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Measles Virus and Its Associated Diseases

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INTRODUCTION

Measles has long been recognized as one of the "inevitable traumas of childhood" (356). Although the advent of a successful vaccination program during the past decade has greatly reduced the incidence of "clinical" measles infections (24, 180, 198), research on measles virus has recently received increased attention. Much of this interest is due to the relative ease with which the virus can establish persistent infections in vitro and in vivo and to the fact that measles infections often involve the central nervous system. The results of recent studies have furthered our understanding of a variety of clinical conditions that may be due to persistent or latent infections with measles virus and other paramyxoviruses. For example, subacute sclerosing panencephalitis appears to result from a latent infection with measles or a variant of measles virus, and there is circumstantial evidence linking measles virus infections to multiple sclerosis and systemic lupus erythematosus.

Measles virus is a member of the family *Paramyxoviridae* (91). Two other viruses, canine distemper and rinderpest, share a close antigenic relationship with measles virus (107, 156, 269, 382, 395), and these three viruses form a distinct group, the genus *Morbillivirus* (91), which differs from the other paramyxoviruses in several respects. These viruses do not possess any virion-associated neuraminidase activity, nor do they adsorb to neuraminic acid-containing cellular receptors (57, 151, 249, 285, 380). In addition, measles virus is the only member of the genus that exhibits hemagglutination. This article will examine the properties of the virus

and attempt to link those properties to various diseases associated with the measles virion and its precursors.

STRUCTURE OF MEASLES VIRIONS

Physical Structure

Measles virions are composed of an outer lipoprotein envelope that is 10 to 20 nm thick and contains short projections, or spikes, and an internal, helical nucleocapsid (Fig. 1). Although the virus particles are roughly spherical in shape, they are very pleomorphic and range in size from 120 to 270 nm in diameter; larger particles have occasionally been observed (244, 380, 381). The virions are somewhat unstable and are easily disrupted when prepared for electron microscopy. Intact, infectious virions have been reported to have a buoyant density of 1.23 to 1.25 g/cm^3 (120, 260, 264). Therefore, as first proposed by Waterson (379), measles virions are morphologically similar to those of other paramyxoviruses, such as Newcastle disease virus (NDV), Sendai virus, and simian virus 5 (SV5), that have been studied in greater detail (for reviews, see [57, 60, 186]).

The major component of the virion is the linear, helical nucleocapsid that contains the genomic ribonucleic acid (RNA) (Fig. 2). Nucleocapsids have an RNA content of approximately 5% and a buoyant density of 1.28 to 1.30 g/cm^3 (120, 377, 378). When examined by electron microscopy, nucleocapsids appear as coiled rods with an outer diameter of 17 to 18 nm and a central, hollow channel measuring approximately 5 nm in diameter (256, 258, 377, 380, 381). When nucleocapsids are isolated without proteolytic enzymes, they have a loosely coiled, flexible appearance; when enzymatic treatment is employed, the nucleocapsids become tightly coiled and rigid (377). These changes have been correlated with alterations in the nucleocapsid protein (see below). The unit length of the nucleocapsid is approximately 1 μm, but they are fragile and fragment readily. Due to this breakage, nucleocapsids sediment heterogeneously between 200S and 300S in sucrose density gradients (120, 245, 256, 377). Aberrant circular and elongated forms of nucleocapsids have also been reported (363).

Structural Components

Genomic RNA. The presence of RNA within measles virus particles was first reported in 1964 (260, 321). This RNA was subsequently shown to be a single-stranded molecule with an approximate molecular weight of 6.2×10^6 and a sedimentation coefficient of approximately 52S in sucrose density gradients (120, 127, 245, 326). Thus, measles RNA appears to be slightly larger than the 50S RNA isolated from other paramyxoviruses (see [57, 186]). However, Hammarskjöld and Norrby (127) reported that measles RNA migrates with other paramyxovirus RNAs in polyacrylamide gels, and Winston et al. (392) found that measles RNA cosedimented with NDV 50S RNA in sucrose density gradients. Like the RNA of other paramyxoviruses, measles virus RNA has a base composition that is rich in uracil (377, 398).

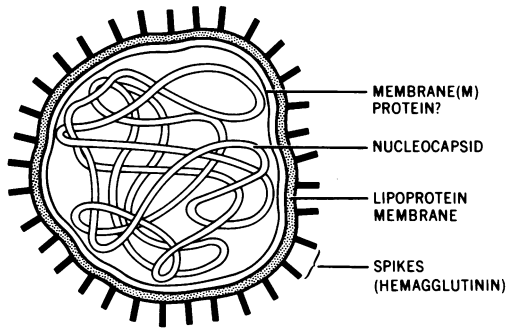

FIG. 1. *Schematic diagram of a representative measles virion.*

Structural proteins. Polyacrylamide gel electrophoresis (PAGE) studies have demonstrated that measles virions are composed of six polypeptides whose approximate molecular weights range between 38,000 and 79,000. In general, the gel patterns that have been obtained for measles virions closely resemble those of canine distemper and rinderpest, and they also exhibit certain similarities to the other paramyxoviruses (41, 120, 372, 376). The major structural protein (molecular weight $\simeq$ 60,000) is the nucleocapsid polypeptide (120, 239, 376). When nucleocapsids were extracted from infected cells by the use of proteolytic enzymes, two smaller polypeptides (molecular weights = 24,000 and 38,000) were obtained. The cleavage of the nucleocapsid polypeptide into subunits has been correlated with its changes in appearance as observed by electron microscopy (377).

The identity of the remaining polypeptides is uncertain. The smallest polypeptide (molecular weight $\simeq$ 38,000) may be analogous to the M (membrane) protein of the other paramyxoviruses (239); this protein is beneath the lipid bilayer of the virus envelope and probably functions in maintaining the integrity of the virus particle (see reference 57). The second largest polypeptide (molecular weight $\simeq$ 70,000) is associated with the nucleocapsid, and it has been proposed that this polypeptide may be part of the transcriptase complex (239).

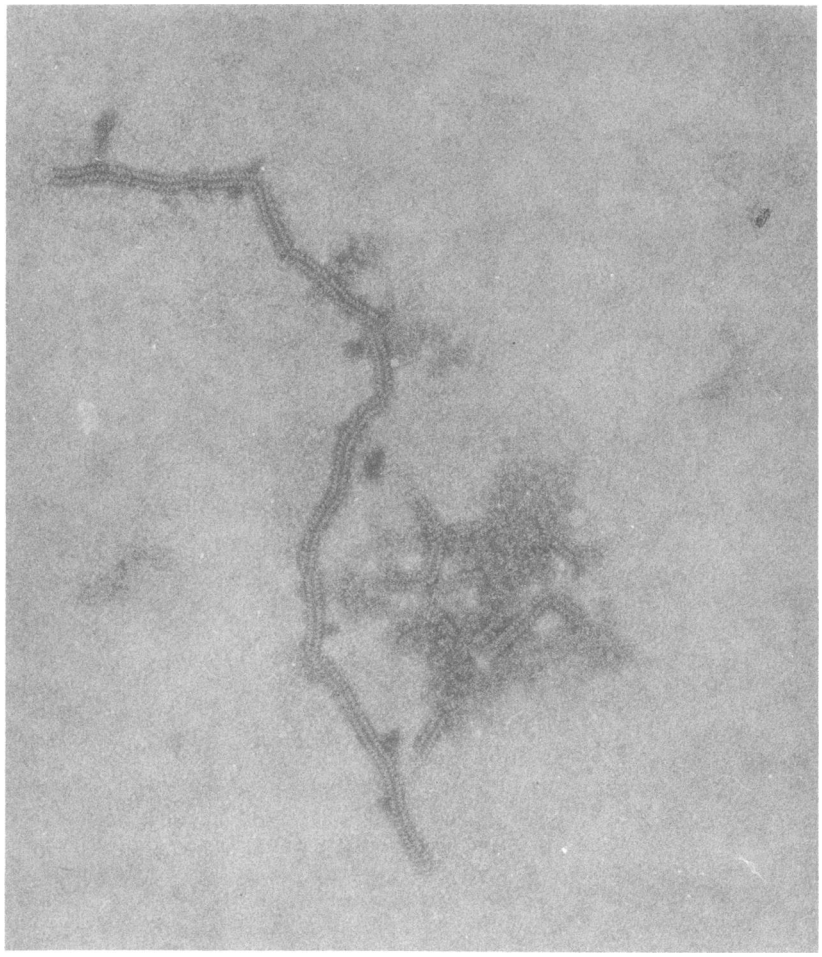

FIG. 2. *Electron micrograph of nucleocapsid fragments spontaneously released from measles virions (×90,000; courtesy of Ronald Glaser).*

There are conflicting data concerning the identity and number of glycoproteins in measles virus. The surface of the envelope is involved in the hemagglutinating (HA), hemolytic (HL), and cell fusion properties of the virion (380). In other paramyxoviruses, these activities, as well as neuraminidase activity, are associated with two surface glycoproteins that form the spikes (see reference 57). There is evidence that the HA and HL activities of measles virus may also be associated with two polypeptides: particles that contain primarily HA activity can be separated in CsCl from infectious virions that contain both HA and HL (251, 258, 260); the HL component is more sensitive than the HA to thermal inactivation and treatment with Formalin, ether, or Tween 80–ether (255, 259); and HA and HL are antigenically distinct (85, 254, 257, 259). However, only one glycoprotein that corresponds to the largest structural polypeptide (molecular weight = 79,000) has been identified in several strains of measles virus (30, 41, 128, 239, 376).

