A MOUSE IS NOT JUST A MOUSE

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Abstract   *Animal Welfare 2000, 9: 193-205*

In this paper we describe the existence and consequences of subspecific and individual variation in the genetic make-up of house mice. The purpose is to illustrate forms of variation that are often neglected in discussions about animal care and experimental design. Towards this end, different inbred mouse strains as well as genetically selected mouse lines are compared in relation to their ecological origin. Firstly, the behaviour of BALB/c, C57BL/6J and CBA mice is described in relation to different habitats. Furthermore, their aggression is compared, as measured by two paradigms. It appears that some inbred lines (eg BALB/c and C57BL/6J) clearly show behaviour that reflects the functional adaptation to the natural habitats in which their ancestors lived. Other strains (eg CBA) show a lack of such behavioural adaptation and their phenotypes appear to be very unstable over time. Secondly, two fundamentally different characters, both present in populations of wild house mice and under genetic control, are described: on the one hand, active copers are characterized by aggressive behaviour; on the other hand, passive copers are reluctant to attack. The active, aggressive animals (manipulators) are well adapted to an invariant environment like their own territory, whereas the passive, non-aggressive copers (adjustors) are well adapted to a changing environment, eg when roaming. We discuss to what extent these coping styles are present in laboratory strains of mice. The major conclusion with regard to both phenomena is that individual and subspecific variation may have significant implications for experimental design and the welfare of the experimental animals.

Keywords: *aggression, animal welfare, behaviour, genetics, inbred lines, mouse*

Introduction

The aim of this paper is to illustrate the importance of genetic variation in animal care and experimental design. This may seem very obvious to the researcher who is well informed about the biology of the experimental animal. However, it is our experience that a significant number of researchers, albeit declining in number, are not well enough educated about this topic – especially those who are working with laboratory animals. This angle is new to the extent that, although species-specific behavioural programmes are attracting more and more attention (see Van Zutphen *et al* [1993] p 76), variation within a species has often been neglected, particularly in the context of experimental design and housing.

To illustrate our point, we will both review previous work and present new findings on the behaviour of different (genetically defined) strains and lines (all belonging to the house mouse, *Mus musculus domesticus*). Firstly, the historical and ecological origin of a number of inbred strains will be compared. Secondly, attention will be paid to individual behavioural variation in a feral population of wild house mice. We hope to convince the reader that not only does the choice of strain have great implications for the outcome of experiments, but sometimes also the choice of individual animals. This may have significance for the welfare of mice (and other animals) kept in the laboratory.

Subspeciation

All living creatures show adaptations to the environment (habitat) in which they live in the wild. If their ancestors have been living in a specific habitat for a long time, the adaptations will, to a certain extent, be fixed in the genes as a result of natural selection: this is often called a co-adaptational gene complex. This is reflected in the construction of the animals' bodies, their physiology and their behaviour. However, not all individuals within a certain species are alike. Different environmental influences during individual development cause variation, as do genetic factors. Populations have sometimes been so spatially separated that natural selection has driven their gene pools in different directions, resulting in the formation of subspecies. In extreme cases, subspecies are no longer capable of interbreeding, something nicely demonstrated in so called 'circular overlap' situations. A chain of overlapping subspecies form a loop in which the terminal links have become sympatric, with no (or difficult) interbreeding between them, as if they had become different species. For example, the dispersion of the great tit (*Parus major*) went from eastern China over the south of Asia to Europe and continued via the northern part of Asia back into China, where the northern subspecies now overlaps with the southern one, although the species does not occupy the central part of Asia. The sympatric Chinese subspecies act very much as if they were different species (Mayer 1963).

Subspeciation is also clearly present in the house mouse. As far as can be determined from molecular studies on genetic variation, this species originated in the north of the Indian subcontinent (Boursot *et al* 1996; Din *et al* 1996). From there it has conquered the world as a commensal of man, resulting in a multitude of subspecies (Marshall & Sage 1981). A fine example is the Robertsonian races found in the valleys of Italy and Switzerland, which differ in their number of chromosomes and are unable to interbreed any more (see, among others, Thaler *et al* [1981]; Nachman *et al* [1994]).

