



## SUSCEPTIBILITY OF MICE INTENDED FOR ESCHERICHIA COLI, PSEUDOMONAS AERUGINOSA, SALMONELLA ENTERITIDIS AND STAPHYLOCOCCUS AUREUS INFECTION

Nikunaj Bhardwaj<sup>1</sup>, Priyvrat Singh Chauhan<sup>2</sup> & Dushyant Kumar Chauhan<sup>3</sup>

<sup>1</sup>Department of Zoology, Meerut College, C.C.S. University, Meerut (UP), India

<sup>2</sup>Department of B. Tech Biotechnology, Noida International University, Greater Noida (UP),  
India

<sup>3</sup>Department of Zoology, C.C.S. University Campus, Meerut (UP), India

### Abstract

Laboratory mice may harbor a variety of viral, bacterial, parasitic, and fungal agents. Frequently, these organisms cause no overt signs of disease. However, many of the natural pathogens of animal may alter host physiology, rendering the host unsuitable for many experimental uses. While the number and prevalence of these pathogens have declined considerably, many still turn up in laboratory animals and represent unwanted variables in research. Investigators using mice in biomedical experimentation should be aware of the profound effects that many of these agents can have on research. What does the future hold regarding the natural pathogens of laboratory mice? Several events can be anticipated. First, the decline in the prevalence of natural pathogens will continue as housing and husbandry methods improve even more. Second, additional effects of currently known pathogens will be reported as new research uses are found for traditional laboratory animals, new questions are asked, and new technologies are applied to those questions. Third, new pathogens will continue to be discovered and reported. Most of these previously unknown agents will not result in clinical disease, but many may affect experimental results. According to Weisbroth (1996), many of these “emerging” pathogens may even be acquired from humans. While the range and magnitude of infections has decreased in laboratory mice, rats, and rabbits, continued diligence and additional study are required to ensure the wellbeing of animals used in biomedical research.

**Keywords:** natural pathogens, biomedical experimentation, traditional laboratory animals



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**Introduction:** Intravenous injection of *Escherichia coli* does not produce pyelonephritis in laboratory animals unless there are preexisting urinary tract abnormalities (Cotran, R. S.,1953). In contrast, normal rats develop pyelitis and pyelonephritis after retrograde instillation of *E.coli*(Cotran, R. S.,1953,Van Ryzin,1961). This later experimental model is probably not strictly comparable to retrograde urinary tract infection in man because normal rats, but not normal man, exhibit urethral reflux. However, in man, whether the route of

infection is ascending or bacteremic, it is evident that urinary tract lesions decrease the resistance of kidneys to *E. coli* infection. Since most people who develop *E. coli* pyelonephritis do not have clinically evident preexisting urinary tract abnormalities, the question rises, are there in apparent renal injuries that may decrease host resistance to the development of pyelonephritis? One possibility that has not been investigated adequately is injury by virus infection.

In man, viruria has been demonstrated in measles, Russian spring summer encephalitis, mumps, rabies, lymphocytic choriomeningitis, Newcastle disease, and in herpes simplex, Coxsackie, cytomegalovirus, and adenovirus infections (Gresser, 1960, Hanshaw, 1961). The mechanism of viruria is obscure (Flanagan, 1963) and little is known about the clinical effects of viuria or of multiplication of viruses in the kidney. Nevertheless, there are indications that Echo 9, mumps, and cytomegalovirus infections may cause renal abnormalities (Sabin, 1958, Wyatt, 1950).

Hartley and Rowe found that adenovirus induced prolonged viruria in adult mice and produced, in infant mice, disseminated lesions in many organs, including the kidney (Hartley, 1960, Rowe, 1962). Mouse adenovirus was found to persist in the mouse kidney for at least 70 days and to produce extensive infiltrates and moderate tubular damage for the same period. The virus induced lesions of the kidney spread is posed infected mice to develop frank pyelonephritis when *E. coli* was injected intravenously or was instilled in the posterior urethra. *E. coli* injected by either route rarely caused pyelonephritis in control mice, the question rises, is there inapparent renal injuries that may decrease host resistance to the development of pyelonephritis? One possibility that has not been investigated adequately is injury by virus infection.

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David R. Ginder, 1964 experimentally find two interesting findings from their experiments. First, the observations of Hartley and Rowe that mouse adenovirus produces lesions in

kidneys of suckling mice (Hartley,1960) were extended to demonstrate that mouse adenovirus produces extensive and persistent lesions in the kidney of adult mice. Secondly, infection with adenovirus was shown to predispose the mouse kidney to develop pyelonephritis when the host was challenged either intravenously or by the retrograde route with *E. coli*.

