WORKING PARTY REPORT

Implications of infectious agents on results of animal experiments

Report of the Working Group on Hygiene of the Gesellschaft für Versuchstierkunde – Society for Laboratory Animal Science (GV-SOLAS)

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Introduction

It is generally accepted that rodent pathogens may not only be hazardous for animals (and humans) but can severely influence the results of animal experiments. Microbiological standardization of laboratory animals is therefore of crucial importance.

It has been known for decades that microorganisms may have an impact on their hosts in various ways. Many years ago, influences of microorganisms were detected on development and growth of tumours. It was shown by various authors that germ-free mice develop fewer tumours (lung, liver, mammary glands, uterus, ovary) after treatment with chemical carcinogens than conventionally housed animals (Burstein *et al.* 1970, Roe & Grant 1970, Schreiber *et al.* 1972). The importance of microorganisms as factors that may influence animal experiments has already been described in review articles more than 25 years ago (van der Waaij & van Bekkum 1967, Hanna *et al.* 1973, Baker *et al.* 1979). A first symposium dealing with this issue was held in 1971, and hitherto known influences of selected microorganisms were published afterwards (Pakes & Benirschke 1971).

Importance of microorganisms

Infectious agents may affect animal populations in various ways. Some are pathogenic and may induce clinical signs with variable morbidity or mortality. However, most microorganisms induce no or only mild disease, at least in cases of endemic infections. Occasionally, loss of animals occurs as a consequence of disease or death. Silent infections are often activated by experimental procedures (stress, immunosuppression, toxic substances, tumours) or environmental influences (transportation, suboptimal humidity or temperature). Frequently, certain strains of a given species are more sensitive to an infection, whereas the same agent may cause milder or different symptoms in other strains, or the infection may be asymptomatic. Clinical signs are usually more serious in immunodeficient animals. Frequently, infections

result in a reduced life expectancy in the absence of specific disease for some individuals or a whole population. Other agents induce silent infections which are asymptomatic even in the case of experimental inoculation.

Many agents may have an impact on physiological parameters and thus on the results of animal experiments independent from their pathogenic potential. Further, infections may increase inter-individual variability. This may result in increased numbers of animals necessary to achieve significant results. Direct effects of infectious agents on experiments may lead to false conclusions or misinterpretation and may be responsible for a lack of reproducibility.

The use of laboratory animals that are free from unwanted microorganisms is an important prerequisite to achieve reliable and reproducible results with a minimum of animals and is therefore a significant contribution to animal welfare.

It is obvious that experimental data obtained from diseased animals should, if ever, be used only with maximal precaution. However, the effect of clinically silent infections may also be devastating because they often remain undetected, and thus modified results may be obtained and published.

The absence of clinical manifestations has no diagnostic value. The presence of unwanted microorganisms and the suitability of an animal population for a specific experiment can only be demonstrated by comprehensive health monitoring before and during experimentation. Health monitoring data are part of the experimental work and have to be considered during interpretation of experimental results by the experimenter and by the reader of a publication. It should, therefore, be self-evident that results of health monitoring are included in scientific publications (Working Committee for the Biological Characterization of Laboratory Animals/GV-SOLAS 1985). Recommendations for health monitoring of laboratory animals have been published repeatedly (Lussier 1991, National Research Council 1991, Kunstyr 1992, Kraft *et al.* 1994, Nicklas 1996, Rehbinder *et al.* 1996, 1998).

Many agents do not only have an impact on animals or animal experiments. Numerous organisms are known to affect experiments conducted with isolated organs or cells. Microorganisms may even persist in cells, tumours or other biological materials for unlimited periods of time and therefore influence *in vitro* experiments. Furthermore, microorganisms resulting from a natural infection might contaminate biological materials (tumours, sera, cells, viruses, parasites) that originate from or have been passaged in infected animals. They may severely influence experiments conducted with such materials, or may be introduced into animal facilities by contaminated samples (Collins & Parker 1976, Nicklas *et al.* 1993).

Unfortunately, research complications due to infectious agents are usually considered artefacts and are published only rarely. Information on influences of microorganisms on experiments is scattered in diverse scientific journals, and many articles are difficult to detect. This text therefore aims to provide an overview on published influences of selected microorganisms on animals as well as on experiments.

To address the problem, several meetings were held on viral complications on research. The knowledge available was summarized in conference proceedings (Melby & Balk 1983, Bhatt *et al.* 1986, Hamm 1986) and has later repeatedly been reviewed (Kraft 1985, Lussier 1988, National Research Council 1991, Hansen 1994, Baker 1998, Mossmann *et al.* 1998).

Aim of this compilation

After detection of an organism in an animal facility the question frequently arises if and how an animal experiment might be influenced. Experimenters and laboratory animal specialists must in such cases be able to evaluate the importance of an infection on research. It is the purpose of this compilation to aid in evaluating the importance of the most relevant microorganisms for animal experiments. Published influences of microorganisms on physiological parameters of laboratory animals have been listed concisely, and the references are cited. In addition, a few other questions which often arise together with infections in populations of experimental animals are addressed (e.g. zoonotic potential, host specificity).

Furthermore, it is the aim of this study to support managers of animal facilities in arguing towards improved microbiological standardization of laboratory animals which will result in better and more reliable results of animal experiments with fewer animals.

The majority of laboratory animals are mice and rats, and most information is available for microorganisms infecting these species. This compilation therefore focuses on rodent microorganisms although there is a general trend towards better microbiological quality also for other animal species (Rehbinder *et al.* 1998).

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Sendai virus

Host species
- mouse, rat, hamster, (guineapig)

Organotropism
- respiratory tract

Clinical disease
- usually inapparent
- severe clinical disease with complicating infections (*M. pulmonis*, CAR bacillus)

Pathology
- focal/segmental necrotizing inflammation of respiratory epithelium
- suppurative or necrotizing bronchitis and bronchiolitis
- foci of interstitial pneumonia

Morbidity and mortality
- up to 100% of a colony infected
- morbidity and mortality depending on host strain (Parker *et al.* 1978, Steward & Tucker 1978, Brownstein & Winkler 1986, Percy *et al.* 1994)

Interference with research
Physiology
- Sendai virus infection in guineapigs and rats enhances airway responsiveness to acetylcholine and substance P (Elwood *et al.* 1993, Yamawaki *et al.* 1995)
- Sendai virus infection aggravates the airway damage in rat lung allografts with chronic rejection (Winter *et al.* 1994)
- Sendai virus infection reduces the life span of the H-2d and H-2b genotypes B10 congenic mice (Yunis & Salazar 1993)

Pathology
- increased number of mitotic cells in bronchial epithelium and in lung parenchyma (Richter 1970)
- increase in bronchiolar mast cells persists for months after infection (Sorden & Castleman 1995)
- Sendai virus nucleoprotein gene is detectable in the olfactory bulbs of intranasally infected mice for at least 168 days post-infection (p.i.) by PCR (Mori *et al.* 1995)
- moderate hypoxia while recovering from a Sendai virus causes pulmonary oedema in young rats (Carpenter *et al.* 1998)

Immunology
- increase in natural killer cell mediated cytotoxicity (Clark *et al.* 1979)
- induction of tumour necrosis factor and other cytokines (Aderka *et al.* 1986, Costas *et al.* 1993, Mo *et al.* 1995, Uhl *et al.* 1996)
- long-term effect on the immune system (55 out of 63 parameters are affected (Kay 1978)
- Sendai virus infection of C57BL/6 mice elicits a strong CD4+ and CD8+ T-cell response in the respiratory tract (Cole *et al.* 1994)
- infected mice have enhanced numbers of cytotoxic T-lymphocyte precursors (>20× background) for life (Doherty *et al.* 1994)
- impairment of macrophage function causing delay in wound healing (Kenyon 1983)
- induces increased TNF-alpha and INF-alpha expression (Milone & Fitzgerald-Bocarsly 1998, Payvandi *et al.* 1998, Uhl *et al.* 1998)

Interactions with other infectious agents
- decrease of pulmonary bacterial clearance (Degre & Solber 1971)
- interaction with bacterial pathogens (Jakab 1981)

Oncology
- production of polyploid variants of tumour cells with increased chromosome numbers and reduced tumorigenicity (Matsuya *et al.* 1978)
- reduced transplantability of hamster tumour cells in combination with augmented cell-mediated immunity (Yamada & Hatano 1972, Ogura *et al.* 1980)
- altered host response to transplantable tumours (Wheelock 1966, 1967, Collins & Parker 1972, Matsuya *et al.* 1978)
- strong influence on chemically induced carcinogenesis (Peck *et al.* 1983)

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Mouse hepatitis virus

Host species
- mouse

Organotropism
- polytropic strains: liver, brain, lymphoid tissue, (other organs)
- enterotropic strains: intestine, lymphoid tissue

Clinical disease
- inapparent in immunocompetent adults, diarrhoea and death in neonates (epizootic infection)
- wasting disease in immunodeficient mice

Pathology
- polytropic strains: acute necrosis and syncytia formation in liver, spleen and lymphoid tissue; necrotizing encephalitis with demyelinization and syncytia formation
- enterotropic strains: villus attenuation, enteroytic syncytia and mucosa necrosis of the terminal small intestine, the caecum and the ascending colon

Morbidity and mortality
- usually 100% of animals are infected
- mortality close to 100% in neonates during an epizootic infection and in immunodeficient mice infected with a polytropic strain
- mortality 0% (or very low) in all other cases

Interference with research
Oncology
- contamination of transplantable tumours (Nicklas *et al.* 1993)
- abnormal tumour invasion pattern, abnormal tumour passage intervals, spontaneous regression or oncolysis of normally stable tumours (Braunsteiner and Friend 1954, Nelson 1959, Manaker *et al.* 1961, Fox *et al.* 1977, Akimaru *et al.* 1981)
- rejection of human xenografts (Kyriazis *et al.* 1979)
- altered response to chemical carcinogens (Barthold 1986a)

