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Review

A new animal welfare concept based on allostasis

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Abstract

Animal welfare is an increasing issue of public concern and debate. As a result, many countries are reconsidering the way animal welfare is embedded in the legislation and rules for housing and care of animals. This requires general agreement of what animal welfare is. Unfortunately, the current science of animal welfare is less scientific than what has been claimed. In our view, it is overly guided by anthropocentric thinking about how animals ought to be handled and neglects the latest concept of physiology: 'The Allostasis Concept'. Allostasis, which means stability through change, has the potential to replace homeostasis as the core model of physiological regulation. Not constancy or freedoms, but capacity to change is crucial to good physical and mental health and good animal welfare. Therefore, not homeostasis but allostasis is at the basis of our new animal welfare concept. This paper is aimed at a broader scientific discussion of animal welfare that includes knowledge from the latest scientific developments in neurobiology and behavioral physiology, and generates views that are extremely relevant for the animal welfare discussion.

Keywords: Animal welfare; Stress; Homeostasis; Allostasis; Allostatic state; Allostatic load; Disease

Contents

1. Introduction

Animal welfare research is facing a fundamental problem. The field is less scientific than claimed, because welfare was part of a social discourse actuated by emotion rather than reason before it became the subject of scientific research [1]. In response to the public outcry over Ruth Harrison's 1964 book, *Animal Machines* [2], the British government commissioned an investigation, chaired by F. Rogers Brambell, into the animal welfare of intensively farmed veal calves, pigs, and chickens [3]. It was concluded that animals should be able to stand up, lie down, turn around, stretch limbs and interact with conspecifics. These freedoms were primarily based on space requirements and not specifically aimed at important welfare needs. In 1993 the UK Farm Animal Welfare Council [4] published "The Five

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Freedoms" of animal welfare, which mainly describe housing conditions and care, and were thought to be an improvement upon what originally was recommended by the Brambell committee. Recently ideas on how to keep animals have rapidly changed in Europe, because in the last decennia society has been confronted with epidemics such as mad cow disease (BSE), foot and mouth disease and avian influenza. This has affected farmers but also society on a large scale. In European law, animals now are defined as "sentient" creatures, indicating that they are considered as conscious feeling animals, no longer just as agricultural products, and they have a value of their own. This is an understandable change, because conscious feeling animals are crucial to animal welfare, but without scientific background it opens the door for anthropocentric (public) thinking of how animals ought to be handled. This increases the risk that subjectivity, cultural and non-scientific opinions will largely affect legislation on how to keep and treat animals. This creates a considerable obstacle for progress on animal welfare on a more global scale.

However, this anthropocentric thinking of how animals ought to be handled should be rejected because the latest developments in neurobiology and behavioral physiology make it possible to objectively investigate the relationships between emotional individual beings and their environment to understand and improve animal welfare where needed. To understand animal welfare in conscious feeling animals it is crucial to investigate both brain and periphery states in relation to the environmental challenges that have led to these states. According to Antonio R. Damasio [5] consciousness highly depends on the image of knowing, which originates in neural structures fundamentally associated with the representation of body (brain and periphery) states, thus the image of knowing is a feeling". Altered brain and periphery states play a crucial role in the concept of allostasis. That's why the concept of allostasis is so important for animal welfare. We have to admit that some scientists have recently started to investigate consciousness, emotions, positive feelings and animal welfare (e.g. [6,7]), but not many are examining the possibility of refining over-arching principles.

2. Why do we need a new concept of animal welfare?

2.1. Freedoms

As mentioned above, the UK Farm Animal Welfare Council formulated the "Five Freedoms" of animal welfare and provisions associated with each of these freedoms are : 1) Freedom from hunger and thirst by ready access to fresh water and a diet to maintain full health; 2) Freedom from discomfort by providing a suitable environment including shelter and a comfortable resting area; 3) Freedom from pain, injury and disease by prevention or rapid diagnosis and treatment; 4) Freedom to express normal behavior by providing sufficient space, proper facilities and company of the animal's own kind; and 5) Freedom from fear and distress by ensuring conditions which avoid mental suffering. Remarkably, this approach is at the basis of present European (EU) legislation on animal welfare [8]. Although the EU claims that its animal welfare legislation should be based on sound scientific evidence, the freedoms principle reflects a more ethical view than a science-based approach. In fact, complete freedom is undesirable. Here, arguments will be given why the concept of the "Five Freedoms" is no longer helpful.

