persist in the individual as chronic or latent infections are common. Often the course of initial infection is similar to that seen in an acute infection followed by efficient clearance, as described previously. In a persistent infection, however, the virus cannot be cleared either because of virus-induced deficiencies in the immune response or because of the virus maintaining infection in localized areas where immunity is not complete. Some persistent infections are characterized by chronic, low-level replication of virus in tissues that are constantly being regenerated so that damaged cells are eliminated as a matter of course. An excellent example described in more detail in Chapter 17, is the persistent growth and differentiation of **keratinized tissue** in a wart caused by a **papillomavirus**. In such infections, virus replication closely correlates with the cell's differentiation state, and the virus can express genes that delay the normal programmed death (**apoptosis**) of such cells in order to lengthen the time available for replication.

Other viruses more distantly related to papillomaviruses include BK virus and JC virus that induce chronic infections of kidney tissue. Such infections are usually asymptomatic and are only characterized by virus shedding in the urine. The completely unrelated **adenovirus** also is characterized by establishment of persistent infections of the lung's (respiratory) epithelial cells.

Herpesvirus infections and latency

As outlined in Chapter 4 and detailed in Chapter 18, hallmarks of herpesvirus infections are an initial acute infection followed by apparent recovery where viral genomes are maintained in the absence of infectious virus production in specific tissue. Latency is characterized by episodic reactivation (recrudescence) with ensuing (usually) milder symptoms of the original acute infection. Example viruses include HSV, EBV, and varicella-zoster virus (chicken pox).

In a latent infection, the viral genome is maintained in a specific cell type and does not actively replicate. HSV maintains latent infections in sensory neurons, whereas EBV maintains itself in lymphocytes. Latent infections often require the expression of specific virus genes that function to ensure the survival of the viral genome or to mediate the reactivation process.

Reactivation requires active participation of the host. Immunity, which normally shields the body against reinfection, must temporarily decline. Such a decline can be triggered by the host's reaction to physically and psychologically stressful events. HSV reactivation often correlates with a host stressed by fatigue or anxiety.

Complications arising from persistent infections

Persistent infections caused by some viruses can (rarely) lead to a **neoplasm** (a cancerous growth) due to continual tissue damage and resulting in mutation of cellular genes controlling cell division (**oncogenes** or **tumor suppressor genes**). Examples include infections with slow-transforming retroviruses such as **human T-cell leukemia virus** (**HTLV**), chronic hepatitis B infections of the liver, certain genital papillomavirus infections, and EBV infections. The latter require the additional action of auxiliary cancer-causing factors (*co-carcinogens*).

Autoimmune diseases such as **multiple sclerosis** (MS) are thought by many investigators to result from an abnormal immune response to viral protein antigens continually present in the body due to a persistent infection. Such persistent infections need not result in the reappearance of infectious virus. For example, infection with measles virus usually leads to rash and recovery although portions of viral genomes and antigens persist in certain tissues, including neural tissue. The mechanism of this persistence is not fully understood, but it is clear that virus maturation is blocked in such cells that bear viral genomes, and viral antigens are present in reduced amounts on the cell surface. The presence of antigen leads to lifelong immunity to measles, but can result in immune complications where the host's immune system destroys otherwise healthy neuronal tissue bearing measles antigens.

The fatal disease of **subacute sclerosing panencephalitis** (**SSPE**), which is a rare complication in children occurring a few years after a measles infection, is a result of such an autoimmune response. SSPE is a rare outcome of measles infection, but other severe sequelae of measles are common. One of the most frequent sequelae is damage to eyesight. The virus replicates in the host and infects surface epithelium, resulting in characteristic rash and lesions in the mouth, on the tongue, and on the eye's conjunctiva. Virus infection of the conjunctiva can clear, but movement of eye muscles in response to light, or in the process of reading, can lead to further infection of eye musculature, leading to permanent damage, which is why individuals infected with measles should be protected from light and kept from using their eyes as much as possible.

Viral and subviral diseases with long incubation periods

Most virus-induced diseases have low or only moderate mortality rates. Obviously, if a virus's mortality rate is too high, infection will kill off all the hosts so rapidly that a potential pool of susceptible individuals is lost. Exceptions to this rule do occur, however. Introduction of viral disease into a virgin population (perhaps due to intrusion into a novel ecosystem) can lead to high mortality. Prime examples are the spread of smallpox in Europe during the Middle Ages, and the destruction of native populations in the Western Hemisphere by the introduction of measles during the era of European expansion. Another exception to the rule comes about as a manifestation of infection with a virus that has an unusually long incubation period between the time of infection and the onset of symptoms of disease.

