This report is required by law (? USC 21 43) Failure to report according to the regulations can result in an order to cease and desist and to be subject lo penalties as provided for in Section 2150

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Interagency Report Control No 0180-DOA-AN

UNITED STATES DEPARTMENT OF AGRICULTURE
ANIMAL AND PLANT HEALTH INSPECTION SERVICE

ANNUAL REPORT OF RESEARCH FACILITY
(TYPE OR PRINT)

1 REGISTRATION NO. 74-R-0073
CUSTOMER NUMBER 1469

FORM APPROVED
OMB NO. 0579-0036

2. HEADQUARTERS RESEARCH FACILITY (Name and Address, as registered with USDA Include Zip Code)

University of Texas
Medical Branch at Galveston
301 University Blvd
Office of the Associate Dean for Research
Galveston, TX 77550

3. REPORTING FACILITY (List all locations where animals were housed or used in actual research, testing, teaching, or experimentation, or held for these purposes. Attach additional sheets if necessary.)

FACILITYLOCATIONS (Sites) *See Attached Listing*

REPORT OF ANIMALS USED BY OR UNDER CONTROL OF RESEARCH FACILITY (Attach additional sheets if necessary or use APHIS FORM 7023A)

A. Animals Covered By The Anima Welfare Regulations	B. Number of animals being bred, conditioned, or held for use in teaching, testing, experiments, research, or surgery but not yet used for such purposes	C. Number of animals upon which teaching, research, experiments, or tests were conducted involving no pain, distress, or use of pain-relieving drugs.	D. Number of animals upon which experiments, teaching, research, surgery, or tests were conducted involving accompanying pain or distress to the animals and for which appropriate anesthetic, analgesic, or tranquilizing drugs were used	E. Number of animals upon which teaching experiments, research, surgery, or tests were conducted involving accompanying pain or distress to the animals and for which the use of appropriate anesthetic, analgesic, or tranquilizing drugs would have adversely affected the procedures, results, or interpretation of the teaching, research, experiments, surgery, or tests. *(An explanation of the procedures producing pain or distress in those animals and the reasons such drugs were not used must be attached to this report)*	F. TOTAL NO OF ANIMALS (Cols. C + D + E)
4. Dogs	3	0	16	0	16
5. Cats	0	0	0	0	0
6. Guinea Pigs	8	6	3	476	485
7. Hamsters	0	75	409	318	802
8. Rabbits	0	12	46	301	359
9. Non-human Primates	0	0	1	0	1
10. Sheep	0	0	393	3	396
11., Pigs	0	0	174	0	174
12. Other Farm Animals					
Goats	0	0	12	0	12
13 Other Animals					
Cotton Rats	0	0	0	10	10
Gerbils	0	0	39	32	71
Ferrets	0	0	0	58	58

ASSURANCE STATEMENTS

1) Professionally acceptable standards governing the care, treatment, and use of animals including appropriate use of anesthetic, analgesic, and tranquilizing drugs, prior to, during and following actual research, teaching, testing, surgery, or experimentation were followed by this research facility

2) Each principal investigator has considered alternatives to painful procedures.

3) This facility is adhering to the standards and regulations under the Act, and it has required that exceptions to the standards and regulations be specified and explained by the principal investigator and approved by the Institutional Animal Care and Use Committee (IACUC). A summary **of all such exceptions is attached lo this annual report.** In addition to identifying the IACUC-approved exceptions, this summary includes a brief explanation of the exceptions, as well as the species and number of animals affected.

4) The attending veterinarianfor this research facility has appropriate authority to ensure the provision of adequate veterinary care and to oversee the adequacy of other aspects of animal care and use.

CERTIFICATION BY HEADQUARTERS RESEARCH FACILITY OFFICIAL

(Chief Executive Officer or Legally Responsible Institutional Official)
I certify that the above is true, correct, and complete (7 U.S.C. Section 2143).

