Health News

Microbiology

The latest health monitoring report indicated no changes in the health status of Göttingen minipigs bred at the full-barrier SPF unit in Dalmoose. In this issue of the Ellegaard Göttingen Minipigs Newsletter we refer to the separately enclosed health monitoring report.

In general, no health problems will occur when microbiologically defined Göttingen minipigs are introduced into a conventional laboratory with good hygiene. Housing pigs and minipigs from several sources at the same facility will subsequently lead to diarrhoea and other health problems. This may also be the case at laboratories with a high stocking density or high animal flow. Vaccination may in such cases offer extra protection.

Vaccination against Erysipelothrix rhusiopathiae and Haemophilus parasuis will protect microbiologically defined minipigs against these infections, and seems to stimulate the immune system to increase general resistance. We have had good experience with these vaccinations during the last half year, and offer this possibility to those who wish to work with vaccinated animals.

Iron treatment

An experiment investigating the level of anaemia in non-iron treated young Göttingen minipigs showed a sever anaemia during the first weeks of life. However, after 13 weeks this situation was reversed to normal as a result of iron uptake from the diet. The conclusion was that prophylactic iron-dextran treatment is necessary to prevent anaemia in young Göttingen minipigs, even though it may be related to siderosis.

Nonetheless is the prevention of silderosis actual, since it may be a disturbing factor in histopathology. A further study, identifying the minimal dose of iron-dextran for the reduction of silderosis and preventing anaemia, has been conducted recently and is due to be published soon.

This year has been another successful year for the Göttingen Minipig. We wish to take the opportunity to thank you for your interest in the Göttingen Minipig, and wish you a merry Christmas and a happy new year!

Workshop anaesthesia and surgery

During last summer we organized in cooperation with the Biomedical Laboratory of Odense University a workshop on anaesthesia and experimental surgery. A group of 20 participants had the opportunity to improve their skills of minipig anaesthesia and cannulation of vessels and ducts extensively, with excellent instructions from Dr. Per Svendsen and Dr. H.P. Olesen. The workshop was received very well, especially since participants had enough time to practice the demonstrated techniques.

Parallel to this workshop a seminar was organized in one of the auditoria. The lectures included the production of the Göttingen minipig, nutrition of minipigs, health monitoring, spontaneous and induced pathology, surgical approaches, minipigs in dermal toxicology and drug metabolism of minipigs.

The proceedings of this workshop will be published in a supplement to Pharmacology & Toxicology, during the first months of next year. If you are interested in receiving the proceedings, please indicate so on the enclosed reply form, also if you are interested in attending a next workshop on anaesthesia and surgery in the minipig. On page 2 and 3 of this Newsletter, you will find the abstracts from last workshop.

The minipig in toxicology

In connection with Eurotox '97, which will be organized in Denmark next year, a satellite symposium with the title The Minipig in Toxicology will be organized on 24-25 June 1997. At this symposium a range of topics from pharmacology and toxicology, as well as general aspects of minipigs will be presented. The enclosed leaflet gives more information about the satellite symposium, and includes a reply slip for further information.

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The Newsletter is a publication from Ellegaard Göttingen Minipigs, edited by Peter Bollen.
Abstracts from the workshop and seminar Anaesthesia and Surgery in the Minipig

Production of a defined quality miniature pig

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One of the primary objectives of Laboratory Animal Science is to contribute to the quality of animal experimentation. Beside reducing the between-experiment variation are, this can be achieved by reducing the within-experiment variation or the inter-individual variation. Both types of variation can be the result of the same source, the variation in the animals and their environment. Standardization of the animals and their environment will contribute to the reduction of such variations, and the establishment of a controlled genetic and microbiological quality and stable environmental conditions. In the production of miniature swine for research purposes, the Göttingen Minipig meets the criteria of a defined quality. One of these criteria is laid down in the recommendations for health monitoring of experimental pig breeding colonies. These recommendations deal with porcine microbiological quality, whereas no such guidelines exist for porcine genetic quality or environmental conditions for pigs. The genetic quality, however, is well documented for the Göttingen Minipig, as are the environmental conditions. The development of the present 17 sub-lines started over 30 years ago at the University of Göteborg. A closely monitored breeding program resulted into a coloured line (8 sub-lines) and a white line (9 sub-lines). Of the white line 8 sub-lines were successfully introduced into an environment controlled full barrier-unit at Ellegaard Göttingen Minipigs ApS. The methods of derivation of the Göttingen Minipig, the present health status, the control of the environmental conditions and the genetic quality control will be presented.