History of laboratory mice

Mice have long been bred by man (Festing & Lovell 1981; Morse III 1981). Until the end of the 19th century they were mainly kept as fancy animals. They were selected for colour and 'funny' mutational variations, like the 'dancing mice'. At the beginning of the 20th century, these fancy mice were taken into laboratories, initially for cancer research. Most colonies, whether intentionally or not, became inbred. Sometimes specific characteristics, like tumour resistance, sensitivity to seizures, alcohol preference and maze performance were deliberately selected. Nevertheless, those characteristics that made them fit for general laboratory conditions were in all cases 'naturally selected for' (as described, for instance, by Bittner [1941]). By now, their basic biology is generally believed to be adapted to such conditions and to be more or less similar for all mice. The most frequently described biological features are the consequence of these conditions and of accessory husbandry (Van

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Zutphen *et al* 1993 ch 3). Most of the strain differences are thought to be caused by founder effects, genetic drift and selection for specific features. However, these differences may also express relics of adaptations to the habitats in which their wild ancestors dwelled, as will become apparent when behavioural differences between mice of three different inbred lines (BALB/c, C57BL/6J and CBA) are compared.

Generally, not much is known about the natural origin of most laboratory strains. However, we do have some knowledge of the origin of the previously mentioned strains (Morse III 1981). C57BL/6J mice originate from a Miss Lathrop, a mouse fancier, who kept a variety of mice from different parts of the world on a mouse farm in Granby, Massachusetts (USA) from 1903 to 1915. BALB/c mice were taken into the laboratory by a Dr Bagg, who bought the mice from an animal dealer in Ohio, USA in 1913. Since these mice were albinos, they were called Bagg albinos (BALB for short). Similar variation in allozymic and mitochondrial DNA indicates that the Lathrop and Bagg mice may be descended from the same gene pool. However, this does not by definition exclude the presence of genetic variation. On the contrary, because of their distinct origins, it is likely that their wild ancestors dwelled in quite different habitats and developed quite different functional adaptations (eg Lynch [1992]). If so, it is plausible that genetic variation still exists that differentially affects their adaptative qualities.

Some inbred strains are the result of a cross between two other inbred strains. Accordingly, such a strain is not original in the sense described above. For instance, CBA mice were bred by a Dr Strong in 1921. He crossed two 'original' strains, namely BALB/c and DBA, the latter strain being in use in genetic studies on coat colours at Cold Spring Harbour, USA.

A comparison of strains: BALB/c vs C57BL/6J
Biotope preferences – a review
A functional and comparative study on the complete behaviour of BALB/c and C57BL/6J mice showed a clear-cut and strain-dependent preference for specific habitats, most probably the ones their ancestors inhabited in the wild. There is no other way to explain the coherent way in which these strains were found to differ in all aspects of their behaviour, once they were given the opportunity to show their specific skills. The strains differed neither in the behavioural elements they used, nor in their general activity (ie all elements taken together). However, the frequencies with which they demonstrated each behavioural element were completely different and served different functions (Van Oortmerssen 1971).

BALB/c mice seem to be adapted to living on the surface. Their exploratory behaviour is mainly directed towards open space. Although they sometimes dig, they never succeed in making proper holes. They are, however, skilled at making beautiful spherical sleeping nests, which do not require the support of any wall, as they fray their nesting material so that it holds together. C57BL/6J mice seem to be hole-dwelling animals that make proper holes, even in a very difficult substrate like loose peat dust. They line the walls of these holes with nesting material which is not prepared in the specific way of the BALB/c mice. Their exploratory behaviour is mainly directed at the substrate (for more details regarding biotope preferences see Van Oortmerssen [1971]). In this respect, it is worth mentioning that nesting behaviour shows substantial heritability and also adaptive variation: mice originating from the northeast coast of the USA build larger nests than those from the southeast (Lynch 1992).

