Veterinary Research Communications, 12 (1988) 199–217
Geo Abstracts Ltd, Norwich—printed in England

POTENTIAL DETRIMENTAL EFFECTS OF RODENT VIRAL INFECTIONS ON LONG-TERM EXPERIMENTS

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ABSTRACT

Lussier, G. 1988. Potential detrimental effects of rodent viral infections on long-term experiments. *Veterinary Research Communications*, **12(2-3),** 199–217.

Healthy animals are of paramount importance in obtaining meaningful, reliable scientific results. Viral infections of rodents often have a significant impact on various types of biomedical research. Laboratory animal specialists and researchers must be aware of the possible consequences associated with the use of infected animals.

The objective of the paper is a discussion of the frequently encountered viral infections that can complicate or invalidate the interpretation of results by altering the host's response.

INTRODUCTION

Rodent viruses are widespread and have a long history of interfering with biomedical research. Although numerous publications have appeared during the past 10-15 years concerning the effects of rodent viral infections on biomedical data, the literature is scattered in diverse scientific journals. Scientists in general are not well informed of such influences on their research. Therefore, the objective of this article is to review the knowledge published in recent years concerning the possible role of a variety of rodent viruses on long-term experiments

Sendai Virus

Sendai virus was isolated from mice inoculated with human clinical specimens and was erroneously described as a virus causing fatal pneumonitis in newborn children (Kuroya *et al.*, 1953). Subsequently the virus was shown to be indigenous in mice (Fukumi *et al.*, 1954). Sendai virus is one of the most prevalent of rodent viruses (Parker & Richter, 1982). The infection may occur in acute clinical or subclinical forms or may be clinically inapparent and can then only be recognized by serology (Zurcher *et al.*, 1977).

In addition to being primarily involved in the respiratory system (Ward, 1974; Burek *et al.*, 1977; Zurcher *et al.*, 1977), Sendai virus may exert a synergistic effect with bacterial and mycoplasmal infections. Increased severity of lesions has been reported in experimental infections of mice with *Haemophilus influenza* (Degré & Glasgow, 1968; Degré, 1970) and *Pasteurella pneumotropica* (Jakab, 1974, 1981) and in mice and rats with Mycoplasma pulmonis (Howard *et al.*, 1978; Schoeb *et al.*, 1985).

Virus-induced impairment of the functional activity of alveolar macrophages has been reported (Degré, 1970; Warr & Jakab, 1979). Sendai virus may cause other subtle and long-lasting effects on humoral and cell-mediated immune responses (Kay *et al.*, 1979). It depresses the antibody response to sheep red blood cells (SRBC) in rats (van Hoosier, 1982), reduces the mitogenic response of lymphocytes to phytohemagglutinin and concanavalin A in mice and rats (Garlinghouse & van Hoosier, 1982), reduces the severity of

0165-7380/88/$03.50

adjuvant-induced arthritis in rats, a commonly used model of evaluating antiinflammatory and immunosuppressive drugs (Garlinghouse & van Hoosier, 1978) and accelerates rejection of skin isografts (Streilein *et al.*, 1981).

Sendai virus may also interfere with experimental carcinogenesis studies. Regenerative and repair lesions characterized by marked proliferation and squamous metaplasia of bronchial and bronchiolar cells with extension into the alveoli are observed following Sendai infection; these lesions have the appearance of invasive carcinomas (Richter, 1970). Sendai virus may also have a strong influence on experimental chemical carcinogenesis (Schreiber *et al.*, 1972). It suppresses the induction of pulmonary adenomas by urethane (Nettesheim, 1974), reduces the number of lung tumours in 10-chloromethyl-9-chloroanthracene-treated mice and increases the number of lung tumours in 7,12,dimethyl-benz(a)anthracene treatment (Peck *et al.*, 1983). Interference with the development of leukemia induced by Friend virus has been reported in DBA/2 mice infected with Sendai virus (Wheelock, 1967). Sendai virus infection of transplantable tumours alters the tumorigenicity of the cells: infection of Ehrlich ascites tumour with Sendai virus produces variants that are less oncogenic (Matsuya *et al.*, 1978). Similarly, the tumorigenicity of a leukemia cell line was shown to be reduced following persistent Sendai virus infection (Takeyama *et al.*, 1979). The latter alterations are probably the result of a virus-induced modification of the cell membrane. However, it has recently been shown that Sendai virus is an effective inducer of tumour necrosis factor by blood mononuclear leukocytes (Aderka *et al.*, 1986) suggesting possible implications of the virus in experimental oncogenesis.

