Opportunistic Infections: Why Worry?

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The papers presented herein have been written by individuals whom I regard as some of the most experienced infectious disease diagnosticians, laboratory animal clinicians, and research scientists in the field of comparative medical/laboratory animal science. Many of us have been in the field long enough to marvel at the improvements in microbiological quality of the animals we use in research. Those changes were spurred in the early 1980s by the implementation of new diagnostic methods that revealed a spectrum of infectious agents indigenous to most rodents from commercial and research colonies. When the extent of the infectious disease problem was finally appreciated, commercial suppliers were pressured to improve the quality of their "products." That challenge required design of new biocontainment/bioexclusion systems that were not only effective but were also more user-friendly than the flexible film isolator (see White and others 1998). However, the laboratory animal community was still left with a problem: how to maintain the pathogen-free status of rodents that arrived at facilities housing animals under both conventional and specific pathogen-free conditions. This is a struggle that continues today, especially at academic institutions that are constrained by insufficient budgets and burgeoning animal populations, represented largely by genetically engineered mice. It is safe to say that new construction plans under development at many institutions will translate into facilities that will be overcrowded on their opening day. How ironic that only a few years ago, laboratory animal specialists were concerned about the future of their profession because censuses were plummeting!

Improvements in serological diagnosis that were implemented in the early 1980s are now being followed by a molecular revolution. Many laboratories have incorporated the polymerase chain reaction (PCR) into their standard diagnostic protocols. The technology, although expensive, is rapid and may be designed as a "universal" test or an agent-specific test (see Weisbroth and others 1998). For instance, a single set of primers can be designed to amplify the nonstructural region of the genomes of all known rodent parvoviruses. Thus, DNA of minute virus of mice, mouse parvovirus, rat virus, H-1 virus, or rat parvovirus can be detected in animal tissues, transplantable tumors, or cultured cells using a single test. The infecting agent may then be identified using primers specific to the capsid genes of each of those viruses. As emphasized by Weisbroth and others in this volume, it is very likely that PCR will reveal many agents that are currently unknown to the laboratory animal community because they cannot be cultured by conventional means. This prediction echoes the sentiments of many speakers at a recent meeting on emerging infectious diseases (summarized by Smith 1998). We are probably aware of only a small proportion of the microbes circulating in nature, and many more will become evident as we continue to change our environment and alter the genetic makeup of animals (ourselves included) and plants.

The power of molecular diagnostics is exemplified by the recent detection of many previously unrecognized Helicobacter species. These organisms are quite difficult to culture due to fastidious in vitro growth requirements. They also grow relatively slowly and are often overgrown by other intestinal flora. The application of PCR methodology to Helicobacter infections in both the diagnostic and research settings has contributed enormously to our understanding of their role in disease processes. These agents also make a cogent case for expanding the role of veterinary pathology specialists in phenotypically defining genetically altered animals. Early characterization of mice with targeted disruptions of diverse cytokine genes and mice with mutations in the T cell receptor gene revealed the development of colitis or inflammatory bowel disease that could not be attributed to any other purposeful manipulations of these mice (Kuhn and others 1993; Mombaerts and others 1993; Sadlack and others 1993). Subsequently, Helicobacter hepaticus and Helicobacter bilis have been shown to induce inflammatory bowel disease both spontaneously and experimentally in immunocompromised and genetically altered rodents (Foltz and others 1998; Haines and others 1998; Shomer and others 1997; Ward and others 1996). The problem was effectively stated in a recent editorial addressed to the laboratory animal medicine community (Brownstein 1998): Many scientists view genetically altered mice as run-of-the-mill laboratory mice with an introduced or deleted gene, not recognizing that the manipulations required for the production and reproduction of these animals may have unanticipated consequences.

We often think of opportunistic infections as those that are superimposed on a host immunocompromised by virtue of genetic makeup or chemical induction. However, it is im-
perative that laboratory animal clinicians, facility managers, and investigators understand that the immune systems of rodents infected with some of the more common pathogens circulating in today’s vivaria can be functionally altered to such an extent that they become unacceptable subjects for immunological assays and/or more susceptible to the deleterious effects of other agents (de Souza and Smith 1991; de Souza and others 1991; McKisic and others 1995, 1996, 1998). We must not assume that an agent is innocuous if the appropriate studies have not been conducted. We must also remember that laboratory rodents have become world travelers and that the stresses associated with transportation may have amplified effects in animals that already have impaired immune function.

CONCLUSION

At the time of this writing, no consensus exists regarding the precise definition of “opportunistic” infections. Many people immediately think of this term in the context of the ongoing pandemic of acquired immunodeficiency syndrome, the victims of which frequently succumb to infections that immunocompetent individuals handle with ease. *Pneumocystis carinii*, the best known of these opportunists, has also become an issue for laboratory animal veterinarians pursuant to the widespread use of immunodeficient rodents, most notably mice bearing the mutation for severe combined immunodeficiency (scid). However, for the purposes of this discussion, I have chosen to use a broader definition of opportunistic: “denoting an organism capable of causing disease only in a host whose resistance is lowered, for example, by other diseases or by drugs” (Stedman’s Medical Dictionary 1995). The list of factors rendering the laboratory rodent host less resistant is steadily growing and now must include not only those drugs or infections that may alter immune function but also the manipulations we impose on the animal genome. In keeping with the above-mentioned counsel of Brownstein, we must remember that genetically altered rodents may have unanticipated phenotypes that include clinical manifestations of disease induced by organisms heretofore unrecognized or thought to be commensals.

**REFERENCES**