Interactions with other infectious diseases
- confusion about origin of virus isolates: Tettnang (Smith *et al.* 1983), multiple sclerosis (Gerdes *et al.* 1981), puffinosis (Nuttall & Harrap 1982)
- reduced susceptibility for viral infections (PVM, Sendai) (Carrano *et al.* 1984)
- potentiation of subclinical MHV infections by urethane and methylformamide (Braunsteiner & Friend 1954), halothane (Moudgil 1973), transplantation of tumours (Barthold 1986b), concurrent infection with *Eperythrozoon coccoides* (Kraft 1982)
- enhances resistance to *Salmonella typhimurium* in mice by inducing suppression of bacterial growth (Fallon *et al.* 1991)

Immunology
- immunodepression and immunostimulation depending on the time of infection (Virelizier *et al.* 1976)
- MHV replicates in macrophages and with or without lysis in both B and T lymphocytes (Bang & Warwick 1960, Lamontage *et al.* 1989, de Souza & Smith 1991)
- enhanced and suppressed macrophage function (Boorman *et al.* 1982, Dempsey *et al.* 1986) and dysfunction of T and B cells (Casebolt *et al.* 1987, de Souza *et al.* 1991, Smith *et al.* 1991, Cook-Mills *et al.* 1992)
- activation of natural killer (NK) cells and alteration of the interferon responsiveness of infected mice (Virelizier *et al.* 1976, Schindler *et al.* 1982)
- reduced levels of cytokines, interleukins and gamma interferon in spleen cells (de Souza *et al.* 1991)
- recovered mice have complete or partial protection against T-cell dysfunctions when re-infected with different strains of MHV (Smith *et al.* 1992)
- macrophage dysfunctions continue in MHV-recovered mice (Boorman *et al.* 1982)
- MHV infection can durably modify unrelated T-cell responses that are initiated at the time of infection (Coutelier *et al.* 1991)
- permanent decrease of skin graft rejection and T-cell dependent antibody responses after recovering from MHV-A59 infection (Cray *et al.* 1993)
- enhancement of concomitant autoimmune reactions (Lardans *et al.* 1996)
- altered pathogenesis in transgenic and knock-out mice (Schijns *et al.* 1998)

Physiology
- alteration of liver enzyme levels, patterns of protein synthesis and other biochemical markers (Piazza 1969, Barthold 1986a, Lucchiari *et al.* 1992)
- induction of alpha-fetoprotein (Kiuchi *et al.* 1974) and increase of iron uptake (Tiensiwakul & Husain 1979)
- changes in peripheral blood such as anaemia, thrombocytopenia, leukopenia and increased monocyte procoagulant activity (Piazza *et al.* 1965, Levy *et al.* 1981)
- decrease of the incidence of diabetes in non-obese diabetic mice (Wilberz *et al.* 1991)
- MHV-3 induces the expression of fgl2 prothrombinase in the liver, the enzyme responsible for fulminant liver failure (Ding *et al.* 1997)
- MHV-JHM induces nitric oxide synthase type II expression in brains of acutely infected mice (Grzybicki *et al.* 1997)

Reproductive technology
- persistent contamination of embryonic stem (ES) cells without diminishing their pluripotency (Okumura *et al.* 1996)
- MHV infection influenced the outcome of fertilization. Infected mice produce more MHC-hetero-

zygous embryos than sham-infected ones (Rulicke *et al.* 1998)

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Sialodacryoadenitis virus, Rat coronavirus

Host species
- rat

Organotropism
- salivary and lacrimal (including Harderian) glands, respiratory tract

Clinical disease
- enzootic: asymptomatic or mild conjunctivitis in suckling rats
- epizootic: nasal and ocular discharge, porphyrin staining, corneal ulceration, swelling of the neck, exophthalmus
- SDAV may persist for at least 6 months in athymic rats (Weir *et al.* 1990, Hajjar *et al.* 1991)

Pathology
- acute: coagulation necrosis of the ductal structure of the salivary and lacrimal glands
- reparative phase: squamous metaplasia of ductal and acinar structures of the salivary and lacrimal glands

Morbidity and mortality
- morbidity: high
- mortality: none

Interference with research
Physiology
- interference with studies involving eyes, salivary and lacrimal glands or respiratory system (Jacoby 1986)
- reduced reproduction and growth rates (Utsumi *et al.* 1980)
- impairing functions such as olfaction and chemoreception for up to 2 weeks post-exposure (Bihun & Percy 1995)

Immunology
- reduction of interleukin production in alveolar macrophages (Boschert *et al.* 1988)
- causes increase of localized graft-*vs*-host disease in salivary and lacrimal glands after bone marrow transplant (Rossie *et al.* 1988)

Interactions with other infectious agents
- increased adherence of *Mycoplasma pulmonis* in tracheas of infected rats (Schoeb *et al.* 1993)
- enhances lower respiratory tract disease in rats following *Mycoplasma pulmonis* infection (Schunk *et al.* 1995)

Oncology
- reduction of epidermal growth factor in submaxillary salivary gland (Percy *et al.* 1988)
- causes higher prevalence of anterior pituitary tumours in male F344/NCr rats (Rao *et al.* 1989)

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Pneumonia virus of mice

Host species
- mouse, rat, hamster, guineapig (Griffith *et al.* 1997), (rabbit)

Organotropism
- respiratory tract

Clinical disease
- asymptomatic in euthymic animals (Smith *et al.* 1984, Griffith *et al.* 1997)
- chronic pneumonia and death in athymic (nude) mice (Richter *et al.* 1988, Weir *et al.* 1988)

Pathology
- mild necrotizing rhinitis, necrotizing bronchiolitis and non-suppurative interstitial pneumonia

Morbidity and mortality
- morbidity: from 20% (in mice) to 50% (in rats and hamsters)
- mortality: none, except in immunodeficient mice

Interference with research
Physiology
- increases the susceptibility to diabetes induction by streptozotocin in BALB/cByJ male mice (Leiter *et al.* 1988)
- causes significant decreases in body weights of F344/NCr rats but not of B6C3F1 mice (Rao *et al.* 1989a,b)

Pathology
- produces an interstitial pneumonia with virus demonstrated in the bronchial epithelium but also in the alveolar walls and alveolar macrophages in germ-free athymic and euthymic mice (Carthew & Sparrow 1980a,b)
- causes hydrocephalus after intracerebral inoculation of neonatal mice (Lagace-Simard *et al.* 1980)

Oncology
- lowers the prevalence of leukaemia in male F344/NCr rats (Rao *et al.* 1989)

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Guineapig adenovirus (GPAdV)

Host species
- guineapig

Organotropism
- lungs, upper respiratory tract

Clinical disease
- dyspnoea (rapid, shallow, laboured or noisy breathing), a hunched posture, piloerection (roughened coat), eventually sensitivity to touch, hypothermia and death in sporadic cases within one hour or one day caused by an acute lobar bronchopneumonia (necrotizing bronchiolitis)

Morbidity and mortality
- Note: The virus alone seems not to be able to elicit the disease; some additional weakening factors are necessary (multi-factorial disease). Nothing is known about the prevalence of the virus in infected colonies. Morbidity is considered to be low and mortality close to 100% (no animal showing clinical dyspnoea recovered). Subclinical infection of the upper respiratory tract has recently been found

Interference with research
- sudden death of experimental guineapigs in sporadic cases (or reaching about 5% mortality of a batch at the most). No other interference is known

Note
Diagnostic method: beside histology and electron microscopy, also PCR (Pring-Akerblom *et al.* 1997). May be used to detect subclinical infection in the upper respiratory tract (Butz & Homberger 1997).

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Minute virus of mice (MVM)

Host species
- natural host: laboratory and wild mice (Parker *et al.* 1970, Singleton *et al.* 1993, Smith *et al.* 1993)
- hamsters and rats are susceptible to experimental infection (Kilham & Margolis 1970, 1971)

Properties of the virus
- highly temperature resistant (Fassolitis *et al.* 1985)
- highly resistant to environmental conditions e.g. desiccation (Tattersall & Cotmore 1986, National Research Council 1991)
- like other parvoviruses, MVM can infect cells only during the S phase of the mitotic cycle (Tattersall 1972)
- two allotropic variants exist which replicate in fibroblasts (MVMp) or in T-lymphocytes (MVMi) (McMaster *et al.* 1981, Spalholz & Tattersall 1983, Antonietti *et al.* 1988, Gardiner & Tattersall 1988)
- oncogenic transformation of cells by radiation, chemical carcinogens, or SV40 increases permissiveness to MVMp (Cornelis *et al.* 1988a)
- transplacental transmission after experimental infection of pregnant hamsters, mice and rats (Kilham & Margolis 1971)
- mouse embryos with intact zona pellucida are not susceptible to infection (Mohanty & Bachmann 1974)

Strain susceptibility
- the host strain may influence the mode and extent of horizontal transmission (Tattersall & Cotmore 1986)
- three susceptibility phenotypes in response to MVMi: asymptomatic infection in C57BL/6, lethal with intestinal haemorrhage in DBA/2, lethal with renal haemorrhage in BALB/c, C3H and other strains (Brownstein *et al.* 1991)
- amount of viral DNA produced during infection is dependent on host strain (Kapil 1995)

Organotropism
- viral replication only in mitotically active tissues e.g. embryos (Tattersall & Cotmore 1986)
- benign fetal infections in mice (Kilham & Margolis 1975)
- MVMi causes generalized infection of endothelium, lymphocytes and haematopoietic cells, and produces bilateral infarcts of the renal papilli (Brownstein *et al.* 1991)

Clinical disease
- natural infection of mice usually asymptomatic (Ward & Tattersall 1982, National Research Council 1991, Jacoby *et al.* 1996)
- subclinical infection in experimentally infected rats or mice and lethal disease in hamsters after experimental infection (Kilham & Margolis 1970)
- infectivity, organotropism, and pathogenesis of infection is dependent on characteristics of the virus (Brownstein *et al.* 1992, Jacoby & Ball-Goodrich 1995)
- growth retardation of mice after experimental infection (Kilham & Margolis 1970)
- MVMi but not MVMp is able to induce a runting syndrome in experimentally infected new-born mice (Kimsey *et al.* 1986)
- fetal death and resorption (Kilham & Margolis 1971)
- periodontal disease and mongolism in hamsters surviving experimental infection (Kilham & Margolis 1970)

Pathology
- intranuclear inclusions in some infected animals (Kilham & Margolis 1971)
- no pathological lesions after natural infection (National Research Council 1991)