In contrast, Hall and Martin (120) have identified in their measles preparations two glycopolypeptides, number 2 (molecular weight = 69,000) and number 4 (molecular weight = 53,000), that form the spikes and that can be removed by proteolytic digestion. When these proteins were further purified and characterized, HA activity was associated with the larger glycoprotein, whereas HL and cell fusion activities required both glycoproteins and membrane lipids (121, 122). However, Mountcastle and Choppin (239) were unable to detect a second glycoprotein in this same strain of measles vi-

rus. The reasons for these discrepancies remain to be resolved.

VIRUS-CELL INTERACTIONS

Cytopathic Effects

The first major advance in modern measles virus research occurred in 1954 when Enders and Peebles (88) successfully isolated measles virus in vitro by inoculating primary human and simian kidney cells with clinical specimens. Shortly thereafter, it was reported that the virus could also replicate in established cell lines and chicken embryos (100, 231), and plaque assay systems were developed (152, 371). It has subsequently been shown that measles virus can be grown in a variety of primary and continuous cell lines, although the best results are obtained with cells of human and simian origin (225).

As first described by Enders and Peebles (88), measles virus infections usually produce very distinctive cytopathic effects (CPE) that are characterized by the formation of multinucleated giant cells (syncytia) (Fig. 3). The chromatin assumes a marginal position and is replaced by intranuclear inclusions; eosinophilic inclusions develop in the cytoplasm. In addition, chromosomal aberrations and breakage have been observed in measles virus-infected cells (65, 97, 207, 247).

The formation of syncytia ("fusion from within") is dependent upon the presence of a virus-specific protein on the surfaces of infected cells. This "fusion factor" may be identical to the HL (51, 57). This is supported by some of the data that have been obtained for the temperature-sensitive mutants of measles virus. Some of these mutants fail to produce syncytia at the nonpermissive temperature, and the infected cells do not contain detectable amounts of the HL polypeptide, as determined by immunofluorescence techniques (132). Fusion factor is also associated with the virion itself. Syncytia formation ("fusion from without") can occur within 5 h when cells are infected at high mul-

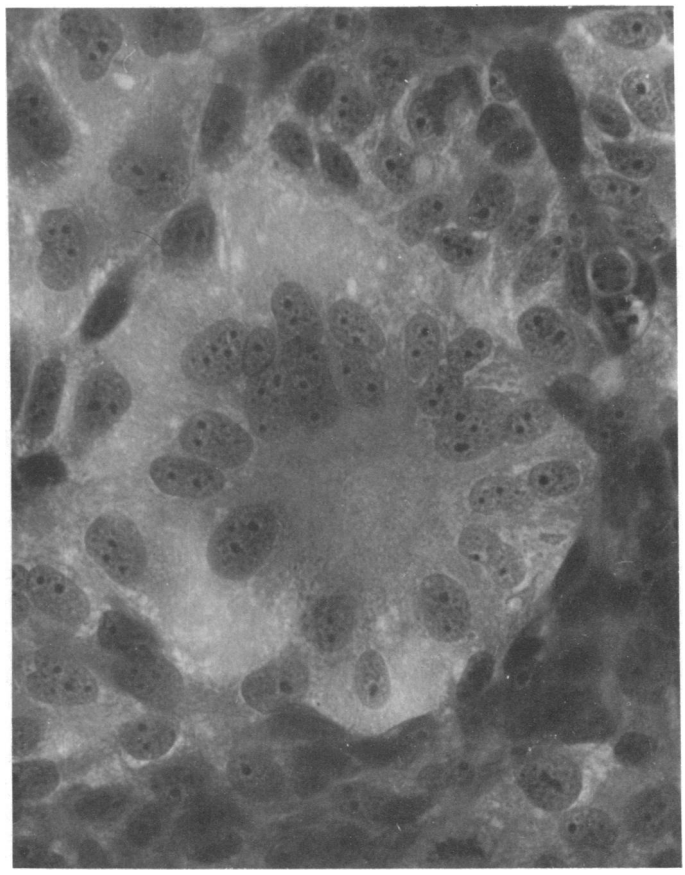

FIG. 3. *Photograph of measles virus-induced syncytia formation in monkey kidney cells (hematoxylin and eosin).*

tiplicities (51). Noninfectious measles virus particles, such as ultraviolet-irradiated virions (367) and the "small HA particles" (251, 325) can also produce syncytia. Therefore, "fusion from without" can occur even in the absence of virus replication.

A second type of measles virus CPE ("strand-forming") has also been described. This is characterized by the appearance of spindle-shaped or stellate cells that have long and irregular cytoplasmic processes (266). Strand-forming CPE often occurs when cells are infected with undiluted, passaged inoculum, and infectious virus yields are often greatly reduced (266, 277).

Interactions with Erythrocytes

Measles virions are capable of several interactions with erythrocytes and the development of HA (248, 249, 284, 314). HA-inhibition (250, 314) and HL (255, 284) assays have greatly enhanced the ease with which virus replication could be monitored and quantified. As first reported by Peries and Chany (284), measles virus will agglutinate only monkey or baboon erythrocytes. Unlike HA by other paramyxoviruses, that by measles virus is maximal at 37°C and, because of the lack of neuraminidase, there is no spontaneous elution of the virions. In addition, HA is not influenced by pH changes between 4.8 and 10.1, and there is a minimal requirement for the presence of mono- and divalent ions (57, 248, 380). In some instances, however, HA titers can be enhanced when HA assays are carried out in buffers containing 0.8 M ammonium sulfate (i.e., salt-dependent HA) (110, 327, 346). Some strains of measles virus will agglutinate only in the presence of high salt (30, 110), and virus can be eluted by resuspending the erythrocytes in isotonic buffer (327).

Late in infection, after the HA protein has been inserted into cellular membranes, infected cells can hemadsorb erythrocytes (16, 74, 191, 313) (Fig. 4). However, some strains of measles virus, especially those that demonstrate salt-dependent HA, produce syncytia that do not hemadsorb (30, 317, 346). Measles virions can also lyse erythrocytes. Although HL and HA activities can be differentiated, HA appears to be a necessary prerequisite for HL (30, 255). HL activity is optimal at pH 8.0 and is markedly inhibited by Ca^{2+} ions (255).

REPLICATION

A generalized growth curve for measles virus is shown in Fig. 5. Only the relative times of appearance of virus-specific functions are depicted. Many variables, such as virus strain, host cell, and multiplicity of infection, have significant influence on the severity of the infection, the length of time required for the appearance of progeny virions, and the amount of virus ultimately produced (71, 245, 294, 305). The replication cycle can be divided into three major events that will be discussed in the following sections.

Adsorption, Penetration, and Uncoating

The virions attach to cellular receptors, presumably by means of the spikes on the virus envelope. One such receptor for measles virus is a glycoprotein that contains only low levels of sialic acid (80). Based upon studies with other paramyxoviruses, it is thought that the virions enter the cell either by "viropexis" (phagocytosis) (61) or by fusion of the viral membrane with the cellular membrane (238). Either process is ultimately followed by the release of nucleocapsids into the cytoplasm (i.e., uncoating), and it is likely that both occur during infection (57).

