Genetic factors in neurotoxicology and neuropharmacology: A critical evaluation of the use of genetics as a research tool

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Abstract. Animals have evolved a detoxication system to enable them to survive in a hostile chemical environment in which foods contain many non-nutrient chemicals. Detoxication depends on enzymes which are often genetically polymorphic. As a result, inter-individual variation is common, and in humans several Mendelian loci have been identified. However, most variation in response is probably due to the action of several genes.
Genetic variation in response to the neurotoxin MPTP and to chemically and physically-induced seizures is reviewed. In the former case, differences between pigmented and white mouse strains have been noted which are consistent with the hypothesis that humans are more sensitive than mice or rats because of the presence of melanin in human brains. However, variation in sensitivity probably also depends on other genes. In the case of audiogenic seizures, a single locus has been identified and mapped, but its relationship with seizures induced by other agents is not clear. Genetic variation in response to alcohol is also discussed.
The failure of most toxicologists to consider genetic variation as a potentially confounding variable, and as a powerful research tool, is discussed critically in relation to non-repeatability of research on the neurotoxic effects of lead, and in relation to the genetic variation in MPTP, seizures, and alcohol response already noted. It seems clear that genetic methods provide a powerful research tool which is largely being ignored by toxicologists.
Key words. Pharmacogenetics; neurotoxicology; toxicology; neuropharmacology; MPTP; seizures; alcohol; inbred strains; detoxication.

Introduction

It is generally accepted that organisms evolve by mutation, natural selection, and genetic sampling to cope with a hostile environment. Their size, shape, physiology and behaviour[45] are the evolutionary consequence of the particular environment to which they have become genetically adapted. Sexual reproduction has evolved as one mechanism by which genetic variability may be conserved, allowing rapid evolution and survival when conditions change. Genetic variation controlling physiological, morphological and developmental characteristics has been widely documented for most laboratory species, including the mouse[61], rat[82], guinea-pig[28] and rabbit[36].
There is also a hostile microbiological environment. Animals would provide an ideal host for pathogenic microorganisms were it not for the protective mechanisms that have evolved. In vertebrates these include an impermeable skin, non-specific elimination of invaders by phagocytosis, and an immune system capable of mounting a specific immunological defense against millions of different microorganisms and antigens. There is also substantial, genetically-determined, inter-individual variation in the immune system[95], allowing populations to evolve which are resistant to new microbiological challenges[94]. In Australia, for example, strains of rabbits soon evolved which were resistant to the myxomatosis virus following its introduction by humans[2].
The genetics of the immune system has been intensively studied for many years, and has been the subject of many books and papers. A notable feature of research in this field has been the wide-spread use of genetically-defined animals, particularly inbred strains of mice. The identification and characterization of individual loci governing many aspects of the immune response has been achieved by making use of 'congenic' strains developed by backcrossing selected alleles to an inbred strain. Klein[55] lists no fewer than 800 such strains. By this means genetic loci controlling the production of immunoglobulins and cell surface antigens such as the major histocompatibility system have been isolated, and cloned[89]. Such studies have made a fundamental contribution to our understanding of the mode of gene action in immunology and related areas such as cancer research[20].
Animals have also evolved mechanisms to allow them to exist in a hostile chemical environment. For example, it has been estimated that each person consumes more than 10,000 different non-food chemicals each day, amounting to a total weight of over one gram[8]. Many toxic compounds including alkaloids, amines, non-protein amino acids, cyanogenic glycosides, terpenoids and phenolics are synthesised by plants in order to protect themselves from attack by microorganisms, insects and herbivores, while others, such as ethanol, are metabolic by-products of microbial metabolism.
Many classes of food contain potential toxins. For example, some legumes such as red kidney beans contain lectins which can be toxic unless inactivated by cooking. Over 150 different chemical substances have been identified in potatoes, and cooking increases this number to more than 225. Toxicity depends critically on dose level. The levels of potentially toxic substances in potatoes can increase dramatically if they are exposed to light or are

allowed to sprout, and many new toxins may be produced in foods that have become spoiled by microbial attack[1].

