



Nr. 19

May 2001

## **Göttingen Minipigs in USA**

Ellegaard Minipigs USA has participated in the Society of Toxicology Annual Meeting in San Francisco, CA and Experimental Biology in Orlando, FL. At both meetings the interest for the Göttingen minipig was significant.

In conjunction with the SOT meeting we hosted a scientific seminar about telemetry as well as reproductive and juvenile studies in the Göttingen minipig. The seminar was well visited and the presentations and following discussion showed high interest in this high quality breed of minipigs. At the 2002 SOT meeting in Nashville, TN, we will continue this successful way of bringing scientists together sharing information on Göttingen minipigs. The subjects for the meeting will be presented on our website and here in our newsletter.

Göttingen minipigs are available from our USDA approved quarantine site in Perkasie, Pennsylvania. We can provide large uniform groups of minipigs well suited for your GLP studies. To ensure even better availability of Göttingen minipigs a breeding facility will be established as soon as the North American market for Göttingen minipigs has grown to a certain extent – hopefully within the next two years.

It is our wish to obtain AAALAC accreditation for our quarantine site in Perkasie as soon as possible, and currently we are working on the necessary preparations.

## **Microsomes for in vitro metabolism studies**

Liver microsomes from Göttingen minipigs are now available from BIOPREDICT, a contract in vitro services laboratory in France. Ellegaard Göttingen Minipigs has established contact to BIOPREDICT, to provide customers working with minipigs also with minipig liver microsomes. Please contact Ellegaard Göttingen Minipigs for specifications.

## **Transportation of Göttingen Minipigs with regard to the Foot and Mouth Disease situation**

In spite of the serious situation regarding Foot and Mouth Disease (FMD) in Europe, distribution of Göttingen minipigs has continuously been possible due to specific permission from veterinary authorities. Our company was granted permission to export Göttingen minipigs by the Danish Veterinary and Food Administration, and national veterinary authorities of the receiving countries, with the exception of the United Kingdom and the Netherlands, due to the high health status of our animals and high level of protection during transportation.

Besides our routine disinfection procedures, extra precautions are taken, and before returning to Denmark vehicles are disinfected at the border in certified truck washing facilities. Additionally, routes are planned to avoid areas with FMD outbreaks with a wide safety margin.

Importation into the USA is still not possible, since all import of life stock and animal products from Europe is banned. However, USDA is considering regionalization of Europe, allowing products from certain regions into the USA. As it looks now, the Scandinavian countries, including Denmark, have a fair chance of being exempted from the general ban, since FMD has not been identified in Scandinavia.

## **Course on experimental surgery**

On 16 May 2001, in connection with the Scand-LAS symposium in Aarhus, we have arranged a course on experimental surgery in minipigs. The course will take place at the Institute for Experimental Clinical Research, Skejby Hospital, Aarhus. The programme and abstracts of lectures can be found inside this Newsletter, and at [www.minipigs.com](http://www.minipigs.com). Registration for the course is closed, and a waiting list exists, but seen the overwhelming interest we plan on repeating this course later this year. Please, let us know if you are interested in attending the next course.

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## Abstracts of lectures at the Surgery Workshop on the Göttingen Minipig

Wednesday, May 16, 2001

Institute for Experimental Clinical Research, Skejby Hospital, Aarhus

### *Programme:*

- 8.30 Welcome (Prof. M. Hasenkam)  
8.45 Introduction to the course  
(Peter Bollen/Frederik Dagnæs-Hansen)  
9.00 Swine: Handling techniques, venipuncture, anesthesia, and perivascular cut downs  
(M. Michael Swindle)  
9.45 Maintenance of long-term vascular access devices in minipigs (Anthony Webb)  
10.30 Coffee break  
10.45 Techniques for use of fully implantable telemetric monitoring implants in monitoring of ECG and BP in large animals and the Ellegaard minipig (Steven Hachtman and Dan Huettelman)  
11.30 Practical introduction to the workshop  
12.15 Lunch  
13.00-17.00 Surgery workshop with six stations