First, freedom from fear and distress is a typical anthropocentric construct. Fear is an emotion produced by the perceptions of impending danger and is normal in appropriate situations. It is a vital evolutionary legacy that leads an organism to avoid threat. Without fear, few vertebrates in the wild would survive long enough to reproduce. Thus, fear has fitness value. However, this does not mean that in the absence of threats animals should feel fear.

Freedom from distress, what does this mean? Recently, the Animal and Plant Health Inspection Service of the U.S. Department of Agriculture requested comments to help it decide on a formal definition of "distress" as part of its responsibilities under the Animal Welfare Act [9]. They came up with a working definition of distress: "a state in which an animal cannot escape from or adapt to the internal or external stressors or conditions it experiences, resulting in negative effects on its well-being". The Federation of American Societies for Experimental Biology objected that this definition is "vague and could lead to widely varying, highly subjective interpretations", and "there are no simple physiological or behavioral criteria to mark the point where an animal that experiences stress becomes distressed" [10]. Previously, it has been concluded that the term (dis)stress has so many different meanings that it becomes counterproductive by inhibiting a proper application and critical interpretation of experimental results [11]. Distress has mostly been associated with negative events and consequences. There is, however, no justification for the assumption that the expression of stress responses always compromise health or welfare. Indeed, the functional aspects of stress have often been neglected [12]. The paradox of stress lies in the simultaneity of its adaptive nature and its possible maladaptive consequences [13,14]. The best known stress hormones are corticosteroids, but their name could also be anti-stress hormones [15], because their primary function is protective and adaptive [16–18]. Corticosteroids are well known for their inverted-U curve of concentration and effect [16] (see also Fig 1). Because these hormones may have damaging effects as well, there may be a price to be paid for the adaptive nature of the stress response. The scientific challenge is to make a cost-benefit analysis, i.e. to determine under which conditions the costs outweigh the benefits and vice versa.

Second, one might expect that natural selection will shape a body for maximum health and longevity. Unfortunately, this is not always true. Health is not the outcome of natural selection, maximal reproduction is. If a mutation causes a disease, but yields a net increased reproductive success, it will be selected for [19]. Here is exactly where fitness and animal welfare depart: something can benefit reproductive success but involve negative experiences for the individual, causing poor animal welfare.

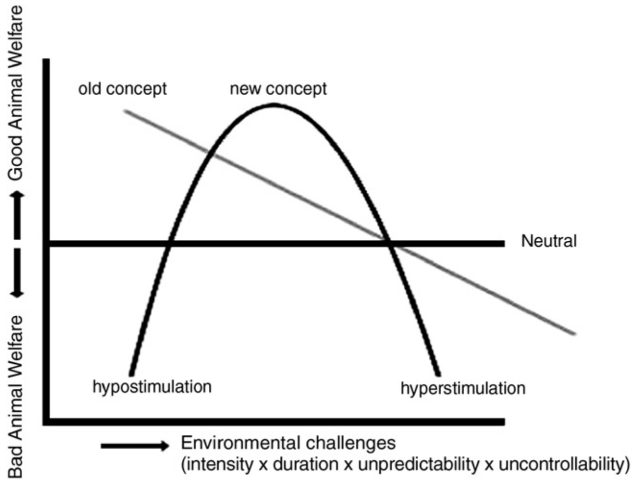

Fig. 1. Animal welfare in relation to environmental challenges as shown by the out-dated concept based homeostasis and the new concept based on the inverted U-curve of (di)stress.

Third, freedom from pain, injury or disease is a utopia. For example, pain is a natural defense mechanism that helps to protect organisms from potential threats and dangerous substances. Pain, nausea, fever, vomiting and diarrhea are products of natural selection. Although they produce suffering, they are defense mechanisms that protect organisms [20].