Animals have also evolved mechanisms to detoxify any such compounds which enter the body via the food, the air, or the skin. The main features of the detoxication system are well understood. According to Timbrell[92], the biotransformation of the xenobiotic usually involves a two-stage reaction. Phase I reactions generally involve an oxidative, reductive or hydrolytic reaction which provides the necessary chemical structure for the phase II reactions, which are generally conjugations. Chemicals which already possess a suitable structure may directly undergo the phase II reaction, the main function of which appears to be to make the compound more hydrophilic so that it can be eliminated in the urine.

The majority of the phase I reactions are catalysed by the mono-oxygenase system based on cytochrome P450 which is a membrane-bound haemoprotein enzyme located in the smooth endoplasmic reticulum. It is particularly abundant in the liver, though it also occurs in most other mammalian tissues. The P450 enzymes represent a superfamily of genes which have probably evolved by gene duplication. They are generally non-specific in their ability to catalyse the oxidation of a wide range of substrates. So far 13 isozymes have been identified in humans and nine in mice. The latter have been mapped to chromosomes 4, 6, 7, 9, 15, 17 and 19[73]. Many of these loci are genetically polymorphic[96,97], though much work remains to be done on the phenotypic effects of such polymorphisms. Not all xenobiotics are metabolised by P450. Some, such as ethanol, have specific enzymes which can metabolize them, though even in this case the cytochrome P450 enzymes may play a part under certain circumstances.

The phase II reactions involve the formation of glucuronides catalysed by glucuronyl transferases, sulphation catalysed by sulphotransferases, glutathione conjugation catalysed by the glutathione-S-transferases, conjugation with amino acids, acetylation, and methylation, all of which are again catalysed by specific enzymes. Again, many of these phase II conjugating enzymes are genetically polymorphic.

It is unfortunate that the chemical detoxication system lacks a succinct name like 'immunology'. The term Xenobiosis, which '...deals with the chemical and pharmacological behaviour of foreign substances in the (human) body'[1] is reasonably satisfactory, but is not yet widely recognised. Pharmacogenetics, the discipline concerned with genetic variation in response to drugs and chemicals, is very much in its infancy in comparison with immunogenetics. While there is ample evidence for genetic variation in response to a wide range of chemicals, the genetic mechanisms are only just beginning to be explored in any depth. Few specialised strains of laboratory animals have been developed to isolate genetic loci of interest, though Nebert[75] has developed six congenic strains and 17 recombinant inbred strains of mice specifically to study the *Ah* gene controlling inducibility of some of the cytochrome P450 loci. Several of the cytochrome P450 loci have been cloned, but relatively little is known about the phenotypic consequences of genetic variation at these loci.

Genetic variation in response to xenobiotics

Inter-individual variation in response to drugs and other xenobiotics is widely observed in humans[11]. For example, according to the Boston Comparative Drug Surveillance Program, about 36% of hospitalized patients show adverse drug reactions. Some of this variation is due to age, health, and interactions with other xenobiotics, but a substantial fraction appears to be due to genetic factors[29]. The genetics of such adverse responses to xenobiotics has been reviewed by Kalow[53], Evans[27], Clark[13] and Nebert et al.[72,74]. Festing[29] summarised much of these data and discussed the implications of such variation for toxicity screening. About 20 Mendelian loci in humans have been associated with adverse reactions to drugs, and in some populations and racial groups the frequency of such genes can be high. For example, about 10% of Europeans are poor metabolizers of the drug debrisoquine, which is associated with adverse reactions to about 20 drugs[54]. More than 100 million people are believed to have a deficiency of glucose-6-phosphate dehydrogenase, which is associated with an adverse reaction (acute hemolysis) to the antimalarial drug Primaquine as well as the disease favism caused by an adverse reaction to eating broad beans[1].