Synthesis of Virus-Specific Macromolecules

RNA. Relatively little is known about the replication of measles virus RNA in comparison to the other paramyxoviruses; however, available data suggest that measles is similar, if not identical, in this respect (for reviews, see references 57, 186, 188). Virus RNA synthesis is initiated shortly after infection (294); synthesis of virus proteins and genomic RNA, which is encapsidated into progeny nucleocapsids, then occurs. All of these events appear to take place within the cytoplasm of infected cells. However, it has been reported that measles RNA can be isolated from the nuclear fraction of infected cell extracts (49, 328), and that treatment of infected cells with actinomycin D causes a reduction in genomic RNA and protein synthesis (124, 329) and in virus yields (329). More recently, Follett et al. (99) studied the growth of measles virus in enucleated cells; the yields of infectious virus were greatly reduced compared with the results obtained in nucleated cells, but virus-specific polypeptides were synthesized in the enucleated cells.

The measles virus genome, like that of other negative-strand viruses, cannot function as a message; the synthesis of smaller, complementary RNAs (plus strands) is necessary. Although enzymatic activity has not been reported for measles virus, other paramyxoviruses contain a virion-associated RNA polymerase (transcriptase) which is associated with the nucleocapsid (155, 310, 350). Virus-specific RNA transcripts, which have approximate sedimentation values of 18S, 22S, and 35S, have

been detected in measles virus-infected cells (50, 184, 392, 398). These RNAs are comlementary to genomic RNA (123, 398), and they have been isolated in association with five different size classes of polyribosomes (184). The complementary RNAs of other paramyxoviruses contain polyadenylic acid tracts at the 3'-termini (224, 390) and are functional in cell-free protein-synthesizing systems (67, 187). Therefore, at least a portion of the complementary RNA functions as message for the synthesis of virus-specific proteins.

At a later stage in the replication cycle, the virus must transcribe complete 52S (plus) strands to serve as templates for the formation of 52S (minus-strand) genomes. It is not known whether the enzyme that is necessary for genomic RNA replication (replicase) represents an alternate function of the transcriptase or whether a separate enzyme or enzyme subunit is required (188). The synthesis of Sendai (293, 311) and mumps (82) 50S RNA is inhibited by cycloheximide, suggesting that genomic RNA replication requires continued protein synthesis. However, there are conflicting reports on whether the synthesis of measles 52S RNA is inhibited by cycloheximide (124, 184). It is apparent that the progeny molecules are rapidly encapsidated, since free paramyxovirus RNA has not been observed in infected cells (188).

Virus antigens and structural proteins. All of the current biochemical data on the nature of measles virus proteins have been obtained from studies on the structural proteins of the virion. To date, there have been no published reports on the synthesis of measles virus proteins in infected cells using techniques such as PAGE. Studies using metabolic inhibitors have shown that protein synthesis can be detected within 3 h after infection and that it reaches a peak long before the appearance of infectious virions (294).

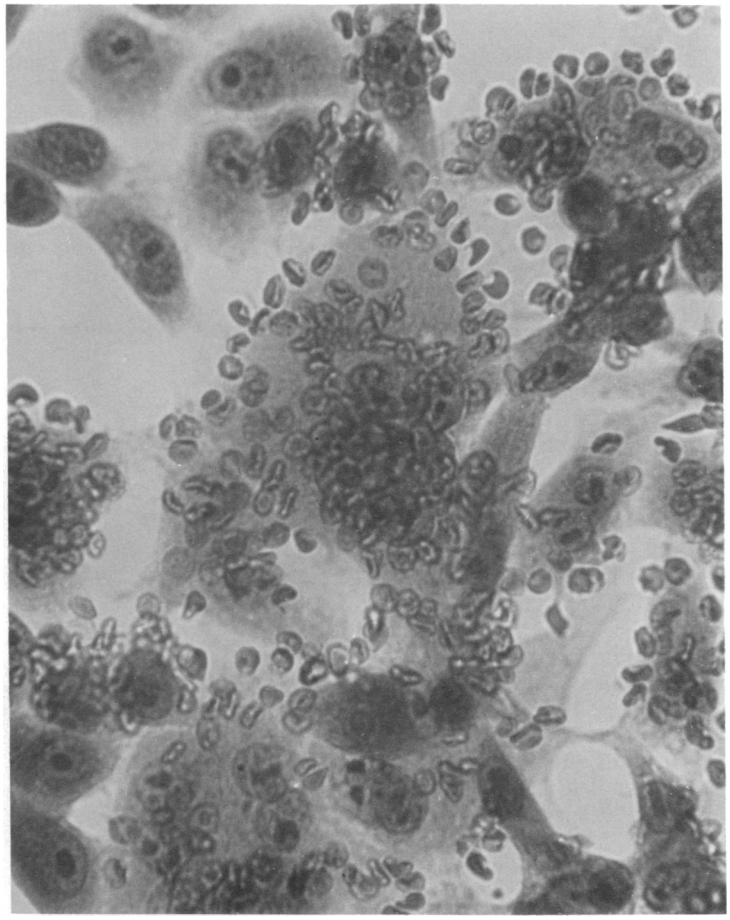

FIG. 4. *Photomicrograph of hemadsorption of African green monkey erythrocytes to measles virus-infected cells (hematoxylin and eosin).*

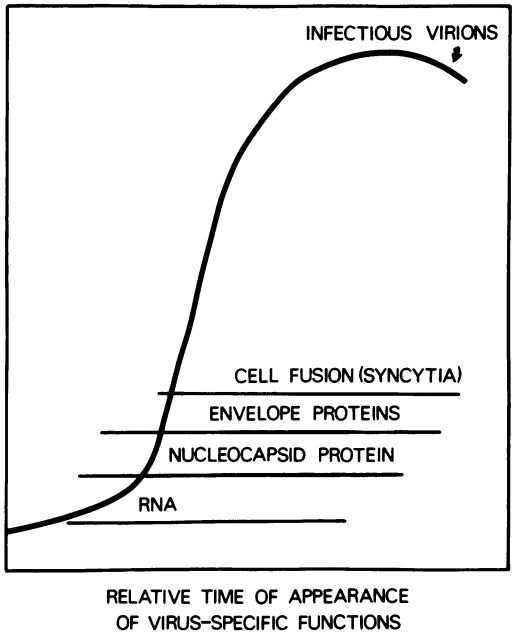

FIG. 5. *Major events in measles virus replication. The relative times of onset of various virus-specific functions are shown in comparison to an ideal one-step growth curve measuring the production of infectious progeny virions.*

The development of virus-specific antigens within infected cells has been studied with immunofluorescence techniques (Fig. 6). Within a few hours after infection, virus-specific antigen (nucleocapsid) can be detected in the cytoplasm. The fluorescence first appears as fine dots, or granules, in the perinuclear region, and, as the infection proceeds and the intensity of staining increases, this fluorescence often completely encircles the nucleus. Ultimately, the nucleocapsid antigens become dispersed throughout the cytoplasm (212, 253, 306). Nucleocapsid antigens can also be detected in the nuclei of some cells; nuclear staining is most prevalent late in infection, and the antigens are associated with nuclear inclusion bodies (88, 212, 253, 272, 306).

The envelope antigens (HL and HA) first appear in the cytoplasm at one pole of the nucleus. In contrast to the nucleocapsid antigen, these antigens produce a meshwork of fine threads of fluorescence (253). Later in infection, the antigens become dispersed throughout the cytoplasm and preferentially accumulate in the cytoplasmic membrane (87, 253, 306). In studies with infected cells that have been treated with trypsin (i.e., stripped of surface antigens), the HA first appears at the poles of cells and then spreads over the surface of the cellular membrane (86). The budding of nucleocapsids to form infectious virions occurs at those sites on the membrane where virus-specific antigens are present (78).

Assembly and Release of Progeny Virions

Much of the current information on measles virus maturation and assembly has been derived from electron microscope studies. Early in infection, intracytoplasmic inclusion bodies composed of nucleocapsid filaments are formed. The inclusion bodies tend to accumulate in the perinuclear region of the cell and are most frequently observed in multinucleated giant cells (78, 244, 245, 273) (Fig. 7). The cell membrane subsequently becomes altered in appearance to more closely resemble the virus envelope; the membrane becomes thicker and more electron dense, and spikes appear. The nucleocapsids assemble beneath these areas of the cellular membrane and align in parallel arrays. The membrane then protrudes (buds) to form progeny virions (78, 244, 245, 273).