Accordingly, when given an experimental choice between living on the surface and living underground, BALB/c animals settled on the surface, whereas C57BL/6J preferred living underground (see Figure 1). For detailed descriptions, see Van Oortmerssen (1971).
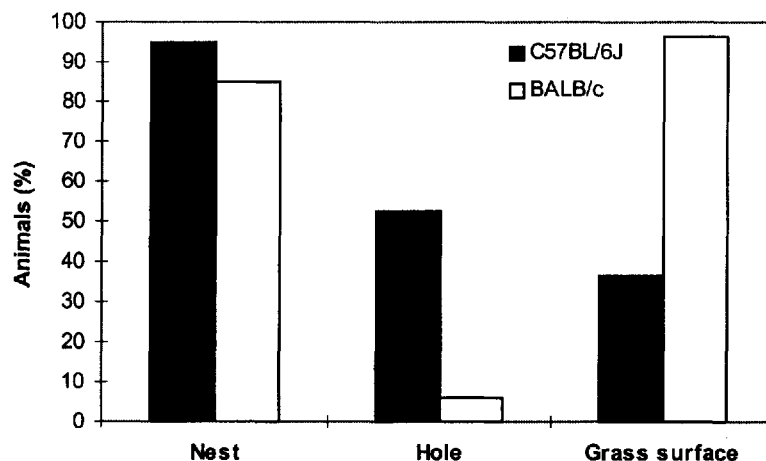

Figure 1   **Biotope preferences in two inbred strains of mice (C57BL/6J and BALB/c). The variable 'Nest' represents the percentage of animals actually building at least one nest. 'Hole' denotes the percentage of those animals building nests in a hole, whereas 'Grass surface' represents the percentage of animals building nests on a grass surface. For more details, see Van Oortmerssen (1971).**

Performance in intermale aggressive behaviour tests

We conducted a series of experiments to compare aggressive responses of BALB/c and C57BL/6J mice under various conditions, as described below. All experiments were performed in accordance with national laws and institutional guidelines.

Subjects

All mice were obtained from Charles River (Japan) and housed in Plexiglas cages (42x27x17 cm) in a room with an artificial 12:12 light:dark cycle (lights on at 0600h). Food (standard laboratory chow; Hope Farms AM2) and water were available *ad libitum*. At the age of 49 days, each male was paired with one female of the same genotype. Starting on day 67, males were tested in the neutral cage paradigm on 3 consecutive days. On day 94, males were separated from their female cagemates; 10 days later they were tested in the resident:intruder test. Seventeen C57BL/6J and 16 BALB/c males were used.

Behavioural testing

Aggression was tested in two different situations: a neutral cage and a resident:intruder paradigm. In both tests, an A/J//Orl male of the same age as the test animal was used as a standard opponent. This strain was chosen because of its low propensity to attack (Carlier & Roubertoux 1986). Standard opponents were used up to once day^{-1}. In neither test did any opponent show any attack behaviour. The neutral cage paradigm employed here has been described in detail by Carlier and Roubertoux (1986) and Roubertoux and Carlier (1988).

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The test was performed in a transparent Makrolon® cage (42x26x18 cm; Bayer, Germany) with a transparent lid. Animals were tested on 3 consecutive days. The floor of the test cage was covered with sawdust from the cages of the different genotypes. This procedure is known to accelerate the appearance of the first attack but has no effect on the proportion of males exhibiting at least one attack (Carlier & Roubertoux 1986). The experimental animal was placed in the test cage and allowed to habituate for 2min, after which a standard opponent was carefully placed in the corner of the test cage. Observations started when the experimental animal sniffed the opponent for the first time and lasted 6min if no aggressive acts took place. The experiment was immediately terminated after the first attack by the experimental animal, thereby minimizing the risk of injury to the standard opponent.

For the resident:intruder paradigm, animals were isolated for 10 days before the actual testing. The rationale of this test has been explained elsewhere (see, among others, Maxson [1992]). Standard opponents were cautiously put in the corner of the home cage of the animal to be tested. The rest of the procedure was identical to that followed for the neutral cage test except for the maximum duration of the test (10min).

The variable that we present here is the percentage of non-attacking males, a parameter shown to be a reliable index of aggression (Carlier & Roubertoux 1986; Roubertoux & Carlier 1988).

Results

The results show that, in the neutral cage paradigm, neither BALB/c nor C57BL/6J males attacked on the first test day. This remained the same for C57BL/6J males, resulting in no aggressive acts on any of the 3 consecutive days for the 17 males. BALB/c males, though, did show aggressive behaviour on the later days: 7 out of 16 males attacked on the third test day (Figure 2).

