



From the working group “Experimental Pathology” to the department “Pathology Unit” – historical development in retrospect

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Abstract. The Pathology Unit of the German Primate Center started as the working group of Experimental Pathology in 1992. This small group with one veterinary pathologist and a technician was founded based on an idea of Prof. Dr. Kuhn, who wanted to strengthen the pathology research activities and to establish a centralized electron microscopy laboratory. Later on, experimental pathology, veterinary services and primate husbandry were integrated as the Department of Veterinary Medicine and Primate Husbandry but subsequently again separated. Prof. Dr. Franz-Josef Kaup, the head of the previously integrated department, remained in his capacity as the leader of the different units. Over the years, the research activities have changed from SIV-associated pathology to other infectious diseases. Today, the main research focus is on the pathogenesis of orthopoxvirus infection, primate pathology, neglected tropical diseases and nonhuman primates as models for chronic respiratory diseases. This paper gives an overview of the historical development and aspects of research activities.

1 Introduction

Following its establishment in the early 1980s, the initial divisional structure of the German Primate Center reorganized its scientific focus towards the end of this decade. In this context, establishment of a new Morphology and Systematics Department was considered, for which acquisition of a transmission electron microscope was planned. In the financial year of 1990, a budget of DM 750 000 was set aside for a transmission electron microscope. Establishment of an electron microscopic device was also supported by the German Council of Science during evaluation of the German Primate Center in January 1990. At the same time, the head of the German Primate Center, Professor Kuhn, considered setting up an independent scientific working group for experimental pathology in addition to the existing Pathology Department headed by Dr. Manfred Brack.

2 Establishment of the working group “Experimental Pathology”: 1992–1996

In the subsequent meetings of the Scientific Advisory Council and the Supervisory Board, establishment of three working groups was decided on in June 1991: Electron Microscopy, Behavior Research, and Experimental Pathology (Supervisory Board Meeting on 4 June 1991). Since an eligible candidate for the head of the Electron Microscopy group could not be found, supervision of the electron microscope as part of the central service facility was assigned to the new Experimental Pathology group.

At the same time, Dr. Franz-Josef Kaup, who at the time was a research assistant in the electron microscopy division of the Institute of Pathology, University of Veterinary Medicine Hanover, was invited to give a talk at the German Primate Center. On 30 January 1992 Dr. Kaup gave a presentation titled “Morphologic Methods of Viral Detection with Special Reference to Immunoelectron Microscopy” at the German Primate Center. After discussion in the Scientific Advisory Council, Dr. Kaup was endorsed as head for the new Experimental Pathology working group. Thus, two