Late in infection, nucleocapsids can also be observed in the intranuclear inclusion bodies in which they often aggregate in crystalline arrays (15, 244, 273, 300). It has not been established whether these nucleocapsids serve any function in the normal replication events. The cytoplasmic and nuclear forms of nucleocapsids

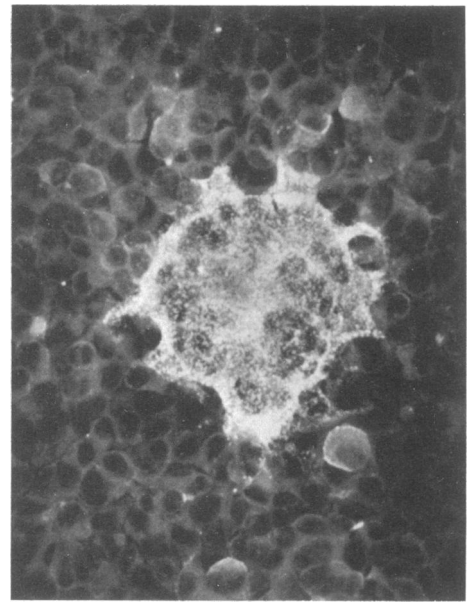

FIG. 6. *Photomicrograph of immunofluorescent staining of a measles virus syncytium.*

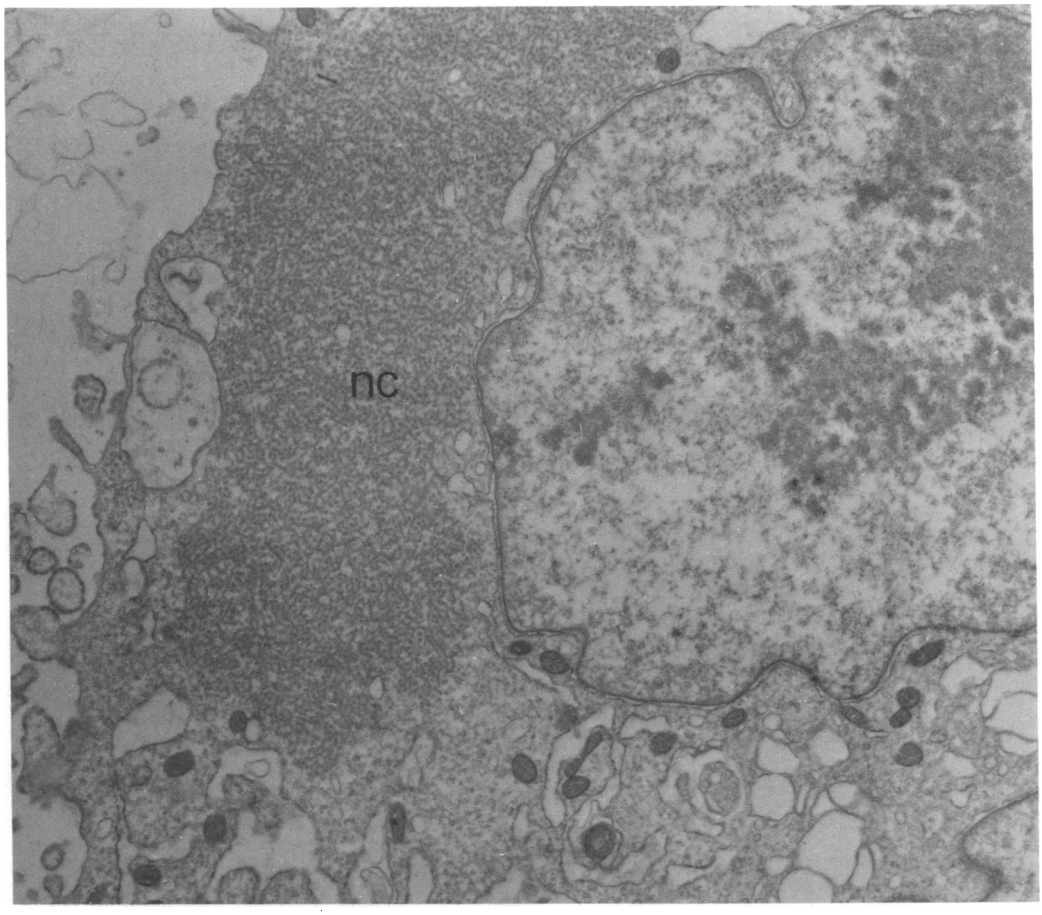

FIG. 7. *Electron micrograph of aggregated measles virus nucleocapsids (nc) in the cytoplasm of an infected monkey kidney cell (×15,600; courtesy of Ronald Glaser).*

may be different; the cytoplasmic filaments often have a granular, "fuzzy" appearance, whereas the nuclear form appears to be smooth (78, 273). Nucleocapsids are rarely observed in both the nucleus and cytoplasm of the same cell, and there is no evidence that they migrate from one site to another. In addition, when the nuclear nucleocapsids are the predominant form in an infected culture, little virus budding from the cell surface is observed and low yields of infectious virus are obtained (245).

GENETICS (TEMPERATURE-SENSITIVE MUTANTS)

Relatively little is known about the genetics of measles and other paramyxoviruses (57). Several groups of investigators have isolated temperature-sensitive (ts) mutants of measles virus, and the preliminary characterization of these mutants has been initiated (25, 132, 396). The measles genome, which has a molecular weight of 6.2×10^6, could theoretically code for 6 to 10 average-sized polypeptides. Since six structural polypeptides have been identified, there should be at least six complementation groups of ts mutants.

Haspel et al. (132) and Bergholz et al. (25) have each isolated three complementation groups of ts mutants, and together these mutants represent five different complementation groups (29; see also Table 1). Twenty-two of the 24 mutants isolated by Haspel et al. (132) are classified as RNA negative (RNA^-) because they do not synthesize virion RNA or detectable virus antigens at the nonpermissive temperature (39°C). Seven of the nine mutants isolated by Bergholz et al. (25) are also RNA^-.

The RNA^+ mutants are defective in functions associated with the envelope proteins. Cells that were infected with the mutants isolated by

TABLE 1. *Properties of the ts mutants of measles virus*[a]

Complementation group[b]	Mutant[c]	Virus-specific functions at 39°C					Neuro-virulence in newborn hamsters
		RNA	Nucleo-capsid antigen	Hemad-sorption	Hemoly-sin anti-gen	Syncytia	
Parental virus		+	+	+	+	+	+
A	*ts*-1	−	−	−	−	−	−
B	*ts* 2-7, *ts* 101, 102, 104-106, 108-112, 115-124 (*ts*-8)[d]	−	−	−	−	−	−
C	*ts*-107	−	−	−	−	−	±
D	*ts*-9	+	+	−		±	−
E	*ts*-103, 113, 114	+	+	+	−	−	+

[a] Modified from Breschkin et al. (29).
[b] Complementation groups determined by Breschkin et al. (29).
[c] Mutants designated *ts* 1-9 were isolated by Bergholz et al. (25); *ts* 101-124 were substituted for the alphabetical designations (A-X) used by Haspel et al. (132).
[d] Although *ts*-8 synthesizes virus-specific RNA and antigens, it appears to belong to complementation group B.

Bergholz et al. (25) did not hemadsorb or produce syncytia, but virus-specific antigens were detected in the cytoplasm and nuclei. The other group of RNA^+ mutants synthesizes virion RNA, nucleocapsids, and HA, but does not form syncytia in infected cells, and no HL antigen could be detected by immunofluorescence tests (132). Some of the properties of these mutants are summarized in Table 1.

INTERFERON

During in vitro and in vivo replication, measles virus induces the synthesis of interferon (72, 73, 142, 235, 286). The sensitivity of the virus to inhibition by interferon was demonstrated in studies showing that virus yields and plaque size were enhanced when infected cells were treated with low concentrations of actinomycin D to inhibit interferon synthesis (12, 235, 305). Recently, it was found that the ts mutants of measles virus fail to induce interferon (221). Unlike the ts mutants of other viruses, e.g., reovirus (201), Sindbis virus (14), and Semliki Forest virus (213), the ts mutants of measles virus do not induce interferon when grown at either the permissive or nonpermissive temperature. In addition, mixed infections involving pairs of ts mutants that produced positive complementation failed to induce detectable amounts of interferon.