Sendai virus infection in pregnant rats results in impaired fetal developmental and neonatal mortality (Coid & Wardman, 1971). Infection of pregnant rats in the early stage of gestation results in resorption of embryos, whereas infection at a later stage increases the gestation period and neonatal mortality. The affinity of Sendai virus for fertilized eggs before implantation has been reported in mice with resulting death of embryos and decreased breeding efficiency (Tuffrey *et al.*, 1972).

Mouse hepatitis virus (MHV)

The first strain of MHV, strain JHM, was isolated from the central nervous system of a spontaneously paralyzed mouse (Cheever *et al.*, 1949). MHV is now considered as a common contaminant of mouse colonies where the infection is often subclinical (Parker *et al.*, 1965; Carthew & Verstraete, 1978; Gannon & Carthew, 1980; Lussier & Descôteaux, 1986). However, MHV may induce different types of disease in several mouse strains (Virelizier & Allison, 1976). Most strains, including strain C57BL, are fully susceptible and die in a few days with hepatitis. Mice of the A strain are fully resistant, develop a mild disease, clear the virus efficiently and survive (Le Prevost *et al.*, 1975). Mice with intermediate susceptibility, including strain C3H, become carriers and develop a progressive neurologic disease lasting for weeks or months (Virelizier *et al.*, 1975). Other strains of MHV may cause enteritis (Broderson *et al.*, 1976). Infectious agents or numerous physical factors may act synergistically with MHV to produce a fulminant disease in colonies where MHV had previously been clinically inapparent (Fox *et al.*, 1977; Kraft, 1982).

MHV may alter various parameters of the immune response including either decreasing or enhancing the humoral response to SRBC, depending on experimental conditions (Virelizier *et al.*, 1976). Furthermore, persistently infected mice show a marked and long-lasting immunosuppression (Virelizier *et al.*, 1976). Infection of mice before antigen administration leads to immunosuppression, whereas simultaneous infection with virus

and antigen results in immunostimulation (Virelizier *et al.*, 1976; Tamura *et al.*, 1978). The presence of interferon correlated with these modifications, interferon peaking before antigen is associated with immunodepression, whereas interferon secretion after antigen is associated with immunostimulation (Virelizier *et al.*, 1976). MHV has been shown to alter host resistance to experimental infection with encephalomyocarditis virus (EMC) and to reduce the protective effects of exogeneously administered inteferon against EMC infections (Dempsey *et al.*, 1986).

MHV infection modifies numerous enzyme systems; it increases certain hepatic enzymes while it decreases several others (Ruebner *et al.*, 1965; Paradisi *et al.*, 1972; Budillon *et al.*, 1972).

In susceptible strains, MHV-3 induces histological modifications of the thymus characterized by a rapidly progressing destruction of the cortex (Virelizier *et al.*, 1976).

Numerous strains of MHV reduce ability of mice to seroconvert to pneumonia virus of mice (PVM) and convert Sendai-virus-susceptible DBA/2 mice to a resistant phenotype (Carraro *et al.*, 1984); antibody titers to PVM in MHV-infected mice are lower than in uninfected animals.

Numerous macrophage alterations caused by naturally occurring MHV have been reported (Boorman *et al.*, 1982; Dempsey *et al.*, 1986). These include increased number of cells, cytoplasmic vacuolations, increased vacuolated membranes, increased erythrophagocytosis and altered macrophage ectoenzyme phenotypes.