Morbidity and mortality
- MVMi more pathogenic for mice than MVMp, MVMi influences growth of mice shortly infected after birth, some die of the infection; non pathogenic in adult mice (Kimsey *et al.* 1986)
- pathogenic in fetal hamsters and rats, no clinical disease in experimentally infected mothers (Kilham & Margolis 1971)

Zoonotic potential
- none

Interference with research
Pathology
- intranuclear inclusion bodies (Kilham & Margolis 1971)
- dental defects in aged hamsters after infection at 5 days of age (Baer & Kilham 1974)

Immunology
- weak induction of interferon *in vivo* (Harris *et al.* 1974) and of IFN-β, TNF-α and IL-6 *in vitro* (Schlehofer *et al.* 1992)
- strong inhibitory effects of the immunosuppressive variant (MVMi) on allogeneic mixed lymphocyte cultures *in vitro* (Bonnard *et al.* 1976)
- inhibition of lymphocyte proliferation and the generation of cytolytic T-lymphocyte activity but not interferon production, inhibition of growth and cytolytic activity of T-cell lines, suppression of an *in vitro* antibody response by MVMi but not by MVMp (Engers *et al.* 1981)
- inhibition of the generation of cytolytic T-lymphocytes by MVMi (McMaster *et al.* 1981)
- reduction of T-cell mitogenic responses and interference with helper dependent B-cell responses *in vitro* (Tattersall & Cotmore 1986)
- depression of splenic T-cell and B-cell mitogenic stimulation *in vivo* (Tattersall & Cotmore 1986)
- neonatal infections by MVMi may have long-term effects on immunocompetence (Kimsey *et al.* 1986)

- inhibition of haematopoiesis *in vitro* by MVMi but not by MVMp (Bueren *et al.* 1991, Segovia *et al.* 1991)
- decreased haematopoiesis in spleen and bone marrow cells (Segovia *et al.* 1995)

Physiology
- degeneration of the lens and the adjacent retinal layers after infection of newborn hamsters, extensive hypertrophy of the Harderian glands (Toolan 1983)

Cell biology
- contaminant of cell lines, leukaemias, and transplantable tumours (Parker *et al.* 1970, Collins & Parker 1972, Zoletto 1985, Garnick 1996, Chang *et al.* 1997)
- persistent infection of cell lines (Ron & Tal 1985, Koering *et al.* 1996)
- disruption of nucleolar functions by virus replication in the nucleolus (Walton *et al.* 1989)
- interference of a virus protein (NS1) with cell DNA replication, cell cycle stops in the S phase (Op de Beeck & Caillet-Fauquet 1997)
- viral DNA replication in fibroblasts co-infected with MVM and adenovirus is markedly dependent on the cell line (Fox *et al.* 1990)

Teratology
- congenital malformation (Margolis & Kilham 1975)
- death and resorption of fetuses (Kilham & Margolis 1971, Jordan & Sever 1994)

Interactions with other infectious agents
- first described as a contaminant of a stock of mouse adenovirus (Crawford 1966)

Oncology
- contamination of transplantable or chemically induced tumours (Parker *et al.* 1970, Collins & Parker 1972, Bonnard *et al.* 1976, Lussier 1991, Nicklas *et al.* 1993)
- inhibition of cell transformation by SV40 (Mousset & Rommelaere 1982)
- stable transformed phenotype is required for complete competence for MVM replication (Rommelaere & Tattersall 1990)
- greater susceptibility of human oncogenic transformed cells and tumour-derived cell lines than of normal untransformed parental cells (Mousset *et al.* 1986, Cornelis *et al.* 1988a, Rommelaere & Cornelis 1991)
- cultures of transformed rat fibroblasts are more susceptible to the cytopathic effect of MVMp than their untransformed homologues (Cornelis *et al.* 1988b, Guetta *et al.* 1990)
- suppression of Ehrlich ascites tumours in mice after co-injection of MVM and acquisition of long-term resistance to additional injections of tumour cells (Guetta *et al.* 1986)
- both strains suppress growth of p815 mastocytoma in mice concurrently infected (Kimsey *et al.* 1986)
- oncogenes from different functional classes cooperate in the responsiveness of cells to attack by MVMp (Legrand *et al.* 1992)
- cooperation of virus proteins (NS1) with oncogenes results in cell death (Mousset *et al.* 1994)

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Mouse parvovirus (MPV)/Rat parvovirus (RPV)

(formerly 'Orphan parvovirus' [OPV])

History

- serological evidence for the existence of additional, antigenetically distinct parvoviruses was found during 1983–1984 in mice and rats
- agents were known as 'orphan' parvoviruses or OPV
- mouse and rat orphan parvoviruses have been identified and characterized and have been renamed mouse parvovirus (MPV) (Ball-Goodrich & Johnson 1994) and rat parvovirus (RPV) (Ball-Goodrich *et al.* 1998)

Host species

- natural host: laboratory and wild rats (RPV) and mice (MPV)

Properties of the virus

- all parvoviruses are highly temperature resistant (Fassolitis *et al.* 1985)
- all parvoviruses are highly resistant to environmental conditions e.g. desiccation (Tattersall & Cotmore 1986, Yang *et al.* 1995, Jacoby *et al.* 1996)
- MPV is distinct from but related to MVM (Ball-Goodrich & Johnson 1994)
- MPV infection persists after seroconversion even in mice inoculated as adults (Smith *et al.* 1993, Jacoby & Ball-Goodrich 1995)
- viral DNA of RPV is detectable in lymphoid tissues for months (Ueno *et al.* 1997)

Strain susceptibility

- none

Organotropism

- viral replication in mitotically active tissues e.g. gastrointestinal tract, lymphocytes, tumours, tropism for lymphoid cells (McKisic *et al.* 1993, Jacoby *et al.* 1996, Shek *et al.* 1998)
- predilection for lymphoid tissues of infant and adult mice (MPV) (Jacoby & Ball-Goodrich 1995) or endothelium and lymphoid tissues of rats (RPV) (Ball-Goodrich *et al.* 1998)
- MPV detectable in pancreas, spleen, lymph nodes, lungs, intestines, kidneys (Smith *et al.* 1993, Besselsen *et al.* 1995)
- RPV detectable in lymph nodes, small intestines, kidneys, spleen, etc. (Ueno *et al.* 1996, Ball-Goodrich *et al.* 1998)

Clinical disease

- infection asymptomatic even in infant and severely immunocompromised mice (SCID mice) (Smith *et al.* 1993, Jacoby *et al.* 1995) and rats (Jacoby & Ball-Goodrich 1995, Ball-Goodrich *et al.* 1998)

Pathology

- no pathology or histological lesions after experimental (i.p., oral) infection (Smith *et al.* 1993, Jacoby *et al.* 1995, Ball-Goodrich *et al.* 1998)

Morbidity and mortality

- infection asymptomatic even in neonatal and infant mice and rats (Smith *et al.* 1993, Jacoby & Ball-Goodrich 1995, Ball-Goodrich *et al.* 1998)

Zoonotic potential

- none

Interference with research

Immunology

- MPV first isolated from a CD8+ T-cell clone that had lost function and viability (McKisic *et al.* 1993)
- inhibition of proliferation of CD8+ and CD4+ T-cell clones stimulated with IL-2 or antigen, but no inhibition of the generation of cytotoxic T-cells in mixed lymphocyte cultures (MLC) (McKisic *et al.* 1993)
- reduced cytolytic capacity of T-cells after MPV infection (McKisic *et al.* 1996)
- MPV diminishes the proliferation rate of lymphocytes from spleen and popliteal lymph nodes, but augments the proliferative response of cells from mesenterial lymph nodes (Jacoby *et al.* 1996, McKisic *et al.* 1996)
- T-cell mediated potentiation of rejection of allogeneic skin grafts by MPV infection, induction of rejection of syngeneic skin grafts (McKisic *et al.* 1998)
- RPV infection may modulate immune function (Ball-Goodrich *et al.* 1998)

Cell biology

- contaminant of cell lines (McKisic *et al.* 1993)
- infection transplantable tumours (Ball-Goodrich *et al.* 1998)

Oncology

- MPV accelerates tumour allograft rejection (McKisic *et al.* 1996)
- contamination of transplantable leukaemia cells by RPV (Ball-Goodrich *et al.* 1998)
- milder disease (reduced hepatosplenomegaly) or delayed onset of clinical signs and leukaemia in RPV infected tumour-bearing rats compared to uninfected rats (Jacoby *et al.* 1996, Ball-Goodrich *et al.* 1998)

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Kilham rat virus (KRV)

Host species
- natural host: laboratory and wild rats
- hamsters and other species such as Mastomys (multimammate mouse) can be infected experimentally (Kilham 1961, Rabson *et al.* 1961, National Research Council 1991)

Properties of the virus
- highly temperature resistant (Fassolitis *et al.* 1985)
- highly resistant to environmental conditions e.g. desiccation (Lum & Schreiner 1963, Tattersall & Cotmore 1986, Yang *et al.* 1995)
- evidence for virus persistence in rats after natural infection (Robey *et al.* 1968, Lipton *et al.* 1973)
- persistent infection after experimental infection of infant and juvenile rats (Paturzo *et al.* 1987, Jacoby *et al.* 1991)
- transplacental transmission (Kilham & Margolis 1966, Kilham & Margolis 1969, Kajiwara *et al.* 1996)
- uterine infection in pregnant rats with severe disease of the fetuses and persistent infection in dams (Gaertner *et al.* 1996)
- persistent infection in T-cell deficient rats (Gaertner *et al.* 1995)
- limited infection in euthymic rats

Strain susceptibility
- none (Jacoby & Ball-Goodrich 1995)

Organotropism
- viral replication only in mitotically active tissues (Tennant & Hand 1970) e.g. embryo, intestines, tumours
- predilection for the developing liver and cerebellum (Kilham & Margolis 1966, Cole *et al.* 1970)