Rabies

Some viral diseases have very high mortality rates despite their being well established in a population. With rabies, for example, injection of virus via the saliva of an animal bearing active disease leads to unapparent early infection followed by a long incubation period. During this time, the infected animal is a walking "time bomb." The symptoms of disease (irritability, frenzy, and salivation) are all important parts of the way the virus is spread among individuals. The very long incubation period allows animals bearing the disease to carry on normal activities, even breed, before the symptoms almost inevitably presaging death appear. A hypothetical viral infection that might lead to these physiological and behavioral changes but that resulted in a quick death could not be spread in such a way.

HIV–AIDS

AIDS, which is characterized by a latent period in which HIV can be transmitted, followed by severe disease, is an example of a "new" viral disease. In humans, virus spread is often the result of behavioral patterns of infected individuals during HIV's long latent period. This pattern of spread makes it unlikely that there is any selective pressure over time toward amelioration of the late severe symptoms.

Prion diseases

We have noted in Chapter 1 that while prions are not viruses, many of the principles developed for the study of viral diseases can be applied to study of the pathology of prion-associated diseases. The prion-caused **encephalopathies** are, perhaps, the extreme example of an infectious disease with a long incubation period. Periods ranging from 10 to 30 years between the time of exposure and onset of symptoms have been documented. Prion-induced encephalopathy does not lead to any detectable immune response or inflammation, probably because the prion is a host protein. Course of the disease is marked by a slow, progressive deterioration of brain tissue. Only when this deterioration is significant enough to lead to behavioral changes can the disease be discerned and diagnosed. No obvious treatment or vaccination strategy is available at this time for such a disease.

SOME VIRAL INFECTIONS TARGETING SPECIFIC ORGAN SYSTEMS

While all the organ systems of the vertebrate host have important or vital functions in the organism's life, several play such critical roles that their disruption leads to serious consequences or death. Among these are the CNS with its influence on all aspects of behavior both innate and learned, the circulatory system, its attendant lymphatic loop, and the liver. Virus infections of these systems are often life threatening to the individual, and the tissue damage resulting from infection can lead to permanent damage. For example, destruction of immune system cells targeted by HIV is the major symptom of AIDS and leads to death. Other viruses can cause as devastating a disease as HIV, but most viral infections are not invariably fatal. A consideration of some CNS and liver virus infections provides some interesting examples of both destructive and limited disease courses.

The different patterns of sequelae following infection of a common target organ are also important demonstrations of several features of virus infection and pathogenesis.

First, specific tissue or cell tropism is a result of highly specific interactions between a given virus and the cell type it infects. Depending on the type of cell infected, the severity of symptoms, and the nature of the damage caused by the infection, different outcomes of infection are evident.

Second, persistent infection is a complex process. It is, in part, the result of a virus interacting with and modulating the host's immune system. Often persistence involves the virus adapting to a continuing association with the target cell itself.

Third, classifying viruses by the diseases they cause is not a particularly useful exercise when trying to understand relationships among viruses.

Fourth, and finally, viruses spread by very different routes can target the same organ. The movement of virus within the host is as important as the initial port of entry for the virus.

Viral infections of nerve tissue

The vertebrae nerve net can be readily divided into peripheral and central portions. The peripheral portion functions to move impulses to and from the brain through connecting circuits in the spinal cord. Viral infections of nerve tissue can be divided into infections of specific groups of neurons: neurons of the spinal cord (**myelitis**), the covering of the brain (**meningitis**), and neurons of the brain and brain stem itself (encephalitis).

The brain and CNS have a privileged position in the body and are protected by a physical and physiological barrier from the rest of the body and potentially harmful circulating pathogens. This barrier, often referred to as the **blood–brain barrier**, serves as an effective but incomplete barrier to pathogens. Viruses that migrate through neurons can breach it and traverse synapses between peripheral and central neurons, by physical destruction of tissue due to an active infection, by direct invasion via olfactory neurons (which are not isolated from the CNS), or by other less well-characterized mechanisms.

Certainly, invasion of the CNS by pathogens is not all that rare since a specific set of cells in the CNS, the microglial cells, function in manners analogous or identical to cells of the lymphatic immune system.

