



InFocus

Center of Comparative Medicine & Pathology
Research Animal Resource Center
Laboratory of Comparative Pathology



New Insights into the Etiology of Ulcerative Dermatitis in C57BL/6 Mice

Ulcerative dermatitis (UD) is a progressive, debilitating, pruritic (itchy) condition commonly affecting C57BL/6 and related mouse strains. UD initially begins with alopecia (fur loss) and a papular dermatitis over the dorsum of the head and thorax. Ulcerations subsequently develop, may progressively enlarge, and often heal by fibrosis, resulting in skin contracture and possible restriction of limb movement or food prehension (Figure 1). Secondary bacterial infection also commonly complicates healing. UD must be differentiated from the pruritus and secondary skin trauma (self-inflicted from scratching) associated with fur mites (such as *Myobia musculi* and *Myocoptes musculinus*) as these mice can also present with skin ulceration.

Initially UD is characterized histologically by profound inflammation of the dermis and epidermis composed of neutrophils, lymphocytes, macrophages, and mast cells. With time and self-trauma, lesions often progress to ulceration of the overlying epidermis with an adhered serocellular crust (Figure 2). The inflammatory response can also involve deeper structures, including muscle, subcutaneous adipose tissue, and nerves. The intact epithelium adjacent to the ulceration is markedly hyperplastic. Chronic lesions have granulation tissue formation progressing to advanced dermal fibrosis. These findings indicate that UD has the potential to confound results in both dermatological and immunological studies.

Despite numerous studies, the exact cause and pathogenesis of UD remains unclear. The current hypothesis is that the condition is multifactorial with both genetic and environmental components. Epidemiologic studies have linked UD to aging, high vitamin A levels, high fat diets (11%), ad libitum feeding, hair-induced periodontitis (secondary to excessive grooming), and deficiency in inducible nitric oxide synthase. It has also been linked with a dermal vasculitis

Cont. on pg. 4

A New Era for Animal Rights Activism

Animal rights activism has officially entered the ranks of terrorism in the United States. In April 2009, the US Federal Bureau of Investigation announced that it had added an extreme animal rights activist to its list of “Most Wanted Terrorists” for acts of domestic terrorism. This places animal rights extremists on a list headed by terrorists such as the leaders of Al Qaeda. According to the FBI, the activist on their most wanted terrorist list may have “advocated violence in connection with animal rights issues” and may have planted a mail bomb alongside another bomb at a research facility “intended to harm or kill the first responders.” According to the FBI, to date, animal rights extremists have been responsible for more than 1800 criminal acts, and more than \$110 million in damages. In 2009, the FBI was investigating approximately 170 animal rights extremist activities across the country (9-23-2009 NY Times, F.B.I. Calls Animal Rights Activist ‘Terrorist’).

Animal rights activities aren’t new to those of us who work daily in biomedical research. We have observed the activism arena intensifying over time. In the late 1990’s, one of the most publicized acts of violence was perpetrated by the group called SHAC, Stop Huntingdon Animal Cruelty. But it happened off our shores, in the United Kingdom. So we felt the impact, but we were buffered by the ocean and continued to believe that animal rights activists would never gain ground to that extent in the US. We were wrong. In 2009, Dr. David Jentsch, a Professor of Neuroscience at UCLA, woke up to an orange flash and a car alarm. Animal rights terrorists had bombed his car. A year later in 2010, he received a letter containing razor blades and threats that his throat would be cut. Now in 2011, the animal rights extremists at NIO, Negotiation Is Over, are harassing university students who use animals across the country, most recently here in New York. They are flooding their email accounts with obscenities and rabid rhetoric. The

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Figure 1. Typical presentation of chronic ulcerative dermatitis with intrascapular ulceration and fibrosis. (Kastenmeyer 2006).

