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Parasitology Research at the School

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Animal health is closely tethered to the health of the general populace. With mankind's heavy reliance on animals for social support and nutritional sustenance, our well-being, in many ways, mirrors that of the various species occupying our realm. In no way, perhaps, is this more apparent than in the field of parasitology.

Global leaders in the study of parasitic diseases, researchers at the School's Laboratory of Parasitology — part of the Department of Pathobiology — combine their diverse academic interests to broaden our understanding of vector-transmitted diseases that impact public health. Funded largely by leading research institutions, including the National Institutes of Health (NIH), World Health Organization (WHO), Burroughs Wellcome Foundation and Merck Foundation, their investigations contribute to the development of treatments and prevention strategies — in animals and people — that are viable in both developed and third-world countries.

Dr. Gerhard A. Schad, professor of parasitology at the School, studies nematode growth and development. The primary focus of his research is on *Strongyloides stercoralis*, a gastrointestinal helminth particularly destructive in immunocompromised individuals. In the U.S., *S. stercoralis* is a significant public health concern in southern Appalachian communities, as well as in institutions, where personal hygiene is often inadequate. It also infects people in poorly-sanitized foci of tropical and subtropical regions, such as Brazil, the Caribbean islands and southeast Asia. *S. stercoralis* larvae penetrate the intact skin of humans who come in contact with fecally-contaminated soil. Three outcomes of *S. stercoralis* infection are possible. One may become a silent carrier and show no clinical signs; in the most common scenario, he or she may develop acute strongyloidiasis, characterized by enteritis and weight loss; in hyperinfection, seen in immunosuppressed individuals, larvae migrate throughout the body, causing tissue destruction and possible death.

"We're trying to understand the developmental biology of strongyloidiasis that

results in hyperinfection, disseminated infection and chronic infection," says Dr. Schad. "This would provide a basis for better control of the disease."

Dr. Schad's lab, one of the few worldwide that investigates *S. stercoralis* infection, performs laser microbeam ablation studies to identify the neurons in the worm's anterior sense organs that are involved in the infection process. This could facilitate an understanding of the signals that reactivate development of infective larvae upon entry into a host, and



lead to new approaches in parasite control. Working closely with Dr. Schad, Dr. Thomas Nolan, adjunct associate professor of parasitology, is studying *S. stercoralis* autoinfection. In autoinfection, larvae develop into egg-laying adults within the host, which is then reinfected by the larvae which hatch within the intestine. Autoinfection occurs most frequently in immunosuppressed patients. Using a gerbil model, Dr. Nolan is working to determine the impact of immunosuppression and certain physiologic factors, such as gut motility, on the development of autoinfection in strongyloidiasis.

Like *S. stercoralis*, several filarial nematodes cause severe systemic disease in humans. Dr. James Lok, associate professor of parasitology, is studying two filarial parasites, *Brugia malayi* and *Onchocerca volvulus*. *B. malayi*, which is transmitted by mosquitoes, afflicts some 100 million people worldwide, primarily in southeastern and northern Asia. Adult worms invade the lymph nodes and lymphatic vessels, causing obstructive disease (the end stage of chronic lymphatic filariasis is elephantiasis, a disfiguring condition). Resulting microfilaremia can

induce allergic responses, including filarial fever, joint inflammation and tropical pulmonary eosinophilia, which is characterized by lung infiltrates that cause paroxysmal coughing.

O. volvulus, which is transmitted by black flies, is implicated in "river blindness" in South and Central America, and Africa. In infected humans, adult worms reside in subcutaneous nodules, causing dermatitis. Microfilaria migrate through the skin and eventually invade the eye, damaging the cornea, retina and optic nerve. Large parasite burdens can, with chronicity, cause permanent blindness.

Because of the "long-term consequences of being incapacitated in underdeveloped economies," says Dr. Lok, the study of filariasis — "a disease of the poorest of the poor," is crucial to improving public health in third-world countries.

In the lab, Dr. Lok is using gerbil models to study the developmental biology of the larvae, which arrest in the vector at the infective stage and resume development upon transmission to a mammalian host.

"One of the reasons there are so few satisfactory drugs to prevent filarial infections in humans is that we don't yet know what causes these larvae to resume development once they are transmitted," Dr. Lok explains.