Fourth, intuitively it is appealing to improve animal welfare by respecting the nature of the animals. However, one has to realize that due to natural selection, nature is by no way a paradise. For instance, mice from some laboratory lines can survive as long as three years, while free-living wild mice are likely to die much earlier from disease, competition, or predators [21]. Male mice will tolerate their own offspring, but will kill offspring born to females that belong to other demes [22]. Wild animals try to increase their genes in a population. In contrast, many farm and laboratory animals are docile, due to artificial selection on the calmest animals. Consequently, behavior, temperament and associated physiology of these animals may have been modified during domestication. It is important to realize that wild, farm and experimental animals differ in the way genetic (natural or artificial) selection takes place with different consequences for ethics and animal welfare (see Table 1).

Fifth, freedom of hunger or ad libitum food availability in farm animals and zoo animals also produces problems [23]. Freedom from hunger together with an impoverished environment may disturb mental health as reflected by stereotypic and compulsive behaviors in zoo, circus and farm animals. Quantitively this is the world's largest animal welfare problem. In addition, mammals that are fed a restricted calorie diet live longer. Thus, longevity and hunger are part of a healthy mammal's life.

2.2. Homeostasis

Broom [24] defined the welfare of an animal as "its state as regards its attempts to cope with its environment". Any evidence of attempting to cope with the environment, whether successful or not, would be reflective of an animal's welfare. Welfare is seen as a continuum, ranging from very poor to very good, and the ethical question becomes one of what level of welfare is considered acceptable.

This approach implies that when an animal is confronted with environmental challenges it reacts with behavioral and physiological feedback mechanisms to maintain constant internal characteristics of the body (milieu intérieur). This is called homeostasis [25]. Homeostasis implies that the controlled physiological variables are kept at their 'set point'. This definition refers in a general way to the balance which exists between the animal and its surroundings. So, implicitly it suggests that without environmental challenges good animal welfare can be guaranteed. In our opinion this is an out-dated concept (see Fig. 1), because it ignores the absence of environmental challenges which produces hypostimulation in the animal and consequently bad animal welfare (see also Section 2.3).

2.3. Allostasis, allostatic state and allostatic load

To be fair to early thinkers about animal welfare; they used professional judgment and available information to come up with concepts like the "Five Freedoms". Until today, however, the latest concept of physiology, the allostasis concept, *has been neglected*. "Stability through change", coined by Peter Sterling *as allostasis*, involves mechanisms that change the controlled physiological variable by predicting what level will be needed to meet anticipated demand [26]. Natural selection has sculpted physiology and behavior to meet the most likely environmental demands plus a modest safety margin [18]. Thus, allostasis considers an unusual physiological parameter value not as a

Table 1
Wild, farm and experimental animals are kept for different reasons, each with different consequences for selection, animal welfare and ethics

	Wild animals	Farm animals	Experimental animals
Purpose	Animal fitness	Animal production	Health and disease
Goal	Reproduction in order to increase genes in the population	Production of food with increased quality and/or quantity	Understanding of Biology and development of both Human and Veterinary Medicine to the treatment of diseases
Consequences	Natural selection	Artificial Genetic Selection (incl. domestication)	Animal models (incl. inducing disease)
Ethics	Survival of the fittest	Maintain mental health and avoid mental diseases Maintain physical health and avoid disease and mutilation	Experiments on living animals should only be carried out when no other suitable alternative methods are available and the expected benefits to mankind outweighs the costs to animals

Table 2
The different mediators of allostasis, associated allostatic state and allostatic load due to hypostimulation or hyperstimulation, respectively

	Mediators of allostasis	Assessment of allostatic state	Measures of allostatic load	
			*Hypo*stimulation	*Hyper*stimulation
Central nervous system	Glucocorticoids, Amino acids, Cytokines, Serotonin, Dopamine, Norepinephrine, Neuropeptides like CRF, etc.	–change in central MR/GR balance – altered hippocampal CA3 dendritic tree atrophy – altered DG cell turnover – expression and function of 5-HT_{1A} /5-HT_{2C}	–violence – impulse control disorders – atypical depression – hypersomnia – chronic fatigue	–cognitive impairment – anxiety disorders – melancholic depression – insomnia – psychotic states
Cardio-vascular system	Catecholamines: e.g. adrenaline	–elevated levels of overnight urinary catecholamines – decreased vagal activity – increased clotting factors	–ventricular arrhythmia's – sudden death	–hypertension – ventricular heart hypertrophy –increased blood clotting
Immune system	Glucocorticoids Cytokines: e.g. IL-1,-4,-6,-10, TNF-α, TNF-γ, etc.	–decreased plasma cortisol levels and decreased mobility of white cells – increased levels of inflammatory cytokines	–infection – impaired wound healing – retarded immunization	–inflammation – autoimmunity
Metabolic system	Glucocorticoids	–elevated and flattened diurnal urinary cortisol – increased insulin and glucose levels	–weight loss	–abdominal fat – atheriosclerosis – muscle wasting – bone thinning – diabetis