Nutrition of Göttingen Minipigs: facts, assumptions and mysteries

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The National Research Council (NRC, 1988) gives detailed scientific information concerning the nutrient requirements of swine under ad libitum conditions. These data cannot be transferred to minipigs as such, because they will become too obese. The data of the NRC (1988) are based on obtaining maximum growth for economic purposes, which is not considered the optimum situation from scientific point of view. The recommendations issued by GV-SOLAS for minipig diets can be used as a guideline (Mitteilungen des Ausschusses für Ernährung der Versuchsstiere, GV-SOLAS, Berlin, 1993). These guidelines are mainly based on empirical findings as no detailed scientific information is available concerning the specific nutrient requirements of the (Göttingen) minipig. Because minipigs easily become obese, a restricted feeding schedule is usually applied. This raises the question whether the needs for individual (essential) nutrients are met, especially when restricted feeding is given to group housed animals. Competition between animals may increase the variation between animals, leading to obese -relatively overfed animals- versus (marginally) deficient animals. In case certain (essential) nutrients are ingested in (marginally) deficient amounts, this may interfere with scientific and toxicological results. In order to establish a solid scientific basis for the recommended nutrient composition of minipig diets, more research is needed.

Health monitoring of laboratory pigs

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During the last five years our department has developed a system for health monitoring of pigs in order to establish a quality of laboratory pigs equivalent to laboratory rodents. This system, which has mainly been used for monitoring barrier-bred pigs from Ellegaard Göttingen Minipigs, has been the basis for a set of guidelines for health monitoring in laboratory pigs published by the Scandinavian Federation for Laboratory Animal Science. The system includes screening for 9 types of viruses, 18 bacterial species as well as ecto- and endoparasites. In the barrier-bred minipigs only rotaviruses are found. This may be shown by both serological antibody detection and by detection of rotaviral antigen in feces. In minipigs from another unit with far less hygienic protection rotaviruses are also found along with certain influenza- and coronaviruses, and Pasteurella spp. were found, and also Haemophilus parasuis was found. It is concluded, that barrier protection improves the quality of pigs for research purposes.

How clean is a mini-pig? - Impressions and suggestions of a pathologist working in the field of toxicology

Matthias Rinke, BAYER AG, PH-PDT Toxic Path, D-42096 Wuppertal, Germany.

Minipigs are occasionally used for toxicological studies. The presented data result from gross and histopathological investigations that were carried out on Trolt minipigs some years ago at the BAYER laboratories. The following points are discussed in more detail.

Findings due to repeated blood sampling. For anatomical reasons the thyroid gland of pigs can be injured during blood sampling. Histopathological investigation of thyroid glands often revealed inflammatory and reparative fibrotic changes of this organ. Depending on the grade of damage thyroid hormone levels may vary. To avoid misinterpretation of results, most careful blood sampling by experienced personal is recommended.

Findings due to viral, bacterial and parasitic infections. These concerned mainly the lungs which often showed pneumonic alterations. In case of parasitic invasions, the skeletal muscles may reveal partly severe degenerative changes due to sarcosporidia (re-infection). Therefore, optimal hygienic conditions, e.g. during blood sampling, and continuing health monitoring are recommended.

