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An appreciation of Diether Neubert and Hans-Joachim Merker's contributions to Reproductive and Developmental Toxicology on their 80th birthday

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ABSTRACT

Diether Neubert, toxicologist, and Hans-Joachim Merker, histopathologist and embryologist, made significant contributions to the field of Developmental and Reproductive Toxicology. They worked under the same roof at the Institute of Toxicology and Embryopharmacology in Berlin, and actively collaborated with each other for over 25 years. Both scientists are now retired and turned 80 this year (2009). This celebratory article reports some remarkable events of their long and prolific scientific careers.

1. Diether Neubert's scientific career

Diether Neubert was born on September 5th, 1929, in Berlin where he also grew up, attended undergraduate school and resided most of the time. He began his medical studies at the University of Heidelberg but returned to Berlin and held his doctorate in medicine from the Free University of Berlin (FU-Berlin) in 1954. At that time Neubert completed a series of internships and postdoctoral studies in internal medicine, pathology and biochemical pharmacology that resulted in at least 19 articles most of which published in the traditional German journal *Naunyn-Schmiedebergs Archiv für experimentelle Pathologie und Pharmakologie* between 1953 and 1960. In the early-1960s, Neubert undertook a postdoctoral research work with Albert Lester Lehninger – one of the founding fathers of modern Bioenergetics – at the Johns Hopkins University, School of Medicine, Department of Physiological Chemistry, in Baltimore, Maryland, USA. The postdoctoral work at Lehninger's laboratory focused on water uptake and extrusion by mitochondria and gave rise to seven papers published in the Journal of Biological Chemistry, Proceedings of the National Academy of Sciences USA, Biochemical Pharmacology and *Biochemica et Biophysica Acta* in 1961–1962. Back to Berlin, Neubert earned his habilitation from FU-Berlin in 1962. In Germany, habilitation is the highest academic qualification a person can achieve by his or her own pursuit and is usually obtained only after a doctorate and several additional years of independent research. A successful habilitation entitles a person to be called *Privatdozent*/*Privatdozentin* and gives him/her the *venia legendi* or permission for lecturing. After his habilitation, Diether Neubert was nominated full-professor in 1968, chairman of Toxicology and Embryopharmacology in 1972, and professor emeritus on the occasion of his retirement in 1997.

Upon his return from the Johns Hopkins School of Medicine in 1962 and until his nomination as full-professor, Neubert investigated oxidative phosphorylation reactions and mitochondrial function. He was one of the pioneers in the study of mitochondrial RNA polymerase of animal cells. By 1968 he turned his attention to the influence of xenobiotics on embryo development and published a study on the effects of drugs on embryonic nucleic acid metabolism (with H-J Merker) [1], a study on the alkylation of embryonic tissue macromolecules by cyclophosphamide [2], and another study on the activity of oxidoreductases in rat embryos [3]. He was also a pioneer in using a biochemical approach to study chemically induced abnormal development of mammalian embryos, and along his career the metabolism of xenobiotic compounds in embryonic tissues remained as one of his main research interests. Looking into the problem of abnormal embryo development with eyes of a biochemist, Neubert gave then the first steps on

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Fig. 1. Diether Neubert (left) and Hans-Joachim Merker (right) at the Institute of Toxicology and Embryopharmacology FU-Berlin about 2 years before their retirement in 1997.

a long and productive journey through the field of Developmental and Reproductive Toxicology. Diether Neubert is an extraordinarily versatile researcher and thus his contributions cover a variety of relevant topics. We comment here only on those we think are the most significant ones.