Abbreviations: CRF — Corticotropin releasing factor; MR — mineralocorticoid receptor; GR — glucocorticoid receptor; DG — Dentate Gyrus; 5-HT — 5 hydroxytryptophan; IL — interleukine; TNF — tumor necrosis factor.

failure to defend a set point, but rather as a response to some prediction [27]. Coordinated plasticity is needed to optimize performance at minimal cost. The emotional brain plays a central role in allostasis [28]. By controlling all the mechanisms simultaneously, the brain can enforce its command and incorporate influential factors such as experience, feelings, memories, and re-evaluation of needs in anticipation of physiological requirements. A shift in the probability of demand should shift the integrated response, and when the prediction reverses, so should the response [27]. This response, involving the release of mediators of allostasis (e.g. adrenal hormones, neurotransmitters, and cytokines (see Table 2)), works via receptors in various tissues and organs to produce changes that are adaptive to metabolism, immune, and cardiovascular systems in the short term [11,13,14,17,22,29,30].

A fit animal has a wide regulatory range of allostatic mechanisms. Activation of these mechanisms outside this range can result in: failure to habituate with repeated challenges, failure to shut off the physiological response if the challenge is over, or failure to mount an adequate response [12]. This produces a state of chronic deviation of the regulatory system from its normal operating level [28]. This new equilibrium, coined by George Koob as allostatic state [28], is characterized by a narrower regulatory range (see Fig. 3) and hence by an enhanced chance of hyper-or hypostimulation. This can be described as the cumulative load to the brain and periphery, coined by Bruce McEwen as allostatic load [11]. When allostatic load is chronically high, pathologies may develop due to "wear and tear" [11] (Table 3). Allostatic load may also be *very* low as a consequence of hypostimulation, for instance, different diseases like allergic reactions, inflammatory/autoimmune disease, fatigue states and atypical depression are associated with blunted hypothalamic–pituitary adrenal axis [31]. Also, in the brain, chronic hypostimulation (e.g. low mental activity) may produce negative effects For instance neuronal survival highly depends on whether the new neural cells are sufficiently activated by incoming signals [32], a process that may be termed "use it or lose it" [33]. Remarkably, voluntary physical activity also increases cell proliferation and neurogenesis in the adult mouse brain, especially the hippocampal dentate gyrus [34]. Voluntary physical activity is also good for muscle tissue (incl. heart) and bone tissue.

In Fig. 2 it is shown that organisms may show different stress response profiles and different types of allostatic load exist [12].

Table 3
Animal welfare and the associated behavioral outcome

Animal Welfare				
Bad	Neutral	Good	Neutral	Bad
Chronic fatigue	Hypersomnia	Arousal	Insomnia	Hypervigilance
Chronic hunger and starvation	Hunger	Foraging	Satiety and obesity	Metabolic syndrome
Violence and stereotypy	Aggression and impulsivity	Exploration	Fear and avoidance	Generalized anxiety
Compulsive desires	Sensation seeking	Pleasure and aversion	Pain	Chronic pain

Normally habituation takes place in the stress response when the stimulus is repeated (see profile a). The response profiles b, c, d may produce costs due to the longer exposure and higher concentrations of stress mediators. In contrast, the hyporesponses (profile e) also produce costs, but these are due to hypostimulation.

3. Dawn of a new concept of animal welfare based on allostasis

Allostasis, which means stability through change, has the potential to replace homeostasis as the core model of physiological regulation [27]. Not constancy or freedoms, but capacity to change is crucial to good health and good animal welfare. Following this line of reasoning, good animal welfare is characterized by a broad predictive physiological and behavioral capacity to anticipate environmental challenges. Thus, good animal welfare is guaranteed when the regulatory range of allostatic mechanisms matches the environmental demands. In captive animals, housing conditions usually require quite some adaptation resulting in an allostatic state characterized by a reduced regulatory capacity.