(b)(6), (b)(7)c

DATE SIGNED
Revised
03/19/2009

(AUG 91)

MAR 20 2009

4	Guinea Pig 96	Following intravaginal or intrarectal virus inoculation animals begin to develop vesiculoulcerative skin lesions on the perineum 4-5 days post inoculation. The skin disease reaches peak severity by 8-9 days post-inoculation and usually resolves spontaneously by 14-15 days post inoculation. During the acute infection the skin disease for each animal is quantified daily using a well-established 4 point severity scale. During the acute infection some animals develop urinary retention. In these animals the bladder is expressed daily in order to release the urine and minimize discomfort. During the primary infection animals may also experience hind-limb paralysis, as with the skin disease the vast majority of these animals recover spontaneously. However, all animals are observed daily. Animals in which hind-limb paralysis does not resolve within 4 days are euthanized by appropriate means. This is a neurotrophic virus thus we cannot use pharmacologic agents that alter the function of neuronal elements. Further the use of such agents which can alter the pathogenesis of disease can also affect the subsequent development of immune responses to infection. This in turn could affect the recurrent disease that is seen following resolution of the primary genital skin disease. During the recurrent phase of infection, animals develop spontaneous recurrent lesions. These lesions are episodic generally lasting 1-2 days and are not associated with any obvious signs of pain or distress in the animal. Historical data from our laboratory demonstrates that without intervention recurrent lesions are seen on ~10-20% of days with the frequency decreasing over time.
5	Guinea pig 45	Animals are used to determine the virulence of knockout strains of the organism and the safety and efficacy of a vaccine for the disease. The goal of the study is to determine the host response to the vaccine and the pathogenesis of the disease. The results of the study will be used to evaluate safety and efficacy of the vaccine for human beings. The infection causes fever in rodents during the early stage and ruffled fur, loss of activity, and weight loss in the late stage of infection. In general, complete or local anesthesia will not be given to the animals because complete anesthesia will affect the observation of the animal activity and the local anesthesia may have no effect on reducing discomfort caused by a systemic infection. We do not plan to give general or local anesthesia or analgesia to the animals during the infection (2-3 days after inoculation) because the animals appear healthy. In order to test the effectiveness of the vaccine, use of therapies that might alter the progression of the disease and recognition of the signs and symptoms of infection would adversely affect the study. When the animals become extremely sick (ruffled fur) or lose appetite, the animals will be euthanized.

6	Hamster 4	The purpose of some of our studies is to test vaccines under development for viral infections. Rodents are the most accurate and relevant model system for studying viral disease and are therefore the animal models used in these studies. Animals will be injected with a vaccine followed by challenge with a virus. Control animals will receive a sham vaccination followed by viral challenge. In order to test the effectiveness of vaccines, measured by the difference in survival between the test and control animals, the viral infection must be allowed to run its course with recognizable signs or symptoms developing in the control animals and in any of the test animals not protected by the vaccines. The use of intervening therapies that might alter the progression or recognition of the signs and symptoms of the viral infection in the animal model, including pharmacologic agents that do not have anti-inflammatory effects, would adversely affect the study.

7	Hamster 2	The purpose of this study is to examine the mechanisms of pathogenesis associated with parasite infections. Rodents are the most accurate and relevant model systems for studying the disease and are therefore the animal models used in the study. Animals will be injected s.c. with parasites. Control animals will receive a sham injection of PBS. To assess immunological and pathological changes during the course of infection, tissue samples will be collected from the skin, lymph node, spleen and liver, and will be used for examining signs and symptoms of parasite infection in the animal models, as well as cytokine/chemokine production in responses to parasite infection. Although skin lesions in diseased human patients do not accompany with pain, discomfort does occur when infected hosts have mucosal involvement, or enlarged spleen and liver. Therefore, it is anticipated that infected rodents will suffer mild-to-moderate pain or discomfort. It is not possible to administer therapeutic agents as they may affect the levels of cytokine/chemokine production.
8	Hamster 105	These are experimental model systems being developed and utilized in a small number of laboratories including UTMB. There are no specific federal regulations, but these protocols have been approved for these studies by the NIH. The objectives of this project are to study development of virus diseases in animals and investigate strategies for treatment including the production and testing of candidate vaccines and other antiviral treatments. Two to four-day-old mice will be injected intracranially while infant hamsters, adult hamsters, and adult mice will be injected in the peritoneal cavity with a viral suspension to initiate infection. The pain and discomfort produced by virus infections consist of headaches, paralysis, and eventual death due to loss of ability to breath or nurse. Animals will be observed daily for two weeks following inoculation or in some cases, animals may be retained for several weeks so that post-exposure blood can be collected to demonstrate viral infection by detection of virus-specific sera. When signs of disease (hind limb paralysis and/or tremors, and/or severe fur ruffling) are detected at a level of severity that will result in death within 24 hours, the animals will be humanely euthanized. The use of intervening therapies might alter the natural progression, or recognition of the signs and symptoms, or the viral infection in the animal model, including pharmacologic agents that do not have anti-inflammatory effects, would adversely affect the study and cannot be used.