Clinical disease
- infection often asymptomatic (Lum 1970, Robinson *et al.* 1971), but can be severe or lethal, especially in athymic infant rats (Gaertner *et al.* 1991, Jacoby *et al.* 1996)
- cases of spontaneous clinical disease with deaths have been reported (Kilham & Margolis 1966, Coleman *et al.* 1983)
- fetal and neonatal abnormalities (Kilham & Margolis 1975)
- jaundice and ataxia in young rats
- cerebellar hypoplasia and ataxia in hamsters after experimental infection (Kilham & Margolis 1964)
- periodontal disease in hamsters (National Research Council 1991)

Pathology
- haemorrhage and infarction especially in the central nervous system (El Dadah *et al.* 1967, Cole *et al.* 1970, Margolis & Kilham 1970, Baringer & Nathanson 1972)
- intranuclear parvoviral inclusions in areas of necrosis among clinically affected rats (Jacoby *et al.* 1979, Lussier 1991)
- mongoloid-type deformity in newborn hamsters after experimental infection (Baer & Kilham 1962)
- cerebellar lesions in cats after experimental infection (Kilham & Margolis 1965)

Morbidity and mortality
- pathogenic in fetal and infant rats (Jacoby & Ball-Goodrich 1995)
- acute disease in hamsters after experimental infection (Kilham 1961)
- prenatal infections in rats (Jacoby *et al.* 1988)

Zoonotic potential
- none

Interference with research

Pathology
- increased leukocyte adhesion in the aortic epithelium (Gabaldon *et al.* 1992)
- hamsters surviving experimental infection develop stunted growth resembling mongolism (Kilham 1961)

Immunology
- infection of T and B-lymphocytes and suppression of various lymphocyte functions (McKisic *et al.* 1995)
- stimulates autoreactive T-lymphocytes specific for pancreatic antigens (Brown *et al.* 1993)
- virus alters susceptibility to autoimmune diabetes in a rat strain which is normally resistant to this syndrome (Guberski *et al.* 1991, Stubbs *et al.* 1994, Ellermann *et al.* 1996, Chung *et al.* 1997)
- alters cytotoxic lymphocyte activity (Darrigrand *et al.* 1984)
- depresses lymphocyte viability and a variety of T-cell functions e.g. *in vitro* lymphoproliferative responses (Campbell *et al.* 1977a,b)
- stimulates interferon production (Kilham *et al.* 1968)
- increased expression of macrophage-derived cytokines (IL-12, TNF-α, IL-1β) and CD4+ T-cell derived cytokines (IL-2, IFN-γ) (Chung *et al.* 1997)

Physiology
- inhibition of lipid formation in rat kidney cells *in vitro* (Schuster *et al.* 1991)
- increased abortion rate (Kilham & Margolis 1969)
- delayed healing of osseous wounds in hamsters (Engler *et al.* 1966)

Cell biology
- contaminant of cell lines (Hallauer *et al.* 1971)
- persistent infection of cell lines and transplantable tumours (Wozniak & Hetrick 1969, Bass & Hetrick 1978, National Research Council 1991)

Teratology
- transplacental transmission in pregnant hamsters and rats (Kilham & Margolis 1969)
- congenital malformation (Margolis & Kilham 1975)
- death and resorption of fetuses (Kilham & Margolis 1966, Jordan & Sever 1994)

Interactions with other infectious agents
- necrosis in the lung may support secondary colonization with other microorganisms such as *Pasteurella pneumotropica* (Carthew & Gannon 1981)
- KRV together with H-1 and *C. piliforme* can influence the prevalence rate of Yersinia-induced arthritis in rats (Gripenberg-Lerche & Toivanen 1993, 1994)

Oncology
- contamination of transplantable or chemically-induced tumours (Kilham & Olivier 1959, Campbell *et al.* 1977, Nicklas *et al.* 1993)
- contamination of leukaemias or leukaemia virus preparations (Kilham & Moloney 1964, Bergs 1967, Spencer 1967)
- suppression of leukaemia induction by Moloney virus (Bergs 1969, Rommelaere & Tattersall 1990)

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Toolan's H-1 virus (H-1)

Host species
- natural host: laboratory and wild rats (Jacoby *et al.* 1979)
- hamsters and other species can be infected experimentally (Kilham & Margolis 1975, National Research Council 1991)
- mouse cells cannot be infected by H-1 (Tattersall & Cotmore 1986)
- antibodies have been detected in humans (Toolan *et al.* 1962)

Properties of the virus
- highly temperature resistant (Fassolitis *et al.* 1985)
- highly resistant at different pH values, desiccation and other environmental conditions (Greene 1963, Tattersall & Cotmore 1986)

Strain susceptibility
- none

Organotropism
- viral replication only in mitotically active tissues e.g. embryo, intestines, tumours (Jacoby *et al.* 1979, Jacoby *et al.* 1996)
- pathogenic for the developing liver and cerebellum (Jacoby & Ball-Goodrich 1995)

Clinical disease
- no clinical signs after natural infection (National Research Council 1991)
- fetal and neonatal abnormalities (Kilham & Margolis 1975)
- cerebellar hypoplasia and chronic ataxia in young animals after experimental infection (Margolis & Kilham 1975)

Pathology
- no lesions after natural infection
- experimental malformations of the central nervous system, skeleton, and teeth (Kilham & Margolis 1975)
- hepatocellular necrosis after partial hepatectomy (Ruffolo *et al.* 1966)

Morbidity and mortality
- no clinical signs after natural infection
- mongoloid-like deformations in hamsters experimentally infected as newborns (Toolan & Ledinko 1968)

Zoonotic potential
- none, but antibodies to H-1 have been detected in humans (Toolan *et al.* 1962)

Interference with research
Physiology
- delayed healing of bone fractures and altered callus formation (Kilham & Margolis 1975)
- inhibition of lipid formation in rat kidney cells *in vitro* (Schuster *et al.* 1991)
- increased abortion rate (Kilham & Margolis 1969, Jordan & Sever 1994)

Pathology
- hepatocellular necrosis after partial hepatectomy (Ruffolo *et al.* 1966)

Cell biology
- contaminant of permanent human cell lines (Hallauer *et al.* 1971)
- infection of human cells is increased after oncogenic transformation (Toolan & Ledinko 1965, Chen *et al.* 1986, Dupressoir *et al.* 1989, Rommelaere & Cornelis 1991)
- human cells naturally or experimentally transformed with DNA tumour viruses are permissive for H-1 infection (Faisst *et al.* 1989)
- a persistent infection can occur in various human lymphoma-derived cells (Faisst *et al.* 1990)

Immunology
- weak induction of IFN-β, TNF-α and IL-6 *in vitro* (Schlehofer *et al.* 1992)

Teratology
- transplacental transmission in pregnant hamsters and rats (Kilham & Margolis 1969)
- fetal deaths and congenital malformation after inoculation into pregnant hamsters (Ferm & Kilham 1964)

Interactions with other infectious agents
- viral inclusion bodies in animals bearing larval forms of tapeworms (Kilham *et al.* 1970)
- H-1 together with KRV and *C. piliforme* can influence the prevalence rate of Yersinia-induced arthritis in rats (Gripenberg-Lerche & Toivanen 1993, 1994)

Oncology
- greater susceptibility of human oncogenic transformed cells and tumour-derived cell lines than normal untransformed parental cells (Cornelis *et al.* 1988, Rommelaere & Cornelis 1991)
- kills preferentially neoplastic cells, little effect on normal human cells (Telerman *et al.* 1993, Van Pachterbeke *et al.* 1993)
- presence of H-1 virus reduces the number of tumours produced by an oncogenic adenovirus in hamsters (Toolan & Ledinko 1968, Rommelaere & Tattersall 1990)
- reduced incidence of spontaneous tumours in hamsters experimentally infected at birth (Toolan 1967, Toolan *et al.* 1982)
- reduced incidence of chemically-induced tumours in experimentally-infected hamsters (Toolan *et al.* 1982)
- inhibition of tumour formation in nude mice from a transplanted human tumour and retardation of tumour growth (Dupressoir *et al.* 1989)

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Lactate dehydrogenase elevating virus

Host species
- mouse (*Mus musculus*, *Mus caroli*) (Rowsan 1980)

Organotropism
- polytropic strains: liver, spleen, lymph nodes, testis tissue
- neurovirulent strain: LDV-C: central nervous system, anterior horn neurons, leptomeninges
- mucosal barrier to viral transmission

Clinical disease
- life-long asymptomatic, low-level viraemic persistence
- immunosuppressed AKR and C58 strain: poliomyelitis with fatal paralysis
- mice are infected by mechanical transfer of tissues or serum from infected animals
- natural transmission between cage mates is rare

Morbidity and mortality
- morbidity and mortality are very low
- morbidity and mortality depend on host strain, immunodeficiency and presence of murine retroviruses

Zoonotic potential
- none

Important notice
- Detection of LDV: measuring LDH levels in mouse plasma, PCR assay (van der Logt *et al.* 1994)

Interference with research
Oncology
- enhancement of tumour growth (Isakov & Feldmann 1981, McDonald 1983)
- suppression of chemically-induced mouse lung tumorigenesis (Theiss *et al.* 1980) and foreign body tumorigenesis (Brinton-Darnell 1977)
- Contamination of transplantable tumours (Riley *et al.* 1978, Isakov *et al.* 1981, Nicklas *et al.* 1993)
- interactions with oncogenic murine retroviruses: ecotropic murine leukaemia virus (Contag & Plagemann 1988, Contag & Plagemann 1989, Inada & Yamazaki 1991, Inada 1993, Inada *et al.* 1993, Anderson *et al.* 1995)

Interactions with other infectious agents
- impaired resistance to bacterial infection (Bonventre *et al.* 1980)
- inhibits eosinophilic and mast cell responses in mice infected with nematodes (Morimoto *et al.* 1998)