However, in the absence of any further environmental demands, welfare is not always at stake (see Fig 3.). In this view, only conditions that produce high allostatic load or inadequately low allostatic load may threaten good health and good animal welfare. Such conditions render animals vulnerable to diseases or pathology including violence, stereotypy, chronic fatigue, atrophy of brain regions, metabolic syndrome etc. (see Table 3).

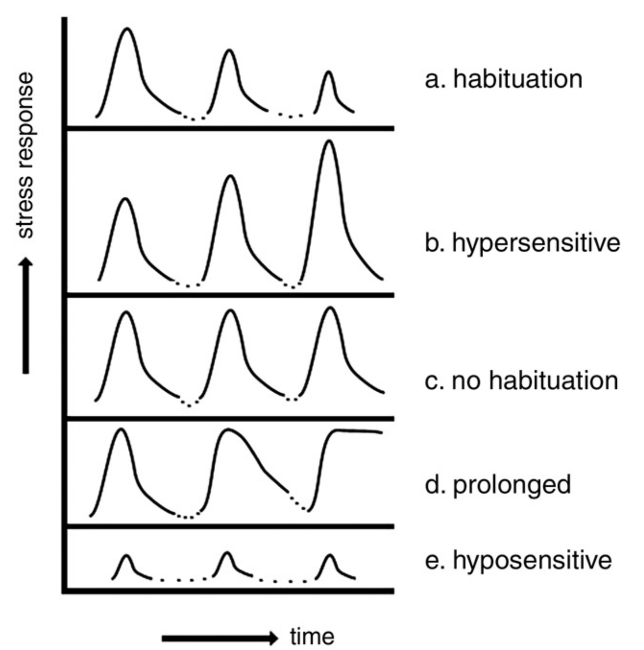

Fig. 2. The different stress response profiles. After repeated exposure to the same stressor habituation of the stress response optimally takes place (a). Due to different gene x environment interactions the organism may show a hypersensitive stress response (b), no habituation (c), prolonged stress response (d), or hyposensitive response (e).

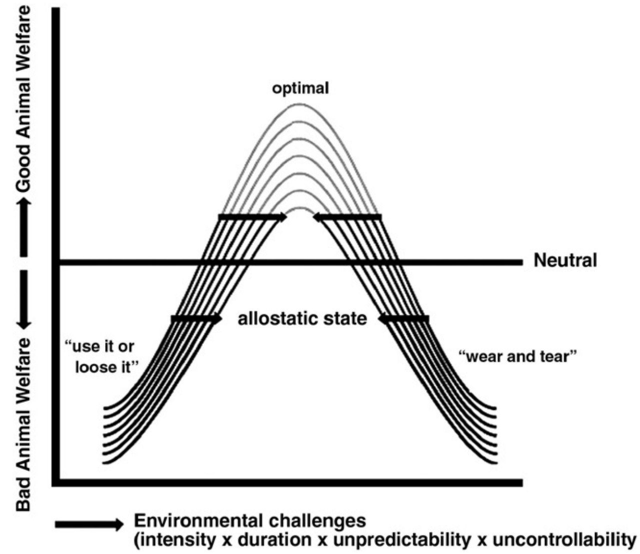

Fig. 3. A new animal welfare concept based on allostasis. Animal welfare is shown in relation to environmental challenges (inverted U-curve). Absence or chronic exposure to environmental challenges produce a state of chronic deviation of the regulatory system from its optimal operating level. This new equilibrium, allostatic state, is characterized by a narrower regulatory range and hence by an enhanced chance of hypo-or hyperstimulation. This is referred to as altered allostatic load which can be respectively described as "use it or lose it" or the cumulative "wear and tear" to the brain and periphery. Inadequately low (very low or zero) allostatic load or high allostatic load are at the basis of many stress-related pathologies.

Consequently, animal welfare research must find a science-based answer to the adaptive nature and maladaptive consequences of the stress response. This is not an easy task, but our line of reasoning implies that allostatic state is reflected by a new equilibrium and a narrower regulatory range (see Fig. 3) with consequences for the reactivity of stress systems rather than merely the level of stress parameters. Moreover, the irreversible nature of changes in reactivity, reduced resilience and consequently the damage to tissues and organs can be used as a measure of allostatic load [12–14,17,28,29]. See also Table 2 for the different types of allostatic load due to hypostimulation or hyperstimulation.

