Editorial Comment

Blood Pressure and Heredity
Is It All in the Genes, or Not?
Klaus Lindpaintner

We have come to appreciate that maintenance of "normal" blood pressure is based on the complex interaction of genetic factors and environmental variables in the context of a highly complicated and sophisticated maze of regulatory and feedback circuits. Primary hypertension (or, probably more accurately, hypertensions) then reflects a breakdown somewhere in this circuitry not explained by a readily apparent physiopathological mechanism that leads to a readjustment of the target set point. We understand today that the genetic background of this entity is both polygenic and heterogeneous and that it is likely to involve both specific gene-gene (epistatic) and gene-environment (ecogenetic) interactions. Add to this the analytic challenges posed by quantitative (rather than qualitative) traits and incomplete penetrance and the confounding phenomenon of a pronounced sexual dimorphism, and it becomes obvious to the most optimistic that the investigation of the genes contributing to primary hypertension in humans is a daunting task. Thus, the use of animal models of "genetic" hypertension has been a mainstay of hypertension research for more than three decades: The creation of fully inbred strains eliminated the problem of genetic heterogeneity, and the (perceived) ability to control and standardize environmental influences stringently was viewed as an effective means to avoid the noise of multifactorial interactions. Recent advances in molecular genetics and theoretical concepts of quantitative trait analysis have been applied to these model systems with the hope of elucidating at least some of the major genes that form the genetic background in animal hypertension, albeit without any certainty that analogies to human hypertension will follow.

Thus, the world of the experimental investigator using animal models of hypertension appeared to be neatly split into unknown genes and conventionally recognized environmental perturbations as the causative principles that lead, alone or in concert, to pathological elevations of blood pressure. Presence of an offending gene mutation (and, in the case of a true ecogenetic interaction, of the associated environmental stimulus) would by necessity result in hypertension. This seemed credible because among a strain of inbred hypertensive animals all individuals, without exception, exhibit the morbid phenotype. The effects of such a gene could be traced from generation to generation in breeding experiments (with the restraints that a quantitative, polygenic trait places on such experiments). The presumption has been that only modification of the flawed gene's effects by various classic breeding strategies or modern gene transfer techniques would provide a lasting change in the blood pressure phenotype. This concept is now being challenged by the results of a study by Wu and Berecek published in this issue of Hypertension.1 The authors report that early (intratrauterine) treatment with angiotensin converting enzyme inhibitors prevents the development of hypertension in spontaneously hypertensive rats, an effect that is maintained even after withdrawal of the drug. Strikingly, in what might even be viewed as a vindication of Lamarckian theory, the reduction in blood pressure is passed on to the offspring of these animals. Thus, despite the preservation of an unaltered hypertensive genetic background, and in the absence of exposure to antihypertensive agents at any time, this progeny displays essentially normal blood pressure values. Therefore, the presence of a hypertensive genetic background alone is apparently not sufficient to lead to the expression of the morbid phenotype, and additional permissive factors must be present. Simplistically put, the milieu of a hypertensive mother seems to be required for the offspring to fully develop and exhibit the hypertensive phenotype.

If the genetic material remains unaffected, what does change in the offspring to account for the difference in phenotype? Probably the most likely explanation, though entirely hypothetical, has to do with the well-established concept of developmental plasticity under the influence of neurohumoral mediators.2,3 Lasting changes in structure and function particularly of neural organization may be introduced by manipulation of these influences, and it is conceivable that they, in turn, result in an altered internal neurohumoral milieu affecting the ontogeny of the succeeding generation, entirely in the absence of the initial, external manipulation. The persistent differences in drinking behavior after intracerebroventricular administration of angio-

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Richard II
Shakespeare, Richard II

That bed, that womb, that mettle, that self mould, that fashioned thee...
tension II found in the offspring of captoril-treated rats in the article under discussion may in fact point to the introduction and propagation of such an effect on central synaptic circuits. This concept is not without precedent: Diabetes mellitus has been induced in F2 rats born to nondiabetic dams exposed to experimental gestational hyperglycemia. The diabetic phenotype is then passed on to F2 progeny, although neither the F2 nor the F2 rats were ever exposed to experimentally induced hyperglycemia, a phenomenon attributed to the metabolic milieu present during ontogeny that has been termed "fuel-mediated teratogenesis" and that one might indeed construe to represent a "neo-Lamarckian" mechanism.

