Physiol. Res. 43: 209–210, 1994

LETTERS TO THE EDITOR

Recombinant Inbred Strains in Hypertension Research [Reply]

We have recently published an Editorial concerning the use of recombinant inbred strains in hypertension research (*Physiol. Res.* **42:** 225–233, 1993). Since we are physiologists, our attention was focused to intermediate phenotypes and pathophysiological aspects of this kind of research. We are therefore happy that our colleagues, who are concerned mainly with the genetic aspects of the above research, disclosed some pitfalls in our genetic terminology. Nevertheless, we do not feel that we have misinterpreted some results or have drawn some unjustified conclusions.

1) The paragraph on mathematical methods used for the analysis of quantitative traits was taken from the paper of Démant & Hart (*Immunogenetics* **24:** 416, 1986) concerning the advantages of recombinant inbred strains and recombinant congenic strains over some older genetic approaches. We are grateful to our colleagues for their expert comments on modern genetic techniques.

2) We apologize for our incorrect genetic terminology. Of course, the respective expressions should be replaced by "*strain distribution pattern for polymorphic loci can be established*" and "*the presence of particular homozygosity at each locus is determined only by the random segregation and crossover events*".

3) The authors are aware of the basic difference between recombinant congenic strains and congenic strains. Both approaches can be used for verification of the role of particular gene(s) in the determination of quantitative traits. It is, however, evident that the latter system represents an easier approach. Moreover, there were available several congenic strains (e.g. SHR.1N versus BN.1K or LEW.1K) possessing contrasting haplotypes of RT1 complex which was found to be associated with blood pressure in the study on recombinant inbred strains. Indeed, the results obtained by using these congenic strains confirmed the earlier findings in recombinant inbred strains.

4) According to the original paper of Pohlová et al. (*Clin. Sci.* **84:** 129, 1993) the presence of SHR allele of the renin gene in particular recombinant inbred strains was associated with 50 % reduction of renal renin activity (RRA) ($p<0.01$) whereas blood pressure was only non-significantly increased by +6 mm Hg. Until now this is one of the most significant associations described in RI strains.

In order to test the hypothesis that lower RRA in RI strains with SHR allele of the renin gene might be a consequence of their elevated blood pressure, we compared RRA in blood pressure-matched RI strains possessing either the SHR or BN allele of the renin gene. It was evident that RRA in RI strains with SHR allele was independent of their blood pressure because it was similar in the strains with low and high blood pressure. Our conclusions were confirmed in a subsequent experiment in which 30 RI strains were studied (Zicha et al. *J. Hypertens.* **11** (Suppl. 5): S66, 1993). Thus the arguments of our colleagues on decreased statistical power of small subpopulations of RI strains are not relevant to our use of blood pressure-matched groups of RI strains. Our comparison clearly demonstrated that RRA was also reduced ($p<0.001$) in those RI strains with the SHR allele of the renin gene in which blood pressure was not elevated. This means that RRA was decreased even in the case when blood pressure was so low as in the RI strains with the BN allele which are characterized by high renal renin activity. To our knowledge, there is no alternative physiological approach how to investigate the long-term effects of blood pressure on other physiological variables than a comparison of groups with similar or different levels of blood pressure.

5) We agree with our colleagues that different results can be obtained when the same genes are studied at a different genetic background or in animals kept in a different environment. Blood pressure association with the RT1 complex and hsp70 gene might be used as a typical example because there is a major discrepancy between the results obtained in Prague RI (SHR x BN) strains (Pravenec et al. *J. Hypertens.* **7:** 217, 1989; Hamet et al. *Hypertension* **19:** 611, 1992) and in Leicester SHR x WKY cross (Lodwick et al. *J. Hypertens.* **11:** 1047, 1993). Another example is the gene for the angiotensin converting enzyme that has no association with blood pressure in Prague RI strains (Pohlová et al. *Clin. Sci.* **84:** 129, 1993) whereas it was strongly associated with blood pressure in the Heidelberg SHR x WKY cross

(Hilbert et al. *Nature* **353:** 521, 1991; Jacob et al. *Cell* **67:** 213, 1991).

In fact, our findings concerning relative organ weights clearly indicated that, at the age of 4 months, the relative kidney and heart weights are determined by other genes than those important for blood pressure determination. Unfortunately, due to a linguistic error (*"we have solved"* instead of *"we have tried to solve"*) our experimental question was considered as a conclusion.

6) The criticized phrase concerning the pedigree analysis in essential hypertension was taken from the conclusions of the paper on platelet aggregation in RI strains by Pravenec et al. (*J. Hypertens.* **10:** 1453, 1992). It is a great pleasure to see the rapid progress in methods used for genetic analysis of essential hypertension (e.g. Lifton R.P., Jeunemaitre X.: Findings genes that cause human hypertension. *J. Hypertens.* **11:** 231–236, 1993; Morris B.J.: Identification of essential hypertension genes. *J. Hypertens.* **11:** 115–120, 1993; Williams R.R. et al.: Genetic basis of familial dyslipidemia and hypertension. *Am. J. Hypertens.* **6:** 319S – 327S, 1993).

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Received May 30, 1994