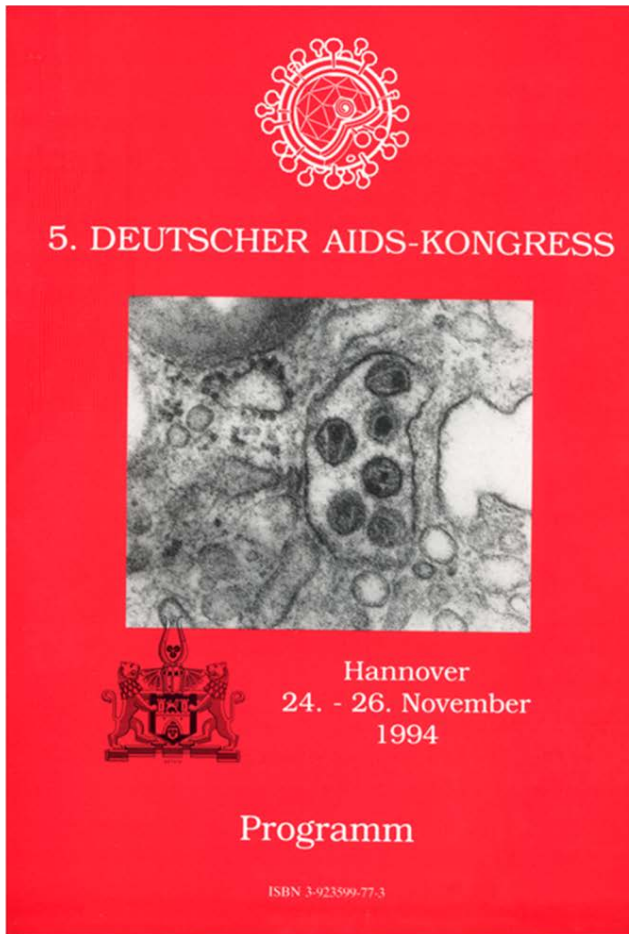


Figure 1. Transmission electron micrograph on the cover page of the program 5th German AIDS congress in Hanover, 1994. The micrograph presents an intracytoplasmic vacuole containing SIV particles. The structure was found in an SIV-induced giant cell from an infected rhesus monkey (*Macaca mulatta*). Photo taken by Kaup, Experimental Pathology, German Primate Center.

recommendations of the German Council of Science (establishment of a unit Electron Microscopy and a unit Experimental Pathology) could be realized by a single occupancy.

After granting of the *Venia legendi* for "General Pathology and Pathologic Anatomy of Domestic Animals" by the University of Veterinary Medicine in Hanover, PD Dr. Kaup took up employment at the German Primate Center on 1 August 1992.

3 From the working group Experimental Pathology to the Department of Veterinary Medicine and Primate Husbandry: 1992–2002

During the first few years, the newly formed working group focused on the pathogenesis of gastrointestinal and respiratory infections, while related ultrastructural studies contributed to the establishment of a central electron microscopy

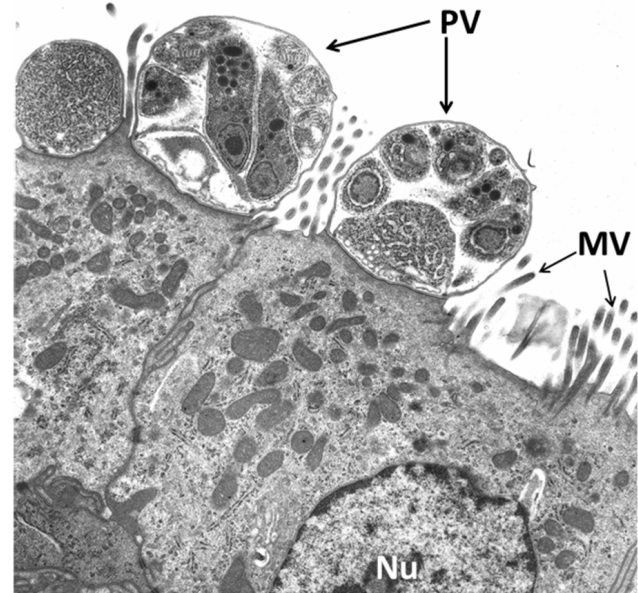


Figure 2. Cryptosporidiosis in an SIV-infected rhesus macaque. Enterocytes (Nu – nucleus) with adjacent parasites. The parasitophorous vacuoles (PV) are probably formed by the microvilli (MV) of the affected enterocytes. The ultrastructure of the vacuoles argue for the morphology of schizonts containing merozoites. Cryptosporidiosis is a typical opportunistic infection in SIV-infected macaques. Transmission electron microscopy.

division (Kaup et al., 1994, 1998, 2005; Kuhn and Kaup, 1996). In this process, the Department of Virology and Immunology proved to be a valuable partner, as both experimental SIV infections in rhesus macaques (Fig. 1) and associated opportunistic infections opened new research fields for the working group (Figs. 2 and 3). At the beginning of 1994, Dr. Kerstin Mätz-Rensing joined the working group as the first research assistant, and spontaneous nonhuman primate disease increasingly became the subject of research.