Further studies have suggested that the inability of these ts mutants to induce interferon may be a result of the selection of virus particles that were unable to induce interferon before mutagenesis. For example: (i) one wild-type revertant of measles virus (28) was also unable to induce interferon; and (ii) stocks of wild-type virus appear to consist of a mixture of virus particles, some of which induce interferon and some of which do not. In fact, the strain of measles virus from which most of the ts mutants were derived (132) consists primarily of non-interferon-inducing particles (222).

The ability (or inability) to induce interferon may be partially under the genetic control of the virion; plaque-purified clones of measles virus that induce interferon generally retain this characteristic upon subsequent passage. However, some cellular factor(s) may also be involved, because some non-interferon-inducing clones regain the ability to induce interferon, and others produce greater amounts of interferon after serial passage in Vero cells (222). An interesting observation is that these various clones cannot be distinguished by any criteria other than interferon induction. The influence that interferon may have on virulence is not known.

PERSISTENT AND LATENT INFECTIONS

Experimental Persistent Measles Virus Infections

Measles virus shares with other paramyxoviruses the ability to establish persistent infections in vitro (57, 309). Although measles infections usually result in widespread cellular destruction, surviving cells can be selected and subcultured and are often found to be persistently infected. One feature that is common to most persistent infections is that the cultures are usually refractory to superinfection with measles virus, but are readily infected with other, unrelated viruses (229, 252, 319). However, the types of persistently infected cultures that can be obtained vary considerably.

One type of persistent infection produced by measles virus is the "carrier culture," in which low levels of infectious virus are continually shed into the medium (20, 106, 109, 130, 220, 232, 234, 252, 318, 319). Such cultures have been maintained for long periods of time (319). Persistent measles infections can be established by growing infected cells in the presence of specific antisera (171, 318), and there is no evidence that they can be "cured" by continued growth in the presence of antisera (109, 252, 320). In addition, interferon induction does not appear to be responsible for the low virus yields (106, 252, 307). There has been one report that cells persistently infected with canine distemper virus release into the medium a factor that selectively inhibits the replication of canine distemper and measles virus (357).

The second type of persistent infection is more latent in that the cultures fail to produce infectious virus. However, these "non-yielder" cultures contain virus-specific intracellular antigens (190, 228, 320) and all size classes of virus-specific RNA (392). It should be noted that distinctions between these two types of persistent infections are not absolute. For example, by subculturing carrier cultures of HeLa cells in the presence of antiserum, Rustigian (319, 320) was able to isolate clones that failed to release infectious virus. Conversely, persistently infected hamster embryo fibroblasts that did not produce infectious virus (190) began to spontaneously release low levels of infectious virus when the cells were repeatedly passaged (130).

At present, the factors involved in the establishment and maintenance of persistent infection are not well understood. It has been postulated that both defective interfering particles and ts mutants may be involved (154, 298; see also following sections). Questions concerning the status of the virus and the virus genome in persistently infected cells have been of particular interest.

Infectious virus has been recovered from cells persistently infected with measles virus by cocultivating the cells with a different, susceptible cell line (190), and increased virus yields have been obtained by lowering the incubation temperature (130, 252) or by treatment with drugs (e.g., iododeoxyuridine, bromodeoxyuridine, or mitomycin C) (307). In another cell line, treatment with inhibitors produced an increase in the number of cells that would hemadsorb, but infectious virus was not detected (98, 228). It has been suggested that the virus may be blocked at a late stage in the replication cycle, since studies demonstrated that infectious virus could be recovered within 6 h after co-cultivation, even in the presence of RNA and protein inhibitors (130). Based on the alterations that occur in nucleocapsids after proteolytic digestion, it has also been proposed that similar changes may occur in persistently infected cells and may result in the accumulation of nucleocapsids that are unable to become incorporated into virions (240, 377). However, there is no evidence that such alterations occur in cultures persistently infected with SV5 (241).

It has also been suggested that the genetic information of non-oncogenic RNA viruses may become integrated into the cellular genome. There have been reports that DNA isolated from cells persistently infected with measles virus contains sequences that are homologous to measles genomic RNA (403, 404). In studies with another paramyxovirus, respiratory syncytial virus, DNA extracted from persistently infected cultures was used to transfect susceptible cells, which subsequently released infectious virus (347). Finally, a variant of NDV that was isolated from persistently infected cells was found to contain reverse transcriptase activity (103). Integration would provide an effective mechanism for maintaining persistent infections; however, other investigators have been unable to confirm these results (143), and their validity remains doubtful.

Role of Defective Particles in Persistent Infections

It has been suggested that defective interfering (DI) particles may be associated with persistent infections in vitro and with certain subacute or latent infections in vivo (154). DI particles, which often arise during serial, undiluted passage of virus stocks, are particles that contain only a part of the virus genome. Although DI particles require the presence of nondefective, homologous virus for their replication, they concomitantly interfere with the replication of standard virus (153). The generation of DI particles has been described for several paramyxovirus systems (189, 192, 312), and there is evidence that DI particles can arise in measles virus infections. However, the association of DI particles with persistent measles virus infections has not been well documented.

The presence of defective measles virus particles was first suspected when species of RNA smaller than 52S genomic RNA were detected in preparations of measles virions (50, 326, 392). In addition, smaller nucleocapsids (<200S), which contain smaller species of RNA, can be isolated from infected cells (183, 185). The smaller RNAs and nucleocapsids can be produced by undiluted passage and can be eliminated when virus stocks are plaque purified

and passaged at low multiplicities (50, 185). It has been reported that undiluted passage of measles virus results in strand-forming CPE that is associated with a decrease in infectious virus yields, and that different types of virus-specific products, such as "noninfectious HA," are produced (261, 266, 267, 277).

More recently, Hall et al. (125) reported the isolation of more slowly sedimenting particles from undiluted, passaged measles virus stocks; these particles demonstrate many of the characteristics of DI particles. The virus stocks containing these DI particles were able to establish persistent infections in Vero cells. In addition, smaller nucleocapsids that contain 20S RNA have been isolated from HEp-2 cells that are persistently infected with measles virus (133).

Role of ts Mutants in Persistent Infections

There is a growing body of evidence which suggests that ts mutants may participate in the establishment and/or maintenance of persistent infections and that they may be selected for during the course of a persistent infection (298). ts mutants have been isolated from cells persistently infected with Sendai virus (243) and NDV (296, 297, 349, 400), and there have been two reports of the isolation of ts mutants of measles virus.

Knight et al. (190) established a "non-yielder" culture of hamster embryo cells which began to spontaneously produce small amounts of virus after 18 passages at 37°C. Greater yields of virus were obtained when the cultures were incubated at 33.5°C, and the virus that was released was ts (130). Gould and Linton (109) also isolated a ts mutant from HEp-2 cells persistently infected with measles. When shifted to 39°C, the cultures appeared to be "cured," based upon the loss of detectable intracellular antigens. However, the antigens reappeared when the cells were shifted back to 37°C and subcultured.

The function(s) of ts mutants in persistent infections remain to be determined. There is evidence from some systems that ts mutants may act in a fashion analogous to DI particles by interfering with the replication of wild-type virus. This suggests that ts mutants may have some type of selective advantage in persistent infections, since there is no evidence for the subsequent isolation of wild-type revertants (297, 401). Additional work is required to determine whether this observation is also true of persistent measles infections: the ts mutant of measles virus was lost from persistently infected hamster cells during further subculture and was replaced with a virus that replicated like the wild-type virus (130, 307).

COMPLICATIONS ASSOCIATED WITH MEASLES INFECTIONS

Measles virus is ubiquitous and "classic" measles infection is a common disease of childhood. The virus is highly infectious, spreads by droplet infection, and initiates infection in the upper respiratory tract of susceptible individuals. The clinical course of the infection has been well documented (e.g., see references 38, 180, 182).

Symptoms that indicate neurological involvement develop in many patients during measles virus infections. It is not known whether the virus invades the central nervous system during the secondary viremic phase. However, during the peak of clinical illness, at least 50% of measles patients have transient electroencephalographic changes (105, 180). Aberrant electroencephalographic patterns have also been detected after vaccination with live virus (274). In addition, significant increases in the number of lymphocytes in cerebrospinal (CSF) fluid (CSF pleocytosis) have been noted in at least 10% of measles patients (180, 268).