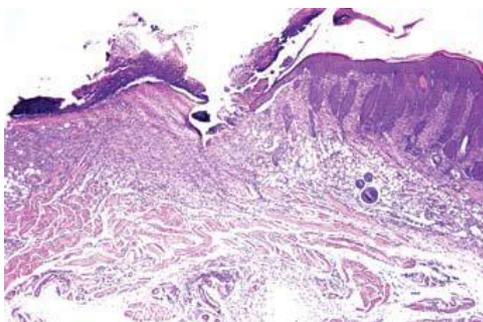


Figure 2. A typical ulcerative dermatitis lesion extending to the subcutis with inflammatory cells and fibrosis (Kastenmeyer 2006).



Noah Berger / AP file

Animal rights activists demonstrate outside the home of a University of California Berkeley professor this year.



**Keep ID card visible
AT ALL TIMES
and never share access!**

Security Enhancements Implemented at RRL

Increasing animal rights activism in the US necessitated a security review of all RARC's vivaria. In order to enhance security in MSKCC's Rockefeller Research Laboratory (RRL), WCMC staff utilizing those facilities are now required to scan their MSKCC ID cards in all RRL elevators to access the 12th floor 24/7 (previously, this was limited to evenings and weekends only). Security Officers will also continue to check ID cards as people enter the building.

It is also important for all vivarium users to remember to keep your ID visible at all times while in the facility. You should never use your card to provide facility access to another staff member if they do not have an ID or their ID card is not working, even if you know them. Staff requiring access should contact RARC administration @ 646-888-2400 for access. It is important to remain alert at all times and immediately report suspicious personnel or activity to Security and/or RARC management.

Finally, also remember that photography and videography within the vivarium is prohibited without IACUC or RARC authorization. If you need to photograph research animals or areas within the vivaria as a component of your project, contact EQA for assistance.

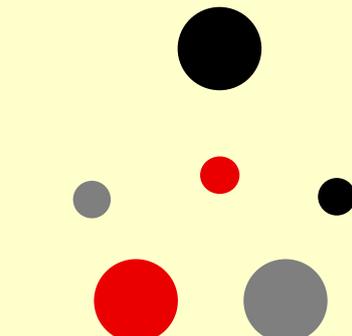
Aseptic Technique in Rodent Survival Surgery: Critical to Research Success

Aseptic technique is the set of procedures used to reduce contamination by microbes to the lowest possible level when performing surgery (4, 9-11). It includes preparation of the patient and surgeon, as well as sterilization of instruments, cleanliness of the surgical environment and proper surgical technique (2, 6, 8-11). The importance of aseptic technique cannot be overstated when performing survival surgical procedures on rodents. Not only are post-surgical complications an animal welfare issue, but they can negatively impact research in terms of lost time, labor and cost, as well as lost research potential (2). These complications include but are not limited to delayed wound healing, wound opening (dehiscence) and subsequent infection, evisceration, pneumothorax, post-surgical pain, inflammation, and even death. While aseptic technique involves multiple steps, this article will focus on patient and surgeon preparation.

When preparing an animal for surgery, the fur should be removed from an area 150% larger than the area where the incision will be made (2,4,10,11). Appropriate methods of fur removal include using a surgical clipper with an appropriate blade or depilatory cream (11). Fur removal serves multiple functions. First, hair can harbor bacteria that, while normally not pathogenic, may contribute to opportunistic infection should they enter the incision (2). Also if fur falls into or becomes entangled in the incision, a foreign-body granuloma may develop which can cause a significant immune response and delay incision healing. It may predispose the animal to wound infection and even result in mortality when not identified rapidly. For example, Veterinary Services staff recently evaluated two mice presenting with ulcerations and cellulitis on the forehead with inflammation extending into the brain. The intense inflammation and subsequent infection was a result of hair shafts becoming embedded in the craniotomy incision (7). Proper preparation of the surgical area in these cases would likely have prevented the need to prematurely euthanize these animals. Removing the hair also preserves the sharpness of scalpel blades and scissors which if dull create jagged wound edges that take longer to heal. Finally, fur removal improves visualization of the