However, the response to most xenobiotics has a more complex 'polygenic' mode of inheritance, being dependent on several genetic loci as well as on environmental factors. In humans it is usually difficult to distinguish between genetic and environmental/social factors due to the complexity of the human social environment. However, the extent to which a response is under genetic control can be studied by comparing monozygous and fraternal twins[93], by studying monozygous twins reared apart, or by comparing adopted children with their biological parents[40]. Festing[29] quotes examples of, and Vessell and Penno[93] give data on, presumed polygenic variation in response to phenacetin, ethanol, amphetamines, diphenylhydramine, diethylstilbestrol, atropine, clioquinol, aminopyrine and several other drugs in humans.

Early work on animal pharmacogenetics was reviewed by Meier[68] and Fuller and Wimmer[38]. Lush[58] reviewed the pharmacogenetics of the mouse. Fewer individual loci have been identified in laboratory mice and rats, even though the identification of Mendelian loci is technically much easier in these species than in humans[29,33]. This is probably because most toxicological studies use only a single strain of mice or rats, so that genetic variation in response is not noted. For example, Festing[34] found that

among 78 'rat' or 'mouse' papers published in *Toxicology* and *Applied Pharmacology* only six (7%) used more than a single strain. A similar survey of 119 research papers published in *Neurotoxicology* between 1986 and 1988 failed to find a single paper which had used more than one strain. The identification of genetic variation, which is most easily seen by using two or more strains of animals is an essential pre-requisite for the identification of Mendelian loci. Thus, Festing[29] only noted seven and two Mendelian loci associated with toxic response to xenobiotics in mice and rats, respectively.

However, many studies have been published which show strain differences among laboratory animals in response to a wide range of xenobiotics. Indeed, it is probably true that in a majority of studies which have used more than one strain, significant strain differences have been observed, suggesting substantial genetic variation in a wide range of responses which have yet to be analyzed in detail. Nobody has attempted a full review of such papers. Festing[31] listed about 40 studies in which strain differences in response to chemicals and physical agents such as irradiation had been observed, but only studies involving five or more strains were considered. Grasso and Hardy[41] listed more than fifty papers in their review of strain differences in the development of liver tumours in mice, a narrowly defined phenotype.

Genetic variation in neurotoxicity

There is an extensive literature on strain variation in response to pharmacologically active agents in mice and rats, all of which could potentially be classed as 'toxins' when given at an appropriately high dose. However, these mostly represent individual 'one-off' studies with little attempt being made to follow up the genetic basis or even the biochemical significance of such observations. Many of the studies relating to opioids and opioid receptors have been reviewed by Frischknecht et al.[37], and it is clear that a large proportion of papers involve a simple comparison of two strains (frequently C57BL/6 and DBA/2) which differ in behaviour, with an attempt to relate this to a biochemical difference. This can often be misleading (see below).

Most of the more detailed work such as multi-strain studies, the use of sets of recombinant inbred strains, selection, and the development of congenic strains has been reported in the genetical or pharmacological journals. As already noted, there is no tradition in toxicology of looking for genetic variation in response to toxic compounds, though there are occasional papers concerned with genetic variation in insects in response to insecticides (e.g. Bloomquist and Miller[7]). Festing[34] pointed out that the frequent use of a single, genetically undefined stock can lead to misleading generalizations, inefficient experimental design, and the neglect of a potentially powerful research tool.

In this review the term neurotoxicity is defined as an *impairment of structure or function of the nervous system.* The genetics of response to alcohol has already been extensively reviewed in this series (Sinclair et al.[86], Phillips et al.[77]) and elsewhere[39], and will only be commented on briefly here as an example of a research field in which a wide range of genetic techniques have been used. It will be compared with two other research topics (MPTP-induced Parkinson's disease, and seizures) in which different approaches have been used. The final section is a critical comment on the use of genetic methods in these three areas.

1. Parkinson's disease induced by MPTP

In 1979 a single case of parkinsonism occurred after self-administration by intravenous infusion of an illicit narcotic analgesic. This was due to an impurity which was found to be 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP). Intravenous administration in the Rhesus monkey caused the same effect[10]. The mechanisms are not well understood, but MPTP selectively destroys dopaminergic cells in the pars compacta of the substantia nigra. Mice and rats are much less sensitive than primates, and this may be due to the presence of melanin containing neurones in this region in primates, but not rodents. Lyden et al.[60] used pigmented C57BL and albino NMRI mice and, by using whole-body radiography with tritiated MPTP, they showed that it had an affinity for melanin. In eyes, the counts (dpm/mg tissue) were 979 $\pm$ 37 in pigmented mice and 127 $\pm$ 15 in albino mice, but in other tissues, including brain, which is unpigmented in rodents, the differences were less marked. This supported the suggestion that the 100-fold decrease in sensitivity of rodents to MPTP is due to absence of pigmentation in the brain, and also established the precedent of using more than one strain of mice in this field of research.

Subsequently, a number of other research workers[9,80,87] used C57BL and albino mice of another strain, and have assumed that any differences noted between the two is associated with MPTP sensitivity. For example, Riachi and Harik[80] used C57BL and CF1 mice which differ in sensitivity to MPTP and correlated this with monoamine oxidase activity in the cerebral cortex, striatum and brain microvessels. Although they concluded that there was an inverse correlation with MOA activity in brain microvessels, they apparently did not appreciate that two such mouse strains can differ in many ways which are totally unrelated to MPTP sensitivity.

Studies of this sort should be replicated across several strains, as was done by Hoskins and Davis[48] who used four pigmented and four non-pigmented (3 albino and 1 black-eyed white homozygous for W^{tox}) mouse strains to study the neurochemical correlates of MPTP sensitivity. They found that sensitivity was related to colour with the 4 pigmented strains being most sensitive. A dose that was near the LD50 for the most sensitive strain had little or

no effect on the least sensitive one. A pair of congenic strains differing at the albino locus (C57BL/10 and albino strain B10-*cc*) were also involved. However, C57BL/10 was the least sensitive coloured strain and B10-*cc* was the most sensitive albino strain, suggesting that although pigmentation is important, other genes are also involved. The extent to which this pair of strains actually differ in MPTP phenotype is not entirely clear from their paper. Ideally, future studies directed at the importance of the albino locus in determining sensitivity to MPTP should use such a pair of congenic strains, while those looking for neurochemical correlates should be replicated across several strains.

2. Seizures

At least twelve mouse mutants, including some of those which cause demyelination such as jimpy and quaking, cause seizures of various sorts[42] and the physiological/biochemical mechanisms are probably different for each mutant. However, a number of chemical and physical agents can cause seizures or convulsions in apparently normal strains of mice and rats. These include chemicals such as caffeine, chlorpromazine, meprobamate, nicotine, pentylenetetrazol, reserpine and strychnine[38], the insecticide lindane[56], and withdrawal symptoms from drugs such as alcohol[16]. Physical factors include noise, such as that causing audiogenic seizures[84], high barometric pressure[63], electric foot shocks[18] and 'kindling' or direct electrical stimulation of the brain or olfactory bulbs in mice[43]. In most studies strain DBA/2 is the prototype strain for high sensitivity, and C57BL/6 is usually insensitive, but it is not always clear whether this is due to chance, or whether DBA/2 is naturally sensitive to all agents which cause convulsions. It has sometimes been suggested that the dilute coat colour gene may be a minor modifier of seizure susceptibility, though it clearly is not a major gene for susceptibility. Dilute-lethal, another mutation at the *d* locus, is also associated with spontaneous seizures.

Deckard et al.[18] compared the sensitivity of six mouse strains to both audiogenic and electroconvulsive seizures at various ages. Strains P/J, BDP and DBA/2 were most sensitive, and C57BL and DBA/1 were least sensitive, with a strong correlation between susceptibility to audiogenic and electroconvulsive seizures, suggesting a common neural mechanism. They suggested that this may be related to levels of biogenic amines and GABA in the brains of these mouse strains, and that similar patterns of sensitivity might be observed with other convulsive agents. Jazrawi et al.[50] concluded that abnormalities of high-affinity noradrenaline uptake do not contribute to audiogenic seizures in DBA/2J mice, and Jazrawi and Horton[51] concluded that the basis of this susceptibility has not been convincingly established, though there is some evidence that it involves serotonergic (5-HT) neurones. Brain 5-HT levels are lower in DBA mice at the time of maximum sensitivity than are those of C57BL, but do not differ at 42 days when DBA are no longer sensitive. Their study shows that there was a greater density, but similar affinity of 5-HT binding sites in DBA cerebral cortex than in C57BL at the time of maximum sensitivity, but not at other times.