Special emphasis was laid on the establishment of immunohistochemical markers for nonhuman primate tissue, which were used in different studies on the pathogenesis of the intestinal SIV infection, but also for tumor differentiation and classification in nonhuman primates (Kuhn et al., 1999; Didier et al., 1999; Mätz-Rensing et al., 1999b; Kaup et al., 2001; Kahnt et al., 2002). Beside pathomorphological methods, new *in vivo* experimental techniques were also implemented. Endoscopic techniques were introduced at the German Primate Center during a study on SIV passage via the intestinal barrier (Kewenig et al., 1999; Schäfer et al., 2002). Since then, endoscopy has been an essential tool that is widely used to this day to obtain gastrointestinal biopsies in experimental infections, for example, with *Helicobacter pylori*. Dr. Kaup, who was meanwhile appointed as an exceptional professor by the University of Veterinary Medicine

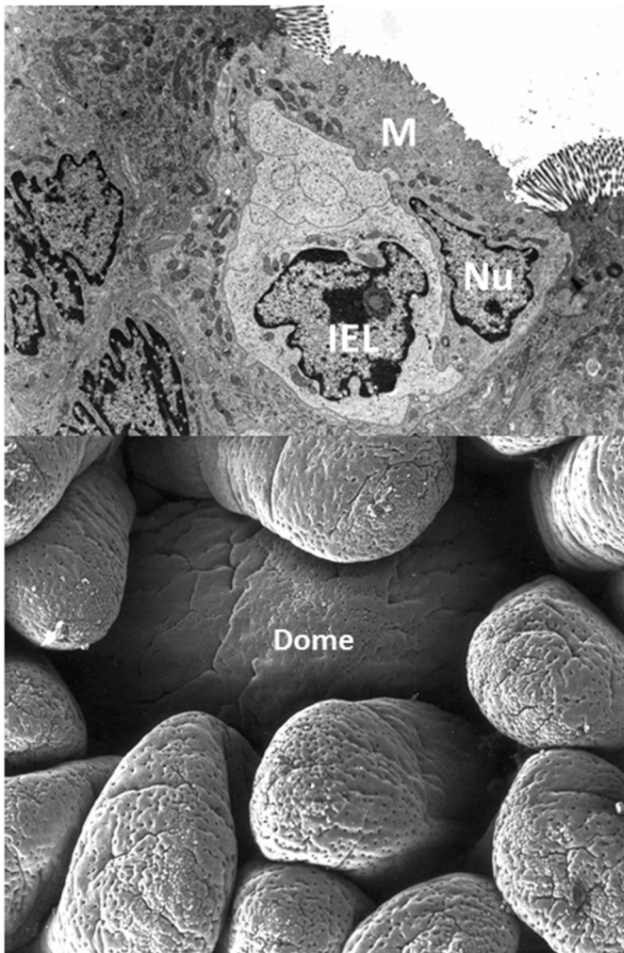


Figure 3. Scanning electron micrograph showing a hemispherical intestinal dome area bulging into the gut lumen and surrounded by intestinal villi. The domes are covered by enterocytes and M cells (M – cytoplasm, Nu – nucleus). Transmission electron microscopy demonstrates the close contact of an M cell with intraepithelial lymphocytes (IEL). Ileum, rhesus monkey (*Macaca mulatta*).

Hanover, succeeded Professor Kuhn as the animal welfare officer of the German Primate Center in February 1996.

After an evaluation in 1996, the Department of Veterinary Medicine and Primate Husbandry headed by Professor Dr. Franz-Josef Kaup was established by merging the Experimental Pathology and the Primate Husbandry working groups (headed by Dr. W. Kaumanns). In addition, the functional Veterinary Care unit (led by Dr. T. Gatesman) separated from the Department of Pathology and was integrated into the new department. The functional division of the pathological diagnostics, along with the necropsy hall, bacteriology lab and parasitology lab remained connected to the Department of Pathology headed by Dr. Brack. The new department consisted of the Functional Pathology, Veterinary Medicine/Primate Husbandry, and Biology of Primate Keeping working groups. The certified biologist Uwe Schönmann