### **Swine: Handling techniques, venipuncture, anesthesia, and perivascular cut downs**

M. Michael Swindle, DVM, Professor and Chairman, Department of Comparative Medicine, Medical University of South Carolina, Charleston, SC, USA, swindlem@musc.edu

Swine are best handled using humane restraint techniques and stressful agricultural techniques such as snout snaring and use of large gauge needles for precaval venapuncture should be avoided. In the size of pigs used in most research settings, 20g, 1.5" needles are usually adequate. Venipuncture can be made in the following peripheral veins: precava, external and internal jugular, cephalic, auricular, cranial abdominal, lateral and medial saphenous, femoral. In addition the following arteries can be accessed peripherally: carotid, medial saphenous.

Endotracheal intubation can be accomplished without special equipment in swine >50 kg. Intubation is readily accomplished with the pig in dorsal recumbency using a laryngoscope blade with a slightly curved tip and an endotracheal tube without a stylette. Small swine can be intubated without a laryngoscope by external manipulation of the larynx.

Peripheral vascular cut downs are readily accomplished in the neck and hind limbs. The external jugular vein, internal jugular vein and carotid artery can all be reached through a single incision in the jugular furrow. The cephalic vein can be accessed through a superficial incision at the level of the thoracic inlet. The femoral and medial saphenous vessels can be accessed through a single incision in the medial aspect of the hind limb.

All of these techniques will be demonstrated during the workshop. The techniques will be discussed during the lecture portion and specific recommendations for anesthesia and analgesia will be made.

## Maintenance of long-term vascular access devices in minipigs

Anthony J Webb BVSc DVR MRCVS, Animal Welfare Group, Pfizer Global Research and Development, Sandwich Laboratories, Ramsgate Road, Sandwich, Kent CT13 9NJ, United Kingdom

### *Introduction:*

Maintenance of long term implanted vascular catheters in minipigs has a significant impact upon the ultimate performance of the device, as well as animal health and welfare. Meticulous attention to detail will help to ensure success. Many of the complications of vascular catheters in minipigs are virtually impossible to eliminate successfully, once established, making prevention of problems paramount in any catheter maintenance programme. Prior to implantation, time should be spent acclimatising minipigs to their working environment and handling. This is an essential step in facilitating good maintenance procedures - by ensuring the animal's cooperation.

### *Responses to implantation:*

A complex interaction occurs from the time of implantation of a vascular catheter between the materials from which it is constructed and the animal body into which it is implanted. Nearly all materials acquire a bio film which influences the long-term behaviour of the catheter and the presence of the foreign material incites responses in the body. Understanding of these interactions is a valuable starting point for appreciating the principles of catheter design, implantation and maintenance. The type of response mounted at the surface of the catheter and by the surrounding tissues will be influenced by the materials used in construction of the catheter.

### *Materials:*

Materials for catheters should combine tissue compatibility with haemocompatibility: these are largely surface properties. Suitable physical properties to provide mechanical strength and resistance to fracture due to repeated movements. The ideal properties for the intravascular portion of the catheter will differ from those running in the skin tunnel and at the skin implant interface. The former need to be smooth and non-adherent but the latter should be capable of forming a bond with the tissues to provide anchorage and a barrier to the ingress of infection. Use of composite materials or surface coatings can help optimise the properties of these implants. In practice, two common materials (silicone and polyurethane) meet these requirements.

### *Catheter locking and flushing:*

The presence of blood within the lumen of a catheter contributes to bio film formation and thrombosis. To exclude blood from the catheter when it is not in use, a suitable solution is used to fill the lumen. This is referred to as a lock solution. Key desirable features of lock solutions are: anticoagulant, haemocompatible, low toxicity, ease of sterilisation together with compatibility with catheter materials, compounds and vehicles being administered. Commonly used lock solutions are generally isotonic although hyperosmotic solutions may be encountered. Use of high viscosity lock solutions (e.g. glycerol or high molecular weight polyvinylpyrrolidone -

PVP) can be helpful in helping to prevent blood ingress into the catheter but consideration must be given to the ease of removing the lock solution. Solutions based on sterile physiological saline (0.9% sodium chloride) with heparin are the most commonly used but have no antimicrobial effect. Hypertonic solutions (e.g. 40% dextrose) provide an antimicrobial environment.