The results in the resident:intruder paradigm confirmed these findings (see Figure 3). However, both strains had significantly fewer non-attacking males in this paradigm, which is in line with previous studies (see, among others, Sluyter *et al* [1999]). Furthermore, these data strongly indicate the importance of different test procedures (eg neutral cage vs resident:intruder; 1 test day vs multiple consecutive days).
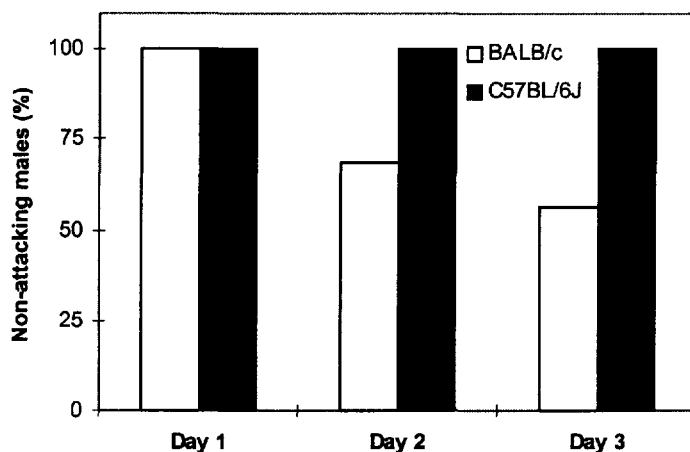

Figure 2   **Percentage of non-attacking males of BALB/c and C57BL/6J strains on 3 consecutive days in the neutral cage paradigm.**
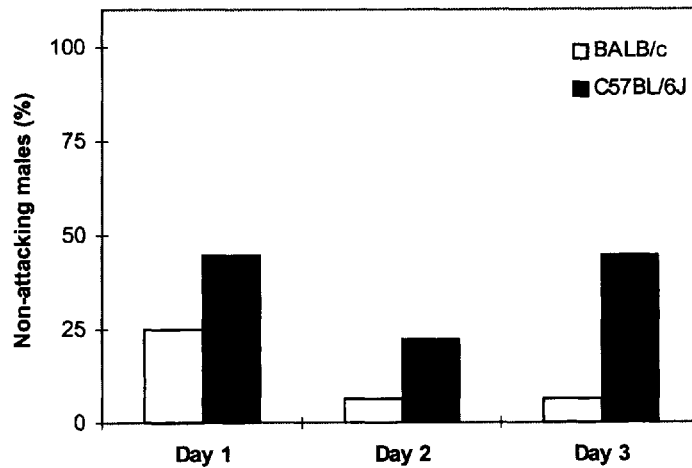
Figure 3 **Percentage of non-attacking males of BALB/c and C57BL/6J strains on 3 consecutive days in the resident:intruder test.**

Discussion
Our neutral cage test results are in agreement with previous studies. C57BL/6J males rarely show aggressive behaviour in this type of test (unless over food when hungry, see Van Oortmerssen [1971]). Guillot *et al* (1994), using a similar paradigm and also the same genotype as the standard opponent here, found that only 1 of 20 C57BL/6J males attacked. Using a different standard opponent (DBA/2), Sluyter *et al* (1999) also observed a low percentage of attacking males. Among BALB/c mice, Guillot *et al* (1994) showed that 40 per cent attacked, a number close to what we found on the third day (44%).

Conclusions regarding the BALB/c and C57BL/6J comparisons
The outcomes of the biotope preference and aggression tests are characteristic for these strains and confirm the concept of a functional ancestral adaptation to different habitats. BALB/c males are territorial and rather aggressive, which seems to be in agreement with their habitat preference. It is more difficult to defend a territory on the surface than underground because of the larger boundaries. In addition, they have a relatively elaborate courtship, necessary to overcome the individual aversion that results from their being aggressive animals. In contrast, C57BL/6J mice seem to be gregarious animals which, although they regularly quarrel, rarely show fierce aggression like BALB/c mice and do not have any courtship. Their sexual behaviour is characterized by speed and their mating behaviour seems to contain only mounting efforts, taking into account neither the gender nor whether females are in heat (Van Oortmerssen 1971). For a comparison of the variation in sexual behaviour, see McGill (1962).