Parasitic mechanisms are not sole determinants of virulence. Just as important are immune responses elicited in hosts. Drs. Jay Farrell and Phillip Scott study host immune responses to *Leishmania*, the intracellular protozoan parasite that causes leishmaniasis. One of six major diseases on which WHO is focusing its efforts, leishmaniasis afflicts over ten million people globally, primarily in northern Africa, southern Europe, India, Pakistan and South America.

Leishmania is transmitted between humans and its primary reservoir hosts, dogs and rodents, by sandflies. Infection generally takes one of two courses: a cutaneous form, in which localized skin lesions develop, and a visceral form, in which infection metastasizes to the liver, spleen and bone marrow. Visceral leishmaniasis carries a 90 percent mortality

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rate. Cutaneous leishmaniasis, however, may resolve over several months. The primary determinant of this outcome rests within the host.

"In humans, non-healing infections are characterized by the production of high amounts of antibody and little cell-mediated response," says Dr. Farrell, professor of parasitology, who has been studying the disease for 25 years.

T lymphocytes, which are required for both humoral and cell-mediated immune responses, are composed of two distinct subsets — T helper 1 (TH1) and T helper 2 (TH2) cells. TH1 cells stimulate the cell-mediated immune response, which is associated with healing cases of leishmaniasis; TH2 cells potentiate humoral immunity, which is typically exhibited in non-healing infections.

Working with mice infected with *Leishmania*, Dr. Farrell, who heads the School's Laboratory of Parasitology, manipulates in-vivo levels of cytokines that control T lymphocyte differentiation. This research, he says, could lead to the development of effective human drug treatment protocols that integrate immunomodulatory agents with conventional drug therapies.

Dr. Scott, who is a member of WHO's steering committee on the development of a *Leishmania* vaccine, is designing

vaccines that incorporate cytokine adjuvants that preferentially induce TH1 cell production and, thereby, cell-mediated immunity. This experimentation will have far-reaching effects, he predicts.

"What we learn from our studies of *Leishmania* may be applicable to other chronic diseases in which inappropriate immune responses can lead to severe disease," says Dr. Scott, professor of microbiology and immunology, who cites leprosy, tuberculosis, AIDS and cancer as a few such examples.

Also exploring immune response to disease is Dr. Chris Hunter, assistant professor in the Department of Pathobiology. An opportunistic infection in immunosuppressed patients, toxoplasmosis is caused by a ubiquitous parasite, *Toxoplasma gondii*. Dr. Hunter, who recently received a Burroughs Wellcome Young Investigator Award, uses immune-deficient strains of mice to study the immune response to *Toxoplasma*. This work has important public health implications.

"We're now at the stage at which we can start to rationally design and formulate new vaccine and treatment strategies," says Dr. Hunter, who has been studying *Toxoplasma* for nearly a decade.

Also key to the development of parasite control strategies is the construction of computer programs that quantify para-

site transmission, therapy and prevention data. Dr. Gary Smith, professor of epidemiology and population biology and director of the School's Center for Infectious Disease and Food Safety, is developing mathematical models for ruminant parasites, including *Fasciola hepatica*, *Haematobia irritans* and several trichostrongylid nematodes; *Ichthyophthirius multifiliis*, a protozoan parasite that afflicts farmed fish; and *Ixodes scapularis*, the tick that transmits the spirochete that causes Lyme disease in dogs and humans.

"The goal in each case is to construct a computer model of transmission dynamics," says Dr. Smith, who developed similar software for gastrointestinal nematodes of cattle, now marketed by Merck AgVet.

The software will help educate the public about parasite transmission, and lay a foundation for comparing existing control strategies and inventing new ones. Dr. Smith says the School's dedication to parasite research plays a key role in enhancing the quality of human life.

"The majority of these infections have a worldwide distribution and threaten human health directly, as in the case of Lyme disease, or indirectly, through their effects on the supply of protein for human consumption." — *Joan Capuzzi*



The Brandywine Polo Club hosted a benefit for New Bolton Center on September 8 at the Brandywine Polo Club grounds. The club played the British Military Polo Team. It was a beautiful, exciting afternoon. Unfortunately, the home team lost. One of its star players was Dr. Cindy Mason, V'96, whose mother, Mrs. Peggy Mason, was instrumental in organizing the event.

The funds raised were for the renovation of the farrier's laboratory. Shown here are Dr. and Mrs. Kelly and the British team.