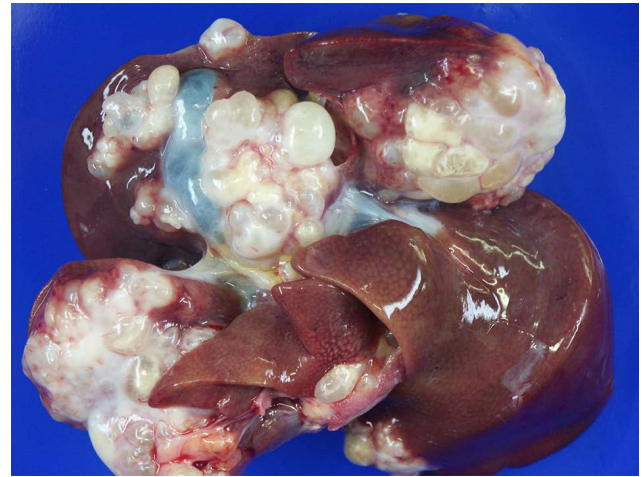


Figure 4. Gross pathology of a hepatic echinococcosis. The parasites invade the liver tissue with multiple cystic transformation. *Echinococcus multilocularis* infection of a rhesus monkey of the German Primate Center.



Figure 5. Macroscopic findings in a cynomolgus macaque (*Macaca fascicularis*) from a diagnostic necropsy. Abundant amounts of encysted parasitic larvae in the abdominal viscera. In this case of a pentastomiasis PCR was done. The sequence matched 98 % that of *Armillifer agkistrodontis*.

became colony manager and head of the Primate Husbandry working group in 1998.

With the retirement of Dr. Manfred Brack in 1999, a long-standing era at the German Primate Center ended. The Department of Pathology was disbanded, and the staff and diagnostic divisions of histology, bacteriology, and parasitology, as well as the operation of the necropsy hall were assigned to the Department of Veterinary Medicine and Primate Husbandry.

Henceforward, the Department of Veterinary Medicine and Primate Husbandry was the central service unit of the German Primate Center. It provided veterinary care with dis-

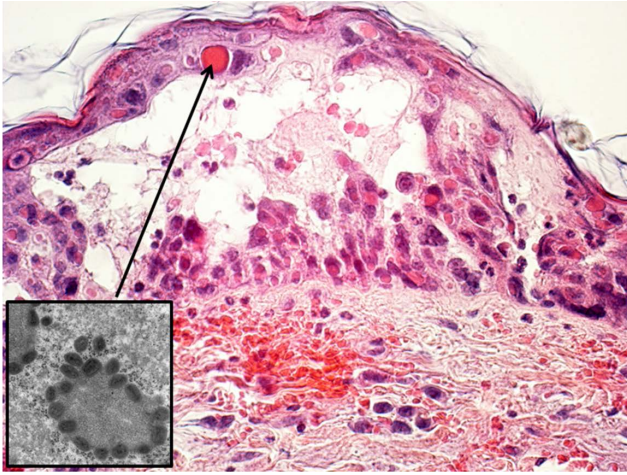


Figure 6. Skin lesions due to a calpox infection in a marmoset (*Callithrix jacchus*). Apart from inflammatory signs calpox lesions are characterized by so-called Guarnieri bodies (arrow) within the cytoplasm of epithelial cells. Transmission electron microscopy of the Guarnieri bodies presents orthopoxvirus particles (inset).

pensary, veterinary diagnostics (pathology, histology, bacteriology, and parasitology), primate husbandry with animal and sample supply, transmission electron microscopy, and animal welfare. This broad service spectrum was intensively used by many internal and external scientists. On 1 December 2000, Professor Dr. Kaup was appointed university professor for laboratory animal pathology at the University of Veterinary Medicine Hanover, which was connected to his position as the head of the Department of Veterinary Medicine and Primate Husbandry at the German Primate Center.