CBA mice: a different story

Van Oortmerssen (1971) reported that CBA mice, which are the result of an initial cross between inbred strains, behave quite differently from BALB/c and C57BL/6J mice in the biotope preference test. Although they show all the behavioural elements characteristic for mice and although they demonstrate similar general activities to BALB/c and C57BL/6J

mice, they nonetheless lack behavioural organization, which is most clearly demonstrated in their nest-building behaviour.

When given the opportunity to build nests and to dig holes, these animals often started digging. However, this digging was never directed at a specific place, resulting in all the substrate being messed up but no hole. This uncoordinated digging was accompanied by carrying nesting material. However, a picture similar to the digging appeared: there was no specific place to take the material to, the nesting material was bitten to pieces and no longer suitable as nesting material. The fraying lacked the fine coordination seen in BALB/c mice. When an individual CBA mouse had a spot where it slept regularly (sleeping nest), this was nothing more than a shallow pit with some small pieces of nesting material scattered in it. A similar lack of coordination was also detected in the social behaviour of these mice.

Consequences of strain-specific behaviour

Most people are not aware of the fact that a number of inbred strains still show behavioural complexes that reflect functional adaptations to specific habitats. Behaviour so well adapted to specific habitats cannot have been learned and is still fully present after many generations of inbreeding in the laboratory. This means that these skills have a genetic basis (present in so-called adaptational gene complexes) and their expression is triggered by the proper environmental stimuli. In theory, these features may also affect the specific laboratory demands of each strain, eg to optimize their welfare, BALB/c mice would need bedding material preferably covered with grass for their nests, whereas C57BL/6Js would need to have the opportunity to dig holes and, therefore, require different types of cages. Of course, we realize the hypothetical nature of these suggestions and reluctantly accept the fact that there are limits to spacial, financial and human resources. Also, we realize that no substantial evidence has been presented that the welfare of the animals is compromised if these facilities are not available. However, it is essential for the people involved in animal care and research to gain as much knowledge as possible about the biology of experimental animals and to be aware of how inbred strains of mice react differently to environmental situations as a result of their ancestral history (for an extensive review of the biology of the mouse, see Berry and Bronson [1992]). If not, the welfare of the animals, as well as the integrity of any experimental design, could risk being seriously compromised.

The typical behavioural disorganization in CBA mice is likely to be a reflection of the physiology behind it. That the F1 progeny of crosses between two lines or (sub)species often show a large variance in behavioural characters is a well-known phenomenon in behavioural genetics, and is sometimes indicated as the Tryon effect (see Caspari [1958]). It has been found in dog aggression (Scott 1964) as well as house mice (see below). Therefore, scientists should consider the potential for these kinds of variation in all F1 animals or laboratory strains resulting from a cross between two original strains or subspecies, and should consider that this variation could induce phenomena that may influence the welfare of animals used for research, as well as the results of research using those animals.

Behavioural strategies of wild house mice: manipulators and adjustors

Differences in the expression of various biological aspects are not limited to interstrain variation, but also exist within one population. A nice illustration of this individual variation is the idiosyncrasy found in populations of wild house mice.

A study of wild mice in western Europe under natural and semi-natural conditions revealed a new aspect of mouse biology, namely the existence of disruptive natural selection

