## Multi-author Review

# Genetic models in brain and behavior research. Part III

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### Extrapolations and perturbations

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Genetic animal models which accurately represent human conditions, both new ones and older ones which are being continuously refined, are being described so often of late that it is becoming difficult to keep up with all of them; models for such diverse problems as, for example, Duchenne and Becker muscular dystrophies (mice and dogs)[2], human senile cataract (mice)[9] and the Chediak-Higashi syndrome (cats and several other species)[8]. In the BB rat, a genetic model for type 1 (insulin-dependent) diabetes mellitus, the neonatal stimulation of pancreatic $\beta$ cells has been recently found to prevent that disease, a finding which has important implications for both understanding the development of, and the treating of, the same genetic condition in humans[1].

It is therefore difficult to comprehend the seemingly evermore-frequent appearances of assumedly well-intentioned, but decidedly poorly-informed, theologians and philosophy professors on "talk-shows" (and other public-directed extravaganzas), righteously proclaiming the impossibility of extrapolating data gained from animal experiments to humans. Indeed, the present series coordinator is aware of several books on animal models which have appeared or will be appearing shortly, being himself the editor of one on genetic models of behavioral dysfunctions, which will not only cover subjects which have been encountered in the present series, such as alcoholism[10,11] and absence of the corpus callosum[12], but also many subjects which have not been, such as Down's syndrome, various myelin disorders and cerebellar mutations, epilepsy, narcolepsy, aggression, and nicotine dependence and sensitivity, among others[6].

Part III of the present review series [Parts I and II appeared in the June 1988 and September 1989 issues of EXPERIENTIA] makes a slight directional change, however, as will be seen by the nature of the contributions. Perhaps even the fore-mentioned theologians and philosophy professors (generally being middle-aged, white men themselves) may have noticed the following titles in a recent issue of a reputable medical journal: "Is there still too much extrapolation from data on middle-age white men?"[3]; "Examples abound of gaps in medical knowledge because of groups excluded from scientific study"[4]. That author went on to question why pregnancy and the menstrual cycle, as well as being non-white or of advanced age, are generally regarded as confounding factors in clinical research, even when most drugs are being designed with the intention of being used on women, non-whites and the elderly. In particular, ethnic differences have often been noted in drug response, probably due to various factors such as metabolism, receptor sensitivity and stress response differences, etc. Even in animal research, the aversion to using female rodents in experiments is well known, as is the preference for using young (inappropriately immature, in many cases) animals and 'random-bred' stocks (which are, unfortunately, not even the rodent equivalent of 'white men'). Our first contributor is one of those[5,7] who, for years, has devoted much of his time and energy to addressing the latter problem as it pertains to toxicological research, in relation to both clinical and pre-clinical studies. Festing's paper, demonstrating that the wide-spread use of "random-bred" rodents in neurotoxicology leads to experiments with low statistical precision, and that the failure by most toxicologists to use more than a single strain deprives them of being able to generalize their experimental results over a range of genotypes, sets the critical tone for Part III. Festing has previously shown that in pharmacological testing the animal population should include several response phenotypes in order to a) avoid problems which might arise from the inadvertent choice of a single, resistant phenotype, b) be able to demonstrate the extent to which the response is genetically determined, and c) eventually incorporate genetic variation in animals at loci which are homologous to those controlling the response to the drug in man[7]. The use of a single stock actually violates the main principal of experimental design, which is to control all variables apart from the treatment[7].

The papers by Gentsch et al., and Ambrogi Lorenzini et al., continue the critical slant of Part III. Gentsch et al. demonstrate that genetically and environmentally induced differences in locomotor activities exist, and that "locomotor activity" is not an entity in itself, but should rather be subdivided into at least two distinct behavioral patterns, an initial reactive locomotor activity and spontaneous locomotor activity. Ambrogi Lorenzini et al., on

the other hand, provide a critical review of the behavioral repertoire of the homozygous and heterozygous Brattleboro rat strains, comparing them with both Long-Evans (pigmented) and Wistar (albino) stocks in regard to consummatory behavior, as well as various activity and emotionality paradigms, including passive and active avoidance.

In a review dealing with female rats, Rivest critically discusses the respective impacts of genetics and environment on sexual maturation, coming to the conclusion that hereditary factors definitely exist, but that their role will be difficult to ascertain so long as the environmental factors are so poorly understood. In addition, both are closely intertwined and are determined by maternal, and by combinations of endocrinological, influences. Endocrinological influences also abound in the background of the studies which are described by Benus et al. Working with male mice, they explore the coping styles of aggressive vs non-aggressive individuals, illustrating the divergent manners in which they reduce environmental stressors, and relating these individual differences to evolutionary processes and natural selection.

Returning to a critical vein, the paper by Brush reviews the work involving most of the major, existing selection/breeding programs for high vs low two-way, active avoidance acquisition in rats. Endocrinological analyses also play an important role here, and Brush proposes what he terms as "important correlates", as distinct from "trivial correlates". The bottom line appears to be pronounced differences in emotionality, uniting all of the low-avoiders at the more emotional end of that line (an "important correlate"). Fernández-Teruel et al. make good use of this same model in the final review-paper, discussing the relationships among the stressful nature of two-way avoidance, individual differences in emotionality and putative endogenous ligands for benzodiazepine receptors. Part IV of this series which is scheduled for publication next year, will cover developmental and maternal influences in genetic models of hypertension.

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