#### *Infection - catheter related sepsis (CRS):*

CRS is an ever-present hazard of long term implanted vascular catheters. The catheter forms a direct portal to the blood stream through its lumen and also, the potential space around the outside of the catheter wall (the catheter track) is a second (and often overlooked) portal of infection. Direct exteriorisation of a catheter through the skin poses additional risks of infection over totally implanted devices (vascular access ports, VAPs). Once bacterial colonisation has occurred on the catheter, the complex reaction between bacteria and the bio film provides an environment, which is highly resistant to attempts to eliminate the contaminants. Provided that catheters are inserted and maintained with suitable aseptic technique, the most likely source of infection is from the animal's own flora - either the skin surrounding the catheter exit site, or a distant focus of infection within the body. Use of Dacron velour cuffs deep to the dermis has proved an effective barrier to the ingress of bacteria. Once CRS is established, it is effectively impossible to eliminate using antibiotic and other therapy. Experience in our laboratories of removing infected catheters and then delivering a course of appropriate systemic antibiotic is that the original infection will recur at the site of implantation of a fresh catheter. Prevention is therefore of the utmost importance and the value of adherence to strict aseptic technique cannot be over emphasised.

#### *Thromboembolic complications ("fibrin cuffs"):*

The pig seems particularly prone to formation of thrombophlebitis associated with vascular catheters. Correct anatomical placement of catheters and optimal construction are important factors in preventing this. For central venous catheters, insertion through a jugular vein with location of the tip just inside the right atrium is our preferred approach. Use of the femoral vein and vena cava have shown a high incidence of thrombosis and "fibrin cuff" around the catheters, significantly reducing longevity. If minor, these complications may not interfere with compound administration but will cause problems with blood removal via catheters.

Special problems of continuous and long-term infusions: Where compounds in solution are infused continuously through a vascular catheter, it is not uncommon to encounter problems associated with chemical incompatibility between the catheter and the compound or vehicle. The particular conditions inside the catheter and connecting tubing may predispose to crystallisation of dissolved compounds, which may potentially block the catheter. Such studies should be carefully planned with due care and attention given to thorough investigation of these compatibilities.

## **Techniques for use of fully implantable telemetric monitoring implants in monitoring of ECG and BP in large animals and the Ellegaard minipig**

Steven Hachtman and Dan Heutteman, DSI, 4211 Lexington Avenue North, Suite 2244, St. Paul, Minnesota 55126-6158, USA.

There are several options for monitoring larger research animals with telemetric devices, the most common of which allows the researcher to measure both systemic pressure and one channel of electrical biopotential, most commonly ECG. These implantable devices are most commonly used in canines, primates and swine. The dog model, although of limited use for ECG, can be a very cost effective and easily maintained animal model for the study of BP for pharmacology and toxicology researchers. They adapt very quickly to the presence of implantable devices and have relatively few post-surgical complications. Primates can provide valuable insights into the more subtle effects of compounds with the addition of a more complex behavioural component in their reactions to experimental protocols. They also add more complexity to the surgical protocols as well. They have relatively thin skin, curious minds and dexterous finger, all factors that complicate SC placement of telemetry devices. Extra care must be taken when considering device placement, SC pouch formation, and wound closure.

Swine, because of their anatomical similarity to humans, are a popular model for acute cardiovascular studies, medical device development, and experimental surgery. Recently their popularity for chronic cardiovascular research using telemetry is on the rise. Several cardiovascular system similarities to human cardiovascular systems provide distinct superiority in specific research protocols. Fully implantable telemetric measurement of heart and BP dynamics in freely moving conscious swine has advanced the accurate sensitive assessment of test compound effects. Ellegaard minipigs offer additional advantages as a model amenable to housing, care, as well as telemetric implantation and monitoring.