A New Era for Animal Rights Activism, cont. from pg. 1

NIO refers to students as the "soft-bellied targets of the vivisection complex" who "can be shut down with relative ease". But they are wrong. University students all over the country are beginning to take a stand. At UCLA, students have banded together to stand up against the lies and misinformation propagated by the animal rights activists and the violence of the extremist groups to form the group Pro-Test for Science. Their goal is to challenge the climate of fear that has descended upon the research community. We at the Center for Comparative Medicine and Pathology are committed to ensuring a safe work environment for all our staff and colleagues who work with animals. We need your help to maintain vigilance and keep an eye out for questionable activity on or around our campuses. If you see something, say something. Contact EQA at RARCEQA@med.cornell.edu.



Pro-Science • Pro-progress • Pro-Test



Cont. on pg. 3

Aseptic Technique: Critical to Research Success

cont. from pg. 2



Materials used in the course of surgery should be laid out and opened aseptically to maintain sterility and allow easy access during the procedure.



A scrub with chlorhexidine or povidone-iodine is used to properly prepare the surgeon's hands before donning gloves.



American Association for Laboratory Animal Science Learning Library, Animal Care and Use in Research and Education

Using a designated well-lit space away from highly trafficked areas can significantly improve surgical success rates.

wound post-operatively making it easier for observers to identify early signs of infection or dehiscence.

The next step of patient preparation is disinfection of the skin (2,4,8,10,11). Chlorhexidine and povidone-iodine scrubs kill many microbial organisms and have residual activity, which is ideal for protecting against infection both during and after surgery (2). Alcohol is a fast-acting bactericidal, fungicidal and virucidal agent, but it does not work against microbial spores (5,6). The use of a chlorhexidine or povidone-iodine scrub alternating with 70% alcohol (isopropyl or ethanol) is best for removal of vegetative bacteria that can be found on the animal's skin (2,11). The scrub is applied first with sterile gauze or a cotton applicator followed by alcohol starting each at the center of the clipped (proposed incisional) area moving outward in a circular pattern. This process is repeated three times, each with fresh gauze. A final application of either a chlorhexidine and povidone-iodine solution (solution does not contain the detergent present in the scrub) to the surgical site before initiating surgery provides additional residual activity.

Draping the rodent patient also minimizes the potential for contaminating the incision. The drape should be sterile and impermeable to water precluding bacterial migration (2, 9). The drape should be large enough to maintain a sterile field to avoid contaminating the surgeon or instruments. Materials used include disposable drape material or adhesive plastic drapes (2, 9). The drape should be large enough to expose the surgical site while covering the majority of the animal's body. Transparent drapes have the advantage of allowing for greater visualization for anesthetic monitoring.

Surgeon preparation is another procedure used to minimize contamination and ensure surgical success. The surgeon should wear a clean lab coat or surgical scrub shirt, a hair net or surgeons cap, a surgical mask, and sterile gloves for survival procedures (2, 9). Surgeons should wash their hands with a disinfectant soap for at least 3 minutes before donning sterile disposable gloves (9). If the surgeon is operating alone, it is important to aseptically set out all materials that will be needed for the procedure before starting. If non-sterile gloves are used, the surgeon

should use a 'tips only' technique so that their hands never come into contact with the tips of the instruments or the surgical site (3,6,8). The goal is to minimize contamination of the wound that may come from the surgeon's normal flora (2).

Key components to minimize post-surgical complications also include reducing surgical time and handling tissues delicately (2,10). By decreasing surgical time, there is less opportunity for bacteria to colonize tissues and, by handling tissues as little as possible; there is often a reduction in surgical inflammation which can be painful. For survival procedures, instruments should always be sterile and the area where surgery is performed should be clean and protected to prevent contamination (2, 4, 8,11).