9	Hamster 182	"The purpose of this study is to characterize the pathogenesis of specific viral infections in Syrian golden hamsters. Syrian golden hamsters are the only laboratory animal that accurately models the pathogenesis and pathology of the viral pulmonary syndrome, which is an acute, potentially fatal disease of humans. Inflammation in infected lung tissue (pneumonitis) appears to be central to the evolution of the life-threatening pulmonary edema in fatal human disease and the similar disease in hamsters. The pathogenicity and virulence of these viruses will be measured in juvenile and adult hamsters. Some of the animals are expected to develop severe pulmonary disease and may even succumb to their infections; however, the animals will be closely monitored and - if they develop severe dyspnea - euthanized by intraperitoneal injection of a lethal dose of sodium pentobarbital. Note that death is not an endpoint and that none of the animals will experience pain that is treatable with an anti-inflammatory medication or analgesic. Also, the use of intervening therapies (i.e., anti-inflammatory medications) that might alter the evolution of the pneumonitis and pulmonary edema (and the progression or recognition of the signs and symptoms of infection) would adversely affect the study."
10	Gerbil 32	All of the animals in our studies will be inoculated with a virus that has the potential to induce pain and /or distress following inoculation. Moreover, we must know how much virus we are giving to the test animals. Thus, it is necessary to titer each virus used and include relatively high doses in the titration. Knowing precisely how much virus is being given test animals is especially important in experiments assessing the protective efficacy of candidate antivirals and vaccines. It is important both in being able to get reproducible results in replicate experiments and in being able to determine if the antiviral or vaccine can prevent infection, illness, severe illness and morality. Stated another way , the amount of challenge virus used in an experiment can significantly affect the apparent outcome of the experiment and the use of too little challenge virus can make a material appear safe and efficacious when it may not have been if more virus had been given the animals. NO other drugs except what is being tested in the experiment can be given to the test animals to reduce any pain or distress since this would make it impossible to evaluate the materials being tested. Use of anesthetic or analgesic agents may alter the

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[redacted]

1	Hamster 12	One of the purposes of this study is to test antiviral drugs for treatment of viral infections. Hamsters are one of the most accurate and relevant model systems for studying this viral disease and are the animal model used in the study. Animals will be injected with an antiviral drug followed by challenge with virus. Control animals will receive a sham injection followed by viral challenge. In order to test the effectiveness of antiviral drugs, measured by the difference in survival between the test and control animals, the viral infection must be allowed to run its course with recognizable signs or symptoms developing in the control animals and in any of the test animals not protected by the antiviral drugs. The use of intervening therapies that might alter the progression or recognition of the signs and symptoms of the viral infection in the animal model, including pharmacologic agents that do not have anti-inflammatory effects, would adversely affect the study.
2	Guinea pig 20	The purpose of this study is to evaluate the efficacy of a virus-specific antiviral compound discovered during the initial SIBR Phase 1 work. A lethal viral infection is required to investigate the efficacy of the drug. Any procedure that might produce pain will be performed under isoflurane anesthesia. The virus can produce clinical symptoms including fever, anorexia, vomiting, muscle aches, malaise, and death. The use of pain relieving drugs is inappropriate for this study. To effectively test the antiviral compound against a lethal viral infection it is imperative to limit the confounding variables of other therapeutic agents that may or may not mask clinical symptoms or have an effect on underlying tissue pathology.

