SOUTHERN RESEARCH

14 November 2019

Reference: Registration No. 64-R-0001, USDA Annual Report of Research Facility

FY 2019 APHIS Form 7023 Column E Explanation:

- 79 rhesus macaques (*Macaca mulatta*) underwent whole body irradiation as a part of an IACUC approved protocol designed to assess the potential of antibiotics as a medical countermeasure to mitigate infection resulting from acute exposure to radiation which could arise in the human population secondary to a radiological or nuclear event, e.g. a "dirty" bomb or nuclear accident. Based on veterinary treatment recommendations, the pain and distress of these animals was mitigated using analgesics, antipyretic agents, food supplements, oral electrolyte supplements, and anti-emetics. The SR IACUC decided that since the pain and distress caused by irradiation and the extent to which that pain and distress was able to be relieved varied, animals undergoing whole body irradiation should be classified into USDA Pain and Distress Category E.

- 1 ferret (*Mustela putorius furo*) used on an influenza challenge protocol developed clinical illness and is considered to have experienced some degree of unrelieved pain and/or distress secondary to influenza challenge. The withholding of anesthetics and analgesics was approved by the SR IACUC after justification by the Study Director who stated:
"Illness experienced by challenged animals must not be treated with analgesics, as this would compromise the scientific integrity of the study, mask the pathogenesis of the disease, obscure secondary efficacy parameters such has amelioration of clinical signs, could inadvertently accelerate the disease process, and confound the interpretation of euthanasia criteria. Importantly, the use of analgesics could alter the pathogenic and immunologic response to infection, thus making it impossible to interpret the data obtained in this study. Narcotic analgesics were shown to interfere with the mechanism(s) responsible for interferon production (Geher, W.F. et al., J. Toxicol Environ Health 2:577-582, 1977; Hugh, C.Y. et al. Proc Soc Exp Diol Med 142:106-111, 1973). Moreover opioids can suppress Natural Killer (NK) cell activity (Beilin, B., et al. Brain Behav Immun 3:129-137, 1989). Also analgesics including buprenorphine can cause histamine release (Marone, G., et al. Int Arch Allergy Immunol 124:249-252, 2001; Stellato, C., Ann NY Acad Sci 406:32-47, 1995). Histamine is a well-known inflammatory mediator and plays a central role in the pathogenesis of allergic and inflammatory diseases by modulating vascular and airway response. Histamine has been shown to induce activation of human macrophages (Mozzoni, A., et al. J Immunol 170:269-2273, 1999), inhibit interferon alpha release from dendritic cells (Marone, G., et al., Int Arch Allergy Immunol, 124:249-252, 2001) and increase the synthesis and release of IL-10 from human macrophages (Sirois, J., et al. J Immunol 164:2964-2970, 2000). Clearly, the

analgesic-induced release of histamine would directly interfere with the inflammatory process. Studies by Piersman et al, (Lab Anim 33:328-333, 1999) provide an additional example of how analgesics may modify the expression of the disease process. These investigators, using an established murine model of endotoxemia, showed that the opioids fentanyl and buprenorphine directly altered the outcome of their experiments by modulating the immune response. In this case, both opioids caused significant decreases in circulating levels of tumor necrosis factor alpha following administration of lipopolysaccharide (LPS)."