Many viruses can infect nerve tissue, and while some such infections are dead ends, other viruses specifically target nerve tissue. Viruses that do infect nerve tissue tend to favor one or another portion, and whereas the discrimination is not complete, many viruses, such as **enteroviruses** and genital HSV (HSV-2), tend to be causative agents of meningitis while others, such as rabies and facial HSV (HSV-1), are almost always associated with encephalitis. Viral, or **aseptic meningitis** tends in general to be less life threatening than are the majority of viral infections associated with encephalitis, but all are serious and potentially dangerous and can lead to debilitating diseases.

While many viral infections of the brain can have grave consequences, such consequences are not always the case. Some viral infections of the CNS have reasonably benign prognoses if proper symptomatic care is provided to the afflicted individual. Viruses that target the brain can be broken into several operational groupings, depending on the nature of brain involvement and whether it and associated tissue are a primary or secondary ("accidental") target.

Examples of viral encephalitis with grave prognosis

Rabies

Once the symptoms of disease become apparent, rabies virus infections are almost always fatal. The virus targets salivary tissue in the head and neck in order to provide itself with an efficient medium for transmission to other animals. Involvement of the CNS and brain is eventually widespread, with ensuing tissue destruction and death. Prior to this, however, the involvement is only with specific cells that lead to alterations in the afflicted animal's behavior and ability to deal with sensory stimuli. During this period, which is often preceded by a **prodromal period** of altered behavioral patterns, the animal can be induced to an aggressive frenzy by loud sounds or by the appearance of other animals. This course is the "furious form" of the disease. This behavioral change is most

marked for carnivores such as dogs, cats, and raccoons, but can be observed in other infected animals such as squirrels and porcupines. The behavioral changes obviously have a marked impact on transmission of the virus, as the frenzied attack is often the instrument of spread.

Despite its association with frenzy (the name *rabies* is derived from the Sanskrit term for doing violence), not all rabies infections lead to the furious form. There is another form of the disease (often termed "dumb") in which the afflicted animal becomes progressively more torpid and withdrawn, eventually lapsing into a coma and death.

The disease's long incubation period between the time of initial inoculation and final death is a very important factor, both in spread of the virus and in its being able to persist in wild populations, but there is also evidence that some animals can be carriers of the disease for long periods with no obvious, overt symptoms. While there are (extremely) rare examples of apparent recovery from the disease even after symptoms appear, generally one can consider the development of the symptoms of rabies as tantamount to a death sentence.

Herpes encephalitis

Encephalitis induced by HSV infection is the result of a physiological accident of some sort. Normally, HSV's involvement with neurons of the CNS and brain is highly restricted, although viral genomes can be detected at autopsy in brain neurons of humans who have died of other causes.

HSV encephalitis occurs only very rarely, but can be a result of either primary infection or an aberrant reactivation. Exactly what features of viral infection or reactivation lead to encephalitis are unknown, but a transitory crisis in immunity appears to be a major factor. Certainly, there is a much higher risk of invasive HSV encephalitis in neonates and infants with primary HSV infection prior to full development of their own immune defenses.

If diagnosed during early clinical manifestations of disease, HSV encephalitis can be treated effectively with antiviral drugs. But within a very short period of time (a few days at most), infection leads to massive necrotic destruction of brain tissue, coma, and death.

Although clinical isolates of HSV are often high in neurovirulence and neuroinvasive indices when they are tested in laboratory animals, there is no evidence that the virus recovered from patients with herpes encephalitis is any more virulent than those isolated from the more common, localized labial or genital infections. Further, there has never been any confirmed epidemiological pattern to the occurrence of herpes encephalitis that would suggest a specific strain of virus as a causative factor.

Viral encephalitis with favorable prognosis for recovery

Many of the viruses that cause encephalitis have RNA genomes and are carried by arthropod vectors from zoonoses, and human involvement is often incidental. Such viruses are often termed **arboviruses**, although this is an imprecise classification that includes two groups of viruses not closely related by other criteria.

The symptoms of encephalitis in wild animals can be difficult to measure, but several equine encephalitis viruses are known to cause serious disease in horses. Often the symptoms of viral encephalitis in humans are drowsiness, mild malaise, and sometimes coma. These mosquito-borne encephalitis viruses do not usually directly invade neural tissue itself, but rather infect supporting tissue. The host response to this infection and resulting inflammation leads to the observed neurological symptoms.