3	Guinea Pig 151 Rabbit 301	The most accepted models for the evaluation of therapeutics for inhalation exposure to bacterial agents are systemic infection models in mice, guinea pigs, rabbits, and non-human primates. The animals are infected by the respiratory route and within 2-3 days a lethal infection occurs. Decreasing the challenge dose does not prolong the period of illness. Animals die rapidly once large numbers of the bacilli multiply in the bloodstream. Mice, guinea pigs, and rabbits exposed to these particular agents do not display any obvious signs of illness, such as fever, agitation, stillness, ruffled fur. They also do not lose weight or stop eating and drinking during the infection. Therefore, it is not possible for us to anticipate whether any of these animals experience pain and/or distress before death. This agent causes an acute infection in which the febrile response is thwarted because the toxins (lethal toxin and edema toxin) diminish the capacity of neutrophils and lymphocytes to secrete cytokines that evoke fever and induce septic shock. Animals do not exhibit signs that they are ill before death, due to the effects of the bacterial toxins that act as immunoavoidance mechanisms. We monitor the condition of the animals a minimum of twice per day (morning and afternoon), and during some studies more often. Typically, the animals continue to eat and drink without any loss in weight right up until death occurs. Death is sudden and occurs when it is least expected. There is no warning that death is imminent. We are investigating the hypothesis that the toxins may act as cardiotoxins, and possibly this may explain why antibiotics and neutralizing antibodies have diminishing effectiveness when given later than 24 h post bacterial challenge. The question of whether there might be any interaction between the new therapeutics and analgesics leading to a different outcome in terms of protection in animals cannot be ruled out. The use of therapies that may alter the progression of the disease, with respect to toxin production and effects on underlying tissue pathology, would adversely affect the study and render suspect the data obtained from the animal model. With regard to selectively euthanizing animals within a study, there would be no basis for selecting those animals, since the animals do not exhibit any signs of discomfort prior to death.

progression of the disease and create variables in recognition of signs and symptoms related to vaccine response. We will not intentionally allow an animal to die. Instead, if an animal becomes moribund or exhibits marked stress or pain, it will be euthanized. Thus, pain and distress will be kept to a minimum by making frequent observations of the animals and euthanizing any that appear to have untoward response.

11	Ferret 30	In general, these viral infections are not considered "painful" although there may be considerable distress, and potentially death, associated with complication from those infections. Clinical signs associated with infection may include fever, anorexia, vomiting, muscle aches, and death. The purpose of the present study is to evaluate the efficacy of certain vaccine candidates against this strain of virus. To do so the animals must be inoculated in an attempt to produce disease in the animal model. We need an animal model that not only becomes ill following inoculation but one that also demonstrates recognizable signs and symptoms of viral infection in order to test the efficacy of the vaccine candidate. The use of anesthetics, analgesics, or sedatives may alter the progression of the disease of the ability to recognize the clinical symptoms associated with the disease process which would preclude us from recognizing the disease state and the effect of the antiviral compound on the disease process.

12	Guinea Pig 154	The purpose of this study is to develop and characterize an aerosol or intranasal animal model for these agents for the investigation of antibiotics and vaccines against those diseases. Although there currently are analogous i.v. based animal models for both diseases, there are few to no small animal models for these agents. In order to establish small animal models, the animals will be inoculated via intranasal or aerosol route and observed for clinical pathology of the disease. Since the initial experiments call for the use of organisms, to which C3H/HeN mice are resistant when these agents are administered by i.v. route, we need to develop and determine the full clinical course of the infection via the aerosol route. To fully characterize the models, the utilization of biosensors will be able to give a sensitive and accurate measurement of the animals' temperature during the course of the disease. The second aim of the project is to determine the effectiveness of therapeutic agents (vaccines, drugs and monoclonal antibodies) in animals that have been inoculated by aerosol challenge and to fully characterize the protective response. The use of intervening therapies may alter the progression of the disease and adversely affect the study. We are using guinea pigs to establish an aerosol model of infection. One of the objectives is to develop in depth and well characterized (molecular, immunological and histological) models in both mouse and guinea pigs. The use of pain and or distress relieving drugs would adversely affect the immunological and molecular markers that are major components of our experiments. They would also alter our observations of the clinical course of the disease.
13	Guinea Pig 10	The purpose of this study is to evaluate the vector competence of different ticks species to transmit specific agents, using guinea pigs as host to and also to perform immunological studies. This animal species is the most accurate and relevant model system and is therefore the animal model used in the study. Animals will either be needle injected or tick-bite transmitted. In order to carry out the study, the disease in the guinea pigs must be allowed to run its course with recognizable signs and symptoms of the infection in the animal model. Including pharmacologic agents that do not have anti-inflammatory effects, would adversely affect the study.