Immunology
- stimulation of B-lymphocyte-activation (Coutelier *et al.* 1990, Bradley *et al.* 1991) and systemic alteration in lymphocyte circulatory pattern (Mongini 1978)
- elevation of immunoglobulin isotype blood levels IgG2a (Cafruny & Plagemann 1982, Coutelier & van Snick 1985, Coutelier *et al.* 1986, Hovinen *et al.* 1990, Li *et al.* 1990)
- LDV modifies the isotypic distribution of antibodies (Gomez *et al.* 1997)
- contaminant of monoclonal antibodies (Nicklas *et al.* 1988)
- induction of interferon production (Evans & Riley 1968, Lagwinska *et al.* 1975, Koi *et al.* 1981, Lussenhop *et al.* 1982, Nicklas *et al.* 1988)
- influence on immunogenic function of macrophages and macrophage-dependent immunoresponse (Isakov *et al.* 1982, Ritzi *et al.* 1982)
- enhancement of natural killer cell activity (Koi *et al.* 1981) and elevation of cytotoxic T-lymphocytes (Even *et al.* 1995)
- reduction of autoantibody production (Hayashi *et al.* 1992, Verdonck *et al.* 1994)
- suppression of cell-mediated immune responses; inhibition of cytokine production IL-4, IL-1 (Hayashi *et al.* 1991, Monteyne *et al.* 1993)

Physiology
- changes in haemopoiesis after tumour transplantation (Motycka *et al.* 1981, Viktora *et al.* 1981)
- suppression of development of glomerulonephritis in autoimmune NZB-mice (Hayashi *et al.* 1993, Kameyama & Hayashi 1994)
- decrease in incidence of diabetes in NOD-mice (Takei *et al.* 1992) and reduction of streptozotocin-induced diabetes mellitus in CD-1-mice (Hayashi *et al.* 1994)
- changes in clearance capacity for several enzymes and proteins (Winkelhake *et al.* 1978, Brinton and Plagemann 1983, Hayashi *et al.* 1988, Nakayama *et al.* 1990, Hayashi *et al.* 1992)
- increase in level of serum lactate dehydrogenase and other enzymes (Brinton 1982)
- mucosal barrier to LDV transmission exists (Cafruny & Hovinen 1988, Cafruny *et al.* 1991, Broen *et al.* 1992)

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Mouse adenoviruses

- mouse adenovirus type 1 (MAd-1) (strain FL)
- mouse adenovirus type 2 (MAd-2) (K87)

Host species
- mouse (positive serological results in rats are most likely due to a yet unidentified rat adenovirus (Smith & Barthold 1987)

Organotropism
- MAd-1: polytropic
- MAd-2: intestine

Clinical disease
- none in naturally infected immunocompetent animals
- wasting disease in athymic mice

Pathology
- MAd-1:
  - only experimental infections described
  - necrotic foci and intranuclear inclusion bodies in various organs (brown fat, myocardium, adrenal glands etc.)
- MAd-2:
  - only intestine affected
  - intranuclear inclusion bodies in mucosal epithelium
  - little inflammation

Morbidity and mortality
- morbidity: no information, mortality: none in natural infections
- significant strain differences in susceptibility (×6000) (Kring *et al.* 1995)

Zoonotic potential
- none

Special considerations
- naturally occurring MAd-1 has not been reported for many years
- prevalence of MAd-2 is largely unknown in Europe (in Australian wild mice: 37% (Smith *et al.* 1993)
- MAd-1 and MAd-2 do not cross-react serologically

Interference with research

Immunology
- transient increase in IL-12 release from macrophages (Coutelier *et al.* 1995)

Interactions with other infectious agents
- raises susceptibility to *E. coli* pyelonephritis during persistent infection (Ginder 1964)
- accelerates experimental scrapie infection (Ehresmann & Hogan 1986)

Physiology
- induces blood-brain barrier dysfunction (Guida *et al.* 1995)

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Lymphocytic choriomeningitis virus

Host species
- natural host (may transmit virus): laboratory and wild mice, pet and laboratory hamsters
- aberrant hosts (no virus transmission): most rodents, dogs, non-human primates, humans
- some continuous cell lines are virus carriers, e.g. mouse neuroblastoma (N18), baby hamster kidney cells (BHK-21) and transplantable tumour cells of infected animals

Organotropism
- kidney
- salivary gland
- lymphohaemopoietic cells
- other organs

Clinical disease
- clinical signs vary with age and strain of infected animals, route of inoculation and strain of virus
- natural infection in mice and hamsters:
  - perinatal: persistent infection, 'late disease' (wasting at 7–10 months of age)
  - adult: acute infection, inapparent
- experimental:
  - parenteral inoculation: visceral form in mice shows asymptomatic conjunctivitis, ascites, somnolence
  - intracerebral inoculation: lymphocytic choriomeningitis
  - autoimmune haemolytic anaemia in different mice strains (Coutelier 1994)
- febrile illness, grippe-like symptoms in humans (Maetz 1976)
- sensorineural deafness and labyrinth damage, meningeal involvement in humans (Hirsch 1976)

Pathology
- natural infection in mice and hamsters:
  - perinatal: antigen-antibody-immune-complex glomerulonephritis at the age of 7–10 months
- experimental infection: T-cell mediated immune disease
  - inflammatory lesions in many organs
  - murine hepatitis (Lohler 1994, Gossmann 1995)

Morbidity and mortality
- LCMV strain ARM is avirulent for different hamster strains and guineapig (Genovesi 1987, Genovesi 1989)
- LCMV strain WE causes 100% mortality in guineapigs (Riviere 1985) and high morbidity of inbred Syrian hamsters
- prevalence of LCMV in different hamster inbred strains is known (Genovesi 1987)

Zoonotic potential
- congenital lymphocytic choriomeningitis virus syndrome in humans (El Karamany 1991, Wright *et al.* 1997)
- LCMV is the causative agent for hamster associated lymphocytic choriomeningitis infection of humans (Maetz 1976, Ackermann 1977, Garman 1977, Lehmann-Grube 1979)
- hamsters transmit the virus to humans (Rousseau *et al.* 1997, Marrie & Saron 1998)
- virus is shed in saliva, nasal secretions and urine of infected animals
- wild mice and rats are a natural reservoir of infection (Ackermann 1964, Smith 1993)

Interference with research
Immunology
- LCMV influences humoral and cellular immune response (Oxenius *et al.* 1998)
- LCMV causes a long-lasting immunodepression with decrease of proliferation capacity of splenic T-lymphocytes (Thomson 1982, Saron 1990, Saron 1991, Colle 1993, El-Azami-El-Idrissi *et al.* 1998)
- LCMV induces polyclonal cytotoxic T-lymphocyte stimulation (Yang 1989, Bocharov 1998)
- neonatally or congenitally infected mice have a lifelong chronic lymphocytic choriomeningitis virus infection (Jamieson 1987)
- enhances the interleukin 12-mediated immunotoxicities (Orange 1994, Orange 1995)
- LCMV induces different expression of alpha/beta interferons (Sandberg 1994)
- LCMV induces a transient bone marrow aplasia (Binder *et al.* 1997)

Oncology
- may influence experimental oncology, enhances the frequency of lymphoma after treatment with carcinogen (Garman 1977)
- enhances the susceptibility for transplantable tumour cell lines (Kohler 1990)

Physiology
- growth hormone deficiency can occur (Oldstone 1985)

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Clostridium piliforme

(formerly *Bacillus piliformis*)

Host species
- all laboratory animals, other mammals (Tyzzer 1917, Fries 1977)

Properties
- spores are relatively resistant to formaline
- relatively sensitive to heat and certain chemical disinfectants (Itoh *et al.* 1987)

Susceptibility
- depending on genetic factors of the host (Waggie *et al.* 1981, Hansen *et al.* 1990)
- antigenetic differences among isolates of bacteria (Boivin *et al.* 1993, Franklin *et al.* 1994)

Organotropism
- intestine
- liver
- heart

Clinical disease and pathology
- anorexia and diarrhoea of different severity
- hypertrophy and inflammation of the ileum
- focal necrosis in the liver and/or heart possible (Fries 1977)
- mesenteric lymphadenopathy
- brain lesions in experimentally-infected *Mystromys albicaudatus* (Waggie *et al.* 1986)

Morbidity and mortality
- inapparent infection, high mortality possible (breeding colonies)
- susceptibility to infection seems to depend on genetic factors of the host (Waggie *et al.* 1981, Hansen *et al.* 1990)
- isolates of different origin show heterogenicity and host specificity (Franklin *et al.* 1994)
- different strains of *C. piliforme* are likely to exist (Boivin *et al.* 1993)

Zoonotic relevance
- one case of human infection in an AIDS patient has been reported (Smith *et al.* 1996)

Notice
- *C. piliforme* is an obligate intracellular parasite forming spores. It does not grow on cell-free media. Cultivation in cell lines and embryonated eggs is possible (Riley *et al.* 1990, Spencer *et al.* 1990)
- diagnosis with IFA (Fries 1977), ELISA and Western blot (Motzel *et al.* 1991), PCR (Duncan *et al.* 1993, Goto & Itoh 1994)

Interference with research

Immunology
- depletion of neutrophils or natural killer cells increased severity of disease in juvenile mice (Van Andel *et al.* 1997)

Physiology
- causes megaloileitis in Sprague-Dawley rats (Hansen *et al.* 1992)
- alters the pharmacokinetics of warfarin and trimethoprim in mice (Fries & Ladefoged 1979)
- alters serum level of hepatic enzymes (Naiki *et al.* 1965)

Toxicology
- dose-related exacerbation of Tyzzer's disease by carbon tetrachloride in weanling mice (Takenaka & Fujiwara 1975)

Interactions with other infectious agents
- lower susceptibility to experimental arthritis caused by *Y. enterocolitica* (Gripenberg *et al.* 1993)

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Corynebacterium kutscheri

Host species
- mouse, rat, (guineapig, hamster)

Organotropism
- respiratory tract (other organs)
- middle ear
- superficial tissue
- generalization

Clinical disease
- inapparent in most strains of immunocompetent mice and rats
- abscesses of superficial tissue with micro-abscessation of various internal organs
- pneumonia in some strains of rats

Morbidity and mortality
- up to 100% of animals are infected
- 5–60% of susceptible strains show clinical signs (Amao *et al.* 1993)
- no age or sex prevalence are known

Zoonotic potential
- *C. kutscheri* was isolated from umbilical cord and other surface in an infant (Fitter *et al.* 1979)

Interference with research
Infection with this agent is usually subclinical in rats and mice and results in disease expression only after severe immunosuppression, by exposure to experimental regimens, dietary deficiencies, or concurrent infection with other agents