The procedure for minipig telemetric module implantation is straightforward and easily accomplished. In today's surgery demonstration we will be using an implantable telemetry device designed to monitor systemic pressure and one channel of electrical biopotential, in this case ECG. A subcutaneous pocket will be formed on the animal's left hip, the transmitting device will be placed in the pocket, and the pressure catheter and ECG leads will be tunnelled to an inguinal incision over the shallow femoral artery branch, the artery will be cannulated and ligated, and the catheter will be advanced into the iliac artery. The positive ECG lead will be affixed to the muscle in the left inguinal area and the negative lead will be tunnelled to the right axillary area and affixed to the muscle for a modified lead II configuration. Surgical issues will be reviewed and as a demonstration data will be collected and analysed from previously implanted minipigs.



## Recent books on (mini)pigs

New handbooks on (mini) pigs have been published recently. In Newsletter 14 (March 1999) *Surgery, anesthesia & experimental techniques in swine*, by Michael Swindle, was reviewed, and since then four new books on (mini) pigs have been published. These are:

Bollen, Peter J.A., Axel Kornerup Hansen and Helle Rasmussen. *The Laboratory Swine*. Boca Raton: CRC Press, 2000.

Lewis, Austin J. and L. Lee Southern (eds.) *Swine Nutrition*, Second edition. Boca Raton: CRC Press, 2000.

Pond, Wilson G. and Harry J. Mersmann (eds.) *Biology of the domestic pig*. Ithaca: Cornell University Press, 2001.

Straw, Barbara E., Sylvie D'Allaire, William L. Mengeling and David J. Taylor (eds.) *Diseases of swine*, Eight edition. Ames: Iowa State University Press, 1999.

## Recent articles on (mini)pigs

Gad, S.G. Pigs and ferrets as models in toxicology and biological safety assessment. *Int. J. Toxicol.* 2000, 19, 149-168.

Quist, M.H., Hoeck, U., Kreilgaard, B., Madsen, F., Frokjær, S. Evaluation of Göttingen minipig skin for transdermal in vitro permeation studies. *Europ. J. Pharmaceut. Sci.* 2000, 11, 59-68.

Skaanild, M.T., Friis, C. Cytochrome P450 sex differences in minipigs and conventional pigs. *Pharmacol. Toxicol.* 1999, 85, 174-180

Vana, G., Meingassner, J.G. Morphologic and immunohistochemical features of experimentally induced allergic contact dermatitis in Göttingen minipigs. *Vet. Pathol.* 2000, 37, 565-580.

More references are available on our website:  
[www.minipigs.com](http://www.minipigs.com)

## Meeting calendar 2001

Ellegaard Göttingen Minipigs and Ellegaard Minipigs USA, Inc. will be represented at the following scientific meetings and exhibitions:

### Scand-LAS Symposium

13. – 16. May, Aarhus, Denmark  
(<http://scandlas2001.au.dk/>)

### AFSTAL 2001

26. – 29. June, Tours, France

Visit us at booth no. 26

### GV-SOLAS Scientific Meeting

10. – 13. September, Ulm, Germany

### Eurotox 2001

13. – 16. September, Istanbul, Turkey  
(<http://www.uta.fi/eurotox/>)

Visit us at booth no. 3

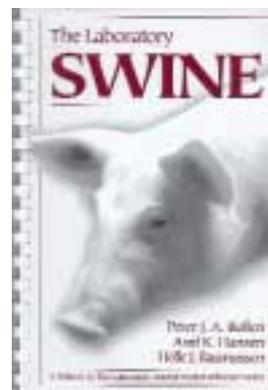
### General Pharmacology/Safety Pharmacology

24. – 25. September, Chicago, USA

### AALAS National Meeting

21. – 25. October, Baltimore, Md. USA  
(<http://www.aalas.org/>)

Visit us at booth no. 620



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