4. Discussion

Why do we need a new concept of animal welfare? First, there is a growing sense that animal welfare science is at an impasse, and that ethical and scientific questions about animal welfare have become hopelessly entangled [35]. Second, the concept of the "Five Freedoms" reflects a more ethical view than a science-based approach. In fact, complete freedom is undesirable. Third, scientific methods are misused by those who seek to obtain so-called "objective" measurement of that which they preconceive to be stress [36], whereas there is growing evidence that stress hormones are also involved in healthy adaptation [13]. Fourth, the welfare state of a sentient animal is a very complex affair and cannot be embraced by any single scientific discipline, be it ethology, physiology, molecular or neurobiology [36]. Fifth, animal welfare should not be based on homeostasis, because not constancy or freedoms, but stability through change (allostasis) and capacity to change are crucial to good health [27]. Sixth, genetic selection specifically on product quantity in farm animals (e.g. broiler chickens) have produced structural designs of organs in the body that are in disbalance. In organisms, structural design (of e.g. all internal compartments of the respiratory system like blood, heart, muscle capillaries, and mitochondria) should match functional demand. This is called symmorphosis [37]. In many farm animals (especially broiler chickens) the structural design of internal organs does not match functional demand [38]. This disbalance is responsible for many health problems in farm animals. It's time to change how we view animal welfare. The "Concept of Animal Welfare based on Allostasis" is a better alternative that incorporates recent scientific developments in behavioral physiology and neurobiology.

The "Concept of Animal Welfare based on Allostasis" can be summarized as follows:

- Stability through change (allostasis) and capacity to change *are* crucial to good health and good animal welfare. "Health" in this concept has the same meaning as defined in the World Health Organization's (WHO) constitution as :"a state of complete physical, mental and social well-being and not merely the absence of disease or infirmity" [39].
- Good animal welfare is characterized by a broad predictive physiological and behavioral capacity to anticipate environmental challenges.
- Good animal welfare is guaranteed when the regulatory range of allostatic mechanisms matches the environmental demands.
- A low allostatic load (not very low or zero) is key for good health and good animal welfare.
- In organisms, structural design should match functional demand (symmorphosis).
- Interpreting behavior and physiology in terms of animal perceptions and not exclusively in terms of human values.

This new concept of animal welfare can help to increase the quality of animal welfare. But first, we want to draw attention to the fact that human's compassion for animals seems to be very inconsequent [40], see also Table 4. As Andrew Moore [41] wrote: "When mice do little more than nibble our food, we justify using some of the most abominable painful mechanical and chemical means (anticoagulants) to exterminate them as a measure of pest control. However, when kept as laboratory animals, we accord them rights". To perform animal experiments with rodents, pigs or chickens in the Netherlands, one must do a lot of paperwork to comply with the regulatory requirements for animal welfare. However, when breeding pigs or chickens for food production many cruelties are allowed, e.g., partial beak amputation in laying hens (beaktrimming) to avoid cannibalism and feather pecking; castration, tail docking and teeth clipping in pigs (without pain killers or anesthesia) to avoid aggression and prevent boar taint in the meat [42]; chronic hunger in broiler breeders because if the parent birds were fed to demand they would become obese and fail to survive through the laying period [43]. In zoos polar bears show the most evidence of severely disturbed mental health, but also in other naturally wide ranging carnivores (e.g. lions) both captive-infant mortality and stereotypy frequency (e.g. pacing) are dramatically high [44]. Remarkably, polar bears in captivity show less pacing and disturbed behaviors when they are treated with the antidepressant Prozac, which is also prescribed in human patients suffering from Obsessive Compulsive Disorders [45].

In the near future, beaktrimming, castration, teeth clipping, tail docking, extreme food restriction etc. should be abolished. These methods do not provide real solutions, but only reduce symptoms. Instead, chronic fatigue, violence and stereotypies in pigs, chronic hunger in broilers; compulsive desires and stereotypies in chickens, and stereotypies in veal calves (tongue playing etc.) must be reduced. In farm animals these behavioral abormalities often reflect inadequately low allostatic loads due to chronic hypostimulation (see Tables 3 and 4).