The use of appropriate suture material with timely removal minimizes tissue reaction and prevents bacterial contamination. If a body cavity, such as the thorax or abdomen is opened, then the body wall should be closed separately from the skin layer. This is best achieved by using a 3-0 or smaller absorbable suture material such as Vicryl®, PDS®, Dexon® or Maxon® (4,8,10,11). For skin closure, monofilament sutures should be used because braided or multifilament sutures promote wicking or capillary transport of bacteria to deeper tissues (3) or alternatively, surgical wound clips applied. In general, non-absorbable sutures should be used for the skin. Skin sutures or wound clips should be removed 7-14 days after placement (9). This includes absorbable sutures because their absorption requires contact with body fluids (3). Ideally, the skin should be closed using either a subcuticular (or other hidden) suture pattern or wound clips, because many rodents will chew at their sutures. In most cases, the skin should be closed using an interrupted pattern to prevent the entire wound from opening if the animal chews at the sutures.

Careful adherence to aseptic technique can minimize post-surgical complications, reduce healing time, improve animal welfare and minimize delays to or impact on research (1,9). For further instructions contact RARC, or refer to RARC's *Rodent Survival Surgery Guidelines*.

References:

1) American College of Laboratory Animal Medicine Position on Rodent Surgery.
http://www.aclam.org/pub_rodent_surgery.html

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RARC Implements New *eLearning* Platform

Both the Animal Welfare Act and the Public Health Service Policy require WCMC to provide training on specific topics to staff using research animals for teaching, training, or research. Electronic or *eLearning* has been demonstrated to be an efficient and effective method of information sharing in a variety of scientific fields and education. In order to meet the needs of investigative staff, RARC has developed and is releasing a web-based *New Investigator Orientation Training Course* which allows new investigative staff to complete orientation online at their convenience. The course curriculum is provided in three modules which ensure that investigative staff utilizing research animals receives essential content.

RARC has employed Lectora[®], a state of the art *eLearning* application that provides RARC the opportunity to offer a dynamic training experience which is both interactive and supports visual and auditory learning. The three modules cover a range of important topics including regulations, safety, as well as applicable institutional and departmental policies and procedures. The modules are accessible 24 hours a day, 7 days a week. As with all RARC training, a knowledge assessment is included at the end of each module to ensure content comprehension. After successfully completing the assessment, investigative staff will receive a certificate of completion which must be submitted to EQA via email (rarceqa@med.cornell.edu). Users requesting access authorization to WCMC's vivaria will have to successfully complete the training modules prior to being granted access. A facility tour will also be required to be completed within 1 month to maintain vivaria access. Future enhancements, to be included in the EnCCoMPass application suite under development, will automate and integrate training activities into both the animal protocol submission and facility access processes. Additional modules, both optional and required, based on specific research activities, are planned. As always, feedback is encouraged and appreciated. RARC strongly believes that an online training curriculum will greatly enhance our education and training program.

New Insights into Ulcerative Dermatitis,

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that caused subsequent epidermal necrosis and ulceration in aged C57BL/6Nia mice.

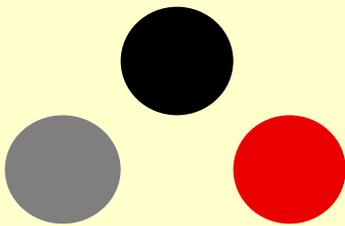
A recently published study by Sundberg et al identified a polymorphism in the alcohol dehydrogenase 4 (Adh4) gene and differential expression of epithelial retinol dehydrogenase (Dhrs9) genes in four C57BL/6 substrains. Adh4 and Dhrs9 are enzymes present in the skin that oxidize retinol (vitamin A) to retinal and retinoic acid. Adh4 oxidizes retinol to retinoic acid which then degrades while Dhrs9 oxidizes retinol to an active form (CRABP2-Retinoic Acid) that can cause toxic levels of gene expression. The Adh4 polymorphism in the C57BL/6 (B6) substrains was previously shown to reduce enzymatic function, suggesting that all four substrains are susceptible to problems metabolizing excess vitamin A. The upregulation of Dhrs9 in two substrains (C57BL/6J, C57BL/6Tac) may explain the increased incidence of dorsal skin alopecia in comparison to the two substrains without upregulation (C57BL/6NCr, C57BL/6Crl) because it increases toxic levels of gene expression. This study provided preliminary evidence that a polymorphism within Adh4 combined with elevated Dhrs9 and a diet high in vitamin A may play a role in B6 dermatitis. In addition, this study found that follicular dystrophy followed by penetration of the hair shaft through the outer root sheath preceded the inflammation characteristic of ulcerative dermatitis.

