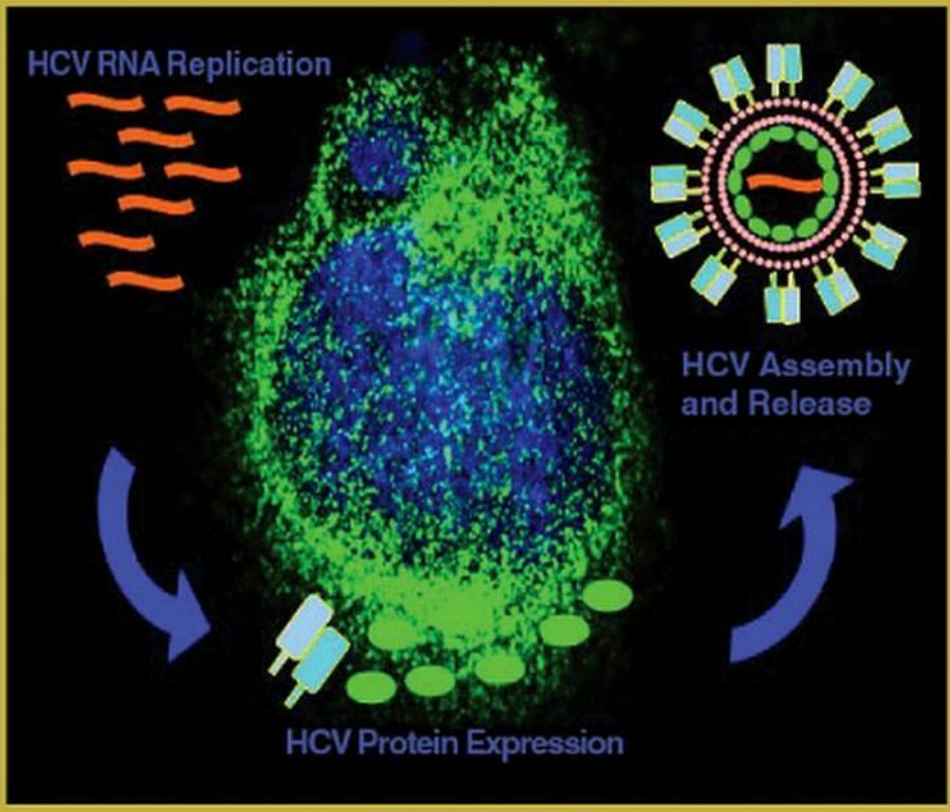
Advances in VIRUS RESEARCH



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Karl Maramorosch
Aaron J. Shatkin
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CHAPTER 1

The Pathogenesis of Poliomyelitis: What We Don't Know

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Abstract

Poliomyelitis has long served as a model for studies of viral pathogenesis, but there remain many important gaps in our understanding of this disease. It is the intent of this review to highlight these residual but important questions, in light of a possible future moratorium on research with polioviruses. Salient questions include: (1) What cells in the gastrointestinal tract are initially infected and act as the source of excreted virus? (2) What is the receptor used by mouse-adapted strains of poliovirus and how can some polioviruses use both mouse and primate receptors? (3) What determines species differences in susceptibility of the gastrointestinal tract to polioviruses? Why cannot PVR transgenic mice be infected by the natural enteric route? (4) Why are neuroadapted polioviruses unable to infect nonneural cells? (5) What is the role of postentry blocks in replication as determinants of neurovirulence? (6) What route(s) does poliovirus take to enter the central nervous system and how does it cross the blood–brain barrier? (7) Why does

poliovirus preferentially attack lower motor neurons in contrast to many other neuronal types within the central nervous system? (8) Does cellular immunity play any role in recovery from acute infection or in vaccine-induced protection? (9) In which cells does poliovirus persist in patients with γ-globulin deficiencies? (10) Is there any evidence that poliovirus genomes can persist in immunocompetent hosts? (11) Why has type 2 poliovirus been eradicated while types 1 and 3 have not? (12) Can transmission of vaccine-derived polioviruses be prevented with inactivated poliovirus vaccine? (13) What is the best strategy to control and eliminate vaccine-derived polioviruses?

I. INTRODUCTION

Poliomyelitis has served as a model for studies of viral pathogenesis, beginning soon after the virus was isolated by Landsteiner and Popper (Flexner, 1931; Landsteiner and Popper, 1909). Since 1990, the development of transgenic rodent models and the ready manipulation of the viral genome have provided new approaches to polio pathogenesis. Beginning about 2000, it was perceived that the world was on the verge of global eradication of poliovirus, leading to proposals for a permanent moratorium on poliovirus research (Dowdle *et al.*, 2006; Thompson *et al.*, 2006). Thus, it is timely to review our knowledge of pathogenesis while opportunity may still exist to conduct research with wild polioviruses.

Surprisingly, there remain many important gaps in our understanding of the pathogenesis of poliomyelitis, and it is the intent of this review to highlight these residual but important questions (Minor, 2004). The interested reader may wish to consult several excellent recent discussions by leading researchers (Mueller *et al.*, 2005; Ohka and Nomoto, 2001; Racaniello, 2006).