A wide variety of complications can arise during measles infections. These most commonly include upper respiratory disorders and secondary bacterial infections. However, other severe, and often fatal, problems can occur (19; see below and Table 2).

Central Nervous System Disorders

Central nervous system complications, the most common of which is encephalomyelitis (230), may occur after the acute phase of measles infection has begun to subside. A number of other neurological sequelae, such as toxic encephalopathy (230, 368), myelitis (230, 368), thrombophlebitis of cerebral veins (368), hemiplegia (230, 368), optic neuritis (230, 368), polyradiculoneuritis (i.e., Guillain-Barré syndrome) (209, 230), and Bell's palsy (292), have also been reported.

Approximately 0.1% of measles patients develop encephalomyelitis (180). The onset is often marked by seizures, altered states of consciousness, and coma, and the appearance of CSF pleocytosis, an increase in CSF protein levels, and electroencephalographic abnormalities (84, 180, 200). The major histological findings include a striking perivascular demyelination which predominates in the white matter, perivascular cuffing, congestion, and hemorrhage. Cytoplasmic, and less often, intranuclear eosinophilic inclusion bodies and multinucleated giant cells have been observed (2, 18, 180). The prognosis for encephalomyelitis pa-

TABLE 2. *Some complications and disorders related to measles infections*

1. Complications due to the primary virus infection:
e.g., bronchiolitis
keratoconjunctivitis
giant cell pneumonia
2. Secondary bacterial infections:
e.g., otitis media
bronchopneumonia
3. Nervous system disorders:
encephalomyelitis
more rarely, e.g., toxic encephalopathy
optic neuritis
Gullian-Barré syndrome
4. Disorders due to slow (or latent) measles infection:
subacute sclerosing panencephalitis
multiple sclerosis?
(systemic lupus erythematosus)?
5. Disruption of immune system:
transient depression of delayed cutaneous hypersensitivity
exacerbation of other diseases, e.g., tuberculosis
autoimmune diseases, e.g., systemic lupus erythematosus?

tients is poor; between 10 and 30% of all cases are fatal and 20 to 50% of the survivors develop significant motor, intellectual, sensory, or emotional sequelae (4, 6, 180, 200).

Giant Cell Pneumonia

Giant cell pneumonia (Hecht's giant cell pneumonia) is a rare, almost uniformly fatal, interstitial pneumonitis that is characterized by the presence of multinucleated giant cells in the respiratory tract (89, 180). Most cases occur in children with malignancies or other severe disorders. In some instances, giant cell pneumonia has developed in patients who had no symptoms of measles (89, 237); in others, it has developed after the subsidence of a normal measles virus infection (27, 236). Measles virus persisted for long periods of time in the few survivors, and their antibody response was impaired; no antibody formation was detected in fatal cases (236, 237).

Disruption of the Immune System

Measles virus infections can affect the immune system in a variety of ways and may involve both humoral and cellular responses. In general, measles virus infections and vaccination with live virus result in antibody formation and lifelong immunity (180, 386). Cell-mediated immunity is also important, because children with agammaglobulinemia respond "normally" to measles infections and are immune to reinfection in the absence of detectable antibody formation (38, 108).

There are relatively few immunological complications that can be directly attributed to measles virus infections. Massive aggregations of thymocytes, formation of large syncytia in the thymus, and destruction of the thymic cortex were repoted in several fatal cases of measles (391).

Measles infections may temporarily impair cell-mediated immunity. In 1908, von Pirquet (373) first noted the loss of the tuberculin response in children with measles. In fact, cases of tuberculosis are often reactivated or exacerbated during measles infections (23). The transient loss of delayed cutaneous hypersensitivity to tuberculin and other antigens has been well documented in measles patients and individuals vaccinated with live virus (34, 96, 227, 407). Some insight into this phenomenon has been provided by in vitro studies. There are several reports that lymphocytes infected with measles virus or obtained from measles patients are unreactive, as determined by their inability to mount a proliferative response to stimulating antigens, such as phytohemagglutinin (PHA) (95, 351, 406, 407). More specifically, helper T-cell function appears to be suppressed in measles virus-infected mice (219). However, other investigators have found that lymphocytes respond normally to PHA (112, 270, 316), and that the response can depend on the antigen employed (96), or on the individual lymphocyte donor (81).

Measles virus can infect lymphocytes in vitro and, depending upon the experimental conditions, both lytic and persistent infections have been obtained (20, 173, 234, 352). Measles virus-infected cells can be lysed in the presence of specific antibody and complement (139, 140, 172, 233), but under conditions that strip virus antigens from the cell's surface (antigenic modulation), infected cells become resistant to im-

mune cytolysis (170, 171). In addition, radioimmunoassays have shown that HeLa cells persistently infected with measles virus bind two to three times less antibody than do acutely infected cells, and these cells are also more resistant to antibody-mediated lysis (174). Osunkoya et al. (271) observed that when lymphocytes from measles patients were stimulated with PHA, measles antigens could be detected by immunofluorescence. These observations provide support for the hypothesis that infected lymphocytes may help to disseminate the virus during infection (38). The survival of infected lymphocytes and other cells in the presence of specific antibody could have implications for certain chronic disorders, such as subacute sclerosing panencephalitis, that have been attributed to measles (see below).

Measles virus may also be involved in autoimmune reactions. It has been proposed that measles encephalitis results from an autoimmune response, because encephalitis develops subsequent to antibody formation, infectious virus is not detectable in the central nervous system or spinal fluid, and there are some similarities between measles encephalitis and experimental allergic encephalitis (4, 180, 200, 279). It is now thought that encephalitis involves central nervous tissue destruction as a result of virus replication, since occasional giant cells are observed in the brain, and virus has been recovered from brain tissue by cocultivation techniques (4, 18, 361). More recently, however, there have been findings which suggest that measles virus could be involved in autoimmune diseases, such as systemic lupus erythematosus (see below).

NEUROLOGICAL DISEASES LINKED TO MEASLES INFECTIONS

Subacute Sclerosing Panencephalitis

Subacute sclerosing panencephalitis (SSPE) is a rare, inflammatory, slowly degenerative disease of the central nervous system which occurs in children and young adults (for reviews, see references 164, 280, 359). The disease progresses through four fairly well characterized stages, beginning with a decrease in intellectual skills and terminating in an almost complete loss of cortical function and death (160, 164, 402). SSPE produces a diffuse encephalitis of the white and grey matter (i.e., panencephalitis) characterized by demyelination, large increases in fibrous astrocytes, infiltration by lymphocytes and plasma cells, perivascular cuffing, and pronounced neuronal loss in the cerebral cortex (164, 167, 278, 359, 402). Eosinophilic Cowdry type A intranuclear inclusion bodies in nerve cells and especially in oligodendroglial cells are also characteristic of SSPE. These bodies were first noted by Dawson (68) in 1933, leading to his proposal that SSPE may be of virus origin. This observation was extended by Bouteille et al. (26) and numerous other investigators, who demonstrated that these inclusions consist of structures resembling paramyxovirus nucleocapsids (70, 101, 137, 176, 283, 342, 354, 355).

Subsequent studies implicated measles virus as the etiological agent of SSPE. It has been repeatedly demonstrated that the sera and CSF of SSPE patients have elevated titers of measles antibody, which increase to extremely high titers during the progression of the disease (35, 63, 64, 115, 150, 205, 287, 338). The ratio of serum to CSF antibody is low relative to the ratios for other virus antibodies, which has led to the proposal that antibody may be produced within the central nervous system (62, 66, 322, 365). In addition, immunofluorescence techniques were used to demonstrate measles virus antigens in brain sections of SSPE patients (63, 101, 205). Although attempts to directly isolate virus from brain material have not been successful, many investigators have recovered measles virus by co-cultivating SSPE brain biopsy material with susceptible cells (22, 52, 146, 147, 282, 358, 369). It has been suggested that SSPE may be a more systemic disease than is clinically apparent, since measles antigens have been detected in lung, kidney, and spleen biopsies, and measles virus has been recovered from the lymph nodes of some SSPE patients (149, 163, 164).