(Van Oortmerssen & Busser 1988). This is brought about by most wild mice living roaming lives, and only a very small number dwelling within territorial families, or demes. By screening a number of metapopulations, Van Zegeren (1980) found that some of the males of such a population showed a high readiness to attack (short attack latency – SAL) when confronted with another male in a resident:intruder paradigm, whereas others showed only a long attack latency (LAL) or did not attack at all (see Figure 4).
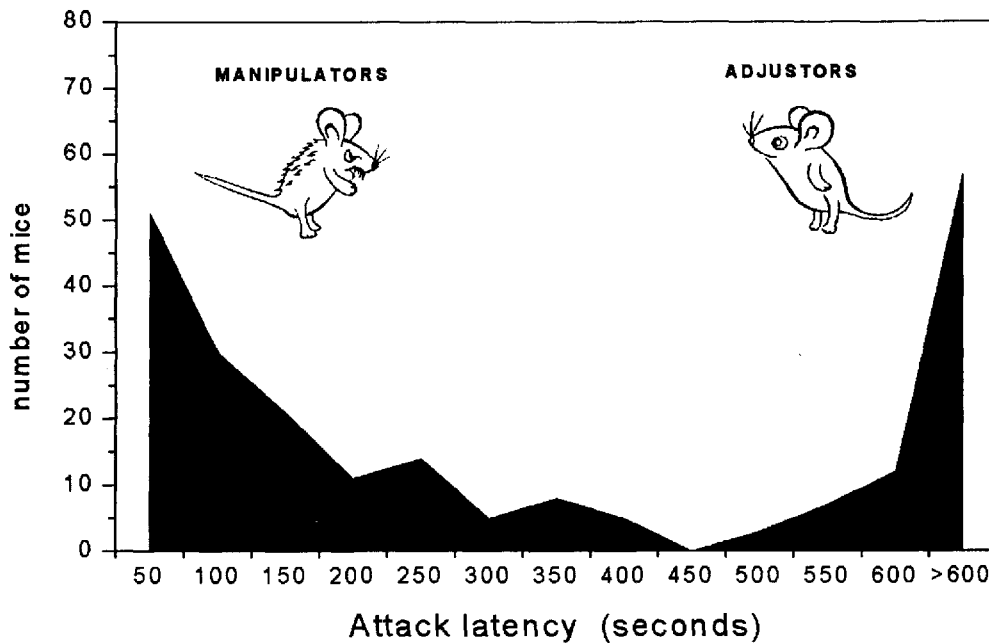

Figure 4   **Bimodal distribution of attack latency scores in wild house mice. For more details, see Van Zegeren (1980).**

This dichotomy is due to the fact that within a deme natural selection favours high aggressiveness whereas outside the demes the non-aggressive types have more advantage (Van Zegeren 1980).

Because of this genetic variation in wild house mice, it has been possible to artificially select for the two types of mice. This resulted in the development of bi-directional selection lines for attack latency, ie offensive aggressive behaviour: i) aggressive animals, characterized by SALs; and ii) non-aggressive animals, characterized by LALs (Van Oortmerssen & Bakker 1981). Further research on SALs and LALs revealed that the difference in aggression is only part of a much more complex difference, related to many aspects of behaviour, that determines how an animal copes with changes in its environment (Benus *et al* 1991). The aggressive (SAL) mice turned out to be active copers (manipulators) which reacted to changes in their environment by manipulative behaviour (of which aggression is a part). They often acted in a very routine manner, often irrespective of details in the environment. Such behaviour makes them best suited to a well-known environment like their own territory (deme).

The non-aggressive (LAL) mice, on the contrary, are passive copers (adjustors) whose behaviour is affected by small changes in the environment (Benus *et al* 1987). While manipulators try to alter the environment to meet their demands, adjustors try to fit into a changing environment. Many additional experiments on these mice have revealed fundamental differences between them. SAL males show more thermoregulatory nest-building behaviour than LAL ones (Sluyter *et al* 1995b); they are also less flexible in social and non-social situations (Benus *et al* 1990). They differ in their physiology, with SAL males having higher plasma testosterone levels than LAL males (Van Oortmerssen *et al* 1987, 1992). Moreover, they vary in their neuroanatomy (Sluyter *et al* 1994), pharmacological reactivity (Benus *et al* 1991; Sluyter *et al* 1995a) and sensitivity to pathogenic influences (Koolhaas & Van Oortmerssen 1988).

Research on this fundamental aspect of rodent populations is now being expanded to include individual variation in a colony of wild rats (Koolhaas *et al* 1999). In wild house mice, SAL mice show more active behaviour than LAL ones when challenged in the shock probe/defensive burying test (Sluyter *et al* 1996). In this test, animals were shocked with an electrified probe. They could then use either an active behavioural strategy, ie pushing bedding material towards or over the probe (defensive burying), or a passive strategy, ie increased immobility or freezing, to cope with the stressor. It appears that the same bimodal distribution also exists in wild rats, with active rats characterized by defensive burying and passive rats characterized by immobility (see, among others, Korte *et al* [1992]; Scoifo *et al* [1996]).