Findings due to preventive iron administration. Months after preventive iron-dextrans administration at the breeding station histopathological examination revealed a siderin accumulation in a number of organs. As a unique finding an intraglomerular siderin deposition in the mesangial cells with subsequent glomerulosclerosis in certain glomeruli was observed. This finding seems to be species specific. Moreover, hematological data make it conceivable that the Fe-binding capacity of the transferrin is exhausted, so that the administered iron is not mobilized. Therefore, iron overdosing in the first days of the piglet's life should be strictly avoided and repeated administration of low doses of an iron dextran complex during their first months of life seems to be more appropriate.

Anaesthesia of the minipig

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After premedication with atropine sulphate (0.05 mg/kg) to reduce the previsus salivation and to stimulate heart action, sedation of the minipig is most efficient achieved by a combination of azaperone (Sedaparone Vet, Stresnil) 4 mg/kg and midazolam (Dormicum) 1 mg/kg i.m. The two compounds can be mixed before i.m. injection. After 15 min. anaesthesia is induced in a quiet environment by i.v. injection of approximately 5 mg/kg propofol (Rapinvent-Diprivan). On the dose is given rapidly, and after one minute additional propofol is slowly injected until the minipig is reflexless, e.g. the mouth can be opened without resistance and muscular contractions of the tongue are completely
abscnt. Spontaneous breathing is an advantage when intubating the animal. After intubation with tube no. 5, the animal is artificially ventilated with a minute volume of 150 mL/kg/min and maintained by halothane (1.2%) in an oxygen/nitrous oxide (1/1) mixture.

Minor surgery may be performed by injection anaesthesia with propofol (Ripogivet, Diprivan) anaesthesia. After sedation and induction with propofol 5 mg/kg i.v. anaesthesia can be maintained by repeated increments of propofol (0.2 mg/kg every 10 minutes). Ketamine should only be used in combination with other anaesthetics. Combining ketamine with midazolam (Dormicum) 1 mg/kg or xylazine (Rompun Vet) 2 mg/kg produces anaesthesia with excellent muscular relaxation lasting 90 and 40 minutes respectively. Decreased heart rate, blood pressure and cardiac output will, however, result.

Venous catheter implantation in the minipig - surgical approaches and refinements

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In spite of requiring invasive implantation procedures, chronic venous catheters offer a number of benefits in biomedical research involving pig:

- avoidance of long term or repeated stress due to restraint for venapuncture
- assured delivery of compounds into venous blood
- sampling is always from the same site
- use of large central veins ensures representative samples, in large quantities
- central venous sites allow rapid dilution or buffering of compounds which may potentially irritate
- facilitate long term and infusion studies

Common sites of access to the venous system are jugular vein or its tributaries and the femoral vein. Experience has shown the jugular approach to the cranial veins cava to give superior performance. The presentation will focus on this approach by surgical exposure of the vessel with reference to the potential use of percutaneous introducer sheaths and Seldinger technique which offer reduced invasiveness of catheter insertion.

Catheters may be either exteriorized through the skin or attached to a totally implanted vascular access port (VAP). The management of the skin-implant interface with materials such as Dacron velour which favour adherence to the animal's own tissue, obliterating space in which infection may arise and providing anchorage is advocated. Fully implantable ports for infusion studies may also be used.

Catheter related sepsis (CRS) is the chief and most significant complication of chronic vascular access in any species. In the pig, CRS is particularly resistant to therapy in comparison with other species. Methods for prevention of catheter related will be outlined.

The selection of materials for vascular catheters is very important in determining their performance and in spite of the many substances available, only a small number of polymers have suitable biocompatibility and ideal physical properties for implanted vascular devices. Silicons and polyurethanes are the two main classes suitable for use in pigs. A number of processes are becoming available which may modify and improve surface properties of these materials (e.g. reduced thrombogenicity, reduced irritancy, reduced coefficients of friction, reduced bacterial and host protein adhesions and intrinsic bactericidal properties). The physio-chemical properties of compounds to be infused and their vehicles will also influence the choice of catheter material.