The extensive and persistent nature of the renal lesions induced by mouse adenovirus raise the possibility that this virus may cause chronic renal disease in addition to making the kidney more susceptible to *E. coli* pyelonephritis. Other viruses, such as cytomegalovirus, canine adenovirus, and routine lymphocytic choriomeningitis virus (Wyatt,1950,Poppensiek,1951,Tranb,1936), produce mononuclear cell infiltrates in the renal cortex and medulla but only mouse adenovirus appears to produce impressive tubular changes. The adenovirus induced renal infiltrate is often so extensive that it might of itself interfere with normal renal function. When infiltrates are associated with tubular necrosis, dilatation, and collapse, it seems possible that the process may cause definite functional abnormalities as a manifestation of a type of chronic interstitial nephritis. The functional effects of mouse adenovirus on the kidney could not be conveniently studied in the mouse; however, canine adenovirus infection should be useful in exploring the long term effects of virus on renal function.

Do other viruses cause histopathologic changes in the kidney? Are there functional sequelae? It seems probable that significant renal lesions are produced by viruric viruses other than murine and canine adenoviruses, cytomegalo-virus, and lymphocytic choriomeningitis virus. Full exploration of the problem requires correlation of renal histopathology with renal function tests and demonstration of virus multiplication in the kidney. There are considerable difficulties involved in fulfilling these requirements yet the problem is an important one because some chronic nephropathies may be virus induced. Indeed there are indications that some virus infections do cause renal abnormalities. Cytomegalo-virus produces extensive interstitial cellular infiltrates in the kidney of infants, but the fragmentary clinical data available do not define the effect of this virus on the kidney (Wyatt,1950). Microscopic hematuria, proteinuria, and transient changes in renal function have been reported to occur in mumps (Utz, J. P.,1964). Hematuria was detected in almost 50 per cent of the patients studied in an epidemic of Echo 9 infection (Sabin,1958). The effects of human adenovirus infections

on renal function and susceptibility to pyelonephritis are being studied at the present time in this laboratory.

Adenovirus infection probably increases susceptibility to pyelonephritis in several ways. During the first 9 days after infection, the predominant virus induced lesions are mononuclear cell infiltrates without evident tubular damage. Increased susceptibility to *E. coli* challenge at this stage may result from increased renal tissue pressure (Freedman,1960,Godley,1964) produced by the extensive cellular infiltrate. In addition, intracellular multiplication and the "toxic" action of adenovirus may decrease resistance to infection by interfering with tubular cell metabolism (Ginsberg,1961). The possible importance of intracellular viral multiplication in lowering resistance to challenge with *E. coli* is underlined by the findings in the experiments with herpes simplex and vaccinia. With both of these viruses, only minimal infiltrate occurred in the cortex of the kidney yet the presence of low titers of virus seemed to decrease significantly the resistance to *E. coli* challenge. The importance of the presence of virus rather than the cellular infiltrate was further emphasized because the decreased resistance to *E. coli* challenge seemed to parallel the presence of vaccinia or herpes simplex in the kidney. From 12 to 54 days after adenovirus infection, when signs of tubular disease (necrosis, dilatation, and collapse) are evident, over 50 per cent of mice challenged with *E. coli* developed frank pyelonephritis in contrast to the 33 per cent incidence of pyelonephritis in mice challenged 3 to 9 days after adenovirus infection. The greater incidence of bacterial pyelonephritis at this time appears to reflect tubular obstruction and consequent increased renal tissue pressure that is believed to be the common denominator of increased susceptibility to pyelonephritis caused by sudden ureteral obstruction, renal artery or renal vein ligation, and electrocoagulation injury of the medulla (Godley,1964,et.al).

### ***Pseudomonas aeruginosa.***

*Pseudomonas aeruginosa* is a gram-negative rod that normally inhabits the nasopharynx, oropharynx, and lower digestive tract of many vertebrate species. The primary importance of *P. aeruginosa* as an opportunistic pathogen (National Research Council,1991). *P. aeruginosa* is commonly found in soil and organic waste and as a normal skin inhabitant, and it is frequently cultured from facility water systems. Active exclusion of the organism from the animal facility is achievable but costly. Transmission is via contact with contaminated water, feed, bedding, and infected rodents and humans (Urano,1995). Clinical signs are generally not observed in immunocompetent hosts, although the host response to *P.*

