



Microbe-related phenotypes, good and bad, its good to be aware

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ABSTRACT Infectious or infesting agents may be introduced intentionally into genetically engineered mice (GEM) for the purpose of eliciting phenotypes that elucidate gene function, but often are examples of environmental (nurture) factors that can impact a wide variety of phenotypes. Induced pathology, disease or phenotypes frequently are strain dependent, and vary with other factors including sex and age of the host, strain and dose of the agent, route of infection, copathogens, spontaneous mutations and genetic manipulations. Infectious agents are more common in laboratory mouse colonies than many of us realize. The most prevalent agents do not cause overt clinical disease in most of the mice we use. They are neither obvious nor uncommon in colonies that are termed 'SPF' or 'barriers'. Worldwide the most prevalent agents include Mouse Hepatitis Virus (MHV, a Coronavirus), mouse parvoviruses, Theilers mouse encephalitis virus (TMEV or GDVII, a Picornavirus), mouse Rotavirus (EDIM), helicobacters, *Pasteurella pneumotropica*, pinworms and mites. While these agents may not cause significant morbidity or mortality, they should be expected to immunomodulate and to cause or impact a variety of other phenotypes, including but not limited to CNS and neurobehavioral phenotypes, enterohepatic and metabolic phenotypes, fecundity, growth, physiology, cancer susceptibility and progression. Infections are not all bad, and their phenotypic effects may improve our understanding of gene functions. However, we should be aware of the agents in our colonies, and of their potential impacts on phenotypes. Phenotypes related to some of the most common agents in our colonies will be discussed briefly.

EXAMPLES of some infected/infested phenotypes

Neurobehavioral

- ▶ Deaf +/- vestibular
 - Otitis - *Mycoplasma*, *Pseudomonas*, *Pasteurella pneumotropica*, etc.
- ▶ Paralysis/paresis
 - Demyelination MHV, TMEV etc.

Inflammatory/Immune

- ▶ Immunomodulation: Cellular responses, cytokine responses - parvoviruses, all ?
- ▶ IBD (rectal Prolapse) - helicobacters, *Citrobacter*, parasites, Norovirus
- ▶ Demyelination - MHV, TMEV
- ▶ Amyloidosis AA - chronic infections, dermatitis, genetic susceptibility