The use of minipigs in dermal toxicity testing

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Pigs have been extensively used for surgical and physiological research for years, due to their similarities to humans. For human medical research, whether the blood and lymph, or circulation, respiration, excretion of urine, digestion, metabolism, nutrition, endocrine and nervous system, and especially the cutaneous system, it appears that the pig is the ideal experimental animal. While rabbits are commonly used for the assessment of primary dermal irritation, pigs have been considered to be a good model for the more sophisticated study of dermal permeability and toxicity. The skin of pigs best fulfills the requirements of a model human skin. Human and porcine skin are similar with regard to sparsity of the pelage, thickness and general morphology, of epidermal cell turnover time and size, orientation and distribution of vessels in the skin. The particularly thin haircoat and lack of pigments of the minipig makes it ideal for dermal studies. The size of the animal also provides the additional practical advantage of abundant surface area for multiple-site and long-term testing. Non-invasive skin examination methods of human dermatology ultrasonography, can be used as monitoring tools in dermal toxicity studies with minipigs. Despite there are some limitations, all in all there is no animal species that mimics human skin better than porcine skin.

Characterisation of the P450 system in Göttingen minipigs

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Knowledge of the xenobiotic-metabolizing cytochrome P450 enzymes and their regulation is important in selection of animal species for pharmacological/toxicological testing of new drugs or chemicals. During the past, the minipig has been a popular alternative to traditional animal species in toxicological testing. However, little information is available on the P450 system in these animals. The objective of the present report is to describe the activities of the various P450 isoenzymes in the minipig, and compare these data with corresponding data from conventional pigs. Furthermore, data are compared to the P450 isoenzyme activities reported in human liver microsomes.

Four Göttingen minipigs (2 males and 2 females, with a body weight (b.wt.) of 10 kg) and 8 Danish Landrace x Yorkshire x Dorco crambred pigs (4 males, 90 kg b.wt. and 4 females, 30 kg b.wt.) were used. Enzyme activity was measured in microsomal fractions using 7-ethoxyresorufin O-dealkylase as probe of CYP1A, of testosterone as probe of CYP1A, 4-hydroxylation of S-4′-methylenetol as probe of CYP2C19, 4-hydroxylation of guanidine-3′-debrisoquine as probe of CYP2D6 and 6-hydroxylation of 2′-3′-chlorozoxazone as probe of CYP2E1. Incubations with liver microsomes showed that minipigs possess high CYP1A activity, high CYP3A activity and high CYP2E1 activity, whereas CYP2C19 and CYP2D6 were absent. A marked sex difference was detected in all enzyme activities with females showing the highest values. The activities of P450 enzymes in Göttingen minipigs were almost similar to those observed in conventional pigs. Except for CYP2C19 and CYP2D6, the P450 enzyme activities were close to the level reported for human beings.
Selected references on the use of minipigs

Below you will find a selection from recent papers on the use of minipigs. If you have special inquiries of literature for your project, please let us help you with abstracts from our database.

ANATOMY, PHYSIOLOGY, BIOCHEMISTRY:


IMMUNOLOGY:


XENOTRANSPLANTATION:

Banerjee, PT; Ierino, F.; Kaynor, GC; Giovino, M.; Sabiniski, T.; Emerly, DW; Rosa, MD; LeGuern, C.; Sachs, DH; Monroy, RL. Retrovirus-mediated transfer and expression of swine MHC class II genes in CD34+ monkey stem cells. Transplant. Proc. 1996, 28 (2): 747-748.

Chao, SH; Chiang, PU; Lee, PH; Chu, SH; Chen, KM. Orotic acid effects on pancreatic graft pancreatitis in inbred pigs. Transplant. Proc. 1996, 28 (3): 1799-1801.


PHARMACOLOGY, TOXICOLOGY:


TERATOLOGY:


Grose, W; Schulz LC; Drommer, W; Ubbersch S; Schafer EA. Kusewitt DF; Burke JP; Tumbleson ME. Test of combination of the agents coumarin and troxerutin for embryotoxic a teratogenic side-effects in Gottingen miniature pigs. Gen. Pharmacol. 1977, 8(S-6): 335-339.


NEUROLOGY:

