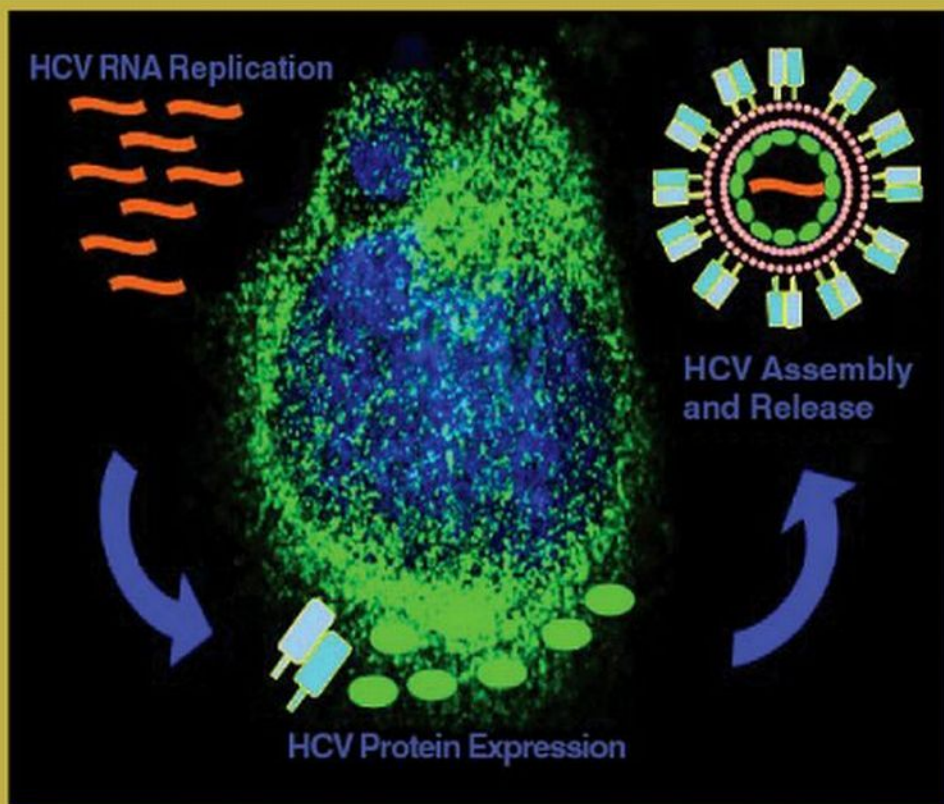


Advances in VIRUS RESEARCH



71

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CONTENTS

1. The Pathogenesis of Poliomyelitis: What We Don't Know	1
Neal Nathanson	
I. Introduction	3
II. Sequential Steps in the Spread of Infection	3
A. Questions unanswered: Cellular sites of replication	4
B. Questions unanswered: Neural invasion from the blood	6
III. Provocation Poliomyelitis	6
A. Questions unanswered: The mechanism of the provoking effect	7
B. Questions unanswered: Neural spread	10
IV. PVR, Tropism, and the Localization of Lesions	11
A. Questions unanswered: Receptor expression is necessary but not sufficient	11
B. Questions unanswered: Localization within the CNS	13
C. Questions unanswered: How poliovirus kills cells	15
V. Host Innate and Immune Response to Infection	15
A. Questions unanswered: The acquired immune response	16
VI. Immune Defenses and Viral Clearance: Mechanisms of Vaccine-Induced Protection	17
A. Primary infections	17
B. Secondary infection in immune hosts	18
C. Poliovirus serotypes	20
VII. Animal Models of Human Poliomyelitis	21
A. Questions unanswered: Determinants of primate susceptibility	22
B. Questions unanswered: The mechanism of rodent adaptation	23
C. Questions unanswered: PVR mice	25
D. Questions unanswered: The tropism enigma	26
VIII. Virulence of Polioviruses	26
A. Questions unanswered: Mechanisms of neurovirulence	32
B. Questions unanswered: Viremia and virulence	32
C. Questions unanswered: Epidemiological properties of polioviruses	33
IX. How Does Poliovirus Persist?	34
A. Questions unanswered: Overt persistence of poliovirus	35
B. The post-polio syndrome and covert persistence of poliovirus	35

X. Eradication	36
A. Questions unanswered: Why is it so difficult to complete the global eradication of wild polioviruses?	37
XI. Vaccine-Derived Polioviruses and the Eradication Endgame	38
A. Questions unanswered: What strategy should be followed if wild polioviruses are eradicated?	39
XII. Reprise	41
Acknowledgments	42
References	42

2. Cutting the Gordian Knot—Development and Biological Relevance of Hepatitis C Virus Cell Culture Systems **51**

Judith M. Gottwein and Jens Bukh

I. Introduction	53
II. Genetic Heterogeneity of HCV—Genotypes, Subtypes, Isolates, and Quasispecies	54
III. The HCV Genome and Its Encoded Proteins	59
IV. Host Cell Factors Supporting the HCV Life Cycle	67
V. Consensus HCV cDNA Clones—Infectious in Transfected Chimpanzees	71
VI. The Replicon System—Autonomous HCV RNA Replication in Hepatoma Cell Lines	73
A. Identification of adaptive mutations led to more efficient replicon systems	74
B. The study of replicon systems led to identification of highly permissive Huh7 cell lines	78
VII. Pseudo-Particles Expressing the HCV Envelope Proteins (HCVpp)—A System for the Study of Viral Entry and Neutralization	79
VIII. The JFH1 Isolate—Generation of Cell Culture Derived HCV (HCVcc) in Full Viral Life Cycle Cell Culture Systems	82
A. The original and adapted JFH1 cell culture system	82
B. The J6/JFH1 cell culture system	87
C. Analysis of HCV buoyant density suggests a role of lipoproteins for the viral life cycle	89
D. Possible causes of special growth characteristics of JFH1 and J6/JFH1	91
E. Applicability of JFH1 and J6/JFH1 cell culture systems	92
IX. Perspectives for Further Development of HCV Cell Culture Systems	95
A. Adaptation of cell culture systems to yield higher viral titers	95
B. Cell culture systems for other HCV genotypes	95
C. Expansion of cell culture systems to different host cells	100
X. Conclusion—Implications of Novel Cell Culture Systems	103

Acknowledgments	104
References	104

3. Poxvirus Host Range Genes **135**

Steven J. Werden, Masmudur M. Rahman, and Grant McFadden

I. Introduction	136
II. Orthopoxvirus Host Range Genes	137
A. SPI-1	140
B. K1L	143
C. C7L	145
D. CHOhr	146
E. p28/N1R	147
F. B5R (ps/hr)	148
G. E3L	149
H. K3L	152
III. Myxoma Virus Host Range Genes	153
A. M-T2	154
B. M-T4	155
C. M-T5	155
D. M11L	157
E. M13L	158
F. M063	159
IV. Molluscum Contagiosum: An Extreme Example of Host Range Restriction	160
V. Conclusions	160
Acknowledgments	162
References	163

4. Receptor Interactions, Tropism, and Mechanisms Involved in Morbillivirus-Induced Immunomodulation **173**

Jürgen Schneider-Schaulies and Sibylle Schneider-Schaulies

I. Introduction	174
A. General aspects of MV- and morbillivirus-induced immunosuppression	176
B. Relationships between tropism of the virus, spread of infection, and immunosuppression	177
II. Leukopenia Associated with Morbillivirus Infections	181
III. Mechanisms and Consequences of T Cell Silencing in Morbillivirus Infections	183
IV. Receptors and Signaling Involved in Suppression of Cell Functions	186

V. Virus Interactions with DCs	190
A. Virus interference with DC functions in animal models	190
B. Experimental models and consequences of DC surface interactions with viral proteins	191
C. Consequences of infection on DC viability and function	192
VI. Conclusions and Perspectives	195
References	196

5. Lyssaviruses—Current Trends 207

Susan A. Nadin-Davis and Christine Fehlner-Gardiner

I. Introduction	208
II. Developments in Diagnostic and Surveillance Tools	209
A. Diagnosis	209
B. Viral typing	210
C. Evolutionary time frames	211
D. Modeling applications	212
III. Fundamental Aspects of Virus–Host Interactions	213
A. What is the basis for RABV pathogenicity?	214
B. Role of viral proteins	214
C. Role of host cell pathways	218
D. Considerations for future studies on rabies pathogenesis	222
IV. Reverse Genetics—Methodology and Applications	222
A. RABV vaccines	224
B. Vaccines for other diseases	225
V. Other Strategies for Rabies Vaccine Development	227
A. Adenovirus recombinants	227
B. DNA vaccines	228
VI. The Challenge of Rabies Biologics for Passive Immunity	230
VII. Novel Applications of RABV	231
A. Use as a neuronal tracer	231
B. Use of RABV proteins for molecular targeting	235
VIII. Concluding Remarks	236
References	237

