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Animals in Hypertension Research

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In this issue of "Hypertension News", two articles will deal with animal experiments in hypertension research. This theme has long been controversial in times of animal protection with its activists, and of recent molecular technologies and computer simulation. For years we have heard the outcry from animal protectionists but also from the political side: "Why can't we replace animal studies by in vitro experiments?"

While molecular and cellular experiments as well as computer simulation both have their own realms and merits – they will be dealt with in a later issue of "Hypertension News"– neither of them will be able to fully replace the experiments in animals, be it to augment our physio-pathological knowledge of hypertensive mechanisms or to develop antihypertensive/cardiovascular drugs.

When I started my scientific carrier as a post-doc fellow in Montréal, Canada, my first task was to look into the dopamine metabolism in dogs. My boss had the idea that conjugated dopamine played a physiological role beyond being an inert metabolite for urinary excretion, and to follow his hypothesis, I had to take blood from the renal and adrenal artery of the animals. The outcome of these experiments was rather unspectacular and, in retrospect, I have to admit that I made the unfortunate dogs suffer without adding much of importance to our scientific knowledge. This may serve as an example were the animal protectionists are right: Unnecessary, ill-designed animal experiments are unethical and have to be avoided.

However, the coin has always two sides: When I returned in 1978 to Heidelberg, Germany, to my next post-doc position, Franz Gross, then director of the Institute of Pharmacology at Heidelberg University and a big shot in hypertension research and drug development, showed me a bottle with a white powder which read "SQ 14 225". This was the name of a new drug to be introduced to the market three years later as "Captopril", the first ACE-Inhibitor. Professor Gross handed the bottle over to me with the words: "Try it but no doubt you will see that it does not lower blood pressure in our spontaneously hypertensive rats since they have a suppressed plasma renin-angiotensin system (RAS)". He followed a widespread hypothesis among hypertension scientists of the time, i.e. that inhibition of the RAS could only unfold antihypertensive actions in individuals with a stimulated plasma RAS. I was ignorant enough to feed the animals with this bitter-tasting powder for a period of several weeks and – I could dose-dependently titrate their blood pressure from about 200 mmHg down to normotensive values.[1] This was certainly not the only study showing this effect but together with animal experiments, mostly in rats and dogs, by many other researchers around the globe, it falsified the hypotheses shared by Franz Gross and many others on the antihypertensive action of RAS inhibitors and paved the ground for our understanding of the actions of ACE inhibitors in general and, finally, for their immense therapeutic success.

A further example: At one point my colleague Juraj Culman and I became interested in the role of tachykinin peptides like Substance P in central stress responses, such as the well-known "defense" reaction of the sympathetic nervous system. In a series of experiments in rats, we could indeed demonstrate that Substance P is a central transmitter involved and, moreover, that the 'love hormone' oxytocin plays an additional, critical role in this complex defense reaction to unpleasant stimuli [2]. Such a gain of fundamental knowledge could have never be attained with in vitro-studies or computerized models; for this one needs the whole set of interacting central and peripheral regulatory systems in an intact organism.

And a third example: Frits Prinzen, an internationally recognized physiologist of Maastricht University in the Netherlands, had developed in dog experiments on electro-mechanics of the heart a way to synchronize the cardiac conduction system and thereby improve the cardiac pumping capacity in heart failure.

In 2007 he and colleagues published in the NEJM how left ventricular apex pacing cured a child [3], and this was confirmed five years later in a large clinical trial. A perfect, convincing example of so-called translational medicine, directly from the animal experiment to the bedside.

Without Prinzen's dog studies, this life-saving success wouldn't have been possible. Some years later, when I was still Scientific Director of CARIM - the Cardiovascular Institute of Maastricht University, the animal protectionist had won the battle: Frits Prinzen was forced to stop his experiments in dogs, and I couldn't avert it. His comment: "Experiments in dogs are a sensitive topic in the general public, related to the strokability of these animals. However, there was a considerable literature and experience from the own laboratory that effects on ventricular pacing were significantly different when testing in other large animals like pigs and goats. Therefore, doing these studies in dogs was the only way to reach the goal of a better treatment for pacemaker patients." And: " The question arises whether it is ethically acceptable to take a dog's life to safe a human life". I would say: Yes, it is. But not everyone shares this opinion. In the Netherlands, for instance, there is a political move to ban all animal experiments by 2025.

So, let us open the discussion on animal experiments in hypertension by a number of articles on the issue in this and a further issue of "Hypertension News". You, the readers, are welcome to send us your comments via any media, and we will try to create a dedicated, lively forum in our journal.

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LEARNING THE ROPES (2)

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Role of animal experiments in hypertension research

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From the early times of hypertension research animal models have been instrumental to acquire novel insights in the regulatory principles defining blood pressure. Moreover they have been essential for the discovery of therapeutic targets and the development of corresponding drugs as particularly exemplified in the renin-angiotensin system. Recent technological revolutions in the detailed analysis and in the targeted alteration of genomes will resume and even accelerate this process in the future. In conclusion, animal experiments have been essential and will remain irreplaceable in hypertension research. Animal experiments have been essential for hypertension research from its beginnings. Already 1898, Tigerstedt and Bergmann injected rabbit kidney extracts into recipient rabbits to discover a hypertensinogenic substance, which they called renin [1] (Figure 1). Nearly 40 years later Harry Goldblatt clipped the kidney of a dog, thereby released renin and induced hypertension in the animal [2] (Figure 2).

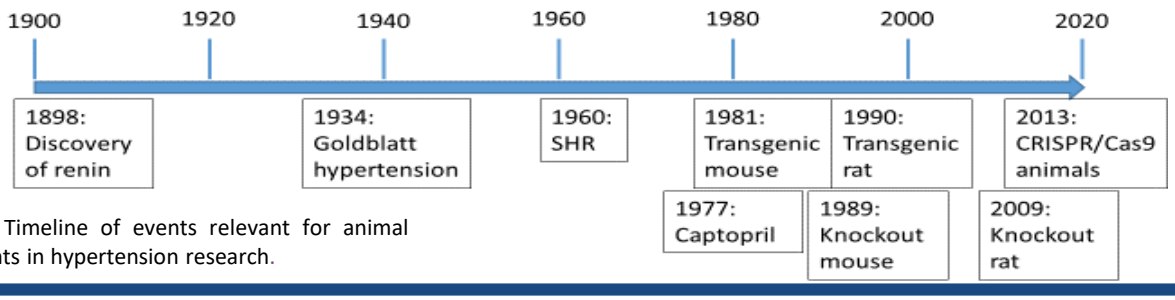

Figure 1: Timeline of events relevant for animal experiments in hypertension research.