Fuller and Wimer[38] summarised the data on susceptibility to audiogenic and electroconvulsive seizures on the one hand, and chemicals on the other, and concluded that in general audiogenic seizure-prone strains were more sensitive to convulsive drugs than resistant ones, though response to Metrazol seemed to be an exception. However, strain differences in effective drug levels were not simple functions of seizure susceptibility. Presumably, metabolic differences as well as CNS sensitivity are important.

Seyfried and Glaser[84] used the BXD set of recombinant inbred strains as well as some *Ah* congenic strains[74] to study the genetic basis of audiogenic seizures. Susceptibility is age dependent, being maximal at about 21 days in strain DBA/2, which is no longer susceptible by 80 days. C57BL mice are mostly resistant at all ages. They considered that seizure susceptibility should be classified as a polygenic threshold character which is dependent on both genetic and environmental influences. However, the differences between these two strains seems to be due to a major gene *Iap* (now designated *aps-1*, Green[42]) with one or more modifiers. The *asp-1* locus is linked to (but not identical with) *Ah*. Among 23 BXD RI strains, with one exception, all the Ah^b strains had a lower incidence of seizures than the Ah^d strains (however, according to the most recent list published by Taylor[90], Seyfried and Glaser made two errors in the *Ah* classification of the lines, which reduces the correlation). The *Ah* congenic strains were intermediate between the parental types. However, it is not known whether the *Ah* congenic strains used by Thurmond et al.[91] still carry a foreign *asp-1* allele, or whether it has been lost by recombination. At one stage there were some problems in the development of *Ah* congenic strains which had apparently become genetically contaminated[57].

Seyfried and Glaser[84] concluded that *asp-1* was probably located on chromosome 8, 9, 17 or 19, but more recently it has been shown that the *Ah* locus, and presumably *asp-1*, are on chromosome 12[59, 78].

A very similar genetic analysis of seizures caused by high pressure was reported by McCall and Frierson[63]. Again, strain DBA/2 was sensitive and C57BL/6 was resistant; a subset of the same BXD recombinant inbred strains was used, and they concluded that sensitivity was dependent on one major and one minor genetic locus with a suggestion of linkage to the H-2 complex on chromosome 17. Unfortunately, they did not even refer to any papers on audiogenic seizures. A comparison of the strain distribution pattern of the strains common to both studies suggests that audiogenic and pressure-induced seizures are inherited independently. If this is the case, it

would be interesting to see which pattern the response to seizure-inducing chemicals follows.

In conclusion, a substantial amount of work has been done on the genetics of seizure susceptibility in mice, but there is a need for more comparative studies to show whether sensitivities to different agents are linked. If there really are identifiable loci governing sensitivity, then sets of congenic strains differing at these loci would be useful.

3. *Alcohol*

As noted above, work on the genetics of the response to alcohol has already been reviewed in this series, and only a brief discussion will be given here. As a paradigm of a genetic system it is of particular interest because of the great range of phenotypes that have been studied. These include voluntary ethanol consumption in mice, with strains C57BL and DBA/2 being the prototypes of high and low-preferring strains[25,67], and a similar response in rats[23]; ethanol-induced hypothermia[15,17,70]; acquired alcohol tolerance[70]; sensitivity to seizures after alcohol withdrawal[16]; neurosensitivity to alcohol[6]; length of alcohol narcosis[24,66]; ethanol-induced depression in cerebellar and hippocampal neurones[88] and sensitivity to fetal alcohol syndrome[81].