The use of the "Concept of Animal Welfare based on Allostasis" can especially be of help in detecting elevated or depressed allostatic loads and in finding ways to reduce or normalize allostatic loads. This approach will lead to new ways to improve animal welfare. By introducing this new animal welfare concept we are convinced that it offers new opportunities for a breakthrough in the animal welfare science impasse, and we hope that more progress in animal welfare can be made on a global scale in the near future.

Acknowledgement

We thank Megan Breuer for editorial assistance.

Table 4
The number of animals used/killed during a person's life (80 yrs) in the Netherlands (Statistics Netherlands (CBS); Netherlands Food and Consumer Product Safety Authority (VWA) data of 2004–2005)

Species	Number	Costs	Benefits
Laboratory mice and rats	<3	Costs that are allowed higly depend on the benefits for mankind; pain killers and anesthesia are often prescribed to reduce suffering	Health and science
Wild mice and rats	ca. 17 [a]	Die slowly from poison	Pest control
Fattening pigs	ca. 48	Violence, compulsive disorders, stereotypies and mutulations	Food
Broiler chickens	ca. 1268	Compulsive disorders, stereotypies and mutulations	Food
Zoo/circus animals (polar bear, tiger, lion etc.)	n.a.	Compulsive disorders and stereotypies	Entertainment

[a] Pest control numbers are from the UK and are corrected for differences in population size and country size [40].

References

[1] Fraser D. The "new perception" of animal agriculture: legless cows, featherless chickens, and a need for genuine analysis. Fraser. J Anim Sci 2001;79:634–41.

[2] Harrison R. Animal machines: the new factory farming industry. London: Vincent Stuart Ltd; 1964.

[3] Brambell FWR. Report of the technical committee to inquire into the welfare of animals kept under intensive livestock husbandry systems (reprinted 1974). London: Her Majesty's Stationery Office; 1965.

[4] Five Freedoms of the Farm Animal WelfareCouncil. http://www.fawc.org.uk/freedoms.htm. Date of access: 17 July 2006.

[5] Damasio AR. The somatic marker hypothesis and the possible functions of the prefrontal cortex. Philos Trans R Soc Lond B Biol Sci 1996;351 (1346):1413–20.

[6] Spruijt BM, van den Bos R, Pijlman FT. A concept of welfare based on reward evaluating mechanisms in the brain: anticipatory behaviour as an indicator for the state of reward systems. Appl Anim Behav Sci 2001;72 (2):145–71.

[7] Panksepp J. Affective consciousness: core emotional feelings in animals and humans. Conscious Cogn 2005;14(1):30–80.

[8] The Community Action Plan on the Protection and Welfare of Animals 2006–2010. http://ec.europa.eu/food/animal/welfare/actionplan/actionplan_en.htm. Date of access: 17 July 2006.

[9] Holden C. Laboratory animals: researchers pained by effort to define distress precisely. News of the week. Science 2000;290:1474–5.

[10] FASEB news dec 2000. http://opa.faseb.org/pdf/newsletter/2000/dec.pdf. Date of access: 30 november 2006.

[11] McEwen B, Lasley EN. The end of stress ass we know it. New York: Joseph Henry Press; 2002.

[12] Korte SM. Corticosteroids in relation to fear, anxiety and psychopathology. Neurosci Biobehav Rev 2001;25:117–42.

[13] McEwen BS. Protective and damaging effects of stress. N Engl J Med 1998;338:171–9.

[14] Korte SM, Koolhaas JM, Wingfield JC, McEwen BS. The Darwinian concept of stress: benefits of allostasis and costs of allostatic load and the trade-offs in health and disease. Neurosci Biobehav Rev 2005;29:3–38.

[15] McEwen BS, Wingfield JC. The concept of allostasis in biology and biomedicine. Horm Behav 2003;43:2–15.

[16] Sapolsky RM, Romero LM, Munck AU. How do glucocorticoids influence stress responses? Integrating permissive, suppressive, stimulatory, and preparative actions. Endocr Rev 2000;21:55–89.

[17] Romero LM, Reed JM, Wingfield JC. Effects of weather on corticosterone responses in wild free-living passerine birds. Gen Comp Endocrinol 2000;118:113–22.

[18] McEwen BS. Sex, stress and the hippocampus: allostasis, allostatic load and the agingprocess. Neurobiol Aging 2002;23:921–39.