aeruginosainfection varies among inbred mouse strains. For example, mice of the BALB/c strain are resistant to *P. aeruginosa* lung infection whereas mice of the DBA/2 strain are susceptible (Morissette,1996). Some immunocompromised mice and rats may develop hunched posture, apathy, dullness, shortness of breath, ruffled coat, emaciation, circling movements around their longitudinal axis, and oblique head posture, and some of them will die (Dietrich,1996.,Johansen, 1993.,National Research Council,1991). Clinical disease is due to invasion of deep tissues, resulting in hematogenous spread of the bacteria to multiple organs. Entry into the vascular system may be facilitated by pseudomonal proteases and bradykinin generated in infectious foci (Sakata,1996). Pathologic lesions are found in affected tissues and consist of multifocal necrosis, abscess formation, and suppuration (Percy,1993). Lesions are often most severe in the lungs (Percy,1993). Vegetative lesions may be found on heart valves of animals with infected indwelling vascular catheters (Percy,1993). Much of what is known of the cell biology of *P. Aeruginosa* infections come from experimentally induced infections. Studies of immune responses to *P. aeruginosa* present evidence of both humoral (Pier,1995) and cellular (Dunkley,1994.Stevenson,1995) contributions to immunity, which is enhanced by vitamin B 2 (13) and IL-1 (691). Type 1 T-helper (Th1) cells may participate in part by triggering TNF- $\alpha$ -mediated hypersensitivity to *P. aeruginosa* (Fruh, R. et al., 1995). Macrophages and neutrophils are important effector cells (Nakano,1994), with neutrophil accumulation mediated through CD11 and CD18 cells (Qin,L.,1996). Also, inbred mouse strains differ in susceptibility (Morissette,1995). Susceptible mice have been shown to have a defect in TNF- $\alpha$  production (Gosselin,1995. Morissette,1996). In addition, strains of *P. aeruginosa* differ widely in virulence (Furuya,1993). Bacterial flagella (Mahenthiralingam,1995), pyoverdine (which may compete directly with transferrin for iron [Meyer,1996]), pyocyanin (Shellito,1992), elastase (Tamura,1992), and potent exotoxins (Gupta,1996,Hirakata,1995,O'Callaghan,1996,Tang,1996) play major roles in determining virulence. Most prominent among the exotoxins is exotoxin A, a super antigen (Miyazaki,1995,Pittet,1996). Numerous publications have reported on the effects of *P. aeruginosa* on research involving immune compromised mice and rats. Most reports are from experimental infections. Effects include early death following exposure to radiation, cyclophosphamide treatment, CMV infection, or cold stress; increased severity of infection following airway trauma; depressed contact sensitivity to oxazolone; stimulation of T-cell

proliferation within splenocytes of nude mice; induction of thymic atrophy via apoptosis; inhibition of wound healing; inactivation of cytokines by bacterial proteases; possible T-cell-dependent immune system suppression mediated by the polysaccharide fraction of LPS; altered fluid transport across the lung epithelium; suppression of delayed hypersensitivity responsiveness; increase in cardiac excitability and enhanced vulnerability to hypoxic insults; inhibition of macrophage function by bacterial rhamnolipids; and altered behavioral and clinical pathologic parameters following experimental infection of surgical wounds (Bradfield,1992,Dixon,1994,Haslov,1992,Heggens,1992,Kwiatkowska-Patzer,1993,Marshall,1993,McIntosh,1992,NationalResearch.Council,1991,Parmely,1990,Pittet,1996,Wang,1994,Yamaguchi,1991). In addition, rodents with streptozotocin-induced diabetes mellitus are more susceptible to *P. aeruginosa* infection (Kitahara, 1981). Rodent-*P. aeruginosa* systems have been developed as models for numerous human diseases and conditions, including indwelling-catheter infections (Ketyi, I. 1995), pyelonephritis (Tsuchimori,1994.), burn trauma (Neely,1994,Stevens,1994), chronic mucosal colonization (Pier,1992), immunization strategies (Cripps,1995), and infection accompanying cystic fibrosis (Johansen,1996, Mahenthiralingam,1994). From these reports, it is apparent that natural infection of immune-compromised mice and rats could affect a variety of research projects, depending upon the organ systems affected.

