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Essays

Human arterial hypertension revisited: How to leap from animal models to individually tailored therapy?

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It all started many decades ago when first data linked arterial hypertension with sudden deaths. The rest is a long history of research and achievements that made us believe in different culprits for this plague of modern man. In fact, this story could have been a fairy tale beginning:

Once upon a time, in the Land of Human Suffering, just beyond the Solid Tumor Swamps lay the waste Land of Arterial Hypertension. In the middle of it is the foggy Hypertension Forest, surrounded by several villages inhabited by scientists of various kinds. The two biggest are held by Nephrologists and by Cardiologists, in the third dwell together many Physiologists and Pathophysiologists.

All these people are hunters, trying to find the magic tree of human hypertension among many trees in the forest. The legend says that if the tree is found and cut down, the whole waste land would disappear, thus ending human suffering from arterial hypertension. The problem is that, due to fog, seeing which tree might be the right one is hard.

These hunters are helped by their pets in this quest. Most of them prefer rats. It is interesting that instead of taking the pets to the wood, they use rats for all kind of tests. Later, hunters use the acquired knowledge to find the path through the wood. There was a rumor that many years ago the Nephrologists used dogs and found an important tree, the legendary Renovascular Hypertension Tree that no longer exists, but this is just a legend, and the Nephrologists are also using rats these days. For instance, few decades ago, rats helped them to find few Natriuretic trees that turned out to be much less important than expected. It was a huge disappointment.

All villagers are supported by traveling magicians called Pharmaceuticals that bring them various magic lotion and other stuff that might help them find and cut down the tree.

The hunters from all villages occasionally meet on rare festive days, usually far away from the wood, somewhere on the seaside, free of fog and dark forests. There they talk mostly about their pets and about the wood. Some says that all trees in the wood are pines, the other has seen only shrubbery, while the third is talking about mighty oaks. It often ends in a quarrel, but, occasionally they realize that all their differences come from the fog and their separate paths through the forest.

Far away, in their high tower, a small bunch of Epidemiologists watch over the Land of Human Suffering using sharp binoculars. On rare sunny days, they can clearly see the Forest of Human Hypertension in the distance,

almost without any fog. Then, it seems to them that the forest has just few huge trees and lots of small ones that look almost like the rat trees. Nevertheless, who will know for shure from that distance, and the quest continues in the deep forest...

During several decades research on arterial hypertension focused on several issues: kidney perfusion in Goldblat's hypertension, dietary salt intake and renal excretion, roles of atrial and other natriuretic factors, increased exposure to vasoconstrictors (norepinephrine, epinephrine, vasopressin, angiotensin II, endothelin-I), reduced local vasodilatatory actions (nitric oxide, adenosine etc.). Recent advancement of molecular biology turned our attention to intracellular mechanisms and gene expression. Less popular but still active field is the link of ageing and suboptimal reparatory angiogenesis that leads to slow increases in peripheral vascular resistance, causing compensatory hypertension in individuals with normal, or hypertrophied heart muscle. It seems reasonably to expect that the less understood areas in human hypertension can be related to epigenetic changes. If these changes accumulate in young individuals, they can alter the hypertension risk in their offspring *(1)*.

The potential problem is that most of our knowledge about arterial hypertension comes from several animal model, usually on rats. After several years of animal testing new drugs are tested on patients in well organized trials and finally compared with standard treatments in large phase III trials that take several hundreds or even thousands of patients.

An example that important data can be lost along the described path is recently recognized fact that ingestion of fructose rich soft drinks can lead to hypertension in human *(2)*. It was only recently found in an epidemiological study, since animal data on this topic from 1987 *(3)* and 1994 *(4)* were not recognized as relevant, despite their publication in a leading journal. So we had to wait two decades for the epidemiology data to correct our dietary salt-centered interpretation of arterial hypertension.

As an illustration, two important topics in human arterial hypertension that seem hardly testable in animal models are listed:

– hypertension due to aging that leads to suboptimal reparatory angiogenesis and vascular damage enhanced by accumulated oxidative stress.

the role of human cognition and stored memories in hypertension. Large clinical studies report that patients with Alzheimer's disease normalize previously elevated blood pressure. Among previously hypertensive, elderly persons, an unexpected minority of hypotensive elderly patients with cognitive decline has been found *(5, 6)*.

When considering size of current clinical trials of antihypertensive drugs, it seems that bitter remarks of D.F. Horrobin *(7)* on oncological trials hold true also here. He said: »... *Many drugs show statistically significant benefits with trial sizes of 20 or 30 patients. With such drugs the prescribing physicians can know that most treated patients will show a response that can be reasonably attributed to the drug by both patient and doctor. But as effect sizes become smaller and trial sizes climb over a hundred, it becomes more and more difficult for anyone to know whether what happens to the individual was caused by the drug.*«

The need for a faster pipeline and smaller, less expensive trials is obvious. Optimal trial size would be the one that can discard any potential drugs unless it is more than just marginally beneficial. This would force pharmaceutical companies to pursue several goals simultaneously instead of their current practice to place all bets on one or few horses.

Since decades of almost a uniform approach to the treatment of hypertensive patients, based on large clinical trials, have already reached their »glass ceiling« of clinical efficacy, any substantial improvement can come from the individually tailored therapy. To achieve that, we need to dissolve the entity of arterial hypertension in several closely related diseases that require different therapeutic approaches. The goal would be to divide patients based on their specific features and then apply optimal, individually tailored, holistic therapy that would address the causative mechanism in that individual. The holistic treatment would need to include preventive measure and lifestyle changes before chronic medication, something completely different from the contemporary practice.

If we try to look in the future of arterial hypertension treatment, a potential path is to put more effort on:

– hereditary traits in relatives with and without hypertension despite different lifestyle habits and exposures to known prohypertensive factors

– exposure risk in unrelated individuals with and without hypertension despite a similar lifestyle and exposures to known prohypertensive factors.

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