Behavioural strategies in the laboratory

The existence of two fundamentally different behavioural strategies is not limited to wild rodent populations, but is also found in laboratory strains. For example, two sets of rat lines (one bi-directionally selected for susceptibility to apomorphine, the other for two-way active shock avoidance) show contrasting behaviour that is quite similar to that seen in the mouse lines selected for attack latency (Driscoll & Bättig 1982; Cools *et al* 1990). Both sets of lines in these studies were selected from an outbred Wistar rat population, which strongly suggests the existence of two fundamentally different, heritable characters in the laboratory too. One may put different labels on the nature of these characters, like emotionality or emotional reaction (Driscoll & Bättig 1982; Brush 1991), differential use of internal and external information (Cools *et al* 1990), aggressive and timid (eg Krsiak & Sulcova [1990]), active and passive (Bohus *et al* 1987; Benus *et al* 1991), or proactive and reactive (Koolhaas *et al* 1999). The fact is that a basic bimodal distribution remains in wild as well as laboratory rodent populations. There may be some quantitative differences between the different sets of strains, though. Laboratory practice in general will have excluded animals with short attack latencies, as animal caretakers do not like to be bitten frequently, especially not by larger rodents. This means that the chance of finding 'true SAL-like' manipulators among them is probably small. Therefore, the outbred rat populations (eg different Wistars), from which the previously mentioned selection lines were developed, are likely to consist of adjustors.

As for the effects of inbreeding on these strain- or line-specific behavioural idiosyncratic phenomena, we can offer only a hypothesis at this moment. Data from the SAL line indicate that the genes for short attack latencies have been fixed by selection and inbreeding (Van Oortmerssen unpublished data). This line is stable, showing very little variation, which also applies to a subline that has been kept 'loose' from generation 14 onwards (ie with no selection). However, the LAL line remains variable, even after 33 generations of selection. It

is probably heterozygous, as some SAL types appear in every generation. In addition, the LAL mice that never attack ('true adjustors') appear to be nearly all infertile, and those that are fertile gradually become more manipulator-like in time, and also show large individual variation with respect to this age effect. Since, in the past, 'SAL-like' and 'infertile LAL-like' animals would have been excluded from breeding, the present inbred lines may have become fixed for alleles that code for 'gradually becoming more manipulator-like'. Accordingly, laboratory strains (at least those descended from the western European house mouse) may have fast, slow or intermediate 'turn-overs', depending on which alleles have been lost by inbreeding. More research is still needed to know what is left of the coping strategies found in the wild. Nevertheless, it is worthwhile realizing that these phenomena play a fundamental role in the 'total' biology of distinct inbred lines.

Also striking is the fact that bimodal distributions are not only found in different lines and (sub)strains of rodents, but also in different species. Studies on juvenile male great tits have shown that these birds differ consistently in their early exploratory behaviour and can be classified as fast and superficial or slow and thorough explorers (Verbeek et al 1994). In addition, fast explorers start and win more fights than slow ones (Verbeek et al 1996). Similar patterns of divergent responses have also been observed in goats (Lyons et al 1988) and pigs (Hessing et al 1994).

Animal welfare implications

The aim of this paper was to show that individual mice are genetically different in several ways. On the one hand, we have compared the behaviour of some inbred strains in relation to their ecological origin; on the other hand we have compared the two types of characters present in a population of wild house mice. We suggest that intraspecific and inter-individual variation, whether the result of distinct functional adaptations between populations (eg BALB/c and C57BL/6J mice), or the product of disruptive natural selection within populations (eg SAL and LAL), will inevitably affect the outcome of experiments. Therefore, we strongly advise that researchers become acquainted with the biology of their particular experimental animals and include this knowledge in husbandry and experimental design. If not, they run the risk of poorly serving the animals' welfare as well as poorly designing the experiment because the animals are being kept under sub-optimal conditions. This, in turn, may lead to the use of more animals than would otherwise be necessary.

Intraspecific and inter-individual variation are important and affect the design of animal experiments as well as the animals' welfare. To illustrate our point, we would like to sharpen the words from Van Zutphen et al (1993) in Principles of Laboratory Animal Science (p 80) by replacing 'species' with 'subspecies' or, even better, 'individuals': '[Individuals] have specific programmes... [of which] ...certain components cannot be omitted without there being consequences for the animal. A good housing system should therefore suit the [individual]-specific behaviour programmes of the animals'.

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