A consistently effective therapy has not been identified despite many studies. In one study, the use of a vitamin-E fortified diet (3000 IU/kg) for a period of 8 weeks was shown to be beneficial for lesion healing with 80% of mice (n=71) showing at least a 50% decrease in lesion size. This suggests oxidative injury may play a role in UD lesion development and/or maintenance. More recently, another group identified maropitant citrate, a neurokinin (NK1) receptor blocker, as a treatment option that works by preventing substance P from binding and inducing pruritus and scratching behavior. In addition, nail trimming has also been shown to decrease lesion severity and healing time.

Guidelines for staging and treatment of UD are available on RARC's website. The



<http://learninggeek.wordpress.com/category/elearning>



C57BL/6 mouse

New study provides preliminary evidence that a polymorphism within Adh4 combined with elevated Dhrs9 and a diet high in vitamin A may play a role in B6 dermatitis.

<http://www.astartebio.com/>

Cont. on pg. 5

New Insights into Ulcerative Dermatitis, Cont. from pg. 4

Stage	Open Lesion Size
1	>1.4 cm ²
2	1.5-2.9 cm ²
3	2.9-4.2 cm ²
4	4.3-5.6 cm ²
5	5.7-7.0 cm ²

Table 1. RARC's 5 stage scale for monitoring ulcerative dermatitis.

end point (stage 5) requiring euthanasia is when lesions on the affected mouse occupy 10% or more (7 cm²) of the animal's body surface area. The 5 stage scale is the maximum allowable body surface involvement (7 cm²) divided into 5 equal measurements of 1.4 cm² (Table 1). Animals with eye or ear involvement are placed in the stage above that dictated by lesion size. Additionally, if limb movement or food prehension is restricted, euthanasia is recommended.

Treatment options offered for UD include nail trimming and topical or oral medications. Nail trimming prevents the animal from causing further damage at the wound when scratching. Oral or topical antibiotic is recommended to prevent or treat secondary bacterial infections. Nail trimming and ointment application can be accomplished by lab members or Veterinary Services can also provide this service for a fee. Feed containing antibiotic (amoxicillin) and elevated levels of Vitamin E are also available through RARC.

References:

Andrews, AG, RC Dysko, SC Spilman, RG Kunkel, DW Brammer and KJ Johnson, Immune complex asculitis with secondary ulcerative dermatitis in aged C57BL/6Nnia mice. 1994. Vet. Pathol., 31: 293-300.

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Nembutal: Withdrawn from Veterinary Market

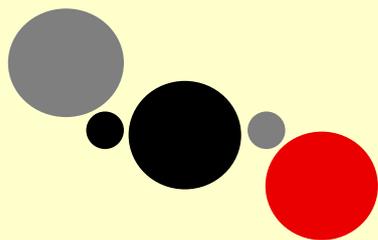
Injectable sodium pentobarbital sold under the trade name of Nembutal® (50mg/ml) is no longer available for veterinary use, including use in research animals, in the United States. To avoid interruption of your research goals, RARC has identified an alternative product, a concentrated formulation of sodium pentobarbital (390mg/ml) that may be suitable for your rodent studies for non-survival use. <http://www.drugs.com/vet/fatal-plus-solution.html>. Veterinary Services' staff can provide a dilute solution of this product to your lab. Alternatively, you may discuss alternative anesthesia options with a RARC veterinarian. Your protocol will need to be amended to reflect this change. For additional information, you may contact Dr. Christine Lieggi (lieggic@mskcc.org, chl2019@med.cornell.edu), Dr. Rodolfo Ricart at WCMC (rjr2004@med.cornell.edu), or Dr. Paula Ezell at MSKCC (ezellp@mskcc.org).