[19] Nesse R. Proximate and evolutionary studies of anxiety, stress and depression: synergy at the interface. Neurosci Biobehav Rev 1999;23: 895–903.

[20] Williams GC, Nesse RM. The dawn of Darwinian medicine. Q Rev Biol 1991;66:1–22.

[21] Rowe FP. Wild house mouse biology and control. Symp Zool Soc Lond 1981;47:575–89.

[22] Sage RD. Wild mice. In: Foster HL, Small JD, Fox JG, editors. The Mouse in Biomedical Research, vol. 1. New York: Academic Press NY; 1981. p. 140–90.

[23] Wechsler B. Stereotypies in polar bears. Zoo Biol 1991;10:177–88.

[24] Broom DM. Indicators of poor welfare. Br Vet J 1986;142:524–6.

[25] Bernard C. Les phénomès de la vie. Paris :Libraire JB Ballière et Fils; 1878.22.Canon WB. The wisdom of the body. The York: Norton WW; 1932.

[26] Sterling P, Eyer J. Handbook of life stress, cognition and health. In: Fisher S, Reason J, editors. Allostasis: a new paradigm to explain arousal pathology. New York: Wiley; 1988. p. 629–49.

[27] Sterling P. In: Schulkin J, editor. Allostasis, homeostasis, and the costs of adaptation. Cambridge University Press; 2004. p. 17–64.

[28] Koob GF, Le Moal M. Drug addiction, dysregulation of reward, and allostasis. Neuropsychopharmacology 2001;24:97–129.

[29] Koob GF. Allostatic view of motivation: implications for psychopathology. Nebr Symp Motiv 2004;50:1–18.

[30] Gold PW, Gabry KE, Yasuda MR, Chrousos GP. Divergent endocrine abnormalities in melancholic and atypical depression: clinical and pathophysiologic implications. Endocrinol Metab Clin North Am 2002;31:37–62.

[31] Sternberg EM. Neural-immune interactions in health and disease. J Clin Invest 1997;100:2641–7.

[32] Jacobs BL, Praag H, Gage FH. Adult brain neurogenesis and psychiatry: a novel theory of depression. Mol Psychiatry May 2000;5(3):262–9.

[33] Swaab DF. Brain aging and Alzheimer's disease. "Wear and tear" versus "use it or lose it". Neurobiol Aging 1991;12:317–24.

[34] van Praag H, Christie BR, Sejnowski TJ, Gage FH. Running enhances neurogenesis, learning, and long-term potentiation in mice. Proc Natl Acad Sci U S A 1999;96:13427–31.

[35] Mench JA. Thirty years after Brambell: whither animal welfare science? J Appl Anim Welf Sci 1998;1:91–102.

[36] Webster AJ. What use is science to animal welfare? Naturwissenschaften 1998;85(6):262–9.

[37] Weibel ER, Taylor CR, Hoppeler H. The concept of symmorphosis: a testable hypothesis of structure-function relationship. Proc Natl Acad Sci U S A 1991;88(22):10357–61.

[38] Korte SM, Sgoifo A, Ruesink W, Kwakernaak C, van Voorst S, Scheele CW, Blokhuis HJ. High carbon dioxide tension (PCO2) and the incidence of cardiac arrhythmias in rapidly growing broiler chickens. Vet Rec 1999;145(2):40–3.

[39] Health is defined in WHO's Constitution: http://www.who.int/about/en/index.html. Date of access: 26 September 2006.

[40] Meerburg B. Zoonotic risks of Rodents in livestock production. Thesis University of Amsterdam, The Netherlands. Wageningen: Musketier; 2006.

[41] Moore A. Of mice and Mendel. EMBO Rep 2001;2:554–8.

[42] Swanson JC. Farm animal well-being and intensive production systems. J Anim Sci 1995;73(9):2744–51.

[43] de Jong IC, van Voorst AS, Blokhuis HJ. Parameters for quantification of hunger in broiler breeders. Physiol Behav 2003;78:773–83.

[44] Clubb R, Mason G. Animal welfare: captivity effects on wide-ranging carnivores. Nature 2003;425:473–4.

[45] Poulsen EMB, Honeyman V, Valentine PA, Teskey GC. Use of fluoxetine for the treatment of stereotypic pacing behavior in a captive polar bear. JAMA 1996;209:1470–4.