Epidemiological data have shown that more than 50% of SSPE patients had clinical measles infections before 2 years of age and that the clinical onset begins at the mean age of 10, resulting in an "incubation" period averaging 6 years (161, 339). Although these data suggest that SSPE may be due to a latent measles infection, the pathogenic mechanism(s) responsible for the onset of disease is not known. The early age at which SSPE patients contract measles suggests that an immature immune system or a heightened susceptibility to a measles virus variant could be contributing factors (33, 38, 161), and immunological abnormalities have been reported in some SSPE patients (5, 104, 196, 216, 355). It has also been proposed that SSPE may result from interactions between latent measles virus and another virus, and particles resembling papovaviruses (17, 195, 272) and herpesviruses (69) have been observed in some SSPE biopsies. Other investigators have reported correlations between SSPE and a second clinical infection; e.g., some SSPE patients

contracted chickenpox 1 to 6 months before the onset of SSPE (75), and there have been three reported cases of coincidental infections involving infectious mononucleosis and SPPE (92). Other viruses may also be capable of producing neurological syndromes almost identical to SSPE, as is the case with rubella virus (366, 387). However, the fact remains that the virus most frequently isolated from SSPE biopsies has been measles virus.

A major unresolved question concerns the nature of the SSPE isolates. Some of these viruses display characteristics that are different from those of "wild" isolates or vaccine strains of measles; others more closely resemble the vaccine strains; and still others are more like wild isolates. Some of the properties of these SSPE isolates are shown in Table 3.

Biochemical studies of genomic RNA, messenger RNA (mRNA), and nucleocapsids have demonstrated that the SSPE viruses are identical to measles (398, 399), but differences in the structural polypeptides and in the extent of homology between the genomes of SSPE and measles viruses have been reported. In one PAGE study, Schluederberg et al. (331) found that the structural polypeptides of an SSPE isolate were identical to those of measles, except that the smallest polypeptide migrated more slowly than the corresponding measles polypeptide. Yeh (398) reported that 18S measles RNA displayed only 60% homology to SSPE genomic RNA. In competition hybridization experiments, Hall and ter Meulen (123) found that measles mRNA competed 100% with SSPE mRNA when hybridized to measles genomic RNA, but only 90% competition was observed with SSPE genomes; these authors interpret the data to infer that the SSPE genome is identical to measles, but that it also contains 10% additional information. In addition, some of the SSPE viruses remain more cell associated and establish cell lines that fail to release infectious virus (39, 76, 79, 344, 369). Electron microscope studies have provided evidence that such infections may be maintained by cell-to-cell transmission of nucleocapsids (159, 344). All of these data tend to support the proposal that SSPE may be due to variants of measles virus, possibly defective variants unable to produce mature virions, and that such variants may be selected within the host during measles infections (126, 281, 301, 302).

Multiple Sclerosis

Multiple sclerosis (MS) is a subacute or chronic disease of young adults that usually follows a course of relapses and remissions over a period of years. Depending upon the individual, MS produces a variety of neurological symptoms (217, 279). The characteristic pathological features include multiple, sharply defined plaques of demyelination and fibrous gliosis (215). The cause(s) of MS is unknown. There is a large body of evidence which suggests that the demyelination in MS may be due to an autoimmune response (279). Based upon such factors as the age distribution curve and geographical distribution, epidemiological studies have suggested that MS may be caused by an infectious agent (1, 11, 32, 83, 295).

It has been suggested that an autoimmune response resulting in demyelination could be initiated by a persistent virus infection of brain tissue (93), and there is indirect evidence implicating measles virus. After the initial report by Adams and Imagawa (3) in 1962, several investigators have found high titers of measles antibody in the sera and CSF of MS patients (36, 37, 136, 262, 275, 276, 322, 323). As in SSPE, MS patients have low serum-to-CSF-antibody ratios, suggesting that the antibody in the CSF is produced within the central nervous system (323). In addition, structures that closely resemble paramyxovirus nucleocapsids have

TABLE 3. *Comparisons between SSPE isolates and wild or vaccine strains of measles virus*

1. Some SSPE isolates exhibit a host range in vitro like those of vaccine strains (126, 148); others are more restricted (126, 280, 358).
2. Some isolates grow slower and produce lower titers of infectious virus (358); others are more cytopathic and produce higher titers of virus than either wild or vaccine strains (126).
3. Some isolates remain cell associated and produce no infectious virus (39, 76, 79, 344, 369).
4. In neutralization tests, some SSPE isolates appear antigenically identical to wild and vaccine strains (148, 280); others are less reactive with antisera than either wild or vaccine virus (281).
5. In general, the SSPE isolates produce more nuclear antigens (nucleocapsids) than wild or vaccine strains (273, 358).
6. In electron micrographs of SSPE virus-infected cells, it is difficult to detect nucleocapsids in budding particles (273, 301).

been observed in MS brain sections (94, 246, 299, 303, 375). However, Shaw and Sumi (341) have noted similar nonvirus nucleocapsid-like structures in biopsies from patients with a variety of neurological disorders. In a recent immunofluorescence study, measles virus antigens were detected in intestinal biopsies from MS patients (226).

There have been many attempts to isolate virus from MS biopsies using the techniques employed to isolate measles virus from SSPE biopsies, but these have met with limited success. There have been reports that herpesvirus (116), measles virus (94), and a virus (6/94 virus) that is virtually identical to Sendai virus (193, 208, 360) have been isolated from MS brain material. Until these results can be confirmed, the question of whether these isolates represent laboratory contaminants remains to be answered (94, 388).

Recently, two groups of investigators obtained evidence that another, as yet unidentified, virus may be involved in MS. When extracts of MS material were injected into mice, a reduction in polymorphonuclear leukocytes was obtained; these extracts also caused a reduction in cell yields in vitro (46, 47, 48, 194). In addition, these investigators have shown the presence of a filterable agent (approximately 50 nm) that apparently grows to high titers in mice and that can be neutralized by sera from MS patients (135, 194). However, these observations require confirmation and extension before their significance can be evaluated.

OTHER DISEASES LINKED TO MEASLES VIRUS

Systemic Lupus Erythematosus

Systemic lupus erythematosus (SLE) is one of several autoimmune connective tissue disorders of unknown etiology. SLE occurs most frequently in young women and is characterized by fluctuating periods of remission and exacerbation. Although synovial and serous surfaces, skin, and kidney are the main targets, SLE can affect any organ of the body. The two most characteristic findings are lesions of the kidney glomerulus and thickening and necrosis of medium-sized arterioles (145, 223). Much of the current knowledge of SLE has been derived from studies of New Zealand black mice, which spontaneously develop signs similar to SLE. Based upon these studies, it appears that genetic susceptibility, a defective immune system, and viruses (both oncogenic and nononcogenic) are contributing factors (59, 158, 223, 364, 405).

In the search for a virus agent in SLE, evidence resembling that obtained for SSPE and MS has raised the possibility that measles virus is involved in SLE. Tubular structures resembling paramyxovirus nucleocapsids have been detected in the cytoplasm of endothelial cells from SLE patients (10, 77, 117, 181, 333, 348). Although these tubular structures are observed frequently enough to be of diagnostic value, other investigators have questioned whether these are of virus origin (59, 111, 119, 134, 144, 263, 290, 324). There has been one report that measles virus antigens were detected by immunofluorescence in SLE cells (10), and there are several reports that SLE patients have elevated measles virus antibody titers (10, 202, 214, 288, 289). Other reports have confirmed the presence of elevated measles antibody; however, antibody titers to a variety of other viruses were also found to be elevated, possibly as a consequence of alterations in the immunological reactivity in SLE patients (144, 289, 315). Finally, there has been one report that deoxyribonucleic acid from tissues of SLE patients contained sequences which hybridized with measles RNA (10). Therefore, although it seems likely that Ziff (405) is accurate in his proposal that SLE may be due to a chronic virus infection which in some way has an adjuvant effect on the immune response and thus results in auto-antibody formation, the role of measles (or any other virus) in SLE remains to be determined.

Other Autoimmune Diseases

Although SLE has been the most widely studied autoimmune disease, there have been reports of paramyxovirus nucleocapsid-like structures and elevated measles antibody titers in other connective tissue disorders. These include rheumatoid arthritis (202), polymyositis (58), scleroderma (263), Goodpasture's syndrome (263), Sjögren's syndrome (343), and Reiter's syndrome (288).