Since tissue at the periphery of neural tissue is the primary target for such encephalitis virus infections, the infection can be resolved and complete recovery will ensue, provided that the host's immune defenses work properly. During the disease's symptomatic period, lethargy and malaise of infected individuals make them vulnerable to other environmental hazards, including infection

with other pathogens. But provided these risks are avoided by means of proper care, the disease generally resolves.

While humans are often accidental targets for encephalitis viruses, it is not clear that symptoms of the disease in humans have any major role in virus spread. As with all arthropod-borne diseases, transmission is by ingestion of blood-associated virus found during the viremic stage of infection, and the behavioral effects are incidental. Still, it may be that the lethargy manifested during active disease makes infected animals more easily bitten by arthropods, and perhaps this is a factor in natural transmission.

Viral infections of the liver (hepatitis)

Diseases of the liver hold a special place in many types of medicine, both because of the important physiological role of this organ and because all circulating blood and lymph pass through the liver frequently. A number of different and unrelated viruses target the liver; these are collectively known as *hepatitis viruses*. All hepatitis viruses cause liver damage that can be devastating to the infected host. Liver failure due to hepatitis infections is a major reason for liver transplantation. Further, a number of these viruses establish persistent carrier states in which virus is present for many months or years following infection. Currently, there are five reasonably well-characterized human hepatitis viruses: A, B, C, delta (D), and E. The severity of the disease caused and the sequelae vary with each.

Hepatitis A

This virus is related to poliovirus. It is spread by contaminated water or food, and causes a potentially severe but controllable loss of liver function and general malaise. Proper medical care will generally result in full recovery of liver function and full clearance of virus from the host, with effective immunity against reinfection. A relatively effective hepatitis A vaccine is available for individuals at risk of infection.

Hepatitis B

Hepatitis B virus is related to but clearly distinct from retroviruses. Unlike the situation with hepatitis A, the B virus is spread mainly through blood, and primary infection is followed by persistent viremia and liver damage. Hepatitis B infection is a special risk to medical personnel owing to the possibility of transmission by needle stick from contaminated blood, and is also a virus endemic among intravenous drug users, commercial sex partners, and their customers. The disease is endemic in Southeast Asia where the virus can be spread from mother to infant by birth trauma.

Infection can lead to symptoms of acute infection or can be asymptomatic, and can be resolved by recovery. Unfortunately, a large number of infected individuals go on to become asymptomatic chronic carriers of the virus. Indeed, chronic hepatitis B infections are a leading factor in certain human liver cancers (carcinomas) prevalent in Southeast Asia. A third form of the hepatitis B (**fulminant infection**) is marked by rapid onset of extensive liver damage and often death.

Hepatitis C

Hepatitis C virus (also called *non-A/non-B hepatitis virus*) is caused by a virus that has some general relationships to a large group of plant, animal, and bacterial viruses, including poliovirus and hepatitis A virus. The virus is transmitted by contaminated blood and blood products, and is thought to cause as much as 25% of worldwide acute hepatitis infections. There is no current evidence of its

being efficiently spread by arthropod vectors, but this possibility cannot be ruled out. Unlike those infected with hepatitis A, a significant proportion of victims do not mount an effective immune response to the infection and have chronic infection that can last for many years with resulting accumulated liver damage.

Hepatitis D

Hepatitis delta (D) virus is, as mentioned, a defective virus in that it cannot replicate without the aid of another virus, the hepatitis B virus. Despite this requirement, it is not particularly prevalent in Southeast Asia, a major center of hepatitis B infection. Hepatitis D and B coinfection in the same individual does not lead to a much higher incidence of acute or chronic liver disease than does infection with hepatitis B alone. In contrast, infection of a person previously infected with hepatitis B is often correlated with acute disease followed by chronic virus secretion and **cirrhosis** of the liver.

Hepatitis E

Like hepatitis A virus, hepatitis E is spread by contaminated water and possibly by food. It is found throughout the world and has caused significant epidemics in India and Russia through problems with drinking water. The disease caused is usually mild, but can have high mortality rates in pregnant women. Recovery from acute infection is generally complete, and there is no evidence of chronic infection following the acute phase.

QUESTIONS FOR CHAPTER 4

1 The disease subacute sclerosing panencephalitis (SSPE) is a complication that may follow infection with measles virus. Discuss the possible mechanisms occurring during development of this rare disease.