Extensive use has been made of genetic techniques including comparisons between inbred strains, the use of recombinant inbred strains, and chimeras between strains differing in alcohol preferences[76]. However, the use of selected strains has been particularly popular. The AA and ANA rat lines[86] and the SS and LS mouse lines[66] are the prototypes, though several other sets have been developed[77]. An important feature of these lines is that they were developed according to well established principles of quantitative genetics[64]. Selection was usually initiated from a synthesised heterogeneous base population, and inbreeding was avoided. In most cases bi-directional selection was used, and in some cases selection was replicated (e.g. Crabbe et al.[15]). Under these circumstances the gene frequency should only change at those loci associated with the selection criterion, and any observed, correlated responses should involve a true genetic association between traits. Thus, a search for correlated responses in these two lines (e.g. Erwin et al.[26] who concluded that the LS and SS mice differed in neural processes activated by specific muscarinic agonists) has more chance of leading to valid conclusions than if two selected inbred strains had been used. In contrast, at least 13 strains of rats have been developed for research on hypertension, but they have all been developed from a relatively narrow base population by selection with simultaneous brother × sister inbreeding (see de Jong[22] for a review). One result is that differences between strains may be due either to selection or chance fixation, and there is no suitable control strain. For example, strain WKY, which is often used as a control strain for the hypertensive strain SHR, differs from it at many electrophoretic loci[30].

The observation that the LS and SS mouse strains differ not in the rate of metabolism, but rather in neural sensitivity was not predicted, and is clearly of immense interest and importance. The fact that these strains appear to differ in their response to many, but not all anaesthetics and other neurotropic drugs suggests that they will be of value in studies of drugs other than alcohol.

In humans there is a well characterised Mendelian polymorphism involving an atypical aldehyde dehydrogenase enzyme which is associated with facial flushing when alcohol is consumed[52]. The gene frequency varies between racial groups, being particularly high in the Mongoloid races. There is some evidence that the resulting unpleasant reactions help to protect carriers from alcoholism[39].

In contrast, in laboratory animals all the phenotypic effects appear to be under polygenic control. Although there is extensive genetic polymorphism for alcohol and aldehyde dehydrogenase and aldehyde oxidase enzymes in mice, so far this appears to be uncorrelated with any known phenotypic effect[46,47].

Critical discussion

Any geneticist who surveys the literature on genetic effects in neurotoxicity must be struck by the almost total failure of toxicologists to take account of genetic variability either as a potential confounding variable, or as a research tool. Cox[14] stated that a well designed experiment should be unbiased, have high precision, have a wide range of applicability, should be simple, and should make provision for the calculation of uncertainty. Failure to take account of genetic variation means that most animal experiments in toxicology can be criticised on at least two of these grounds.

McClearn et al.[65] showed that heterogeneous stock mice were more variable than inbred strains for all behaviour characteristics tested. Jay[49] showed that the standard deviation of barbiturate sleeping time among five inbred mouse strains was 2–4 minutes, while in two outbred stocks it was 12–15 minutes. Variability of experimental material leads to low statistical precision. Thus, Festing[34] has shown that using Jay's data, and assuming that on average inbred mice are as sensitive to an experimental treatment as outbred ones, an experiment to detect a 10% change in sleeping time using a 1% significance level and a power of 90% would require 27 inbred mice per group, or 290 outbred mice per group. Alternatively, if only 20 mice per group were available, there would be a 12% chance of detecting a 10% change in the mean using the outbred mice, and an 87% chance using inbred ones. Thus, the widespread use of outbred animals in neurotoxicology must lead to experiments with low statistical precision.

Failure by most toxicologists to use more than a single strain means that the generality of the experimental results over a range of genotypes is never tested. This must be partly responsible for the lack of repeatability of many experiments in which subtle effects of toxic agents are explored. However, an even more important consequence is that they fail to use genetic variation as a research tool. Anyone reading the literature on genetic variation in response to alcohol must be struck by the great value of the AA and ANA, or SS and LS, selected strains.