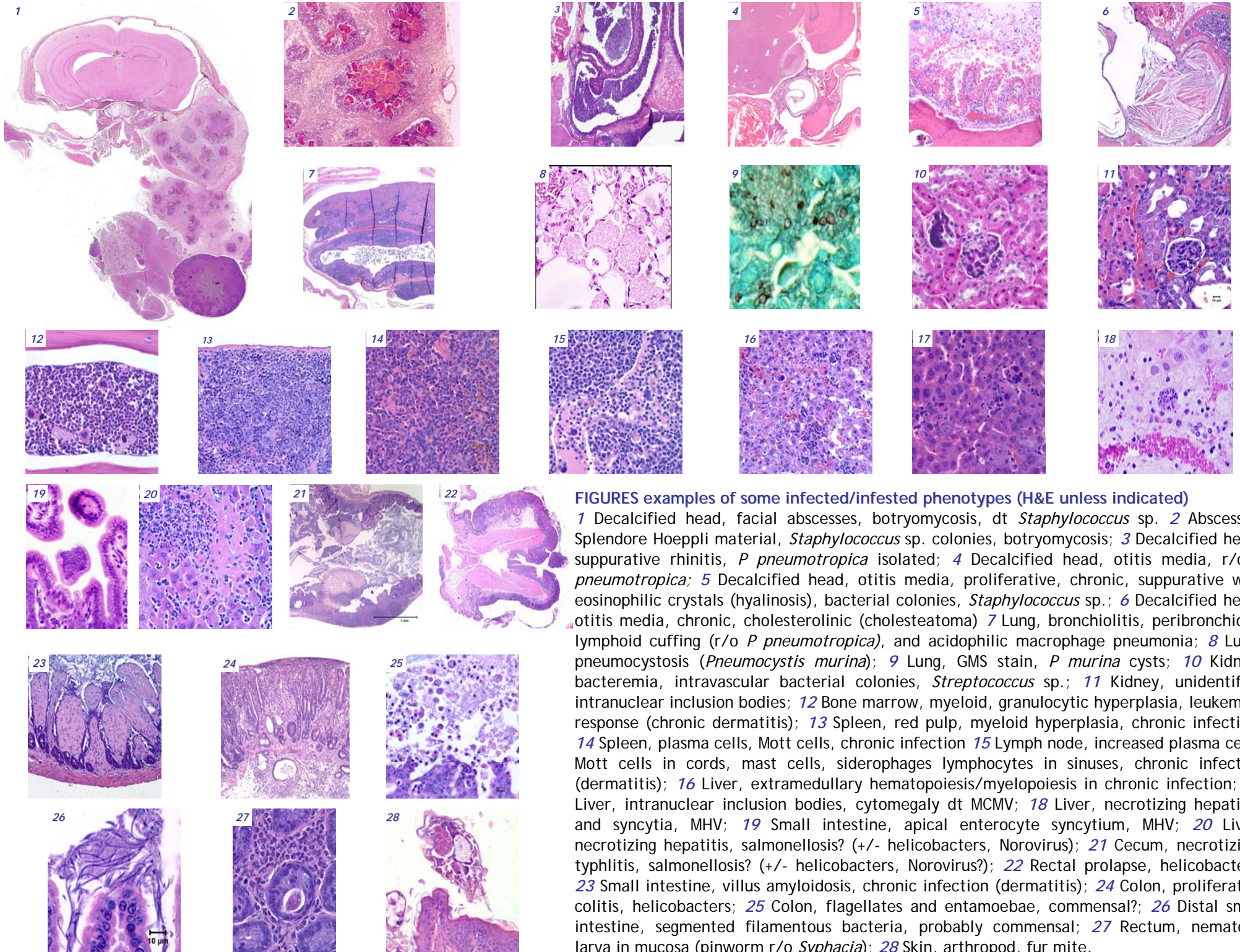
Cancer

- ▶ Parvoviruses - oncosuppressive?
- ▶ Liver tumors - helicobacters (+ single housing, diet etc factors)
- ▶ Lymphoma, mammary tumors, etc - retroviruses

DISCUSSION/CONCLUSIONS The pictured examples (representing multiple institutions) are from mice that were supposed to be **Specific Pathogen Free (SPF)** and/or 'barrier' housed. **SPF** status should be defined by the agents from which the animals are 'free'. **Barriers** should be defined by the excluded agents, and by the special precautions and practices used. Contemporary research colonies should have preventive medicine programs with quarantine and surveillance strategies to exclude agents that can interfere with research. Microbial or parasitic agents that do not cause overt clinical disease in most mice may cause or contribute to phenotypes in susceptible mice. Appreciation of microbial influences on phenotypes can contribute to optimizing surveillance programs for diverse research needs. The (5) most (sero)prevalent viruses in US and EU mouse colonies usually are reported to be MHV, parvoviruses (MVM, MPV), EDIM, TMEV. Recent evidence indicates that seroprevalence of murine Norovirus may exceed 30% in research colonies. This 'emerging' agent has been recognized as a potential pathogen in immunodeficient mice. Cell cultures, tumour lines and mouse sera are well documented sources of Ectromelia virus, MHV, parvoviruses, LDH elevating virus, also herpesviruses, adenoviruses. Thus inoculated biologicals pose a risk that can be minimized by appropriate testing. The most prevalent potentially pathogenic bacteria usually are reported to be rodent helicobacters, with *Pasteurella pneumotropica* and other opportunists frequently identified as a problem in immunocompromised animals. Pinworms, fur mites, and other parasites remain common in some situations.

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FIGURES examples of some infected/infested phenotypes (H&E unless indicated)

1 Decalcified head, facial abscesses, botryomycosis, dt *Staphylococcus* sp. 2 Abscesses, Splendore Hoeffli material, *Staphylococcus* sp. colonies, botryomycosis; 3 Decalcified head, suppurative rhinitis, *P. pneumotropica* isolated; 4 Decalcified head, otitis media, r/o *P. pneumotropica*; 5 Decalcified head, otitis media, proliferative, chronic, suppurative with eosinophilic crystals (hyalinosis), bacterial colonies, *Staphylococcus* sp.; 6 Decalcified head, otitis media, chronic, cholesterolinic (cholesteatoma) 7 Lung, bronchiolitis, peribronchiolar lymphoid cuffing (r/o *P. pneumotropica*), and acidophilic macrophage pneumonia; 8 Lung, pneumocystosis (*Pneumocystis murina*); 9 Lung, GMS stain, *P. murina* cysts; 10 Kidney, bacteremia, intravascular bacterial colonies, *Streptococcus* sp.; 11 Kidney, unidentified intranuclear inclusion bodies; 12 Bone marrow, myeloid, granulocytic hyperplasia, leukemoid response (chronic dermatitis); 13 Spleen, red pulp, myeloid hyperplasia, chronic infection; 14 Spleen, plasma cells, Mott cells, chronic infection 15 Lymph node, increased plasma cells, Mott cells in cords, mast cells, siderophages lymphocytes in sinuses, chronic infection (dermatitis); 16 Liver, extramedullary hematopoiesis/myelopoiesis in chronic infection; 17 Liver, intranuclear inclusion bodies, cytomegaly dt MCMV; 18 Liver, necrotizing hepatitis, and syncytia, MHV; 19 Small intestine, apical enterocyte syncytium, MHV; 20 Liver, necrotizing hepatitis, salmonellosis? (+/- helicobacters, Norovirus); 21 Cecum, necrotizing, typhlitis, salmonellosis? (+/- helicobacters, Norovirus?); 22 Rectal prolapse, helicobacters; 23 Small intestine, villus amyloidosis, chronic infection (dermatitis); 24 Colon, proliferative colitis, helicobacters; 25 Colon, flagellates and entamoebae, commensal?; 26 Distal small intestine, segmented filamentous bacteria, probably commensal; 27 Rectum, nematode larva in mucosa (pinworm r/o *Syphacia*); 28 Skin, arthropod, fur mite.