Physiology
- disease has been active in animals used in studies of dietary deficiency (Zucker & Zucker 1954), gamma irradiation (Schechmeister & Alder 1953), cortisone administration (Takagaki *et al.* 1967), or by other infectious disease, for example infectious ectromelia (Lawrence 1957)

Immunology
- components of *C. kutscheri* may stimulate type-1 helper T-cells to produce IL-2 and IFN-gamma and the enhanced cytokine production could contribute to the non-specific resistance induced by this bacterium (Kita *et al.* 1992)

Oncology
- a T-cell mitogen of *C. kutscheri* induced a tumourlytic factor in mice (Kita *et al.* 1995)

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Citrobacter rodentium
(formerly *C. freundii* 4280)

Host species
- mouse

Organotropism
- large bowel

Clinical disease
- pasty dark faeces and dehydration
- variable incidence of rectal prolapse in mice of all ages is indicative of infection (Brennan *et al.* 1965 and others)
- increased morbidity and mortality in immunocompromised transgenic mice (Maggio-Price *et al.* 1998)

Morbidity and mortality
- usually low in an affected population
- mortality or runting is seen in weaning-age mice
- diminished reproduction, and failure to thrive in affected population

Zoonotic potential
- none

Interference with research
Physiology
- experimental stress can precipitate more severe disease among infected mice

Oncology
- *C. rodentium*-induced hyperplasia can alter the large bowel chemical carcinogenesis (Barthold & Jonas 1977, Barthold & Beck 1980)
- hyperplastic lesions may be confused with neoplasia because cytokinetics share several common features with neoplasia (Pullinger & Iversen 1960, Barthold 1979)

Immunology
- altered immune response in infected mice (Maggio-Price *et al.* 1998)

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Mycoplasma pulmonis

Host species
- rat, mouse: some inbred mice strains are highly resistant to disease, e.g. C57/BL (Cartner *et al.* 1996)
- rarely found in rabbits and guineapigs (Cassell & Hill 1979)

Organotropism
- respiratory epithelium
- middle ear
- genital tract

Clinical disease
- common chronic respiratory infection in rats and mice (Lindsey & Cassell 1973)
- acute bronchopneumonia in combination with other pneumotropic infections or extrinsic factors found in poorly managed conventional colonies such as high NH_3 exposure (Broderson *et al.* 1976, Schoeb *et al.* 1982) or nutritional deficiencies
- sneezing, conjunctivitis, otitis media
- genital tract infections with reduction in fertility
- arthritis after experimental infection of mice and rats (Barden & Tully 1969, Cole *et al.* 1975, Cassell & Hill 1979)
- hydrocephalus after experimental infection of neonate rats and hamsters (Kohn *et al.* 1977)

Morbidity and mortality
- both low under optimal husbandry conditions
- high morbidity and mortality in combination with other pneumotropic infections or extrinsic factors

Interference with research
Oncology
- influence on carcinogenesis (increase or decrease in tumour induction following exposure to carcinogen) (Cassell *et al.* 1986)

Physiology
- *M. pulmonis* infections in rats result in 'neurogenic inflammation', an increased immunoreactivity of substance P due to increased expression of NK1 receptors (McDonald *et al.* 1991, Bowden *et al.* 1994, Baluk *et al.* 1997, Norlander *et al.* 1997)
- *M. pulmonis* infection in the rat induces a degenerative loss of nerve fibres in the peribronchial area (Nohr *et al.* 1996)
- *M. pulmonis* infection and interaction with the tracheal epithelial cells triggers the expression of peroxidase activity (Brennan & Feinstein 1969, Moriguchi *et al.* 1989, Kinbara *et al.* 1992)
- *M. pulmonis* infection modulates experimentally-induced arthritis in rats (Taurog *et al.* 1984)
- *M. pulmonis* induces alteration in epithelial ion transport in tracheal epithelial cells of mice *in vitro* (Lambert *et al.* 1998)
- respiratory tract: damage of airway epithelial and alveolar epithelial cells, mucus secretion, in severe cases bronchitis, bronchiectasis, emphysema and abscesses in the lungs (Cassell *et al.* 1986)
- elevated lung lysophospholipase activity after experimental infection of rats (Laubach *et al.* 1978)
- chronic mycoplasmal infections interfere with gerontological studies, nutrition, toxicology and behavioural research (Lindsey *et al.* 1971)
- marked leukocytosis, mainly caused by increased lymphocyte numbers (Cole *et al.* 1975)

Immunology
- *M. pulmonis* activates the mitogenic activity of both rat B and T-lymphocytes (Naot *et al.* 1979)
- *M. pulmonis* infection augments splenic NK cell activity in mice (Lai *et al.* 1987, Kamiyama *et al.* 1991)
- *M. pulmonis* infection in mice is associated with modification of gene expression of various cytokines in the respiratory tract (Nishimoto *et al.* 1994, Faulkner *et al.* 1995)
- *M. pulmonis* infection in rats and mice suppresses the humoral antibody response to sheep red blood cells (Aguila *et al.* 1988, Lai *et al.* 1989)
- *M. pulmonis* possesses a chemo-attractant protein for resting rat B-lymphocytes (Ross *et al.* 1992)
- non-specific mitogenic effect upon lymphocytes (Cassell *et al.* 1986)
- suppression of interferon induction (Cassell *et al.* 1986)
- since *M. pulmonis* and *M. arthritidis* can persist for months and years in many organs (also spleen) a diversity of effects on the immune system have been described. Cassell *et al.* (1986) have postulated three general mechanisms: (i) delay or prevention of antigenic recognition, (ii) derangement of immune regulations, or (iii) evasion of effector mechanisms
- mice deficient in the fifth component of complement (C5) develop more severe arthritis after artificial infection with *M. pulmonis* than immunologically normal mice (Keystone *et al.* 1978)
- mitogenic stimulation of lymphocytes is dependent on the rat strain (Naot *et al.* 1984, Davis *et al.* 1985)

Interactions with other infectious agents
- *M. pulmonis* exacerbates rat coronavirus infection in rats (Schunk *et al.* 1995)
- synergistic effects of *M. pulmonis* and viruses have been demonstrated *in vitro* (Westerberg *et al.* 1972)

Reproductive physiology
- genital tract: negative influences on *in vitro* and *in vivo* fertilization, on fetal development and drop in fertility (Fraser & Taylor-Robinson 1977, Brown & Steiner 1996)
- rats infected during the third trimester had severe fetal losses, earlier infection caused fetal resorption (Steiner & Brown 1993, Brown & Steiner 1996)
- *M. pulmonis* infection causes male and female infertility in rats and mice (Cassell *et al.* 1981, Swenson, 1982)

- *M. pulmonis* binds to and degrades sperm sulfogalactosylglycerolipid in rats inducing infertility (Lingwood *et al.* 1990)
- intrauterine infection of rat embryos (Juhr *et al.* 1988)
- *M. pulmonis* is not eradicated from fertilized eggs by washing and may be transmitted during embryo transfer or embryo freezing (Hill & Stalley 1991)

Teratology

- modification of teratogenesis of cyclophosphamide (Juhr & Ratsch 1990)

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Helicobacter spp.

Host species

Helicobacter spp. have been isolated from many species of laboratory animals. Different bacterial species have been found, e.g. in mice, rats, hamsters. Various isolates exist which have not yet been identified, and it is expected that several additional species colonizing laboratory rodents will be described in the near future.

- mouse: *H. hepaticus* (Fox *et al.* 1994), *H. bilis* (Fox *et al.* 1995), *H. muridarum* (Lee *et al.* 1992), *H. rodentium* (Shen *et al.* 1997), '*Flexispira rappini*' (Schauer *et al.* 1993)
- rat: *H. troglontum* (Mendes *et al.* 1996), *H. muridarum* (Lee *et al.* 1992), *H. hepaticus*, *H. bilis* (Haines *et al.* 1998)
- hamster: *H. cholecystus* (Franklin *et al.* 1996), *H. cinaedi* (Kiehlbauch *et al.* 1995)

Organotropism

- intestinal tract
- liver

Clinical disease

- chronic proliferative hepatitis (Fox *et al.* 1996, Franklin *et al.* 1998)
- increased risk of hepatic tumours (Ward *et al.* 1994, Fox *et al.* 1996)
- inflammatory large bowel disease in immunodeficient mice (Ward *et al.* 1996, Cahill *et al.* 1997, Shomer *et al.* 1997, Foltz *et al.* 1998) and rats (Haines *et al.* 1998)
- may induce gastritis (*H. muridarum*) (Phillips & Lee 1983)

Pathology

- single to multiple yellow to grey foci in the liver with coagulative necrosis of the hepatocytes and variable infiltration of lymphocytes, macrophages and neutrophils (Fox *et al.* 1996)
- chronic active hepatitis in SCID mice (Franklin *et al.* 1998)
- hepatoma and hepatocellular carcinoma in A/JCr mice (Ward *et al.* 1994)
- various degrees of typhlitis, colitis and proctitis and rectal prolapse with severe proctitis in immunodeficient mice (Ward *et al.* 1996, Cahill *et al.* 1997, Shomer *et al.* 1997)

Morbidity and mortality

- up to 100% of a colony affected
- only 10% of the infected mice show changes in the liver
- infections are usually subclinical
- about 5% of the immunodeficient mice developed rectal prolapse (Ward *et al.* 1996)

Zoonotic potential

- not known (e.g. '*Flexispira rappini*' has been isolated from humans (Schauer *et al.* 1993)

Interference with research

- the consequences of infection have not been completely characterized

Physiology

- infection changes serum enzyme values and bile acids (Ward *et al.* 1994)

Toxicology

- infection may influence toxicologic studies which are produced by hepatotoxic substances (Taylor *et al.* 1995)

Oncology

- may influence experimental oncology (spontaneous development of hepatomas; Fox *et al.* 1996, 1998)
- increased the incidence of induced hepatocellular adenomas, accelerated the development of liver tumours, and increased the multiplicity of the lesions (Diwan *et al.* 1997)

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Pneumocystis carinii

Host species
- laboratory animals (Smulian & Walzer 1992)
- wide range of domestic animals, monkeys, humans

Organotropism
- lungs
- occasionally other organs or generalization to eyes, skin, etc.