The original aim of this review was to consider genetic variation in response to some of the compounds of particular interest to neurotoxicologists. Lead, for example, is known to be highly toxic when absorbed at high levels, and to produce more subtle effects, such as poor learning ability in children, at lower levels [12]. However, although there are numerous scientific papers on the neurotoxicity of lead, it has proved to be impossible to find any in the recent literature in which more than one strain has been used. According to Mailman and Lewis [62], 'The effects of small doses of lead on CNS development have been difficult to quantify or study mechanistically', and Hammond et al. [14] note that '...the response of individual animals is extremely variable, both as to the pattern of lead build-up and as to the degree of exposure'. In discussing this variability, they make no mention of any possible effect of using genetically variable experimental rats.

Similarly, Shellenberger [85] in reviewing the effects of lead on neurotransmitter systems noted that 'Reports of effects are highly variable and many observations lack confirmation by other laboratories or have not been replicated', yet again no account is taken of the fact that different workers use different strains of rats, and the importance of strain differences was not considered. Possibly, genetic factors in response are unimportant. This seems unlikely, however, as low levels of lead in the diet increase voluntary ethanol consumption [71], and it seems unlikely that such an effect would not interact in any way with known genetically-determined voluntary alcohol intake.

The studies of genetic variation in response to MPTP are of value because genetic methods were used to test a simple hypothesis, namely that the low sensitivity of mice and rats compared with humans could be attributed to the presence of melanin in the brain of humans. Most of the work can be criticised on the grounds that the research workers obtained C57BL mice and albino mice of another strain, and called these 'black' mice and 'white' mice, with the implicit assumption that the only difference between them was colour. However, the study by Hoskins and Davis [48] involving eight strains, two of which were congenic for pigmentation, tended to give some support for the over-all hypothesis, while suggesting that other genes were important.

The work on genetic variation in seizure sensitivity represents a much higher level of sophistication. Study of inbred strains and sets of recombinant inbred strains suggested that both audiogenic and pressure-induced seizure sensitivity depended on one major gene with modifiers, and in the case of audiogenic seizures the gene has been mapped to chromosome 12. However, much of the neurochemical work in this field continues to use DBA/2 and C57BL/6 as sensitive and resistant strains, respectively, with the dangerous assumption that observed differences are related to sensitivity. What is really needed now is for someone to pull this area of research together. The first step would be to produce some congenic strains by backcrossing *asp-1* alleles to DBA/2 and C57BL/6 inbred strains. Once these were available, it would be easy to determine whether the locus also controls sensitivity to other types of seizures, and the strains would also be much safer for studying the neurochemical correlates.

Finally, the work on alcohol probably already represents the largest, coherent body of work in pharmacogenetics that has yet been published. Several active research groups are involved, and a large number of strains have been developed by selection as research tools. The selection experiments have been well designed, according to principles of quantitative genetics.

However, these workers will need to give some thought to the future. Selected strains are powerful tools for looking at correlated responses, but they are of no value for the isolation of individual loci. The aim of much of modern genetics is to identify individual genetic loci controlling susceptibility to complex diseases. Any person who could clone a gene for alcoholism would be assured of a place in the history books. There may not be such a gene. At present, sensitivity to alcohol seems to be controlled by many genes, each with a small effect. However, that may be partly due to the use of selection as a means of studying it, and partly because no serious attempt has yet been made to tease out individual loci. The dissection of the component genes of a polygenic character is one of the major challenges of the future. In a few cases substantial progress has been made. For example, time to reject a skin allograft is a typical polygenic character, dependent on several loci and environmental influences. Yet, many of the individual major and minor histocompatibility genes have been isolated using suitable backcrossing programs [3].