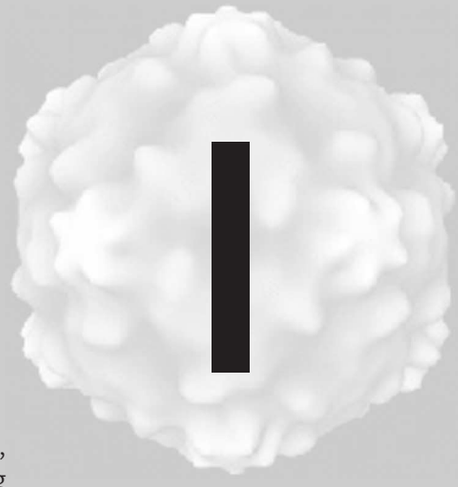
2 What features of pathogenesis are shared by measles virus, varicella-zoster virus, and variola virus?

3 What are some of the unique features of infection by rabies virus?

4 What features distinguish an acute from a persistent infection?

5 Distinguish encephalitis produced by herpesvirus from that resulting from infection with an arbovirus such as La Crosse encephalitis virus.

Problems



PART I

1 This part described the various patterns of viral infection that can be observed, among them acute, persistent, and latent. What common features may exist among these three types of infection? What are the distinguishing characteristics of each of these three types of infection?

2 The five hepatitis viruses have the same tissue tropism (the liver) and yet each is in a different virus family. One of them (hepatitis D or the delta agent) is actually a defective virus, sometimes called a subviral entity.

a In the table below, indicate the mode of transmission of each of these agents:

Agent	Transmitted by
Hepatitis A virus	
Hepatitis B virus	
Hepatitis C virus	
Hepatitis D (delta) agent	
Hepatitis E virus	

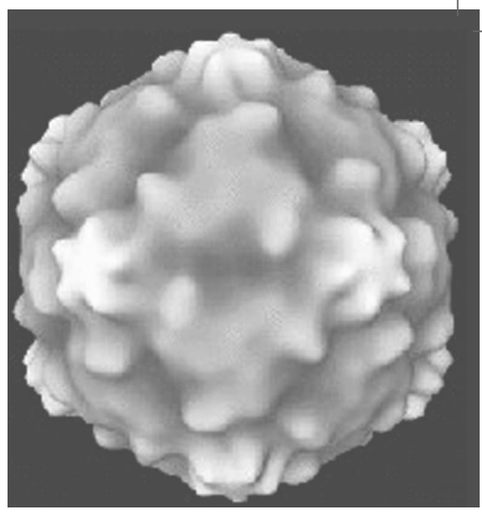
b What functions of the liver may allow all of these agents to have a common tissue tropism, despite their differing modes of transmission?

3 As part of a larger project, you have been given five unknown viruses to characterize. Your job is to determine, given the tools at your disposal, the host range and tissue tropism of these unknown viruses. You will be using two kinds of cells: human and mouse. In each case you have a cell line that grows continuously in culture and is therefore representative of the organism, but not of a particular tissue (human: HeLa cells; mouse: L cells). In addition, you have cells that are derived from and still representative of specific tissues: muscle or neurons. For each virus, you have an assay system that indicates if the virus attaches to ("+") or does not attach to ("–") a particular type of cell. Using the data in the table below, determine, if possible, the host range and tissue tropism of each unknown virus.

	Human			Mouse		
Virus	HeLa	Muscle	Neuron	L	Muscle	Neuron
#1	+	–	–	–	–	–
#2	+	+	–	+	+	–
#3	–	–	–	+	+	+
#4	–	–	–	–	–	–
#5	+	–	+	–	–	–

Here is the report form you will send back with your results. Indicate with a check mark (✓) what your conclusions are for each of the unknown viruses.

				Virus		
		#1	#2	#3	#4	#5
Host range	Human					
	Mouse					
	Both					
	Neither					
Tissue tropism	Muscle					
	Neuron					
	No tropism					
	Cannot be determined from data					



Additional Reading for Part I

Note: see Resource Center for relevant websites.

Domingo, E., Webster, R.G., and Holland, J.J., eds. *Origin and Evolution of Viruses*. San Diego: Academic Press, 1999.

Morse, S.S. Examining the origins of emerging viruses. In Morse, S.S., ed. *Emerging Viruses*. New York: Oxford University Press, 1993: chapter 2.

McNeill, W. Patterns of disease emergence in history. In Morse, S.S., ed. *Emerging Viruses*. New York: Oxford University Press, 1993: chapter 3.

