We also examined the role of CVB in human inflammatory heart diseases (myocarditis and dilated cardiomyopathy). From this work grew the realization that CVB can persist for relatively long periods of time, well past the acute infectious stage. This led to the characterization of a novel enteroviral persistence mechanism in which the virus deletes terminal 5' end sequence information from its genome. These terminally deleted viruses (TDs) replicate orders of magnitude more slowly than the parental (wildtype) virus and demonstrate very interesting and peculiar biological characteristics. We also demonstrated that TDs can arise naturally in human infections as well, indicating a potential pathogenic role for these hitherto unknown populations.

More recently, the laboratory characterized the role of human enteroviruses, modeled by the CVB, in type 1 diabetes (T1D), using the non-obese diabetic (NOD) mouse as the host. It was shown in these studies that enteroviruses play a dual role in the etiology of T1D, a role defined both by the virus strain and by the host. The virus can initiate rapid T1D onset in a host with pre-existing autoimmune islet inflammation, results that are consistent with clinical reports of 'sudden onset' T1D in people following a 'cold' or 'flu' episode. The virus can also act beneficially on the host if infection occurs prior to development of insulitis, likely through the generation of regulatory T cells that work to suppress the autoimmune attack on the insulin-producing beta cells in the pancreatic islets. This work indicates that it may be possible to inhibit T1D through a vaccine approach. These studies are all consistent with what we know of the disease in our past, when it was rare, and is linked to human hygiene.
[see also http://www.unmc.edu/pathology/enterovirus_research_group.htm]

Developing new antibacterial agents

There is a clear need for new, safe antibacterial agents that suppress the growth and kill all types of bacteria including antibiotic resistant strains. It was recently reported that 1 patient in 25 (4%) of hospital patients across the country contract severe bacterial infections during their stay in hospital. Toward this end, we have begun studies to isolate and characterize new and effective antibacterial agents.

Together with Thomas McDonald (Professor; tmcdonal@unmc.edu) in this department, we discovered that protonated creatinine (CRN) functions effectively as a broad spectrum antibacterial agent when used in the low millimolar range (10-100mM). Creatinine (not creatine) is considered to be a waste product without function, normally excreted in urine in the 100uM range; thus, the finding that it is highly effective against all bacteria tested, was very interesting. When tested against numerous Gram positive and negative bacteria, as well as against clinically important drug resistant bacterial strains such as MRSA, VRE and others, CRN suppressed logarithmic growth and begins to kill within an hour of exposure. Bacteria do not evolve resistance to CRN as they can do against standard antibiotics. Creatinine has no suppressive action against eukaryotic microorganisms such as yeasts and fungi. We have shown that CRN can be easily added to over the counter creams and ointments, thereby making them effective antibacterial agents. CRN is a small molecule and not antigenic, is a natural product that is normally excreted by everyone, and is safe to use. [J Antibiot (Tokyo) 2012 65(3):153-156. "Creatinine inhibits bacterial replication." McDonald T, Drescher KM, Weber A, Tracy S]

The potential for using CRN in clinical settings such as hospitals is high. Topical antibiotic therapy and/or dilute antiseptic washes could well be replaced by this more effective approach. Using CRN on the skin prior to insertion of catheters, on suture sites, cuts and abrasions, should also reduce infections due to bacterial contamination. Limited internal use can be envisaged such as

nasal/sinus cavity washing/treatment and colonic treatment to eradicate, for example, C. difficile infections. Numerous other veterinary and industrial applications can be readily imagined.

The effective manner, in which CRN completely inhibits the growth of bacteria, but not eukaryotic microorganisms, has been employed to isolate diverse fungi from environmental samples in order to screen for new antibiotics. In this manner, we have isolated several fungi that produce apparently novel antibiotic compounds which kill Gram positive and negative bacteria as well as drug-resistant strains such as MRSA and VRE. We employ an initial screen against a Gram positive and a Gram negative bacterial species, selecting only those activities that suppress both, then testing against multidrug resistant bacteria, selecting only those with that activity. Using CRN rather than antibiotics (expensive and not necessarily broadly effective at suppressing prokaryotic growth) or acidic pH (as in Sabourrad's agar which is inefficient at suppressing bacterial replication) permits us to use any growth medium for these explorative studies, thereby helping to broaden the chance of isolating useful fungi.