### **Salmonella enteritidis.**

The primary importance of *Salmonella* spp. is as zoonotic agents and as pathogens in immune-compromised mice and rats. *S. enteritidis* serotype typhimurium is the most common serotype infecting laboratory rodents, although the prevalence of asymptomatic carriers is unknown but probably low. Transmission is via ingestion of contaminated feed ingredients and water and by contact with contaminated bedding and animal facility personnel (NationalResearchCouncil,1991). When clinical effects are observed, reproduction is most prominently affected, while other signs are nonspecific (Lentsch,1983). Following ingestion, the mucosa and Peyer's patches in the distal ileum are initial sites of invasion. From those sites the organism reaches the mesenteric lymph nodes and gains access to the vascular system, to be distributed throughout the body. Lesion development depends upon the distribution of the pathogen. The organs most commonly infected include the terminal small intestine and the large intestine, lymph nodes, liver, and spleen. Hallmarks of the infection include local hyperemia, focal necrosis, and pyogranulomatous inflammation, consistent with

septicemic disease; they also include crypt epithelial hyperplasia in the intestine (NationalResearchCouncil,1991, Percy,1993). Immunodeficient rodents are more severely affected. Numerous virulence factors have been identified, each of which contributes to the pathogenic potential of various *S. enteritidis* isolates (Stone,1995,Suzuki,1994,Thorns,1996). A combination of humoral and cellular immune mechanisms control infection with *S. enteritidis*, while gamma interferon (IFN- $\gamma$ ) may contribute to pathology in septic shock (Heinzel,1990). Cellular mechanisms participating in immunity include L3T4<sup>+</sup> and Lyt-2<sup>+</sup> T cells (535, 571) and T lymphocytes that express a g/dT-cell antigen receptor (Mixter,1994). Reported interference of *Salmonella* spp. with research includes increased rates of crypt cell proliferation, resulting in substantial growth of the small intestine (Naughton,1995). These effects include mitogenic activity (Sveen,1992); stimulation of cytokine production (Cohen,1991); lung damage and decreased circulating leukocyte counts (Rose,1994); recruitment of neutrophils to the lung, probably due to the chemo-attractant properties of macrophage inflammatory protein type 2 (Gupta,1996); induction of vasodilation of isolated rat skeletal muscle arterioles (Glembot,1996); decreased amino acid incorporation into proteins (Holecek,1995); altered guanine nucleotide regulatory (G) protein function (Makhlouf,1996); activation of the nuclear transcription factor kappa B and expression of E-selectin mRNA in hepatocytes, Kupffer cells, and endothelial cells (Essani,1996); mortality in neonates and stimulation of adherent splenic cell thromboxane B<sub>2</sub>, IL-6, and nitrite production (Cochran,1995); altered development of the hypothalamic-pituitary-adrenal axis with long-term effects on stress responses (Shanks,1995); altered glucose metabolism (Goto,1994); increased expression of Mac-1 (CD11b/CD18) adhesion glycoproteins on neutrophils (Witthaut,1994); increased calcitonin gene-related peptide and neuropeptide Y levels in plasma (Wang,1992); and altered liver levels of 1,2-diacylglycerol and ceramide (Turinsky,1991). It remains to be discerned which of these observations extend to the mouse or rat infected with *S. enteritidis*. Mice and/or rats infected with *S. enteritidis* serve as models of enteritis (Naughton,1996), typhoid fever, and other septicemic diseases (Genovese,1996).

### **Staphylococcus aureus.**

A variety of clinical presentations have been reported in rats and mice. These include tail lesions, ulcerative dermatitis, and traumatic pododermatitis in rats; and facial abscesses, ulcerative dermatitis, preputial gland abscesses, and penile self-mutilation in mice (National Research Council,1991). Infected rats have alterations in the fibrinogen level in plasma, the

glucose level in serum, total leukocyte counts, and wound histology scores (Bradfield,1992). Immunity to *S. aureus* primarily via complement-mediated killing by neutrophils (National Research Council,1991). Cell-mediated immunity may also be important and may secondarily contribute to the pathogenesis of some lesions (National Research Council,1991). Nitric oxide, IFN-g, TNF, and IL-6 are induced during infection (Florquin,1994,Nakane,1995). *S. aureus* produces several biologically active products, including hemolysins, leukocidins, nuclease, coagulase, lipase, hyaluronidase, exotoxins, fibronectin- and collagen-binding proteins, protein A, and enterotoxins (Jett,1994, Ren,1994,Rozalska,1994). Many of these may be degraded by phagocytic cells into other active products (Fincher, 1996). The effects of these products are numerous and include cell lysis (Hildebrand,1991); increases in pulmonary microvascular permeability (Seeger,1990); contractile dysfunction (Bhakdi,1991); shock and multiple-organ failure (DeKimpe, 1995); epidermolysis (18); and induction of excess sleep, fever, TNF, cytokine, IL-1, and IL-1 receptor antagonist (Fincher, 1996). Staphylococcal enterotoxins have been termed superantigens based on their ability to stimulate polyclonal proliferative responses of murine and human T lymphocytes (Gelfand,1995). In addition, infection with *S. aureus* has been shown to alter immune responses (Benedettini,1984).

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