14	Ferret 28	In general, viral infections are not considered "painful" although there may be considerable distress, and potentially death, associated with complication from those infections. Clinical signs associated with infection may include fever, anorexia, vomiting, muscle aches, and death. The purpose of the present study is to evaluate the efficacy of certain vaccine candidates against the virus. To do so the animals must be inoculated in an attempt to produce disease in the animal model. We need an animal model that not only becomes ill following inoculation but one that also demonstrates recognizable signs and symptoms of viral infection in order to test the efficacy of the vaccine candidate. The use of anesthetics, analgesics, or sedatives may alter the progression of the disease of the ability to recognize the clinical symptoms associated with the disease process which would preclude us from recognizing the disease state and the effect of the antiviral compound on the disease process.
15	Sheep 3	The goal of our experiments is to determine changes in pain thresholds to mechanical stimuli under nerve injury conditions. Accurate pain thresholds in test animals will not be obtainable if pain relief drugs are administered.

16	Hamster 13 Cotton rat 10	Infection by these viruses may cause encephalitis and lymphoid depletion in animals. All of these viruses may cause nonspecific symptoms including muscle aches, headaches and fever in these animals. A goal of these studies is to determine the level of viremia in animals after infection with viruses. It would be impossible to interpret our results if anti-inflammatory or any other analgesic drugs are used, because they might affect the viremia levels. Also, all analgesics interact in some way with the inflammatory response, which is integral part of the disease development, and some can affect the blood brain barrier, which could affect pathogenesis. i) Analgesics, such as non-steroidal analgesics (ibuprofen, acetyl salicilate, etc.) have anti-inflammatory effects that could affect virus replication and dissemination and/or affect thrombocytes that are important mediators in local inflammation (Breddin 2004) (Darling, Romero et al. 2004)(Hodges, Ireland et al. 2001). ii) Cerebral endothelial cells can release/express various products of arachidonic acid cascade with both vasoactive and pro-inflammatory properties, including prostaglandins, leukotrienes, and platelet-activating factor. These metabolites induce platelet and neutrophil activation and adhesion, changes in local cerebral blood flow and blood rheology, and increases in blood brain barrier permeability. iii) Inhibition of COX-1/2 as in the case of ibuprofen, aspirin and other non-steroidal anti-inflammatory drugs could modify the response of these cells after viral infection (Stanimirovic and Satoh 2000; Zhang, Smith et al. 2000). iv) Steroids such as cortisol affect the production of Leukotriens and influence the blood brain barrier directly (Muruganandam, Smith et al. 2000). v). Some studies demonstrated that activation of opioid receptors within the central nervous system alters various immune system parameters. Specifically, natural killer cell cytolytic activity and lymphocyte proliferative responses to mitogen appear to be modulated predominantly through central opioid receptors (Mellon and Bayer 1998; Mellon and Bayer 1998). This could influence the response to viral infection if additional opioids are used.

74R0073

2008 USDA Annual Report – Attachment
UTMB Galveston
Galveston, TX
74-R-073

Exceptions to Regulations and Standards
Approved by the Institutional Animal Care & Use Committee
University of Texas Medical Branch, Galveston, TX

Three hundred and ninety-three (393) sheep were housed in metabolic stanchions up to 4 weeks. The sheep were maintained in stanchions for 48 hours prior to surgery for psychological adaptation to this type of housing. The stanchions allow the sheep to stand or lie down in sternal recumbancy. The sheep were surgically instrumented with specialized equipment (chronic indwelling vascular catheters, etc.). These sheep are provided the most intensive care of any animals on campus. They are monitored 24 hours a day by research staff during the work week and observed minimally 4 times daily on weekends and holidays. In addition, they were observed daily, seven days a week by Animal Resources Center (ARC) veterinary and/or husbandry staff.

Three (3) sheep were housed in metabolic stanchions up to 2 weeks. The stanchions allow the sheep to stand or lie down in sternal recumbancy. When the animals recover from surgery, depending on the procedure, they are either returned to their housing area and monitored daily thereafter, or maintained in stanchions and monitored 24 hours a day by research staff during the work week and observed minimally 4 times daily on weekends and holidays.

Eight (8) nonhuman primate (rhesus macaques) on a long term/chronic study. To prevent damage to the surgically implanted indwelling scientific devices in each animal, pair housing was not possible. Mutual grooming and the possibility of fighting between the monkeys could dislodge or expose the delicate medical instrumentation. Environmental enrichment is provided in the form of toys, puzzle feeders, and food treats. These nonhuman primates were also maintained in restraint chairs periodically, as required for the research study. During these sessions the monkeys receive treats/rewards and are not chaired longer than 4 hours in a 24 hour period.