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Persistent and Slow Virus Infections

John Hotchin

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With 26 figures and 11 tables

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Preface

This monograph by JOHN HOTCHIN represents an up-to-date review concerning presistent and slow virus infections. Included is a comprehensive bibliography of approximately 1200 references. The viruses capable of persisting within the infected host for long periods of time, sometimes for the life of the host, are heterogeneous in many respects, but there are important points of similarity. Their importance in a wide range of human and animal diseases is increasingly becoming recognized. It is not too much to conjecture that they may play a role in still other chronic degenerative diseases whose etiology is as yet unknown. Most appropriately the current status and future prospects of this fascinating and significant field are discussed in this volume by one of its pioneers, whose investigations, particularly in lymphocytic choriomeningitis, have contributed much toward moving the field forward and opening up new areas for its study.

As announced previously, suitable manuscripts in active areas of virus research for this series are welcomed by the editor. However, investigators who wish to submit material for a monograph are requested to make prior arrangements with the editor.

JOSEPH L. MELNICK

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To ERIC TRAUB who started the whole thing

Contents

Introduction

It has become increasingly clear that the persistent viruses constitute an important, numerous and variegated group, which is responsible for a wide range of human and animal diseases. At the present time it is impossible to judge the limit of pathological effects of these viruses, which appear to involve the entire field of medicine. The close relationship between persistent virus infection and slow virus disease is self-evident. The spectrum of action of these agents suggests that no realm of biology is free from their impact. Although theoretically many cancer viruses qualify as persistent, they are excluded from this review, which will be confined to animal agents which are not usually regarded as tumorigenic and which can be readily isolated over a period of months from the infected host.

Arenaviruses

Lymphocytic Choriomeningitis

Lymphocytic choriomeningitis (LCM) virus has several claims as the primary model system of persistent virus infection. TRAUB's [1935a, b, 1936a, b, c] early studies of LCM constituted the first description of a persistent animal virus and stimulated BURNET and FENNER [1949] to suggest the concept of immunological tolerance as an explanation for the behavior of LCM virus in mice. This virus was last comprehensively reviewed by FARMER and JANEWAY in 1942, although VOLKERT and LARSEN [1965c] recently reviewed the question of tolerance to it and SCHEID [1957] has reviewed its neurological aspects. The findings of the many workers who have studied the pathogenesis of LCM appear to this writer to form the basis of a working concept of the mechanism of persistent infection which is used in this monograph as a basis of comparison for other persistent virus infections. The group is defined as those infections in which free virus is readily found, (without recourse to technics such as tissue culture or administration of immunosuppressive agents), for a period of months, in some or all tissues of the host.

Properties of LCM Virus

History

The discovery of LCM was made by ARMSTRONG and LILLIE [1934] on November 2, 1933, [KREIS, 1937] during investigation of the 1933 St. Louis encephalitis (SLE) epidemic, as a monkey isolate derived from a fatal human case. The agent behaved like SLE virus for five monkey passages, and since the final monkey had been immunized against SLE, it seems likely that the LCM originated from one of the monkeys and did not in fact arise from the human case. This possibility is supported by the isolation of LCM virus from tissue culture of an in-

fected monkey by COUGHLIN and WHITNEY [1957]. In 1935 TRAUB [1935a, 1935b] isolated LCM virus from mice which had become sick only after intracerebral (IC) inoculation with sterile broth, and also from the blood of the animal caretaker who looked after the LCM-infected mice. Thus, very early in its history LCM demonstrated its now notorious propensity for inducing airborne laboratory infection. The virus was reported by ARMSTRONG and LILLIE [1934] and by TRAUB [1935b] to cause latent infection in mice.

BURNET and FENNER [1949] first drew attention to the possibility that LCM induced immunological tolerance in the host during intrauterine infection acquired from the mother. This concept was based on TRAUB's extensive work [1935a, b, 1936a, b, c, 1937, 1938a, b, 1939; TRAUB and SCHAFER, 1939] on the pathogenesis of this virus disease in mice.

Nomenclature and Classification

TRAUB pointed out [1936c] that the name lymphocytic choriomeningitis does not describe the disease naturally occurring in mice, since choriomeningitis is rare in such animals and naturally infected mice usually show no symptoms at all. The name applies mainly to the results of IC inoculation of mice and the meningitic complication of the human disease. The name *Armlillia erebea* was proposed [MERCHANT, 1961] for LCM but does not appear to have been used. The virus called pseudo-lymphocytic choriomeningitis [MACCALLUM *et al.*, 1939] appears to have been a strain of ectromelia [MACCALLUM *et al.*, 1957]. LCM virus has been experimentally transmitted by various bloodsucking insects [VIGOVSKII and GUTSEVICH, 1962] including the Rocky Mountain wood tick (*Dermacentor andersoni, Stiles*) [SHAUGHNESSY and MILZER, 1939], mosquitoes *(Aedes aegypti)* [COGGLESHELL, 1939], bedbugs *(Cimex lectularius)* [MILZER, 1942], fleas [FEDOROV and IGOLKIN, 1959] and trichinella spiralis nematodes [SYVERTON *et al.*, 1947] and grows in insect tissue cultures [REHÁČEK, 1965]. LCM can be regarded as an arthropod-borne virus, and it has been suggested [SHAUGHNESSY and MILZER, 1939] that other blood sucking arthropods such as culicine mosquitoes, stable flies and body lice may transmit LCM from rodent to rodent and possibly to man. LCM pathogenesis reveals some resemblance to the mouse hepatitis virus group [GLEDHILL and SEAMER, 1960; SEAMER *et al.*, 1961]. However, LCM is capable of growing in many species of animals, fertile eggs, and tissue cultures in which mouse hepatitis virus will not grow. Both of these agents show a common, unexplained potentia-

tion by coincident infection with the harmless murine blood parasite *Eperythrozoon coccoides* [GLEDHILL and SEAMER, 1960; GLEDHILL *et al.*, 1960; SEAMER *et al.*, 1961]. Recent work (see 'Physical and chemical properties') indicates that LCM is a lipoprotein-enveloped RNA virus with some similarities to the myxovirus group. The finding of multiple discrete electron-dense bodies within the virion gives a unique appearance, and the identical appearance of the Machupo-Tacaribe group [MURPHY *et al.*, 1969] and Lassa virus [BUCKLEY and CASALS, 1970; FRAME *et al.*, 1970; LEIFER *et al.*, 1970] suggests that LCM and these agents constitute a distinct new group. CASALS (personal communication) has found tentative evidence of some reciprocal complement-fixation (CF) cross reaction between Lassa, LCM and some Tacaribe strains. It has been proposed, on the basis of these and other findings, that this group be called the arenaviruses [ROWE *et al.*, 1970].

Strain Differences

TRAUB [1936a] showed that different strains of mice varied in the degree to which they became persistently infected with virus and that different strains of virus varied in pathogenicity. Similar results have been well established since then by other workers for both host [HOTCHIN and WEIGAND, 1961a; HOTCHIN and BENSON, 1963; ROGER and ROGER, 1963a, b, 1964a; HOTCHIN and COLLINS, 1964; VOLKERT and LARSEN, 1964; OLDSTONE and DIXON, 1968a, 1969] and virus [TRAUB, 1938a, 1960a; SCHWARTZMAN, 1946; HOTCHIN and WEIGAND, 1961a; HOTCHIN *et al.*, 1962; HOTCHIN and BENSON, 1963]. Strains of virus which have been passaged to develop viscerotropic properties readily induce tolerance, whereas those which have been passed in the brain, and are regarded as neurotropic, tend not to induce tolerance, but to kill newborn mice [HOTCHIN *et al.*, 1962]. Lethal strains were referred to as aggressive, and non-lethal as docile. Most wild strains of LCM virus are the docile or tolerance-inducing type. In spite of the occurrence of strains of LCM of different pathogenicity, no serologically distinct variants have been described, and all strains share common CF and neutralizing antigens [WILSNACK and ROWE, 1964; LEHMANN-GRUBE, 1964a, b; BENDA *et al.*, 1965]. One strain designated 'MP' virus [MOLOMUT *et al.*, 1965] has been shown to react in CF [MOLOMUT and PADNOS, 1965], mouse cross-protection, neutralization and footpad (FP) tests in the same way as LCM virus[1] and therefore it appears to be a strain of LCM. On the oth-

[1] J. HOTCHIN, unpublished results.

er hand, PADNOS *et al.* [1968] also reported that the MP strain produced a hemagglutinin for sheep red blood cells (SRBC) in serum and organs of infected mice [MOLOMUT and PADNOS, 1965; PADNOS *et al.*, 1968]. However, it was admitted by the authors that the mouse sera contained natural antibody to SRBC, and that the MP strain of LCM merely increased this existing SRBC hemagglutinin. The hemagglutinin was absent from the sera of tolerant mice. The hemagglutinating ability of the MP virus is therefore not comparable to other viral hemagglutinins, but appears to be related to an adjuvant-like property of the virus to enhance non-specific immunity. In all other respects, this strain behaves like LCM virus, and control mice used at the time of the original isolation were positive for LCM by CF test, suggesting that they carried LCM [MOLOMUT *et al.*, 1965; PADNOS *et al.*, 1968]. The biological, biochemical and biophysical properties of three LCM virus strains were compared by CAMYRE and PFAU [1968]. It was found that, although clearly belonging to the same group, the strains differed in terms of their stability to different physical agents. No difference could be detected between the virus from tolerant and acutely infected mice in terms of sedimentation, RNase susceptibility or neutralization [VOLKERT *et al.*, 1964].

Physical and Chemical Properties

The size of LCM virus was first determined by SCOTT and ELFORD [1939] to be 37 to 55 nm by centrifugation studies, while ultrafiltration gave a particle size of 40–60 nm. The virus can be separated from a soluble antigen by centrifugation [SMADEL *et al.*, 1939a]. PFAU [1965a] found it to be unstable in density gradients of RbCl or CsCl, but surviving virus was found in two bands at densities of 1.15 and 1.24. Morphological studies by DALTON *et al.* [1968] suggested that LCM virus was a pleomorphic agent with a variable size range from 50 to greater than 200 nm. While it usually appeared to be spherical, it was often cup-shaped. All the particles were found to contain 1 to 8 or more electron dense granules which were removed by ribonuclease. The virus particles were formed by budding from the plasma membrane and appeared to have spikes. These findings have been confirmed by ABELSON *et al.* [1969], who used peroxidase-labeled anti-virus sera to locate the virions by light and electron microscopy, and by KAJIMA [1970] (fig. 1). Electron microscopy of the MP strain was reported by PADNOS *et al.* [1968] to show spherical particles 80 nm in diameter, having a double limiting membrane with a corona of attached particles 10 nm in diameter.

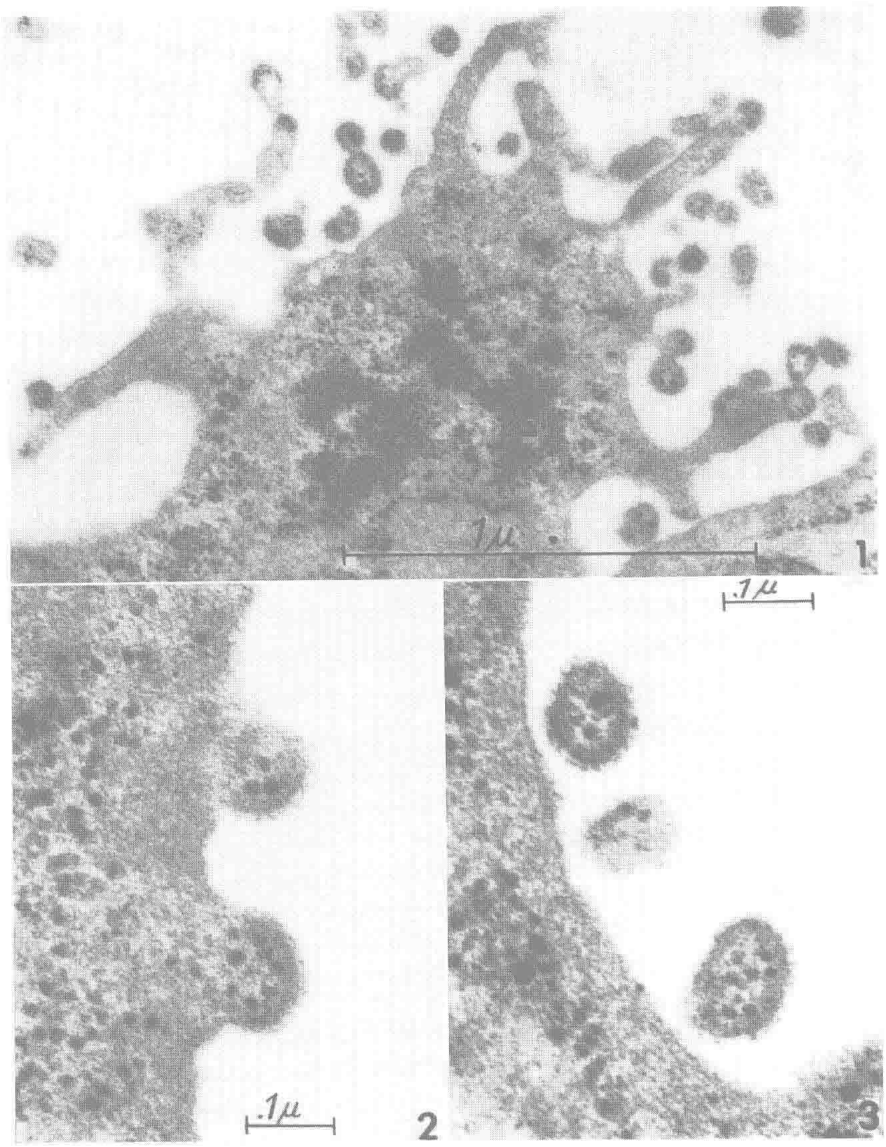

Fig. 1. Electron micrographs showing thin sections of Earle's strain L-929 cells infected with LCM strain CA1371. Virus particles can be seen budding from the cell surface, and electron dense bodies (20 nm) can be seen inside both cells and mature virus particles. Reproduced by permission of Dr. MASAHIRO KAJIMA. Figure 1.1 ×53,000. Figures 1.2 and 1.3 ×150,000.