<i>Index</i>	251
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Color plate section at the end of the book

CHAPTER 1

The Pathogenesis of Poliomyelitis: What We Don't Know

Neal Nathanson

Contents		
	I. Introduction	3
	II. Sequential Steps in the Spread of Infection	3
	A. Questions unanswered: Cellular sites of replication	4
	B. Questions unanswered: Neural invasion from the blood	6
	III. Provocation Poliomyelitis	6
	A. Questions unanswered: The mechanism of the provoking effect	7
	B. Questions unanswered: Neural spread	10
	IV. PVR, Tropism, and the Localization of Lesions	11
	A. Questions unanswered: Receptor expression is necessary but not sufficient	11
	B. Questions unanswered: Localization within the CNS	13
	C. Questions unanswered: How poliovirus kills cells	15
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VII.	Animal Models of Human Poliomyelitis	21
	A. Questions unanswered: Determinants of primate susceptibility	22
	B. Questions unanswered: The mechanism of rodent adaptation	23
	C. Questions unanswered: PVR mice	25
	D. Questions unanswered: The tropism enigma	26
VIII.	Virulence of Polioviruses	26
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	C. Questions unanswered: Epidemiological properties of polioviruses	33
IX.	How Does Poliovirus Persist?	34
	A. Questions unanswered: Overt persistence of poliovirus	35
	B. The post-polio syndrome and covert persistence of poliovirus	35
X.	Eradication	36
	A. Questions unanswered: Why is it so difficult to complete the global eradication of wild polioviruses?	37
XI.	Vaccine-Derived Polioviruses and the Eradication Endgame	38
	A. Questions unanswered: What strategy should be followed if wild polioviruses are eradicated?	39
XII.	Reprise	41
	Acknowledgments	42
	References	42

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

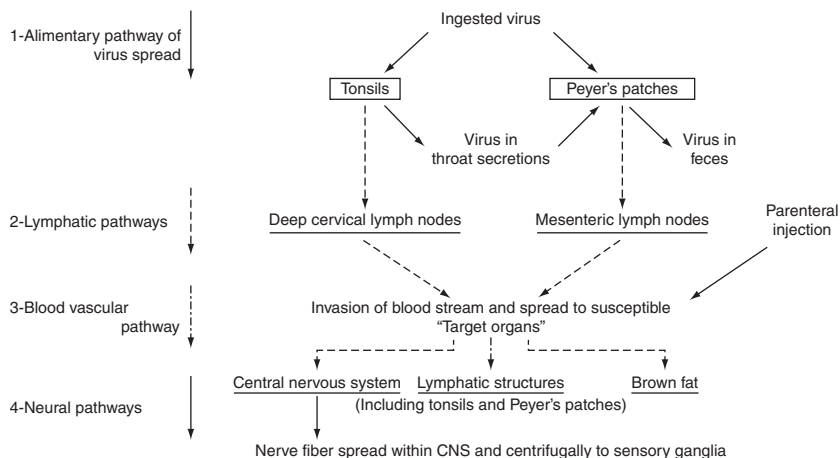


FIGURE 1 The sequential events in poliovirus infection in chimpanzees. Boxes indicate primary sites of implantation while the secondary and tertiary sites of multiplication are underlined [from Bodian D. (1955a). Emerging concept of poliomyelitis infection. *Science* 122, 105-108. Reprinted with permission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

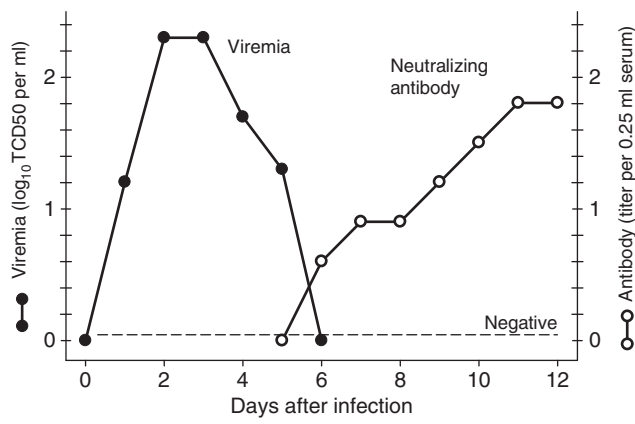


FIGURE 2 Viremia in experimental poliomyelitis. In this model, cynomolgus monkeys were infected by intramuscular injection of Mahoney virus, a virulent strain of wild type 1 poliovirus [after Nathanson and Bodian (1961), with permission].

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