The mode of teratogenic action of thalidomide is one of the challenging topics that caught Neubert's attention throughout his journey. He was a young medical doctor when the drug was first marketed in Germany in 1957 and already an experienced biochemical pharmacologist when Widukind Lenz revealed its teratogenic effects in 1961, and thus it seems plausible to think that the thalidomide tragedy exerted a great influence on his shift in research interests towards chemically induced abnormal embryo development. The ideas of Neubert on the mode of action of what he called "the most intriguing human teratogen" are found in several articles published as scientific correspondence, review papers and book chapters. With his sharp critical mind and objective style of writing, Neubert has dissected a number of hypotheses on the mode of action of thalidomide uncovering their weaknesses. In "*Never-Ending Tales of the Mode of Teratogenic Action of Thalidomide*" [4] he listed some factors that, in his opinion, a hypothesis must take into account to explain the teratogenic action of thalidomide. According to him, any hypothesis should allow for facts such as: (1) the mechanism should occur in the embryo of a known thalidomide-sensitive species (preferably in primates), (2) it must take into account the species-specificity of thalidomide, i.e., it was teratogenic in all primates tested so far, has little effect in rabbits and no effect in rats and mice, (3) it must take into account the thalidomide-susceptible stage of embryonic development (a short but well defined period), (4) it must take into consideration the organ specificity, i.e., besides phocomelia/amelia, thalidomide induces malformations of some organs such as the heart, but not of others such as the brain, and (5) it should also be able to explain the defects induced in other organs by a common mechanism. The above listed factors still stand as guidance to anyone who intends to face the challenge of offering a consistent explanation of thalidomide mode of teratogenic action.

Before investigating the thalidomide mode of action at the bench, Neubert and coworkers successfully established a colony of a non-human primate at the Institute. At the time, this colony was one of the largest, if not the largest and best handled indoors colony of marmosets (*Callithrix jacchus*) available for research purposes. Using marmosets, Neubert, Merker and colleagues performed a number of studies of thalidomide and its analogues (e.g., EM-12) and described the chiral inversion of enantiomers, their toxicokinetics as well as their effects on the embryo growth and skeleton development, the susceptible periods and the variability of embryonic stages [5,6]. Most of these studies were published in 1988–1994. At the time, in a series of studies on the action of thalidomide on the immune system, he also demonstrated that, in human and marmoset blood cells, it downmodulated the expression of integrins, a key family of cell surface adhesion receptors [7,8]. In a further paper [9], he provided evidence that adhesion receptors (β1-, β2- and β-3 integrins and selectin) are expressed on cells of essentially all primordia of *C. jacchus* embryos at early embryogenesis stages, and additionally showed that the thalidomide highly teratogenic analogue EM-12 downmodulated the expression of these receptors on limb bud cells and on cells of other primordia of marmoset embryos. Based on the aforementioned findings, Neubert and coworkers advanced a hypothesis that the primary mechanism of thalidomide teratogenic action involves the downmodulation of adhesion receptors, a change that would result in a disruption of ongoing cell–cell and cell–extracellular matrix interactions during embryo morphogenesis [9]. Along this line it was further reported that thalidomide also modulates the expression of surface molecules involved in the adhesion cascade in an endothelial cell line in vitro [10], a finding consistent with Neubert's early observations (Figs. 1 and 2).

In the 1990s it was found that thalidomide was a potent inhibitor of angiogenesis [11] and an effective drug for treatment of refractory myeloma, a type of bone marrow cancer in which there is an extensive angiogenesis [12]. Since angiogenesis is a critical step in the proliferation and spread of neoplasms (and also in the embryogenesis), it has been regarded as a potential target for a new generation of anticancer drugs. The aforementioned reports therefore elicited a renewed interest in evaluating the possible efficacy of thalidomide and its analogues as anticancer, anti-inflammatory and immunomodulatory agents. The mechanism by which thalidomide inhibits angiogenesis and delays the growth of some tumours, however, is unclear. Thalidomide has been shown to depress the production of TNF-α by enhancing the degradation of TNF-α mRNA, and to exert a myriad of other effects. Within this rather complex scenario, since integrins are emerging as important players in cancer metastatic behavior [13], the possibility exists that thalidomide anticancer and immunomodulatory effects are also mediated by the drug modulatory effects on the expression of adhesion receptors reported by Neubert and coworkers.

The toxicokinetics and reproductive toxicity of polyhalogenated-dibenzo-dioxins/furans (PHDD/Fs) also deserved a great deal of attention from Diether along his career. During the last four decades, health hazards posed by PHDD/Fs or "dioxins"