Clinical disease
- inapparent in immunocompetent hosts
- slowly progressive chronic pneumonia with weight loss in immunocompromised host

Pathology
- slight infection: multifocal alveolar aggregates of cysts and interstitial/perivascular non-purulent infiltration (Walzer *et al.* 1980, Chen *et al.* 1990)
- severe infection: consolidated lungs; extensive lung areas involved with alveolar aggregates of cysts (eosinophilic, honeycombed material), proliferation of type II pneumocytes and severe interstitial fibrosis
- extrapulmonary manifestation of *P. carinii* infection by haematogenous or lymphatic spread is possible; major sites are lymph nodes, bone marrow, liver, and spleen, characterized by eosinophilic honeycombed material with inflammatory response
- multinucleated giant cells in murine *P. carinii* pneumonia (Hanano *et al.* 1996)

Morbidity and mortality
- conventionally bred colonies may be persistently infected because of subclinical nature in immunocompetent hosts (Frenkel *et al.* 1966)
- high morbidity and mortality with chronic progressive pneumonia in immunosuppressed animals

Zoonotic relevance
- *P. carinii* is not universally transmissible between mammalian species (Gigliotti *et al.* 1993)
- respiratory mode of transmission (Hughes 1982)
- most common opportunistic infection and leading cause of morbidity and mortality in AIDS patients

Interference with research
Physiology
- *P. carinii* pneumonia leads to alterations in compliance and lung mechanisms (Brun-Pascaud *et al.* 1985, Stokes *et al.* 1986)
- *P. carinii* may alter the amount and type of surfactant produced: *P. carinii* pneumonia in rats leads to a decrease in surfactant phospholipids in bronchoalveolar lavage (Kernbaum *et al.* 1983, Sheehan *et al.* 1986). *P. carinii* organisms can directly inhibit secretion of phosphatidylcholin from type II cells (Rice *et al.* 1993). Bronchoalveolar lavage phosphatidylglycerol is reduced in rats with *P. carinii* pneumonia (Su *et al.* 1996). Surfactant protein-A levels increase during *P. carinii* pneumonia in the rat (Phelps *et al.* 1996)
- attachment of *P. carinii* to alveolar macrophages occurs by a fibronectin- and calcium-dependent mechanism, but does not trigger a phagocytic response (Pottratz & Martin 1990a,b). *P. carinii* glycoprotein A binds macrophage mannose receptors, thereby mediating binding and uptake of *P. carinii* by alveolar macrophages (Ezekowitz *et al.* 1992, O'Riordan *et al.* 1995). Surfactant protein A can function as a ligand between *P. carinii* and alveolar macrophages (Williams *et al.* 1996)
- attachment of *P. carinii* to type I pneumocytes leads to their degeneration and to proliferation of type II pneumocytes
- following attachment of *P. carinii* to type I cells, surface glycocalyx is decreased and alveolar-capillary permeability is increased (Lanken *et al.* 1980, Yoneda & Walzer 1980, 1981, 1984). As a consequence of dysplasia and disruption of the epithelium, underlying material gains access to the alveolar space and impairs normal lung function
- *P. carinii* attachment increases expression of fibronectin-binding integrins on cultured lung cells (Pottratz *et al.* 1994)
- *P. carinii* and IFN-gamma induce rat alveolar macrophages to produce nitric oxide (Sherman *et al.* 1992)
- the mitochondrial ATPase 6 gene is upregulated in *P. carinii*-infected rat lungs (Asnicar *et al.* 1996)
- *P. carinii* infection alters GTP-binding proteins in the lung (Oz & Hughes 1997)
- *P. carinii* inhibits cyclin-dependent kinase activity in lung epithelial cells (Limper *et al.* 1998)
- fibrinogen expression is induced in the lung epithelium during *P. carinii* pneumonia (Simpson-Haidaris *et al.* 1998).

Immunology
- high risk for all congenitally immunodeficient hosts and for experimental models of immunosuppression
- *P. carinii* from different host species are immunologically distinct (Gigliotti & Harmsen 1997)
- *P. carinii* induces activating and inhibitory innate cellular immune response mechanisms (Warschkau *et al.* 1998)
- cellular immunity is important for protection against *P. carinii* pneumonia (Furuta *et al.* 1984, 1985)
- *P. carinii*-reactive CD4+ lymphocytes may contribute to the host's response via secretion of macrophage-activating cytokines (IFN-gamma and others) as well as by the production of signals that induce foster expansion of the antibody-forming pool of B-cells and cytotoxic CD8+ lymphocytes (Beck *et al.* 1993)
- protective immunity against *P. carinii* is mediated by CD4+ T-cells (reviewed by Hanano & Kaufmann 1998)

- neutrophils, alveolar type II epithelial cells, B-cells, CD8+ lymphocytes, antibodies and cytokines, such as IFN-gamma and TNF, participate in host effector mechanisms against *P. carinii* (Masur & Jones 1978, Von Behren & Pesanti 1978, Shear *et al.* 1989, Pesanti 1989, 1991, Chen *et al.* 1992, Beck *et al.* 1996, Marcotte *et al.* 1996, Garvy *et al.* 1997, Kolls *et al.* 1997)
- *P. carinii* induces TNF-alpha production from monocyte and macrophage cultures with a peak within 8 h of incubation (Tamburrini *et al.* 1991)
- *P. carinii* glycoprotein A stimulates IL-8 production and inflammatory cell activation in alveolar macrophages and cultured monocytes (Lipschik *et al.* 1996)
- *P. carinii* induces expression of ICAM-1 and IL-6 in lung epithelial cells (Yu & Limper 1997, Pottratz *et al.* 1998)

Interactions with other infectious agents

- neutrophils in bacterial pneumonia may participate in host effector mechanisms against *P. carinii* (Pesanti 1982)

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Toxoplasma gondii
(description for intermediate hosts)

Host species
- cat (definitive host) (Jones 1973, Wong & Remington 1993)
- all laboratory and domestic animals, birds and humans (intermediate hosts)
- differential host species susceptibility is reviewed by Innes (1997)

Organotropism
- central nervous system (Jones 1973, Wong & Remington 1993)
- muscle and other organs may also be involved

Clinical disease
- usually inapparent
- occasionally neurological symptoms and/or febrile disease

Morbidity and mortality
- largely depending on the route of infection, parasite strain and dose, and the immunologic state of the host (Dubey & Frenkel 1973, Fernando 1982, Suzuki *et al.* 1988)
- clinical disease most likely in young animals or immunocompromised hosts
- resistance to acute infection and formation of cysts in the brain of mice are genetically controlled (Araujo *et al.* 1976, Williams *et al.* 1978)
- in mice, differences in the gene(s) of MHC, within the H-2D region, correlate with resistance or susceptibility to development of *Toxoplasma* encephalitis (Jones & Erb 1985, Suzuki *et al.* 1991, Blackwell *et al.* 1993)
- age, gender, and pregnancy influence susceptibility to *T. gondii* infection in mice (Johnson *et al.* 1995, Thouvenin *et al.* 1997, Walker *et al.* 1997).

Zoonotic relevance
- transmission to man from other intermediate hosts only by ingestion of uncooked tissues containing *T. gondii* (Dubey 1994)

Interference with research
Physiology
- mice infected with *T. gondii* exhibit ovarian dysfunction with uterine atrophy and thyroidal dysfunction (decline in serum thyroxine levels), probably due to impaired release of hypothalamic releasing hormones (Stahl *et al.* 1995a,b, Stahl *et al.* 1998)
- *T. gondii* infection increases toxicity of some drugs (e.g. neostigmine) (Starec *et al.* 1997).

Pathology
- central nervous system: organisms intra- or extracellular in the neuropil, within granulomatous encephalitis, glial nodules or perivascular infiltration; occasionally accompanied by meningitis and/or scattered neuronal degeneration; occasionally fibrinoid necrosis of vessel walls in association with microthrombi in the centres of small necrotic foci (Sasaki *et al.* 1981, Hay *et al.* 1984, Kittas *et al.* 1984, Ferguson & Hutchinson 1987, Ferguson *et al.* 1991)
- lesions in immunocompromised hosts may lack inflammatory infiltrates and solely consist of small necrotic foci and scattered cysts (Buxton 1980, Johnson 1992)
- muscle and other organs may be involved with necrotic foci, granulomas and pseudocysts

Immunology
- acute and chronic *T. gondii* infection modulate the immune responses in mice (Nguyen *et al.* 1998)
- *T. gondii* is able to induce transient immune downregulation (Channon & Kasper 1996, Denkers *et al.* 1996, Khan *et al.* 1996)
- *T. gondii*-infected cells are resistant to multiple inducers of apoptosis (Nash *et al.* 1998)
- gamma delta T-cells induce expression of heat shock protein 65 in macrophages of mice infected with *T. gondii*, thereby preventing the apoptosis of infected macrophages (Hisaeda *et al.* 1997)
- intracellular *T. gondii* interferes with the MHC class I and class II antigen presentation pathway of murine macrophages (Luder *et al.* 1998)
- CD4+ and CD8+ T-lymphocytes appear to act in concert to prevent reactivation of chronic *T. gondii* infection (Brown & McLeod 1990, Araujo 1991, Gazzinelli *et al.* 1992c)
- NK cell activity and production of IFN-gamma are increased during the course of *T. gondii* infection in mice; IFN-gamma plays a critical role in preventing cyst rupture and toxoplasmic encephalitis (Hauser *et al.* 1982, Suzuki *et al.* 1989, Sher *et al.* 1993, Hunter *et al.* 1994a)
- cytokine levels are elevated in infected humans and in murine models of toxoplasmosis. Overview about immunopathology of *T. gondii* infection: Beaman *et al.* 1992, Gazzinelli *et al.* 1993, Subauste & Remington 1993, Hunter & Remington 1994, Hunter *et al.* 1994b
- IL-12 is crucial for the generation of both innate resistance mechanisms during the acute phase of infection and T cell-dependent acquired immunity during the chronic phase (Johnson & Sayles 1997)
- various other cytokines, such as IFN-beta, IL-1, IL-4, IL-6, IL-10, TGF-beta, and TNF-alpha, are implicated in the pathogenesis of *T. gondii* infection (Chang *et al.* 1990, Orellana *et al.* 1991, Gazinelli *et al.* 1992b, Sher *et al.* 1993, Hunter *et al.* 1995a,b, Roberts *et al.* 1996, Bessieres *et al.* 1997, Neyer *et al.* 1997, Deckert-Schluter *et al.* 1998, Jebbari *et al.* 1998)
- inducible nitric oxide is essential for host control of chronic *T. gondii* infection (Scharton-Kersten *et al.* 1997)
- innate resistance mechanisms during *T. gondii* infection are reviewed by Alexander *et al.* (1997); T

cell-mediated immunity during *T. gondii* infection is reviewed by Denkers and Gazzinelli (1998)