ANIMAL MODEL SYSTEMS

There have been many attempts to establish animal models to investigate measles virus infections and the associated neurological disorders. Measles virus causes encephalitis in many laboratory animals, such as hamsters (7, 162, 383, 393), mice (7, 157, 385), and monkeys (7, 265, 337), after intracerebral inoculation. The outcome of the disease in hamsters and mice is highly age dependent. Most newborns develop a rapidly fatal, acute disease. Some weanlings also develop acute disease, but most survive and develop a more chronic infection. Most adult animals survive without any symp-

toms, although some may develop acute disease (7, 42, 43, 45, 114, 138, 374).

The ts mutants of measles virus differ in their ability to produce encephalitis in newborn hamsters (Table 1). All of the mutants isolated by Bergholz et al. (25) were avirulent, as were 21 of the RNA^- mutants isolated by Haspel et al. (131, 132). Of the remaining mutants, the RNA^+ mutants were as virulent as the parental virus, although the mean survival time for the infected animals was increased (131). One RNA^- mutant (*ts*-107) that appears to be of intermediate neurovirulence also induces hydrocephalus at a high frequency (28, 129, 393); but it is likely that, under the appropriate conditions, most strains of measles virus can cause hydrocephalus (A. M. Breschkin and F. Rapp, unpublished observation). There is increasing evidence that several other paramyxoviruses may also induce hydrocephalus (168, 169, 345).

Persistent measles virus infections are receiving increasing attention because similar infections may be involved in clinical disorders in humans. There is evidence that persistent measles virus infections can be established in laboratory animals. Wear and Rapp (384) demonstrated that when newborn hamsters that had high levels of maternally derived antibodies were inoculated with measles virus, the onset of encephalitis was blocked; only 17% developed encephalitis as compared with a 100% incidence in unprotected animals. When the survivors were subsequently immunosuppressed with cyclophosphamide, 30% developed chronic neural involvement, and infectious measles virus could be recovered. A similar observation has been reported in monkeys inoculated with a brain-adapted strain of measles virus. The animals developed a "clinically silent" infection, but severe disease resulted after they were inoculated with cyclophosphamide (8).

Attempts have also been made to establish animal models for SSPE, but these have not been entirely successful. Intracerebral inoculation of SSPE virus or SSPE virus-infected cells produces encephalitis in hamsters (45, 165, 166, 204), ferrets (175, 177, 362), dogs (178), and mice (113). Although the animals develop some symptoms of SSPE, not all of the requisite symptoms have been reproduced in a single host, and some of the major pathological features of SSPE, such as demyelination, have not been observed. As with other strains of measles, the symptoms and severity of the disease in hamsters vary with age and the state of the immune system (42, 43, 44, 166).

Recent studies with monkeys have been more promising. Ueda et al. (370) reported preliminary evidence that subcutaneous inoculation of an African green monkey with a cell-associated SSPE isolate resulted in symptoms closely resembling SSPE in humans. Albrecht et al. (9) were able to produce chronic, progressive panencephalitis in rhesus monkeys by intracerebral inoculation with a cell-associated SSPE isolate. These animals exhibited many of the features of SSPE in humans, including the presence of high titers of measles antibody in the CSF and intracellular virus inclusions in the brain lesions. In addition, only those monkeys that had a history of natural measles infection (positive antibody titers) developed chronic disease; the nonimmune animals developed acute, rapidly fatal encephalitis.

MEASLES VACCINES

Since the introduction of measles vaccines in 1963, it has been estimated that 24 million cases of measles and 2,400 deaths have been prevented (21). Most of the vaccines presently in use were derived from one of the viruses isolated by Enders and Peebles (88), which has been designated the Edmonston strain. This virus was subsequently passaged 24 times in primary human kidney cells and 28 times in primary human amnion cells, and then adapted to growth in chicken embryos and chicken embryo cells (90). Some of the earliest vaccines were prepared from Formalin-inactivated Edmonston virus; however, these vaccines did not produce lasting immunity (102, 180). In addition, atypical, often severe measles infections have been reported in some children who were vaccinated with the killed vaccines and subsequently exposed to measles (24, 31, 102, 118, 242). In some instances, especially when children were revaccinated with live vaccines, delayed hypersensitivity reactions have occurred (40, 336).

The vaccines in use today contain live, attenuated measles virus. The first of these, Edmonston B, was derived by further passage of Edmonston virus in chicken embryos and chicken embryo cells (90, 179). However, it was found that the Edmonston B strain produced fever and/or rash in approximately 50% of all those vaccinated, although the side effects could be reduced by simultaneous administration of immunoglobulin G (199, 218). The Schwarz vaccine strain was developed by passing the Edmonston virus an additional 77 times in chicken embryo cells (334). This produced a vaccine that was more attenuated than the Edmonston B strain and that was less likely to cause side effects (334, 335). Another vaccine strain, Moraten ("more attenuated Edmonston"), was also developed by passing the Edmonston strain an additional 40 times in chicken embryo cells

(141). The use of these live vaccines appeared to produce lasting immunity, and relatively few complications were reported (54, 203), although there have been reports of children who developed SSPE after immunization with live virus (56, 203, 332).

In spite of the dramatic decrease in the incidence of measles during the past 14 years, sporadic outbreaks have continued to occur, even in supposedly immune populations. The three groups of individuals most often affected are: (i) those who were never immunized; (ii) those who received killed vaccines; and (iii) those who received live vaccines, but who did not seroconvert (55, 197, 198, 210, 291, 330, 394, 397). The reasons for live vaccine "failures" are varied, but the factors most often cited include: (i) the suppressive effects of maternal antibody in children vaccinated prior to 1 year of age (53, 197, 198, 210, 291, 308, 340, 397); (ii) the suppressive effect of simultaneous inoculation with vaccine and immunoglobulin G (13, 197, 198); (iii) loss of vaccine potency due to improper storage (197, 198, 206, 291); and (iv) administration of live vaccine within 1 month after killed vaccine (197, 198). The most common of these appears to be due to vaccination of children less than 1 year of age, and the latest guidelines suggest that no child should be vaccinated before age 15 months, except in the event of a measles outbreak (197).

Simply changing vaccination procedures may not solve all the problems. Questions have been raised concerning the ability of the attenuated vaccines to produce long-lasting immunity (389); measles antibody titers are directly related to the time interval after vaccination (21), and in one 14-year study, the mean antibody titers were lowest in children who had received live vaccines (198). Declining antibody titers may be a consequence of the reduction in natural measles and the subsequent lack of a natural booster effect (21). However, others have noted that previously immunized, seronegative children still demonstrate an anamnestic antibody response to a second vaccination or during reinfection, suggesting that the presence of an antibody response to measles may not be a reliable indicator of protection (211, 330, 389). The fact that such immunized children can be reinfected has caused the peak incidence of measles to shift from preschool children to adolescents (304, 397), some of whom develop atypical measles infections (53, 54, 330, 389). With the change in incidence and the lack of large-scale natural exposure, there are also adults in the population who lack measles immunity and severe, fatal measles infections have been reported in some individuals (304). Although the statement that the "outlook for the ultimate prevention and elimination of measles is bleak" (53) may be too pessimistic, the elimination of measles may be more difficult than once believed, and the course of the disease in the future remains somewhat uncertain.

CONCLUSION

There have been significant advances in measles virus research during the 23 years since Enders and Peebles (88) successfully isolated and cultivated the virus. The need for an effective attenuated vaccine and the evidence linking measles virus to SSPE have been two of the major forces that have provided the impetus for this research. However, as can be seen throughout this article, a large number of observations and questions remain unexplained and unanswered. The central, most important question is: What are the factors that are involved in the reaction between measles virus and its host (or host cell) that can result either in a "normal" infection or in a slow, latent infection?

To supply the answer(s) to this single question, more information is needed concerning: (i) the biochemistry of the virus: its structure, functions and mode of replication; (ii) the ways in which variants in a virus population (e.g., DI particles, ts mutants, non-interferon-inducing particles) can affect or modify virulence, and the role such variants may have in establishing and/or maintaining persistent infections; and (iii) the effect of virus on the immune system and the ways in which virus can escape the host's immune surveillance.

Measles virus is one of many viruses that were once thought to cause only acute disease, but are now implicated in a variety of chronic infections. As such, it represents the challenge of the future for virologists and those dedicated to improving the health of the human population.

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