II. SEQUENTIAL STEPS IN THE SPREAD OF INFECTION

The general outlines of the sequential events in an infection with poliovirus (Fig. 1) were delineated by Bodian, Sabin, and others in the 1950s (Bodian, 1955a; Sabin, 1956). Polio is an enterovirus that is ingested and travels through the gastrointestinal tract where it can initiate infection at several sites, including the tonsils and Peyer's patches of the small intestine. From the initial sites of entry, the virus travels to the draining lymph nodes where it replicates further and spreads via the efferent lymphatic vessels and thoracic duct to enter the bloodstream. In some instances, virus spreads to the central nervous system (CNS) and rarely (estimated 1 case

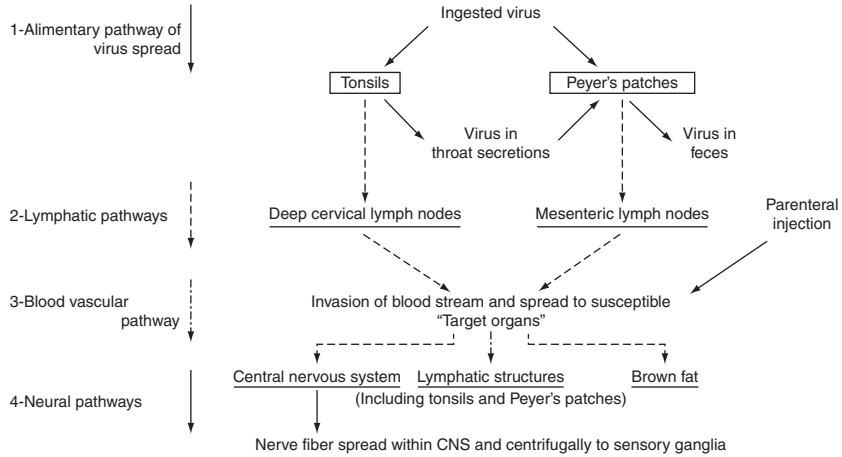

FIGURE 1 The sequential events in poliovirus infection in chimpanzees. Boxes indicate primary sites of implantation while the secondary and tertiary sites of multiplication are underlined [from Bodian D. (1955a). Emerging concept of poliomyelitis infection. Science 122, 105-108. Reprinted with permission from AAAS].

per 100–200 infections) leads to permanent flaccid paralysis. Infected humans shed poliovirus in the pharyngeal secretions and feces, usually for 2–8 weeks, implying that virus replicates in the intestine. Presumably, virus contaminates the hands of the infected person and is transmitted by hand to hand contact to the next person in the chain of infection. There is little published information on the relative importance in transmission of pharyngeal versus fecal shedding that could be relevant to the impact of polio vaccines on herd immunity (see below).

Poliovirus can spread in a susceptible host by either of two different routes, viremia or the neural pathway. The dominant route of spread depends upon the strain of virus. All polioviruses are neurotropic and most primary isolates are also pantropic (enterotropic and viremogenic) as shown in Fig. 2. A few neuroadapted strains behaved as obligatory neurotropes, defined by experimental data of the kind shown in Table I (Nathanson and Bodian, 1961).

A. Questions unanswered: Cellular sites of replication

Many significant details about the sequential steps in infection remain unanswered. There is considerable evidence that poliovirus invades the gastrointestinal tract by transcytosis via microfold (M) cells that express the poliovirus receptor (PVR) on their surface. *Ex vivo* fragments of human Peyer's patches have been reported to endocytose poliovirus

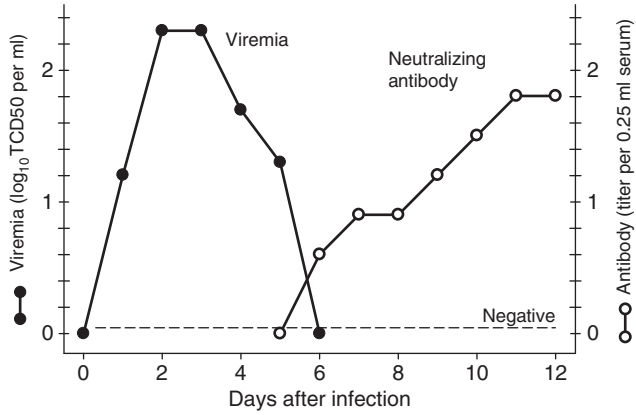

FIGURE 2 Viremia in experimental poliomyelitis. In this model, cynomolgus monkeys were infected by intramuscular injection of Mahoney virus, a virulent strain of wild type 1 poliovirus [after Nathanson and Bodian (1961), with permission].

TABLE I Different tropism of two strains of poliovirus, the neuroadapted MV (mixed virus) and the viremogenic Mahoney virus

	Neuroadapted MV strain		Viremogenic Mahoney strain	
	Control	Nerve block	Control	Nerve block
Paralysis	25/26	0/11	19/19	18/20
Site of initial paralysis				
Injected leg	24	–	3	5
Other	1	–	16	13
Incubation to paralysis (median)	5 days	–	7 days	7.5 days

After injection into the gastronemius muscle, the MV strain spreads only by the neural route, causes initial paralysis in the injected limb, and is impeded by a neural block, while the viremogenic Mahoney strain spreads by viremia, does not cause localized initial paralysis, and is not impeded by nerve block. Neural block was achieved just prior to virus injection by freezing the innervating sciatic nerve with dry ice proximal to the site of virus injection [after Nathanson and Bodian (1961), with permission].

and similar observations have been made in a human monolayer culture containing M-like cells (Iwasaki *et al.*, 2002; Ouzilou *et al.*, 2002; Siciski *et al.*, 1990). Following transcytosis, one or more types of lymphoreticular cells are infected at the sites of primary infection. Although freshly isolated human blood monocytes are not very susceptible to infection (Eberle *et al.*, 1995; Freistadt and Eberle, 1996; Freistadt *et al.*, 1993), when cultured under conditions that promote differentiation into