

ESTP Newsletter 2013 (2)



Editor Zuhal Dincer (Zuhal.Dincer@novartis.com)

Twenty Years of "Classic Examples in Toxicologic Pathology": reflections and feed-back from the presenter, participants & collegial perspective

(Dr Paul German's speech at The 20th Anniversary of the "Classic Examples in Toxicologic Pathology" at Hannover)

Dear Mr President, Dr Greif, and Dear Colleagues,

It is my personal honour and pleasure at this evening to reflect some moments about the history and the achievements of the Classic Examples in Toxicologic Pathology. I would like to take this opportunity to give the organizers of this outstanding seminar with a little bit of a personal feed-back on how they have performed during the last two decades. Especially, I would like to dedicate this feed-back to Prof. Wolfgang Drommer and Prof. Eberhard Karbe who are the heart and the soul of this seminar. Prof. Wolfgang Baumgärtner and Prof. Ulrich Deschl are "the body and the muscle" of this course, providing permanent substantial logistics including financial backbone to this seminar, which is the successful base to the continuum of the Classical Examples.

Who is the heart? Who is the soul? And most importantly, who is the brain? I would like to come back to this question later.

Twenty Years of Classic Examples in Toxicologic Pathology: that is a really long time for an educational seminar conducted by a non-profit organization. These 20 years also tell a story, an amazing success story: a story standing for commitment and dedication of the organizers and the speakers on one side. But also a story of consistent interest, "no, sorry", permanently increasing

interest of the participants shown by the voting by feet, which reflects the high quality of this course.

There are three success criterias which can be identified:

Flexibility
Consistency
Personal touch

Flexibility in science and content:

Twenty years in biological science is an eternity. It is estimated that the doubling time of medical knowledge in 1950 was 50 years; in 1980: 7 years; and in 2010: 3.5 years. In 2020 it is projected to be 0.2 years - just 73 days. To keep the scientific content in such rapid fast evolving field up to date is mandatory. The name "Classic Examples" might lead outsiders to the assumption that old classical cases have been presented here. Instead the contrary is the case. The term "**Classic Examples**" was sometimes (at least I did so) used within the contributing pharmaceutical and chemical companies to get the approval from management to publish the most recent hot topics as case presentation. The content was mostly quite actual which I can judge, having participated in 15 out of 20 years.

Another example for the flexibility of the organizers is the adaptation to the needs & changes in audience. When this seminar started in 1993, it was a small but growing event, mainly focused on the PhD students of the University for Veterinary Medicine Hannover, Foundation and colleagues from the industry. A participant number around 40 people was the projected initial target audience. By buzz marketing and personal recommendation, the number of participants was constantly increasing over the years and now this number is around 110 attending from all over the world. As adaptation to these audiences needs the language changed to English, the hand-outs are now in English too including a lot of high resolution coloured histological pictures and also the number of requested slide sets is now at 70 sets.

The third example how this course is handled as a living, flexible and adaptive organism is the opening towards the (at that time) new media: For example: New ways to advertise and educate: Announcement and registration on the ESTP-Homepage, publishing the content on the CD-Roms, now in the third edition containing 101 scientific papers on them. Finally the inclusion of the Classic Examples into the PhD modules lecturing program as a commitment to a larger educational context at the university, is another sign of flexibility.

Consistency: the second topic as a surety of high quality is exact the contrary of the first qualifier

Wolfgang and Eberhard have been consistent with the basic principles of their seminar: “The microscopical evaluation of slides is one fundamental basis of toxicological pathology”. I don’t know how often I heard this sentence from Eberhard and Wolfgang, but they are right on this. Consistently requesting to provide slide sets instead of pictures from the presenters, they put the emphasis on the main topic: the histological evaluation of slides with a light microscope, detecting and discussing the pathological lesions with colleagues is a central part of this seminar. In modern words: one of its USP’s, unique selling points.

Secondly: The personal commitment to high scientific quality: Easy sentence, but not easy to achieve in reality. Wolfgang and Eberhard have consistently worked in a positive critically way to provide a seminar with high quality of the presentations. In a permanently changing and growing scientific area this was not easy to do. However with their consistent to get high quality in the scientific contributions, I personally think that they have achieved it very well!

Finally their personal commitment to educational quality: the focus on the audience, their stimulation and facilitation of the discussions, involvement of the PhD students in the whole exercise: this is for me a clear sign of dedication for training toxicopathologists.

The Personal Touch of Eberhard and Wolfgang: the third and last success factor

For me, this seminar was, is and will be always a “meet the family” seminar.

This is on the one hand a merit of Prof. Wolfgang Baumgärtner, as Head of the Institute for Pathology. Wolfgang with his team really enabled this event now for many, many years. Dear Wolfgang my personal thanks for your support. For me all the PhD students from Wolfgang’s Department who served for the success of this seminar are very important too. They deserve a big hand from us for their support. Wolfgang Drommer and Eberhard Karbe with their personal touch and communication style are essential as for good open atmosphere, which creates this “meet the family” spirit.

Finally, I would like to take the liberty to make also some very personal comments:

My first comment is to you Eberhard: the person, who looks for the content of the presentations. Let us call Eberhard the “hunter” or even better “predator” of this seminar. Dear Eberhard, thank you very much for your drive to get everything on time and in high quality. This kind of predator behaviour, having the upcoming presenters in your “claws”, permanently chasing the timely deliverables was a surety to the success of the seminar. And beg my pardon Eberhard: it was sometimes a pain in the neck! for us as presenters.

Second comment is to you Wolfgang as the networker of this Seminar. Let us call you the “spider” or “pusher” of this seminar. Dear Wolfgang, I admire your networking capabilities to smooth all ways to achieve a successful course series over so many years. Coming from the perspective as a presenter, your push like: “Paul, come on, you and your people have to present also something next year.” was always a given statement, it was not for discussion. But that’s ok, as you had always the success in your mind.

To conclude my short reflections, I owe you, dear audience, personal answer to the question: who is the brain? who is the heart? and who is the soul of this success story?

I would say, Wolfgang is the heart and Eberhard is the soul of the seminar. The brains of the Classical Examples series are Wolfgang and Eberhard, the presenters and the audience from the University and the Industry. They contribute to the science, the educational purpose and the interactive dialogue which makes this event for me unique in Toxicological Pathology. Dear Wolfgang, dear Eberhard, let me thank you for your personal commitment and persistence which really enabled this 20 years outstanding achievement. With your enthusiasm, you have convinced the companies over the years to provide the necessary slides for free. From these slide seminars I learned a lot content wise and from you both I personally learned a lot anyway. Please give these two Colleagues a big hand for their tremendous and successful work!

Dear Colleagues, thank you very much for your kind attention.

Dr Paul-Georg Germann
Paul-Georg.Germann@takeda.com

Classic Examples in Toxicologic Pathology: succession plan, acknowledgements & 5th CD edition

Dear Members,

On the occasion of the 20th anniversary of our annual seminar, Classic Examples in Toxicologic Pathology, Prof Drommer and I announced that we have decided to

terminate our responsibilities as organizers. Our President, Dr. Frédéric Schorsch, asked me to inform you about the succession plan.

Just before the last seminar on February 22-23, 2013, all the organizers, Profs. Baumgärtner, Drommer, Karbe and Deschl, met and agreed that Prof. Ulrich Deschl will take over the responsibilities covered so far by Profs. Drommer and Karbe. Prof. Deschl will be assisted by Drs. Thomas Nolte and Florian Colbatzky.

My responsibility was to set up the program of the seminars and negotiate with the speakers about handouts and slides. This was facilitated by the fact that I retired from the Bayer Company 15 years ago and thereafter worked only part-time as consultant. Since Prof. Deschl has a full-time job, he needs to be assisted by Drs. Nolte and Colbatzky. Please support the new team of organizers in their new function so that our seminar will thrive in the future as it has in the past with your engagement as speakers and participants.

We are grateful to Prof. Baumgärtner, who will continue to be the organizer responsible for local arrangements. He will continue to make available the great seminar room, costly 150 microscopes and excellent equipment of the TiHo, and the competent graduate students to assist him.

This is a perfect opportunity for us to thank our speakers for the fruitful cooperation we have had over the past 20 years. With their meaningful input it was possible to have a top-notch seminar for the benefit of graduate students, young and even senior pathologists. We appreciated the high quality of the speakers and scientific presentations, the lively discussions, and the collegial atmosphere we had together.

We also wish to thank our 10 ESTP presidents and the many executive committee members, who supported our seminars during the last 20 years by agreeing not to increase the seminar fee and by accepting to run the seminars in a university style. This was made possible by the reliable and flexible engagement of our graduate students under the leadership of Prof. Baumgärtner. Many thanks to this team for providing the basis for smoothly run seminars. That allowed us to keep the seminar fees low, by avoiding costly external seminar organizers. Special thanks also to our speakers, who succeeded in obtaining permission, even for new compounds, and gave their presentations without an honorarium, and to their companies for providing speakers, slides and handouts free of charge. We hope that our successors can carry on this tradition.

Our seminar provides the opportunity to improve our diagnostic skills. We have insisted on using the standard "old fashioned" glass slides and paid special attention to the mechanisms of wanted effects and unwanted side

effects. The seminar also offers opportunities for contact and cooperation between pathologists in industry and university for the benefit of both. Obviously all these functions could remain in the future.

Prof. Drommer and I hope that this seminar continues to be successful for many years to come. Our younger successors may introduce modern approaches to improve their seminar. We wish them all the best for the future.

We are in the process of harmonizing the manuscripts of the last two seminars for the 5th edition of our CD "Classic Examples in Toxicologic Pathology", to be released at the ESTP conference in Ghent on September 10-13, 2013. All 20 speakers have been approached and asked to transform their handout versions to CD manuscripts. Previous speakers, whose Classic Examples have not yet appeared on the CD, now have a good opportunity to make up for it. Please let me know if you are interested. This should broaden the scope of our CD and, at the same time, give authors an additional publication, merely by transforming their handouts to the CD version. This new CD edition will contain at least 125 Classic Examples and probably be the largest collection worldwide of published induced lesions, each illustrated by colored photomicrographs, totaling more than 1000 images in 75 organs and 12 species. It is intended to assist our members and other pathologists in their daily work, aiding them in their task of ensuring the safe use of compounds reaching the market for everyone's benefit.

Best wishes from

Prof. Baumgärtner, Drommer

Prof. Eberhard Karbe
eberhard.karbe@t-online.de

Professor Dr. med. vet. Franz Hartig in memoriam

On March 20, 2013 our honorary ESTP member, Professor Hartig, died suddenly and unexpectedly at his summer house in Gamburg near Tauberbischofsheim, west of Würzburg, Germany. His funeral service took place on March 27 in Ladenburg near Heidelberg, where he had lived since 1973 raising three children with his wife Christine, who died two years ago. Professor Hartig was born in Gamburg in 1929, where he attended elementary school. He graduated from high school in Tauberbischofsheim in 1948 and went on to study veterinary medicine at the University of Munich, where he received his Dr. med. vet. in 1955. In the same year he obtained his license to practice veterinary medicine and had his own practice in Werbach and Gamberg for seven years. During that time he fulfilled the requirements to

take and pass the examinations to become state veterinarian in Heidelberg from 1962 to 1966. His multidisciplinary experience allowed him to pass additional exams to become a licensed veterinarian for microbiology and serology in 1970, pathology in 1971 and clinical veterinary medicine in 1975.

Professor Hartig began his career in toxicologic pathology in 1967, when he joined the pharmaceutical company Boehringer Mannheim (now part of Hoffmann-La Roche). In 1969 he was named head of pathology, in 1987 major division head and in 1992 deputy head of pathology and toxicology. After 28 years as an industrial pathologist he retired from Boehringer in 1994 at the age of 65.

Parallel to his work at Boehringer, Dr. Franz Hartig began an academic career in 1972 at the Institute of Pathology of the veterinary faculty at the University of Giessen supervised by Professor Eugen Weiss. There he gave seminars on the pathology of laboratory animals. His habilitation in 1975 was based on research results on the coagulability of blood of different animal species. He lectured on lab animal diseases, becoming Privatdozent in 1978 and visiting professor (Honorarprofessor) in 1982. He was very highly respected by veterinary pathologists in Europe, leading to his election as president of the European Society of Veterinary Pathology from 1992 to 1993.

Due to his broad experience and reputation in various fields, with an emphasis on pathology, and his career in both academia and industry, Professor Hartig was extremely helpful when we wanted to found the **Gesellschaft fuer Toxikologische Pathologie (GTP)**, the German-speaking Society of Toxicologic Pathology for industrial pathologists, mainly in Germany and Switzerland. Two attempts to found such a society had previously failed. In 1986 four veterinary pathologists met several times in Wiesbaden to prepare for the founding assembly: Prof. Franz Hartig, Dr. Gerd Königsmann, Dr. Wilhelm Dieckmann and me. Professor Hartig, as the best known of the four, and highly respected for his vast experience in tumor diagnosis in many long-term rodent studies, assumed the role of explaining at the founding assembly the great need to finally establish the diagnostic criteria and a unified nomenclature, especially for neoplasms in rats and mice, arguing that the society to be founded would be the suitable body to achieve these goals. During the discussion that followed several colleagues argued vehemently against the foundation. Finally twenty of the large group of pathologists present became founding members, thus surpassing the legal minimum. Professor Hartig's presentation had obviously been crucial and convincing. The society was founded in October 1986. Throughout his career he attended all its meetings, as a highly respected speaker and/or session chairman.

Two years later, the **Registry of Industrial Toxicology Animal-data (RITA)** was founded by Professor Ulrich Mohr and directors of pharmaceutical/chemical companies at the Fraunhofer Institute in Hannover. Here pathologists from participating companies jointly diagnosed, with a multi-headed microscope, tumors and hyperplasias of control animals of standard long-term rat and mouse studies, collected in a tumor data base for mutual use as historical controls. The formulation of diagnostic criteria was the crucial aim, in order to reduce inter-pathologist variability in diagnoses and ensure consistent evaluation of the effects of test compounds, needed for risk assessment, and their safe use by humans and domestic animals. As nearly all the pathologists in the RITA group were members of the GTP, it was decided to accelerate the process by having RITA establish the diagnostic criteria and unified nomenclature for tumors of rats and mice. Here again, Professor Hartig contributed substantially with regard to proliferative lesions, especially in the liver and endocrine organs. The results were harmonized by expert panels of pathologists from all over the world to encourage international acceptance. The outcome led to the WHO publications that now represent an international standard. Professor Hartig was again a leading colleague in the RITA group, as in the GTP, and never missed a meeting. His opinion was always sought and appreciated.

The annual seminar "Classic Examples in Toxicologic Pathology" at the University of Veterinary Medicine in Hannover began in 1994. Professor Hartig was a speaker at the first seminar, presenting his research results on oral antidiabetics. He spoke again in 1997, three years after his retirement from Boehringer, this time on streptozotocin. This is further evidence of his strong interest in research and teaching. His high moral standards as a pathologist were obviously driven not only by responsibility and capability, but also by professional enthusiasm.

In 1999, in recognition of his outstanding contributions to our society, Professor Hartig became the first honorary member of the GTP, which was transformed to the European Society of Toxicologic Pathology in 2002. With Professor Hartig we have lost an exemplary personality and scientist. His remarkable achievements will remain in our minds and his convincing and thoughtful personality in our hearts.

Prof. Eberhard Karbe
eberhard.karbe@t-online.de

Progress of the INHAND nomenclature

Introduction

Beginning in 2005, the STP in the United States and the ESTP in Europe, in conjunction with RITA (Registry of

Industrial Toxicology Animal-data), developed a collaboration to review, update, and harmonize existing nomenclature documents and databases. In 2006, the British Society of Toxicologic Pathology (BSTP) and the Japanese Society of Toxicologic Pathology (JSTP) joined the INHAND (International Harmonization of Nomenclature and Diagnostic criteria) initiative, so that the project has become truly global.

Aims and structure of INHAND

The goal of INHAND is the publication of a standardized nomenclature for all organ systems describing microscopic lesions observed in laboratory rodents (rats and mice) in toxicity and carcinogenicity studies and giving the differential diagnoses. Project oversight is provided by the Global Editorial and Steering Committee (GESC), which consists of members from each of the major societies of toxicologic pathology.¹ ESTP is represented by Wolfgang Kaufmann, Thomas Nolte, and Susanne Rittinghausen. The GESC is currently chaired by Charlotte Keenan (STP).

Fifteen organ system working groups (OWGs) for rodent nomenclature were defined by the GESC. The terminology and criteria are based on the SSNDC (Standardized System of Nomenclature and Diagnostic Criteria) guides for non-proliferative lesions and on the RITA/WHO/IARC classification (International Classification of Rodent Tumors, Rat and Mouse) and "International Harmonization of Rat Nomenclature" for proliferative lesions.

The OWGs develop a primarily descriptive nomenclature and describe findings which can be found in the review of routine H&E histologic sections. Shortly after the draft nomenclature has been compiled, the GESC conducts an initial review, followed by a period of two months during which all members of participating societies are requested to review the proposed nomenclature. At the beginning of every comment period, ESTP members are notified by e-mail with a call for comments. The OWG subsequently finalizes the nomenclature based on the comments received from the GESC and general members.

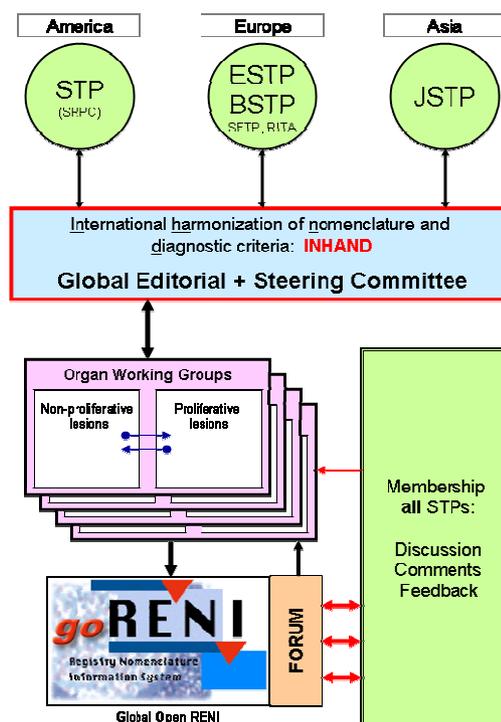


Figure 1. Organization of INHAND²

Future developments

Currently, four non-rodent species working groups are being formed for dog, minipig, rabbit, and monkey nomenclature. Each group is composed of up to three expert toxicologic pathologists from each of the participating societies responsible for developing preferred nomenclature and diagnostic criteria.

In future, diagnoses discussed by an OWG may be extended or amended; a change control process will be published by the GESC this year. The drafted forms were already reviewed by the ESTP board and will be available on the ESTP homepage (www.eurotoxpath.org) and on the goRENI website (www.goreni.org).

The plan is to finalize all organ systems in 2014 at the latest. The INHAND nomenclature will be adopted by FDA for use on SEND (Standard for the Exchange of Non-clinical Data)³.

¹ Vahle, J et al. (2009) The International Nomenclature Project: An Update. *Toxicologic Pathology*, 37: 694-697.

² Mann, P et al. (2012) International Harmonization of Toxicologic Pathology Nomenclature: An Overview and Review of Basic Principles. *Toxicol Pathol.* 40 (4 Suppl): 7S-13S.

³ Keenan CM and Goodman DG (2013) Regulatory Forum Commentary: Through the Looking Glass -SENDING the Pathology Data We Have INHAND. *Toxicol Pathol.* 2013 Apr 18. [Epub ahead of print]

Availability and status of the INHAND nomenclature

An important key for the use of the INHAND nomenclature is the *go*RENI (global open Registry Nomenclature Information System, www.goreni.org) website as a web-based platform to both review and comment draft nomenclature and published final nomenclature. Originally developed by Fraunhofer ITEM with RITA, *go*RENI provides access to members of all Societies of Toxicologic Pathology as well as government regulators.

Published organ systems

- Respiratory system⁴
- Hepatobiliary system⁵
- Urinary system⁶
- Nervous system⁷
- Male reproductive system⁸
- Mammary, Zymbal's, preputial and clitoral glands⁹

The four published INHAND supplements comprising the above mentioned organ systems have been sent to the ESTP members.

Reviewed by ESTP members

- Integument (to be published in 2013)
- Soft tissue (to be published in 2013)



In process

- Female reproductive system
- Lymphoid and hematopoietic system
- Digestive system
- Endocrine system
- Skeletal system
- Cardiovascular system
- Special senses

With best regards

Susanne Rittinghausen

Representative for Nomenclature and RITA

susanne.rittinghausen@item.fraunhofer.de

⁴ Renne, R et al. (2009) Proliferative and nonproliferative lesions of the rat and mouse respiratory tract. *Toxicol Pathol.* 37 (7 Suppl): 5S-73S.

⁵ Thoolen, B et al. (2010) Proliferative and nonproliferative lesions of the rat and mouse hepatobiliary system. *Toxicol Pathol.* 38(7 Suppl): 5S-81S.

⁶ Frazier, K et al. (2012) Proliferative and Nonproliferative Lesions of the Rat and Mouse Urinary System. *Toxicol Pathol.* 40 (4 Suppl): 14S-86S.

⁷ Kaufmann, W et al. (2012) Proliferative and Nonproliferative Lesions of the Rat and Mouse Central and Peripheral Nervous Systems. *Toxicol Pathol.* 40 (4 Suppl): 87S-157S.

⁸ Creasy, D et al. (2012) Proliferative and Nonproliferative Lesions of the Rat and Mouse Male Reproductive System. *Toxicol Pathol.* 40(6 Suppl): 40S-121S.

⁹ Rudmann, D et al. (2012) Proliferative and Nonproliferative Lesions of the Rat and Mouse Mammary, Zymbal's, Preputial, and Clitoral Glands. *Toxicol Pathol.* 40(6 Suppl): 7S-39S.