Cerebral damage leading to hydrocephalus has been induced in rats following intracerebral inoculation of strain A59 of MHV. However, anomalies were not detected following inoculation of nine other strains of MHV (Hirano *et al.*, 1980).

Pneumonia virus of mice (PVM)

PVM was isolated by Horsfall and Hahn (1940) by serial passages of mouse lung in mice during attempts to isolate viruses from cases of human respiratory disease. Serial intranasal passage of lung tissue infected with PVM may result in interstitial pneumonia on the second or third transfer (Tennant *et al.*, 1966). High incidence of hydrocephalus has also been produced following intracerebral inoculation of newborn mice (Lagacé-Simard *et al.*, 1980).

Lactate dehydrogenase-elevating virus (LDV)

LDV has been well reviewed (Riley, 1974; Rowson & Mahy, 1975). The virus was orginally detected as a contaminant of transplantable mouse tumours (Riley *et al.*, 1960). The mouse is the only susceptible host to LDV in which the infection is non-lethal and life-long. Laboratory mouse colonies are not often found to be infected, but LDV is a contaminant of most transplantable tumours and other biological materials maintained by passages in mice (Riley *et al.*, 1960, 1978; Rowson & Mahy, 1985). The infection may then be introduced inadvertently into a mouse colony. Infected mice exhibit a fivefold to tenfold elevation in plasma levels of LDH (Riley *et al.*, 1960; Riley, 1974) and increased levels of a certain number of other plasma enzymes (Plagemann *et al.*, 1962). The level of enzyme activity in the plasma, however, is not directly related to the level of viral infectivity (Motycka *et al.*, 1976). Impaired functioning of the enzyme clearance mechanism by macrophages has been incriminated as the cause of increased enzyme level (Bailey *et al.*, 1964; Notkins, 1965; Mahy *et al.*, 1965*a,b*). The functional capacity of the reticuloendothelial system as measured by carbon clearance is markedly depressed (Notkins & Scheele, 1964).

One special characteristic of the virus is its site of replication that appears to specifically favour the antigen-presenting macrophages (Porter *et al.*, 1969; Schlesinger *et al.*, 1976; Rowson & Mahy, 1975; Inada & Mims, 1985, 1986). LDV infection causes numerous immunological perturbations. When the virus is given shortly before the antigen, it has an apparent adjuvant action on the humoral immune response. (Notkins *et al.*, 1966; Mergenhagen *et al.*, 1967; Michaelides & Simms, 1977, 1980; Isakov *et al.*, 1982; Rowson & Mahy, 1985). In chronically infected mice, the humoral response is depressed (Oldstone *et al.*, 1974; Riley *et al.*, 1976). LDV infection stimulates interferon production and activates NK cell activity (Koi *et al.*, 1981). LDV has also been shown to affect lymphocyte circulation (Chang & Turk, 1977). The infection increases the levels of circulating immunoglobulins (Notkins *et al.*, 1966; Notkins, 1971); the increase is mainly in the IgG 2a subclass (Michaelides & Simms, 1977). LDV infection depresses the cell-mediated response (Howard *et al.*, 1969; Inada & Mims, 1986). An increase in spleen and lymph node mass and a slight transitory fall in thymus weight have been recorded (Riley & Spackman, 1974, 1976; Rowson & Mahy, 1975; Stauber *et al.*, 1975). Histological examination of the lymphoid tissue may reveal hyperplasia of the germinal centers and a reduction in the concentration of lymphocytes in the thymus-dependent areas (Snodgrass & Hanna, 1970; Snodgrass *et al.*, 1972; Proffitt *et al.*, 1972). Thymic atrophy can be prevented by adrenalectomy, suggesting the effect is steroid-mediated (Fritzmaurice *et al.*, 1972). The virus persists in the circulation in the presence of excess neutralizing antibody. The deposition of circulating virus-antibody complexes in the kidneys of LDV-infected animals may lead to the development of an immune-complex type of glomerulonephritis (Porter & Porter, 1969; Oldstone & Dixon, 1971).

LDV plays a role in the progress of a variety of neoplastic conditions. Tumour development may be stimulated or depressed. Several investigators have reported suppression of the growth of certain transplantable tumors in LDV-infected mice (Notkins, 1965; Bailey *et al.*, 1965; Riley, 1966, 1974; Riley *et al.*, 1978). However, tumour enhancement and normal tumour growth have also been observed in LDV-infected animals (Turner *et al.*, 1971; Michaelides & Schlesinger, 1974). The timing of the LDV infection appears to be a critical factor in its effect on the growth of tumours. Mice are more susceptible to tumour formation during acute infection (Michaelides & Schlesinger, 1974), while chronic infection inhibits or delays tumour formation (Riley & Spackman, 1976; Brinton-Darnell & Brand, 1977; Michaelides & Schlesinger, 1974; Isakov *et al.*, 1978, 1982; Henderson *et al.*, 1979; Theiss *et al.*, 1980; McDonald, 1983; Johnson & Shin, 1983). Minor alterations in timing or dose of tumour cells can alter the results. The growth-enhancing effect of the acute infection may be related to the depression of cell-mediated immunity.

As an example of the confusion that LDV can cause in an experiment, splenectomy had been reported to protect BALB/c mice against tumour formation when animals were inoculated with syngeneic methylcholanthrene-induced tumour cells (Chang & Turk, 1977). However, it was subsequently discovered that the tumour had become infected with LDV and that splenectomy had no effect on tumour induction following inoculation with LDV-free tumour cells (Henderson *et al.*, 1979).

A fatal paralytic neurological disease characterized by an inflammatory destruction of motor neurons is observed in LDV-infected mice immunosuppressed by aging or by immunosuppressive agents (Duffey *et al.*, 1976; Nawrocki *et al.*, 1980; Martinez *et al.*, 1980; Bentley *et al.*, 1982); the only strains of mice susceptible are C58 and AKR.

Lymphocytic choriomeningitis virus (LCMV)

LCMV was first isolated from a patient with acute aseptic meningitis (Armstrong &

Lillie, 1934). LCMV was one of the first viruses to be recognized as a latent infection in mice (Traub, 1935); it is a pantropic virus that infects the central nervous system and causes persistent infection in mice and other rodents (Parker *et al.*, 1976). Wild mice are considered as a natural reservoir of the virus and laboratory mice are easily infected from wild mice. Hamsters are also highly susceptible to LCMV. Although not widespread in laboratory rodent colonies, when present, LCMV can interfere with experimental results and poses a health hazard for humans. LCMV has also been found to be a contaminant of many mouse transplantable tumours (Collins & Parker, 1972; Pike, 1979; Bhatt *et al.*, 1986).

Infection in the adult mouse may result in death or, depending on the strains of mouse and the route and dose of virus, may be followed by immunity and clearance of the virus. Mice infected neonatally develop a persistent non-clinical infection that is maintained through successive generations. As the mouse ages, there is development of immune complex disease characterized by glomerulonephritis, arteritis, and widespread interstitial lymphoid infiltration (Hotchin, 1962; Oldstone & Dixon, 1970; Kajima & Pollard, 1970). In certain strains of mice, persistent infections affect the synthesis of growth hormone (Oldstone *et al.*, 1982). Infected animals undergo significant decrease in body weight and become defective in glucose metabolism.

Immunological research may be compromised when persistently infected mice are used. LCMV replicates in mononuclear cells of blood and lymphoid tissue: B-lymphocytes, T-lymphocytes, and macrophages contain replicating virus (Doyle & Oldstone, 1978). Depression of humoral and cell-mediated immune responses of infected mice have been reported (Mims & Wainwright, 1968). LCMV can ameliorate the *in vivo* growth of transplantable tumours (Jungblut & Kodza, 1963; Nadel & Hans, 1956; Youn & Barski, 1966). Enhanced activity of NK cells correlates with decreased receptivity for syngeneic stem cells in bone marrow and spleen (Thomsen *et al.*, 1986). Rejection of skin grafts prepared from syngeneic donor mice chronically infected with LCMV has been observed (Holtermann & Majdc, 1971). LCMV causes a marked activation of NK cells and macrophages (Welsh, 1978; Blanden & Mims, 1973; Thomsen *et al.*, 1986) and stimulates the production of interferon (Ronco *et al.*, 1981).

LCMV may persist in β cells of the islets of Langerhans of certain strains of mice resulting in metabolic and pathologic findings resembling those of type II diabetes mellitus (Oldstone *et al.*, 1984; Rodriguez *et al.*, 1985).

Immunopathologic destructive lesions of the cerebellum have been reported following inoculation of suckling rats (Monjan *et al.*, 1974).

Rodent parvoviruses

Parvoviruses that can infect rodents include Kilham rat virus (RV), Toolan rat (H-1) virus and minute virus of mice (MVM). Although experimental infection can be established in a number of other species, the rat is the only natural host for RV and H-1 viruses and the mouse is the only natural host for MVM (Kilham & Margolis, 1970; 1971).

RV was first identified in rat embryo tissue cultures inoculated with materials from tumour-bearing rats (Kilham & Oliver, 1959). The infection is common in laboratory and wild rats (Kilham, 1966; Robey *et al.*, 1968; Robinson *et al.*, 1971). RV is apparently species-specific during naturally occurring infections but can produce cerebellar hypoplasia or skeletal deformities in experimentally infected hamsters and cats (Kilham, 1961*a*, 1961*b*; Bear & Kilham, 1962; Kilham & Margolis, 1965). In adults, RV produces usually a latent infection, but the virus can be activated by immunosuppression to cause hemorrhagic encephalopathy (El Dadah *et al.*, 1967). Similar lesions accompanied by

cerebellar necrosis can be induced experimentally by intracerebral or parenteral inoculation of suckling rats (Cole *et al.*, 1970; Margolis & Kilham, 1970). RV has been isolated as a contaminant of murine leukemia virus preparations (Kilham & Moloney, 1964) and of transplantable tumours (Kilham & Oliver, 1959; Lum & Schreiner, 1963). The virus can replicate in rat lymphocytes and has been shown to inhibit the lymphoproliferative response to mitogens or allogeneic lymphoid cells (Campbell *et al.*, 1977) and to alter the natural cytotoxicity of rat spleen cells to lymphoma target cells (Darrigrand *et al.*, 1984).

H-1 virus is an antigenically distinct rat parvovirus (Moore 1962) first isolated from a human tumour cell line that had been passaged in rats (Toolan *et al.*, 1960; 1962). H-1 virus can cause neurological and skeletal aberrations and fetal resorption in experimentally inoculated rodents but it is believed to be nonpathogenic in naturally infected rats (Kilham & Margolis, 1969; Toolan, 1960). H-1 virus can contaminate transplantable tumours and established cell lines (Toolan, 1961; hallauer *et al.*, 1971). The virus also reduces the incidence of fibrosarcomas induced in hamsters by 7,12,dimethylbenzanthracene (Toolan *et al.*, 1962).

MVM was originally isolated as a contaminant of the mouse adenovirus (Crawford, 1966) and is considered only moderately pathogenic for mice. However, the virus is highly prevalent in mouse colonies (Parker *et al.*, 1970*a*; Lussier & Descôteaux, 1986) and is a frequent contaminant in transplantable mouse tumours and leukemia stocks (Parker *et al.*, 1970*a*; Collins & Parker, 1972). The infection can be introduced into a colony through inoculation of contaminated cell lines or biological materials. Experimental inoculation of MVM induces lethal infections in suckling rats and runting in mice. The virus is pathogenic for hamsters causing a lethal infection (Kilham & Margolis, 1970). A variant of MVM has been isolated from a murine T lymphoma cell line that differs from the prototype virus in being selectively lytic to T cells *in vitro* (Bonnard *et al.*, 1976; Bloom, 1984). MVM alone or as a contaminant of biological material has been reported to suppress or completely inhibit cell-mediated immune responses of mice (Bonnard *et al.*, 1976; Herberman *et al.*, 1977).

Reovirus 3

Reovirus 3 produces hepatitis, enteritis, encephalitis, and pancreatitis in affected animals (Seamer, 1967) and can adversely affect research directed at these organs. Reovirus 3 has also been shown to influence DNA replication *in vitro* (Jasney *et al.*, 1980). If the latter effect is also observed *in vivo,* the subtle effect of the infection would be more significant.

Reovirus 3 may also play an important role in the host response to environmental carcinogens and may act as an immunostimulant. The incidence of pulmonary adenomas following urethane administration is markedly reduced when the mice are exposed to reovirus 3 (Theiss *et al.*, 1978). Reovirus 3 also significantly affects the therapeutic value of 1,3-bis-(2-choretyl)-1 nitrosourea (BCNU) in the experimental model using transplantable EL4 lymphoma cells (Kollmorgen *et al.*, 1975; 1976). Similar results have been shown when reovirus 3 was used to protect mice from the A-10 murine mammary adenocarcinoma (Sansing *et al.*, 1977).

Mouse adenovirus (MAdV)

Two pathologically distinct strains of MAdV have been described. The FL strain isolated as a contaminant of the Friend's leukemia virus (Hartley & Rowe, 1960) and the K87 strain isolated from the feces of normal mice (Hashimoto *et al.*, 1966). The FL strain

causes acute fatal disease in suckling mice and a generalized persistent, inapparent infection in adult mice with viruria lasting for months or years (Heck *et al.*, 1972; Van der Veen & Mes, 1973). In contrast, MAd K87 produces only an intestinal infection in neonatal or older mice without observable signs of disease (Sugiyama *et al.*, 1967). Immune spleen cells from mice infected with MAdV strain FL were shown to be cytotoxic to target mouse embryo cells or lymphoid cells infected with MAdV (Inada & Uetake, 1978). It has been postulated that a virus-induced surface antigen may be recognized as a new antigen which may serve as a target site for cell-mediated immunity (Inada & Uetake, 1978).

MAdV strain FL persists in the kidneys of infected mice for months, producing infiltrates and moderate tubular damage for a considerable period (Wigand, 1980). Virus-induced lesions in the kidneys predispose to the development of frank pyelonephritis following *Escherichia coli* inoculation (Ginder, 1964). MAdV strain FL significantly alters experimental scrapie disease in mice causing significant acceleration of clinical signs of scrapie (Ehresmann & Hogan, 1986).

Murine cytomegalovirus (MCMV)

MCMV infection has adverse effects upon several parameters of the host defense mechanisms including antibody response to a variety of antigens (Osborn & Medearis, 1967; Osborn *et al.*, 1968; Howard & Najarian, 1974; Booss & Wheelock, 1975; Howard *et al.*, 1974; Tinghitella & Booss, 1979). Similarly, marked suppression of the host's ability to respond to stimulation with T and B cell mitogens has been described (Howard *et al.*, 1974; Booss & Wheelock, 1975, 1977*a,b*; Selgrade *et al.*, 1976; Kelsey *et al.*, 1977, 1978; Cruz & Waner, 1978; Wu & Ho, 1979; Sell *et al.*, 1985). The induction of interferon by multiple agents (Osborn & Medearis 1966, 1967; Kelsey *et al.*, 1977; Stringfellow *et al.*, 1977) and the inversion of the helper to suppressor T-lymphocyte subsets ratio has been reported (Sell *et al.*, 1985). Skin graft survival is significantly prolonged in MCMV-infected recipient mice (Howard *et al.*, 1974; Lang *et al.*, 1976). In certain strains of mice, sublethal MCMV infection induces an early suppressive phase and a later enhanced phase of T cell reactivity to foreign histocompatibility antigens (Grundy & Shearer, 1984). *In vitro* T cell lysis of EL4 tumour cells by splenocytes was significantly suppressed in BALB/c mice grafted with EL4 ascites allograft if the animals had previously been infected with MCMV (Hamilton *et al.*, 1978, 1979). Mice infected with MCMV have temporarily increased rates of carbon clearance compare to uninfected controls (Howard & Najarian, 1974), a signficant reduction in neutrophil migration (Howard *et al.*, 1982; Bale *et al.*, 1983; Lineaweaver *et al.*, 1984) and defective neutrophil functions (Leung & Hashimoto, 1986). Activation of the reticulo-endothelial system by MCMV has been reported (Schleupner *et al.*, 1979). MCMV has also been shown to cause alterations of the respiratory function (Shanley *et al.*, 1982; Reddehase *et al.*, 1985), to potentiate bacterial, fungal, and viral infections (Hamilton *et al.*, 1976; Bale *et al.*, 1982; Howard *et al.*, 1982; Leung & Hashimoto, 1986), and to affect the breeding efficiency of infected colonies (Baskar *et al.*, 1985). Pre-existing or concurrent MCMV infection enhances resistance to development of pulmonary tumour nodules after intravenous inoculation of syngeneic mammary tumour cells; while MCMV infection during tumourigenesis may enhance tumour growth and shorten survival time (Olsen *et al.*, 1976).

Peritoneal macrophages harvested from mice infected previously with MCMV were tumouricidal *in vitro* for a syngeneic mammary tumour cell line and have shown antiviral activity by repressing replication of vaccinia virus in cell cultures (Schleupner *et al.*, 1979).

Macrophages harvested from MCMV-infected mice showed augmented phagocytosis of yeast particles *in vitro* (Schleupner *et al.*, 1979). On the other hand, enhanced protection against *Listeria monocytogenesis* has been demonstrated in infected mice (Schleupner *et al.*, 1979).

Rats are susceptible to MCMV after intraperitoneal inoculation (Smith *et al.*, 1986). MCMV infection in rats is associated with transient reversals of T helper/suppressor cell ratios and alterations of immune cell functions as detected by spleen cell proliferation (Smith *et al.*, 1986).

Rat cytomegalovirus (RCMV)

RCMV was first isolated by Rabson *et al.* (1969) from salivary glands of wild roof rats shown to contain characteristic cytomegalovirus inclusions. Encephalitis has been induced in suckling rats by intracerebral inoculation of the virus (Kilham & Margolis, 1975; Priscott & Tyrell, 1982). RCMV has been used as a model for studying the immunopathology of persistent and reactivating infection in immunocompromised rats (Bruggeman *et al.*, 1983; 1985). The virus has an immunosuppressive effect on the immune response to SRBC (Bruggeman *et al.*, 1985). It has also been shown to induce enhanced levels of chemiluminescence emitted during phagocytosis of zymozan particles, and to enhance the host's capacity to kill *Staphylococcus aureus* (Hendrix *et al.*, 1986).

Sialodacryoadenitis virus (SDAV) and rat coronavirus (RCV)

Two antigenically related coronarviruses, SDAV and RCV, which share a common antigen with MHV (Bhatt *et al.*, 1972), have been isolated from rats. Sialodacryoadenitis is a common, naturally occurring, highly infectious non-fatal disease that is characterized by inflammation of lacrymal and salivary glands as well as of upper and lower respiratory tracts. Ocular lesions including keratoconjunctivites, corneal ulceration, anterior synechiae, exudate in the anterior chamber, and secondary bacterial infections often develop late in the disease (Weisbroth & Peress, 1977). These lesions make infected animals unsuitable for research in which the eye is the target organ (Innes & Stanton, 1961; Lai *et al.*, 1976).

SDAV virus has been shown to be infectious for mice, causing interstitial pneumonia; it is transmitted from mouse to mouse and is detected most readily in the trachea and lung (Bhatt *et al.*, 1977). The main importance of the infection in mice appears to be the serologic cross-reaction between SDAV and MHV. Unless one is aware of SDAV and its cross-reaction with MHV, it may be difficult to distinguish serologically between the two infections in a mouse colony (Bhatt *et al.*, 1977). In contrast to SDAV, RCV is primarily pneumotropic, causing little or no sialodacryoadenitis (Parker *et al.*, 1970*b*).

SDAV and RCV may have a significant impact in certain types of experiments. For instance, lesions of the upper respiratory tract may predispose rats to other respiratory pathogens and may interfere with anesthesia or inhalation in toxicology research (Parker *et al.*, 1970*b*; Jacoby *et al.*, 1979). Decreased breeding efficiency has been reported in female rats exposed to SDAV early in pregnancy (Utsumi *et al.*, 1980); this may affect reproductive research and teratology studies.

K virus

K virus was first isolated as a contaminant of the mouse mammary tumour virus (Kilham, 1952) and has been found to be different from polyomavirus, another member of

the papovavirus family (Bond *et al.*, 1978). The virus is known to infect weanling or adult mice without producing overt disease and is endemic in many wild mouse colonies (Holt, 1959; Rowe *et al.*, 1961). However, inoculation of newborns with biological material containing K virus may produce a fatal illness characterized by a severe interstitial pneumonia (Fisher & Kilham, 1953; Kilham & Murphy, 1953; Greenlee, 1979). Infection in weanling mice with K virus enhances the acute hepatic necrosis and inflammation produced by subsequent infection with MHV (Tisdale, 1963).

Polyomavirus

The virus was first identified by Stewart (1960) and Eddy (1960). It normally causes an inapparent infection of mice; however, inoculation of the virus causes a variety of tumours in numerous species including suckling mice, rats, guinea pigs, rabbits, and ferrets (Eddy, 1969). Polyomavirus can be transmitted to the fetuses when the mother is infected at various stages throughout gestation (McCance & Mims, 1977). The virus persists at low levels for long periods in organs such as the kidney (Rowe *et al.*, 1960) and can be reactivated (McCance & Mims, 1979). Neonatal thymectomy enhances its tumourigenicity in newborn and adult hamsters (Defendi & Roosa, 1965). A wasting disease has been reported in infected nude mice (Sebesteny *et al.*, 1980).

Mouse thymic virus (MTV)

MTV was first described as a contaminant of mouse mammary tumour homogenates (Rowe & Capps, 1961). Neonatal infection of mice with MTV induces a non-fatal disease characterized by extensive but temporary necrosis of the thymus which is maximal 10 to 14 days after infection (Rowe & Capps, 1961; Cross *et al.*, 1979). In addition to the severe histological lesions produced in the thymus, MTV induces profound suppression of a number of immunologic functions mediated by thymus-derivated cells (Cohen *et al.*, 1975; Morse *et al.*, 1976). Spleen cells have markedly diminished reactivity to T cell phytomitogens and to allogenic cells and are incapable of effecting a primary *in vitro* or *in vivo* response to a T-dependent antigen (Cohen *et al.*, 1975). Infection with MTV results in a profound reduction in the direct graft-versus-host reactivity of thymocytes (Cross *et al.*, 1976). Responses to B cell mitogens and to a T-independent antigen appear unimpaired (Cohen *et al.*, 1975; Cross *et al.*, 1976; Morse *et al.*, 1976).

CONCLUSION

These numerous examples of alterations of research data stress the need for monitoring rodent colonies as well as transplantable tumours and murine viral stocks. If experiments are performed with infected animals or with contaminated materials they may lead to erroneous conclusions. This problem is particularly important in immunology, toxicology and experimental pathology. Therefore, health of experimental animals is absolutely essential to the production of accurate reproducible research and test results. Consequently, it is imperative that investigators pay considerable attention to the viral profile of their research animals.

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(Accepted: 23 September 1987)