INTRODUCTION. Chronic infection and the development of antibiotic resistance are major problems in many aspects of health including space flight (which may result in long-term exposure to specific strains of bacteria) and in food borne disease. In regard to food-borne illness, the transfer of antibiotic resistant bacteria from animals to humans may occur via contact, including occupational exposure, and via the food chain. Resistance genes may transfer from bacteria of animals to human pathogens in the intestinal flora of humans. Prevention of the development of resistance in humans necessitates good animal husbandry and hygienic measures to prevent cross contamination, as well as decreased use of antibiotics. Appropriate use of antibiotics for food animals will preserve the long-term efficacy of existing antibiotics, support animal health and welfare, and limit the risks of transfer of antibiotic resistance to humans (1,2). In order to study the cellular and molecular mechanisms involved in both chronic infection and antibiotic resistance, and to develop better therapies, we propose to develop a rabbit model of chronic infection that is suitable for the study of antibiotic resistance.

Ovarectomy in rabbits results in a marked thinning of the mucosal lining of the urinary bladder, increased bacterial adherence to the mucosa, and significantly increased mucosal permeability (3-5). These same changes occur in women post menopause, and results in a significant incidence of recurrent and chronic infection. It is proposed that the ovarectomized followed by acute overdistension of the rabbit bladder will induce a chronic infection, and that treating the rabbit with sub-therapeutic concentrations of specific antibiotics, antibiotic resistant organisms can be induced and utilized as a model for investigation. Some of the specific aspects of chronic infections and antibiotic resistance that can be studied include: a. Alterations in virulence of the organisms associated with both chronic infection and antibiotic resistance; b. Changes in phenotype associated with the development of antibiotic resistance. c. Changes in phenotype associated with the development of chronic infection compared to acute infection. d. Development of cross-resistance and cross-sensitivity of the strain to specific classes of antibiotics. e. Rate of loss of antibiotic resistance once therapy is terminated.

METHODS. Female rabbits will be ovarectomized to induce a marked thinning of the mucosa, increased permeability and increased bacterial adherence. Colonization of the bladder will be established by first overdistending the bladder, which further damages the mucosa, then introducing the specific strain of bacterium via the urethra. The process of overdistending the bladder and introducing bacteria into the bladder will be repeated three times at three-day intervals. This should establish a permanent colonization of the mucosal surface of the bladder that should be maintainable simply by overdistending the bladder at weekly intervals. The normal bladder has no endogenous flora. The bladder’s primary mechanism for eliminating infection is by rapid mucosal synthesis of mucin, which has strong antibacterial adherence properties, sloughing off the surface layer of mucosal cells as the basal cells undergo hyperplasia, and washing out the cells and bacteria during voiding. In the absence of estrogen (via ovarectomy) the mucosal lining thins, mucin synthesis is significantly reduced and hyperplasia of the basal cells in significantly inhibited. Acute overdistension on a weekly base should maintain the mucosa damaged and colonized. Rabbits will be treated chronically with sub-therapeutic doses of the antimicrobial agents selected for study. The specific strain of bacteria under study will be placed in the bladder via catheter/cystoscope and allowed to grow. At weekly intervals, when the bladder is overdistended, the bladder will be swabbed; the resident bacteria will be cultured and evaluated for the presence of bacterial resistance. The resistant bacteria then can be cultured and the molecular characteristics compared to the original strain.

CONCLUSIONS. Although the rabbit bladder model will not exactly mimic the effects of a systemic infection and the associated complications that may occur in a human, it will provide relevant information about the bacteria and their membrane interactions in the presence and absence of antimicrobial resistance and thus will add information to the database evaluated when developing new antimicrobial agents.


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