Interactions with other infectious agents

- macrophage clearance and killing of *Listeria monocytogenes* and *Salmonella typhimurium* are decreased in mice infected with *T. gondii* (Wing *et al.* 1983)
- infection with murine leukaemia virus may lead to reactivation of chronic *T. gondii* infection (Gazzinelli *et al.* 1992a, Watanabe *et al.* 1993)
- infection with murine cytomegalovirus results in reactivation of *Toxoplasma pneumonia* (Goetz & Pomeroy 1996)
- mice infected with *T. gondii* are resistant to proliferation of *Cryptococcus neoformans* cells in the brain (Aguirre *et al.* 1996)

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Encephalitozoon cuniculi

Host species
- rabbit (principal host), guineapig, hamster, rat, mouse (Wilson 1979, Canning *et al.* 1986)
- dog, some wild and zoo animals

Organotropism
- brain/spinal cord
- kidney
- liver

Clinical disease
- usually inapparent (Schmidt & Shadduck 1983, Liu *et al.* 1988, Illanes *et al.* 1993)
- occasionally (most often seen in rabbits) neurological disturbances such as torticollis, paralysis, blindness, aggression

Pathology
- nervous system: multifocal parenchymal and perivascular cell infiltrations, granulomas with pseudocysts, occasional necrotic foci, occasional meningeal lymphocytic infiltrates (Shadduck & Pakes 1971, Cox & Gallichio 1978, Gannon 1980b, Majeed & Zubaidy 1982)
- kidneys: multifocal interstitial nephritis, occasional granulomas with pseudocysts
- liver: occasional granulomas
- in immunocompromised hosts possibly aggregates of pseudocysts with minimal inflammatory reaction in various organs
- two to three weeks after intraperitoneal inoculation, mice develop ascites

Morbidity and mortality
- because of the subclinical nature and multiple routes of transmission, undetected infection can persist in a colony with up to 95% infected animals (Gannon 1980a)
- morbidity and mortality depend on host strain, generally very low with only single cases of clinical disease in immunocompetent animals
- different susceptibility to *E. cuniculi* in different inbred strains of mice (Niederkorn *et al.* 1981)

Zoonotic relevance
- spores are excreted via urine, infection of humans is possible. However, only rare cases of human disease have been reported, and susceptibility of man to *E. cuniculi* is not well known

Interference with research
Physiology
- rabbits infected with *E. cuniculi* have lower levels of catecholamines than non-infected rabbits (Levkut *et al.* 1997)

Immunology
- uptake of *E. cuniculi* by host macrophages (Weidner 1975, Cox *et al.* 1979)
- T-cells may act by releasing lymphokines to activate macrophages which can then kill the parasite (Schmidt & Shadduck 1984)
- murine peritoneal macrophages can be activated with LPS and IFN-gamma to kill *E. cuniculi in vitro* (Didier & Shadduck 1994). Reactive nitrogen intermediates may contribute to the parasite killing (Didier 1995)
- during early stages of *E. cuniculi* infection, murine spleen cells express significantly lower blastogenic responses to T-cell mitogens than uninfected mice (Didier & Shadduck 1988)
- depressed T-lymphocyte response to blastogenic stimuli, together with hypergammaglobulinemia (IgG, IgM) was found in neonatal dogs (Szabo & Shadduck 1987). In rodents, transient suppression of cell mediated immune responses and no evidence of hypergammaglobulinemia was found, thus indicating species specificity of immune effects
- rabbits infected with *E. cuniculi* show inconsistent response to neural device biomaterial and are thus inadequate test systems for tissue compatibility testing of such materials (Ansbacher *et al.* 1988)
- immune response to the immunogen *Brucella abortus* is altered (elevated IgM, depressed IgG) in rabbits naturally infected with *E. cuniculi* (Cox 1977).

Interactions with other infectious agents
- mice infected with *E. cuniculi* are more resistant to intracerebral inoculation with *Chlamydia trachomatis* than non-infected mice (Lepine & Sautter 1949)

Oncology
- infected rats which were injected with sarcoma cells had a 50% longer survival time than controls (Petri 1965)
- in infected mice, the growth of several transplantable tumours was reduced and the life-span of the host was prolonged (Arison *et al.* 1966)

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Oxyurina (Pinworms)
(*Syphacia obvelata*, *Syphacia muris*, *Aspiculuris tetraptera*)

Host species
- *Syphacia obvelata*: mainly mouse (also rat, hamster, gerbil, wild rodents)
- *Syphacia muris*: mainly rat (also mouse, hamster, gerbil, wild rodents)
- *Aspiculuris tetraptera*: mouse, rat (rarely), wild rodents

Organotropism
- intestinal tract: *Syphacia* spp. primarily caecum/rectum; *Aspiculuris* spp. primarily colon

Life cycle
Syphacia
- direct cycle which requires only 11–15 days. Gravid females deposit their eggs in the perianal region. The eggs become infectious within 6 h
- three possible infectious routes:
  - direct: by ingestion of embryonated eggs from the perianal region
  - indirect: by ingestion of food or water contaminated with embryonated eggs
  - retroinfection: when eggs hatch in the perianal region and the larvae migrate back into the colon by way of the anus (Flynn 1973)

Aspiculuris
- direct cycle requires 23–25 days. Females lay their eggs in the colon and the eggs leave the host on faecal pellets. The eggs become infectious after 6–7 days at room temperature
- infection by ingestion of infectious eggs (Flynn 1973)

Clinical disease
- subclinical
- symptoms are: poor condition, rough hair coats, reduced growth rate, rectal prolapse (Hoag 1961, Harwell & Boyd 1968, Jacobson & Reed 1974)
- animals infected experimentally with *S. muris* grew more slowly than uninfected animals (Wagner 1988)
- infection with *S. muris* retards the growth of young mice and accelerates the development of their hepatic monooxygenase system (Mohn & Philipp 1981)
- no clinical signs in experimentally infected animals (Flynn 1973, Wescott 1982)

Pathology
- the prevalence of pinworms in an infected rodent population depends on age, sex and host immune status
- in enzootically infected colonies, weanlings develop the greatest parasite loads, males are more heavily parasitized than females
- *Syphacia* spp. numbers diminish with increasing age of the host (Wescott 1982)
- athymic (nu/nu) mice have increased susceptibility (Jacobson & Reed 1974)
- *Mastomys coucha* is more susceptible than the BALB/c mouse (Higgins-Opitz *et al.* 1990)
- in rats the infestation rates of *S. muris* were higher in the WKY strain than in the SHR strain (Lübcke *et al.* 1992)
- increase in resistance to pinworm infection with advancing age of rats (Wagner 1988)
- pinworms of laboratory rodents are generally not considered pathogens (Flynn 1973, Wescott 1982)

Morbidity and mortality
- morbidity: low
- mortality: none

Zoonotic potential
- there are early reports that *S. obvelata* may occur in people. These reports have not been accurately confirmed. It is certain that the infection has no known health significance (Flynn 1973, Ross *et al.* 1980, Kellogg *et al.* 1982, Wescott 1982)

Interference with research
- infection with pinworms reduces the occurrence of adjuvant-induced arthritis (Pearson & Taylor 1975)
- infection alters the humoral response to non-parasitic antigenetic stimuli. This indicates that infection might modulate the immune system (Sato *et al.* 1995)
- infection with *S. obvelata* induces a proliferation of T- and B-lymphocytes in spleen and lymph nodes and occasional germinal centre formation (Beattie *et al.* 1981)
- athymic mice infected with pinworms develop a lymphoproliferative disorder which eventually leads to lymphoma (Beattie *et al.* 1980, Baird *et al.* 1982)
- animals infected with pinworms are not suitable for growth studies (Wagner 1988)
- infection with *S. obvelata* in mice causes a significant reduction of activity in behavioural studies (McNair & Timmons 1977)
- in rats, intestinal transport of water and electrolytes is significantly decreased due to pinworm infection (Lübcke *et al.* 1992)

Notice
- the eggs of pinworms survive for weeks in the animal room environment (Flynn 1973, Klement *et al.* 1996)

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Mites

Host species
- mouse, rat, hamster, guineapig, rabbit, etc.

Organotropism
- skin

Clinical disease
- varies according to host strain, sex, age, individual differences in sensitivity and ectoparasite load (Csiza & McMartin 1976, Dawson *et al.* 1986)
- scruffiness, pruritus, hair loss, scratch wounds, ulcerative pyodermatitis

Morbidity and mortality
- up to 100% of a colony affected
- morbidity: variable
- mortality: low

Zoonotic potential
- some mites (e.g. *Ornithonyssus bacoti*) (Fox 1982)

Interference with research
Physiology
- *Myocoptes musculinus* reduces contact sensitivity to oxazolone in mice (Laltoo & Kind 1979)

Pathology
- *Myobia musculi* causes secondary amyloidosis (Galton 1963, Weissbroth 1982)

Immunology
- induce IgE response in mice (Laltoo *et al.* 1979) and rats (Inagaki *et al.* 1985, Gilabert *et al.* 1990)
- dust mites and dust mite parts in feed and bedding induce IgE and delayed-type hypersensitivity response in mice (Nakano *et al.* 1989, Motegi *et al.* 1993)
- induction of allergic reaction in mice (Weisbroth *et al.* 1976)

Interactions with other infectious agents
- dust mite proteases augment influenza virus replication in ferrets (Akaike *et al.* 1994)
- serve as vectors for other infectious diseases such as dermatophytes (Hajsig & Cuturic 1969), cotton rat filariasis (Kershaw & Storey 1976) and epidemic haemorrhagic fever virus (Zhang 1987)

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