4 New trends of research

During this time, the scientific spectrum of the department also expanded. In 2001, Dr. Uwe Hahmann and Professor Walter Bodemer established a new working group named Spongiform Encephalopathies, which focused on the pathogenesis of prion diseases and was notably funded by the EU during the BSE crisis (Krasemann et al., 2010; Kiesel et al., 2012a, b). The SIV/SHIV macaque model was continuously serviced pathomorphologically for the Department of Virology and Immunology (headed by Professor Dr. Hunsmann) and later on the Department of Infection Models (Dr. Stahl-Hennig). Dr. Mätz-Rensing succeeded to establish a macaque model for experimental *Helicobacter pylori* infections (Mätz-Rensing et al., 1999a; Mätz-Rensing et al., 2001) as well as detection systems for alveolar echinococcosis (Tappe et al., 2007), a tapeworm infection that has been increasingly diagnosed in the breeding colonies of the German Primate Center (Fig. 4).

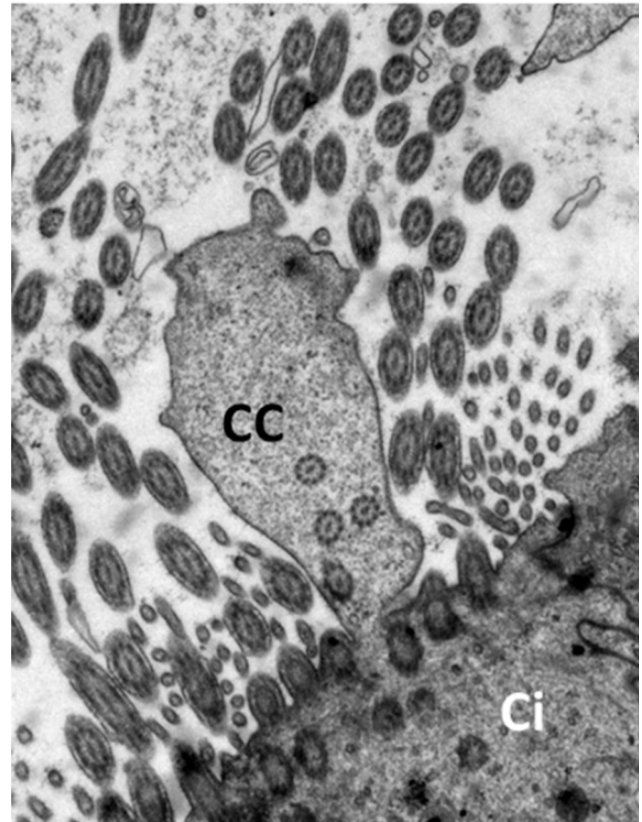


Figure 7. Transmission electron micrograph of a ciliated cell (Ci) originating from the tracheal respiratory epithelium of a newborn marmoset (*Callithrix jacchus*). In the airway lumen numerous cross-sectioned cilia present normal axonemes consisting of a central pair of filaments surrounded by nine other pairs. In addition to normal cilia an atypical cilium (CC) is demonstrated. This malformation belongs to compound cilia of bulging type which contains loosely and randomly embedded axonemes.

5 From the “Department of Veterinary Medicine and Primate Husbandry” to the department “Pathology Unit”: 2002–2015

With the appointment of Professor Dr. Treue as the new scientific director, the six existing departments and three working groups were reorganized. The Department of Veterinary Medicine and Primate Husbandry were separated and a new Pathology Unit (which was also part of the new Infection Research Section) was established. The Primate Husbandry and Veterinary Medicine groups were renamed into Cost Center Primate Husbandry. As both facilities were headed by Professor Kaup, the duties and responsibilities of this group remained unchanged (Table 1).

In 2004, the Pathology Unit set up two new working groups. The Dermatopathology group, headed by Dr. Bärbel Löblich-Beardi, worked on alopecia in rhesus macaques (Beardi et al., 2007; Steinmetz et al., 2005, 2006) and the herpesvirus group, headed by Dr. Dieter Jentsch. Follow-

Table 1. History of the Pathology Unit at the German Primate Center (1992–2015)

Date			
1 August 1992	Working group Experimental Pathology Head: Dr. Kaup	Division Pathology and Veterinary Services Head: Dr. Brack	Breeding and Husbandry Head: Dr. Kaumanns
1 January 1997	Dept. Veterinary Medicine and Primate Husbandry (Functional Pathology, Breeding and Husbandry, Veterinary Services) Head: Prof. Dr. Kaup	Dept. Pathology Head: Dr. Brack	
1 December 1999	Dept. Veterinary Medicine and Primate Husbandry (Primate Pathology, Primate Husbandry with Veterinary Services) Head: Prof. Dr. Kaup		
1 January 2003	Pathology Unit Head: Prof. Dr. Kaup		Cost Center Primate Husbandry (with Veterinary Services) Head: Prof. Dr. Kaup Manager: Uwe Schönmann
1 April 2010	Pathology Unit Head: Prof. Dr. Kaup with Airway Immunology (Satellite station of Fraunhofer ITEM Hanover): actual head: Dr. F. Dahlmann		Cost Center Primate Facilities (with Veterinary Services) Head: Prof. Dr. Kaup Manager: Uwe Schönmann

ing the retirement of Professor Bodemer, Dr. Jentsch, and Dr. Löblich-Beardi, research activities became more focused within the Pathology Unit.

The Primate Pathology group concentrated on spontaneous diseases in nonhuman primates for many years (Mätz-Rensing et al., 2012a) (Fig. 5). The group, led by Dr. Mätz-Rensing, established a new orthopoxvirus model in marmosets based on a diagnostic case of an orthopoxvirus infection in New World monkeys (Fig. 6). This model was used to investigate the clinical and pathological changes of this novel infection and enabled translational evaluation of vaccine efficacy.

This orthopoxvirus model was developed in response to a disease outbreak in a private primate husbandry in 2002. Several New World monkeys, among them common marmosets (*Callithrix jacchus*), died within a very short period of time. Necropsy of some animals with subsequent histological and electron microscopic examinations at the German Primate Center revealed an orthopoxvirus infection. In collaboration with the Robert Koch Institute (RKI), a cow pox virus was isolated. Sequence analyses and phylogenetic investigations showed that it was a novel cow pox virus, which was named calpox virus after its host species (“*Callithrix*”

(Mätz-Rensing et al., 2006, 2012b; Kramski et al., 2010; Schmitt et al., 2014).

The virus was cultured from different organs, and a virus stock was generated by means of a permanent cell line. Meanwhile, different studies were conducted to determine the infectious dose and the optimal inoculation route for experimental infection and to characterize the pathogenesis and the spread of the virus to different organs. Vaccination studies with intranasal virus challenge (8.3×10^3 PFU of calpox virus) showed that the old vaccine, which had many adverse effects (vaccinia virus Elstree VACV LE-BN), provided adequate protection in comparison to subsequently developed vaccines (MVA: modified vaccinia virus Ankara; MVTT: modified vaccinia virus Tiantan), which did not induce reliable immunization.

In April 2010, a cooperation was established with a working group of the Fraunhofer Institute for Toxicology and experimental Medicine (ITEM) Hanover (today headed by Dr. Franziska Dahlmann), which works on primate models for COPD and asthma (Seehase et al., 2011, 2012). This group is supported by a working group of the Pathology Unit named Anatomy/Pathology of the respiratory tract headed by Dr. Martina Bleyer (Hoffmann et al., 2013, 2014) (Fig. 7). Furthermore, a new research group studies neglected tropical

diseases in particular *Treponema* infection in baboons. This group (head Dr. Sascha Knauf) combines laboratory investigations in infectious diseases with field studies in free-living nonhuman primates (Knauf et al., 2012, 2015).

6 Outlook

Over the past few decades, the German Primate Center has continuously focused on nonhuman primate pathology. Results of the research activities are documented in more than 200 publications and 41 veterinary medical dissertations. In addition to its great contribution to research, the pathological diagnostics with associated etiological examinations and extensive sample supply represent important services offered by the German Primate Center that have been used extensively by external scientists and vets. At the German Primate Center, seven veterinarians have completed their five-year training to become veterinary specialists in pathology. The research activities and the diagnostic services of the Pathology Unit are of special value to the Infection Research Section because of the profound expertise in primate diseases and pathology, which is essential for a primate center.

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