The observations by Wu and Berecek, if confirmed, raise a number of important points. Most importantly, they may open a tantalizing door through which an expanded concept of pathogenetic mechanisms might be formulated: Instead of the neat dichotomy of genetic vs environmental factors we have become accustomed to, a third class of epigenetic phenomena would be established as etiologic factors in hypertension. These would display a somewhat chimeric behavior: What begins as an environmental manipulation (such as angiotensin converting enzyme inhibition) in the progenitor results in lasting and heritable effects in the offspring who never experienced the original environmental manipulation and in the absence of any structural (sequence) alteration of genomic or mitochondrial DNA. (Conformational changes, induced in trans by factors that are part of the postulated altered neurohumoral milieu, or chemical modifications such as different DNA methylation patterns, certainly are a possible source of this heritability.) To further add to the complexity of this expanded concept, the origin of the postulated epigenetic influences may well be conserved in genetic information: If exposed to a conducive environment, the relevant genes are expressed, leading to developmental changes that in turn exert the postulated epigenetic influences on the next generation, resulting in a self-amplifying and, eventually, self-perpetuating mode of inheritance. The trend toward higher blood pressures in the F2 progeny reported by Wu and Berecek may indicate that such a mechanism is operative in their model.

Once confirmed, the findings described by Wu and Berecek will spawn important follow-up studies. These will have to address the persistence of altered phenotype in subsequent generations, the effect of other classes of antihypertensive agents administered in a similar protocol, the relative contributions of maternal and paternal lineage to the observed effect, and the possible induction of heritable hypertension in pharmacologically manipulated normotensive animals. It is likely that, according to the mechanism proposed above, the inherited hypertensive effect will gradually wane over subsequent generations. One may speculate that an effect on central nervous system cardiovascular control centers will be an essential mechanism of action for drugs with which this experiment can be repeated. Most likely, the observed effect is transmitted exclusively through maternal lineage by means of the intrauterine milieu; in addition, the postnatal environment may also contribute, either through chemical mediators (secreted in the milk) or via psychobehavioral factors (nursing behavior), which have been found to correlate with blood pressure in pups. As yet, the converse of Wu and Berecek's experiment, namely, the induction of heritable hypertension, has not been possible in experimental animals, and reports of a higher incidence of hypertension in the offspring of preeclamptic mothers are difficult to interpret because of the overlap between preeclampsia and primary hypertension.

Lastly, the report by Wu and Berecek raises an issue germane to most of our animal models of hypertension that is rarely addressed, yet in fact is critically important: Although blood pressure is certainly the easiest parameter to measure and assess, is it truly the most important and relevant phenotype for the investigation of "hypertensive" cardiovascular disease? The spontaneously hypertensive rat and other hypertensive strains are overwhelmingly used as models for elevated blood pressure but not as models for the expression of long-term morbidity and mortality that makes the disease such an important pathological entity in humans. Although hypertension, at some point, presumably becomes an autonomous risk factor, it should probably more appropriately be viewed as an intermediate phenotype that initially represents only the consequence of a primary abnormality of cardiovascular growth, structure, or function. This is illustrated by the well-described dissociation of blood pressure and ventricular mass in hypertension. It remains unclear, thus, whether the reduction in blood pressure seen as a "heritable trait" in the paper by Wu and Berecek reflects a similar modulation toward "normal" of the presumed underlying primary biological derangement. To ask the question differently: Does the alteration of blood pressure phenotype result also in a reduction of cardiovascular morbidity and mortality in these animals and their offspring, or is it a mere epiphenomenon?

These are intriguing results yet difficult to interpret; if confirmed, it will take major investigational efforts to fully understand the mechanisms behind them. The immediate importance of Wu and Berecek's article for today's hypertension researcher is more mundane: It reemphasizes in striking fashion that we have yet to establish and comprehend the full magnitude of complexity that the etiology of primary hypertension encompasses. Once again (and probably not for the last time), we must revise our conceptual views and rethink some of our investigational approaches. On a practical level, we are again reminded that we simply cannot be circumspect and careful enough in the design of our experiments. Perturbations such as drug treatment are obvious and perturbations will increase, as will, in parallel, the danger of reaching wrong or misleading conclusions. Only the integration and comparison of results reached by different investigators will prevent this from happening. This emphasizes the importance of rapid and complete communication between investigators and the use of interchangeable, standardized methodologies.

As has been pointed out before, modern molecular biological and genetic techniques provide us with the
instruments to tackle the intellectual challenges presented by hypertension; it is up to us to orchestrate them in such a way that we continue to make progress toward the goal of solving the riddle in a symphonic and meaningful way.

References


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