When using any new anesthetic agent, or an anesthetic agent from a different source, it is advisable to test a small number of animals first, to observe the anesthetic effects. Doses may be strain and sex dependent. The appropriate dose to use is the lowest dose needed to achieve the appropriate level of anesthesia. The recommended dose of sodium pentobarbital to induce anesthesia in mice ranges from 50-90 mg/kg and the recommended dose for rats is 40-60 mg/kg. Please note that sodium pentobarbital has a long duration of action and a narrow margin of safety in most species. A dose of 300mg/kg is required for euthanasia.

EnCCoMPass: New Application Suite

In conjunction with SKI Research Computing and the development firm EPAM, CCMP is in the process of a complete overhaul and enhancement of all the CCMP, RARC and LCP's computer applications. The new application suite, to be called EnCCoMPass, will replace the various independent systems currently in use and provide substantial efficiencies by eliminating duplicate data entry and enhancing current workflows. The new system will also provide electronic animal health records as well as tools for organizing and documenting staff training

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Nembutal® no longer available for veterinary use in the US.



UPCOMING SEMINAR**Research, Animals, and Ethics**

**Friday November 18, 2011
10:30 AM to 12:00 PM**

**MSKCC's Hoffmann
Auditorium (C-186) - 444
East 68 Street**

Speaker: Susan Kopp, DVM, Professor of Health Sciences in the Veterinary Technology Program at LaGuardia Community College (CUNY) and Affiliated Scholar, Yale Interdisciplinary Center for Bioethics. Her clinical interests focused on shelter medicine and later, as chief veterinarian for the New York City animal shelter system, in related fields of veterinary public health and the human-animal bond. Dr. Kopp is a recipient of the New York State Humane Association Award for Exemplary Veterinary Service.

Society and regulatory agencies dictate that ethical principles be considered when maintaining research animal well-being.

Bioethics is the study of the ethical questions that arise in the relationship between the disciplines of philosophy, law, biotechnology, life sciences, medicine and politics.

Dr. Susan Kopp will provide an introduction to Bioethics as it relates to animal-based research. The seminar will provide a framework for discussion for the research community at our collaborative institutions and outline successful methods for investigative staff to address their research interests to the general public. The animal rights interpretation and perspective will also be addressed for discussion.

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**and
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Pathology**

EnCCoMPass Development, Cont from pg. 5

and a colony management tool to be used by laboratories in the management of their mouse and rat colonies. Application functionality will be accessible to both CCMP and research staff. In the interim, we continue to use our current systems such as *eCensus* (for performing cage census), *eAnimal* (for animal procurement), *eTransfer* (for intra-institutional animal transfers), *eCertificate* (for inter-institutional animal transfers and biosecurity activity scheduling and tracking), *eSirius* (for animal use protocol development, submission, and review) and Visual Lab's Laboratory Information System (for LCP submissions and results reporting), in addition to our existing recharge and billing system.

The project will be completed in three phases with specific modules rolled out in each phase. The first phase, scheduled for completion in mid-2012, will include the protocol management (formerly *eSirius*), animal requisition and billing management (formerly *eAnimal*) modules.

EnCCoMPass will provide a seamless interface to faculty and staff utilizing the CCMP and its constituent sections, RARC and the LCP. Each user will have an individualized application-wide dashboard that will provide most important tasks and workflows on a single screen. Because all modules will be built on a single platform, users will be able to access the entire system with a single log-on and password. The application will allow the CCMP to substantially reduce manual and paper-based processes providing a streamlined and manageable user experience.



EnCCoMPass - CCMP's new comprehensive animal resource program management application promises organizing and documenting capabilities useful to investigative staff.

Aseptic Technique, Cont. from pg. 3

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