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Genetic models in brain and behavior research, Part I

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Introduction

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Key words. Genetic models; selective breeding of rats; mouse strains (C57/DBA); depression; anxiety; stress; alcoholism; rotational behavior; learned helplessness; social interaction; emotionality.

This multi-author review, published in several parts, under the title 'Genetic models in brain and behavior research', was inspired by a symposium organized by the present coordinators at the IVth World Congress of Biological Psychiatry, held in Philadelphia (USA) in September, 1985. One of the most enduring impressions to be gained from that imposing and all-encompassing meeting was the realization of the rapidly-growing importance of genetics in all facets of psychiatry and of psychopharmacological research [16]. Even at this stage of our knowledge, it is obvious that genetic factors are intricately involved in such clinical entities as anxiety, depression, schizophrenia and alcoholism, to name but a few of the most important ones.

Therefore, when one wishes to develop therapeutic solutions for these and other conditions through the study of behavioral alterations in rats and mice, why do the majority of laboratories attempt to do so by studying so-called 'normal' animals? Indeed, the *biggest* problem involved in using 'normal' rats or mice is that such animals *do not exist* and, in reality, these laboratories are merely using undefined genetic material; i.e. introducing an unknown quantity into their research. This would undoubtedly become obvious if complete bibliographies were constructed of each of the thousands of strains and stocks available. Such a compilation might actually also help explain the vast flood of contradictions extant in the literature in many fields, such as serotonin and behavior, the mechanisms of action of benzodiazepine drugs, hippocampal function, etc. It may well be, that unless more attention is payed to the genetic background of the subjects used, or unless more use is made of genetically-selected animal models, these problems will *never* be properly dealt with. The following examples from the literature, which have compared different stocks of 'normal' rats in three widely-used behavioral tests, may be used to illustrate the points made above.

In the first, males of eight stocks of rats were tested in regard to susceptibility to training in a 'learned helplessness' test [19]. The subjects consisted of three outbred lines (Sprague-Dawley, Charles River-Holtzman and Sasco-Holtzman) and five inbred strains (Lewis, Buffalo, Wistar-Kyoto, Brown Norway and Fischer F-344). Four of the eight were virtually non-susceptible to training, two were intermediate, and two were deemed acceptable for use. The authors noted that the few statements which had previously addressed this issue in the literature would lead new investigators in the area to believe that high percentages of training were common in learned helplessness research. This problem has, of course, been confounded by the fact that the only issue which has interested most scientists working with this test has been merely to find the 'most acceptable' rat to use (even though such subjects are, apparently, actually in the minority; i.e. not 'normal'), rather than to find out *why* some rats are acceptable for use, whereas most are not.

Using another test, it has been found that spontaneous, nocturnal, rotational behavior varied from between 5 and 40 rotations among Sprague-Dawley-derived rats obtained from seven different breeders [10]. Reactions to amphetamine also differed among the groups of Sprague-Dawley rats from three of these suppliers. It was concluded that interindividual differences among 'similar' (i.e. Sprague-Dawley) stocks appear to contribute importantly to reported differences in results among laboratories (all of which probably, consider themselves to be using 'normal' rats).

In the third example, striking differences were found in social interaction, locomotion and exploratory activity among hooded rats from different sources, at a laboratory which has become well-known largely as a result of developing a particular test which makes use of these behavioral parameters. In that study, which was conducted several years ago, those rats (the NIMR line) with the lowest levels of all three behaviors also showed the highest defecation rates, as well as elevated plasma corticosterone [8]. It was stated, in the same publication, that researchers using rats from external suppliers should be aware of possible variations which could account for some of the discrepancies in the literature, since the behavioral response to a drug, for example, may depend upon the baseline rate of responding, and response to stress upon the pre-existing level of hypothalamic-pituitary-adrenal activity. Despite the potential advantages of continuing work with this test by pharmacologically comparing two lines of rats which differed emotionally and behaviorally, however, work was apparently discontinued with the NIMR line and continued only with a line of hooded rats which showed high baseline levels of social interaction. As it turned out, during the course of a recent literature review (several years after the study in question), the same laborato-

ry has put forward the idea that there seem to be crucial differences between normal animals and people on the one hand, and clinically-depressed patients on the other. Furthermore, the usefulness of screening for potential antidepressants by looking at the behavior of 'normal' animals (which, as we have seen, probably aren't even that) was questioned[9].

The above are three examples which, besides illustrating the fact that there is no such creature as a 'normal' rat, indicate, directly or indirectly, the value of comparing subjects which differ genetically. The same holds true for mice, perhaps even more so, given the larger volume of literature which has already been produced regarding basic differences in brain and behavior parameters to be found among the many strains and substrains which are available. On this note, we should direct our attention to the reviews comprising Part I of this series.

The paper by Overstreet et al. is an example of how it may be possible to produce a rat model of human depression through selective breeding. This unique approach to the study of depression is particularly timely, as it is becoming increasingly obvious that endogenous depressive illness and/or susceptibility to depression have a strong genetic basis. Selective breeding of rats has also produced useful models for the study of other genetically-determined, or genetically-influenced disorders of humans, such as anxiety (emotional reactivity to stress) and alcoholism[2,3,5–7,13]. The paper by Gentsch et al. shows that symptoms of anxiety in rats may be arrived at by direct, or indirect, selective breeding or by manipulating the environment of rats. It also shows that there appears to be no direct relationship between those symptoms and the benzodiazepine- or imipramine-binding sites compared within the groups of rats reviewed. After presenting a historical review of the selectively-inbred Maudsley Reactive and Non-Reactive rat strains, the paper by Blizard effectively proposes the possibility that a specific neuroanatomical region, the locus ceruleus, may be a focus for gene-action in that animal model of emotionality.

Finally, the paper by Frischknecht et al. introduces the wide, wide world of mouse genetics, reviewing much of the pertinent literature regarding opioids and behavior as concerns obese mice (and rats), recombinant strains of mice and, especially, the C57 and DBA inbred mouse strains. Using C57BL/6 and DBA/2 mice, they construct a genetic model for proneness to drug-induced analgesia, drug abuse, drug addiction and drug-induced locomotor responses. Considered in the light of work with these two substrains at numerous other laboratories, where they have been used as contrasting genetic models in many types of research dealing with brain and behavior[1,4,11,12,14,15,17,18,20], one is tempted to believe that a set of volumes could be written on this theme (C57BL/6 vs DBA/2) alone.

Future reviews in this series will continue to deal with specific aspects of selective breeding and genetic comparisons in rats and mice, as they relate to particular neurochemical, neuroanatomical and/or behavioral topics of interest. It may be hoped that by the time this series of multi-authored reviews is concluded, at some later date, it will no longer be considered feasible (or even expedient) to simply ignore the importance of the vital, genetic elements involved in brain and behavior research.

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