The set of recombinant inbred strains produced from the LS and SS lines may provide more powerful tools for genetic and biochemical analysis [19], though it is difficult to see how they could be used to isolate individual loci. The approach used by Holmes [47] of looking at Mendelian loci concerned with alcohol metabolism should prove profitable, but differences in neural sensitivity, rather than metabolic rate, seem to be of critical importance, and it is not immediately apparent which loci should be studied. Other possible approaches have been outlined by Festing and Blackwell [35] and Festing [32]. They might involve the use of sets of recombinant con-

genic strains[21] or examination of differences among existing congenic strains. Bailey[4,5] used this approach with some success to study genes that affect the shape of the murine mandible. Another approach is to search for mutations. These are often found as subline differences among inbred strains. For example, Moisset[69] reported that a mutation appeared to have occurred in BALB/cJ mice changing them from highly sensitive to highly resistant to ethanol. The BALB/cJ strain is known to differ in a number of ways from other substrains of BALB/c[79]. The use of transgenic strains[83] should also be considered. Such strains are already having considerable impact in certain types of research.

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Genetic and environmental influences on reactive and spontaneous locomotor activities in rats

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Abstract. Paired groups of rats (derived from divergent, selective breeding or living in divergent environmental conditions) were compared with regard to locomotor activities. Intrapair differences were found to vary non-systematically, depending upon whether the rats were initially exposed to a test-environment with or without a slight environmental modification (reactive activities), or were allowed to habituate extensively to the environment (spontaneous activity). Since the behavioral patterns were found to represent distinct entities, this pointed to the necessity of differentiating clearly between spontaneous and reactive activities and indicated, once again, that both genetic and environmental influences are important in these behaviors and must be taken into account. Accepting and controlling for these variables makes it possible to use the factor of individual differences in laboratory animal behavior to advantage.
Key words. Locomotor activity; RHA vs RLA rats; SHR vs WKY rats; Fawn hooded rats; Wistar rats; individual housing; selective breeding; spontaneous activity; reactive activity.

Individuality is an accepted characteristic of human beings; that is, it is accepted that each individual's physiological and behavioral responses are different, depending upon his or her genetic background and prior experience. Even in domestic animals (e.g. dogs, cows, etc.) the importance of both genetic and environmental influences is appreciated and accepted. In contrast, where laboratory animals are concerned, scientific communications of otherwise high quality often contain such sentences as 'normal rats were used' or 'studies were carried out in albino mice'– ignoring, in particular, the potential importance that the genetic background of the subjects used could have for the experiments in question [5, 13]. This is especially true for pharmacological and toxicological studies on laboratory animals, in which it has been demonstrated on many occasions that the action of any drug clearly depends upon the animals's genetic background, age, sex and previous experience, as well as upon the time of day and other environmental considerations.

As most animal studies aim to improve our understanding of physiological and pathophysiological processes in humans, we feel that individuality in animals should be accepted and accounted for. In other words, such factors as 'genetic predisposition', 'transcultural differences' and 'life events' should also be recognized in studies on experimental animals. The advantage of animal studies, of course, as compared to human studies, is that one can profit from the shorter generation-time involved, as well as take advantage of being able to control the genetic and environmental circumstances. Furthermore, the additional knowledge gained about genetic and environmental influences on an animal's physiology and/or behavior could help to clarify further the enormous influence of these factors in humans. Keeping these goals in mind, the present review will be devoted to a description of several aspects of locomotor activity in rats, a behavioral parameter which has been extensively studied in this laboratory for several years.

Terminology

The determination of locomotor activity is probably one of the most frequent behavioral measurements in experimental animals, as sophisticated equipment is not a necessary prerequisite. In addition, locomotor activity has proven to be very susceptible to the influence of drugs as well as to genetic and environmental manipulations. However, in behavioral studies, and especially those concerned with locomotor behavior, superficial, and often misleading, terminologies are frequently encountered. 'Activity' or 'locomotor activity' in experimental animals, or 'differences in activity' between distinct groups of animals, have frequently been reported without any detailed information on the nature of the behavioral act. In order to avoid these linguistic problems, we would propose that non-specific terms such as 'activity' or 'locomotor activity' should always be properly defined and used, if at all, with much reservation.

We would define the term 'locomotor activity' as the sum of all horizontal movements of an animal's body from its present position to an adjacent area of its surroundings. Distinct types of locomotor activity can be differentiated,