Oldstone, M.B.A. *Viruses, Plagues, and History*. New York: Oxford University Press, 1998.

Scheld, W.M., Armstrong, D., and Hughes, J.M., eds. *Emerging Infections*, vol 1 and 2. Washington: ASM Press, 1998.

Shope, R.E., and Evans, A.S. Assessing geographic and transport factors and recognition of new viruses. In Morse, S.S., ed. *Emerging Viruses*. New York: Oxford University Press, 1993: chapter 11.

DeFilippis, V.R., and Villarreal, L.P. An introduction to the evolutionary ecology of viruses. In Hurst, C.J. *Viral Ecology*. New York: John Wiley, 1999: chapter 4.

Villarreal, L.P. On viruses, sex, and motherhood. *Journal of Virology* 1997;71:859–65.

Nathanson, N. Epidemiology. In Fields, B.N., and Knipe, D.M., eds. *Virology*, 4th edn. New York: Raven Press, 2001: chapter 14.

Preston, R. *The Hot Zone*. New York: Random House, 1994.

Ahmed, R., Morrison, L.A., and Knipe, D.M. Persistence of viruses. In Fields, B.N., and Knipe, D.M., eds. *Virology*, 3rd edn. New York: Raven Press, 1995: chapter 8.

Fenner, F.J., Gibbs, E.P.J., Murphy, F.A., Rott, R., Studdert, M.J., and White, D.O. *Veterinary Virology*, 2nd edn. San Diego: Academic Press, 1993: chapters 4, 6, 7, 8, and 9.

Nathanson, N., and Tyler, K.L. Entry dissemination, shedding, and transmission of viruses. In Nathanson, N., ed. *Viral Pathogenesis*. Philadelphia: Lippincott-Raven, 1997: chapter 2.

Haase, A.T. Methods in viral pathogenesis: tissues and organs. In Nathanson, N., ed. *Viral Pathogenesis*. Philadelphia: Lippincott-Raven, 1997: chapter 19.

Smith, A.L., and Barthold, S.W. Methods in viral pathogenesis: animals. In Nathanson, N., ed. *Viral Pathogenesis*. Philadelphia: Lippincott-Raven, 1997: chapter 20.

Lemon, S.M. Type A viral hepatitis. In Gorbach, S.L., Bartlett, J.G., and Blacklow, N.R., eds. *Infectious Diseases*. Philadelphia: WB Saunders, 1998: chapter 90.

Koff, R.S. Hepatitis B and hepatitis D. In Gorbach, S.L., Bartlett, J.G., and Blacklow, N.R., eds. *Infectious Diseases*. Philadelphia: WB Saunders, 1998: chapter 91.

Koff, R.S. Hepatitis C. In Gorbach, S.L., Bartlett, J.G., and Blacklow, N.R., eds. *Infectious Diseases*. Philadelphia: WB Saunders, 1998: chapter 92.

Koff, R.S. Hepatitis E. In Gorbach, S.L., Bartlett, J.G., and Blacklow, N.R., eds. *Infectious Diseases*. Philadelphia: WB Saunders, 1998: chapter 93.

Baum, S.G. Acute viral meningitis and encephalitis. In Gorbach, S.L., Bartlett, J.G., and Blacklow, N.R., eds. *Infectious Diseases*. Philadelphia: WB Saunders, 1998: chapter 158.

Porterfield, J.S., and Htraavik, T. Encephalitis viruses. In Webster, R.G., and Granoff, A., eds. *Encyclopedia of Virology*. New York: Academic Press, 1994.

Baer, G.M., and Tordo, N. Rabies virus. In Webster, R.G., and Granoff, A., eds. *Encyclopedia of Virology*. New York: Academic Press, 1994.

Shope, R.E. Rabies-like viruses. In Webster, R.G., and Granoff, A., eds. *Encyclopedia of Virology*. New York: Academic Press, 1994.

Fan, H., Conner, R.F., and Villarreal, L.P. *The Biology of AIDS*. Boston: Jones and Bartlett, 1989.

Rotbart, H.A. Viral meningitis and the aseptic meningitis syndrome. In Scheld, W.M., Whitley, R.J., Durack. D.T., eds. *Infections of the Central Nervous System*. New York: Raven Press, 1991.

Prusiner, S.B., Tellingm, G., Cohen, G., DeArmond, S. Prion diseases of humans and animals. *Seminars in Virology* 1996;7:159–74.