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David B. Morton

*University of Birmingham*

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## **Distress in animals: its recognition and a hypothesis for its assessment**

*David B. Morton*  
*University of Birmingham, UK*

This essay deals with the recognition of non-painful emotional experiences in animals, how they relate to animal wellbeing and animal welfare, and how they can be assessed, monitored and mitigated. While it is written often from a mammalian perspective, the general principles will apply to all animals that are sentient.

### **Definitions and descriptions**

The impact of poor health, pain, distress and other adverse states on animals will often have a direct effect on their welfare and their quality of life. The question is how do we know that it is having this effect and how can we measure its degree of impact? The umbrella term used to describe such adverse states in the USA research regulations is “pain and distress” whereas in Europe the equivalent phrase is “pain, suffering, distress and lasting harm”. Perhaps the US Congress, when it approved those words, was interpreting the word “distress” as ‘any adverse state other than pain’. After all, pain is a common, well-defined experiential phenomenon, well understood by the public, well characterized in terms of its anatomy, physiology, neurology and pathology, and several modalities are available for its treatment and avoidance. Distress, on the other hand, is nowhere near as clear-cut, and Europe is in a similar state to the US, as there are no accepted definitions or measurements of “distress” or “suffering”. (“Lasting harms” can be identified as experimentally induced or genetic conditions such as diabetes, blindness, deafness, paraplegia, and so on.) However, in Europe, despite any universal agreed definitions of distress and suffering, there is a general understanding of what distress etc might encompass in terms of animal wellbeing. It would, for example, include adverse feelings such as hunger, thirst, excessive hotness or cold, disorientation, frustration, boredom, deprivation (e.g. maternal, social), grief, and so on. All these may require definitions or descriptions but perhaps the important thing is to be able to recognize such states when they occur, to be able to assess them (qualitatively or quantitatively), to know how to avoid causing them and how to treat them if they are not the desired experimental outcome or goal for study. It is not important to come up with a ‘definition’ *per se*, i.e. these adverse states need to be ‘operationalized’.

### **The integrated responsiveness of animals**

While pain can be separated as a mental and physiological phenomenon, it would be wrong to assume that it occurs in isolation. All vertebrates and many invertebrates are complex organisms that have evolved with mechanisms to protect themselves from physical damage and to maintain an internal physiological homeostasis. In vertebrates it is clear that the nociceptive system, the sympathetic adrenal medullary axis (SAM), the hypothalamic-adrenal cortical axis (HPA) and the inflammatory response, together with the senses of sight, hearing, touch, olfaction and taste, form part of an integrated system for the protection of the whole animal. As such they may all respond together or separately, but more often all these systems are activated at roughly the same time as part of a longer-term harm-preventing strategy, together with healing, to restore an animal to normal health and vigor. Take, as an example, a dog with a broken leg going to the veterinarian. It is in pain from the fracture and its corticosteroid levels will be raised along with the inflammatory ‘repair’ response. The vet manipulates the leg in order to determine where it is broken and in so doing causes that animal some pain (probably fairly severe). The next time the vet approaches, the dog remembers the pain that was caused

by this person and it becomes frightened (mental feeling) leading to the SAM and HPA responses. Consequently, the animal has now been motivated to respond not only to the pain but also to the fear; i.e. it responds as an integrated whole and not as a series of separate systems. In research and as clinicians we only measure part of this overall responsiveness depending on our interests.

The reductionist approach by analyzing each of the component systems is part of our scientific analysis or clinical judgment. In order to understand the situations better, both physiological and behavioral outcome measures are needed, and for a correlation to be made between them. However, which should we believe if they are not coincident? The behavioral signs may represent a truer indicator of what an animal feels as, in effect, they reflect the final integrated step for what an animal is feeling. Take an example closer to home. Who wants to be told in the hospital that they are not in pain as their hormone levels are not high enough, or their EEC pattern does not show the right form, and as a consequence you cannot receive any pain relief (or have any food as you are not really hungry)! Our good fortune is that we can communicate. However, for those who cannot, we have to interpret as best we can, normally on the basis of clinical signs and laboratory measures.

### **Distress**

Distress (as well as pain) is of concern as it affects the wellbeing of many of the higher developed animals such as mammals, birds and other vertebrates but we really have no idea about invertebrates, although judging by their behavior many species seem likely to be sentient in some way. I have suggested that "an animal's welfare is compromised when its physiological health and/or its psychological wellbeing, in relation to its cognitive capacity and life's experience, are affected negatively". Several points should be noted with this description. First, disease (physiological health), both infectious and non-infectious, will often, at some stage, affect wellbeing. Second, mental health (psychological wellbeing) is important and the main impact of poor physiological health is that it makes us (and probably animals) feel that our wellbeing and quality of life is not good at that time. That is, the importance of poor physical health lies in its impact on our state of mind. No mind, no problem with wellbeing! Hence the cognitive capacity of the species, and indeed the individual, has also to be considered! For example, any animal unable to carry out activities that it is motivated to carry out may become distressed regardless of whether it is in pain or not. Take separation anxiety in dogs whether it be from humans or other dogs; or an animal unable to walk because of paraplegia or fracture may become mentally distressed as it cannot walk, run or play. The reader will note that I have moved away from consideration of the general to the specific, that is, to a single animal as it is the individual that is of primary importance and not the group which, after all, is simply a collection of individuals. Consideration of the group raises its own separate considerations ethically and practically. That is why the biography of an animal, i.e. its prior experience of life, forms a key part of its mental response to what it perceives as an adverse situation.

Suffering follows from poor wellbeing or an impoverished quality of life, or mental states that cause negative emotions such as unhappiness. Suffering can be described as "a negative emotional state which derives from adverse physical, physiological and psychological circumstances, in accordance with the cognitive capacity of the species and of the individual being, and its life's experience". As with the description of animal wellbeing above, the individual animal is of paramount importance because of its unique cognitive capacity. Animals with more developed central nervous systems e.g. with long memories, may suffer more than those that are not developed to that degree. They may have a greater capacity for 'imagination' and have an idea of what could happen in the future, and so try to take avoiding actions.

Indeed they may even be capable of retrodution, i.e. an ability to form options for future actions and to choose the 'best' one.

The USDA proposed a definition of distress as "A state in which an animal cannot escape from, or adapt to, the external or internal stressors or conditions it experiences, resulting in negative effects upon its well-being". This definition starts to separate what I have labeled as 'mental distress' from 'dystress' and the role of stressors.

*Stressors*: are those environmental circumstances that an animal perceives as 'negative' and which are capable of causing feelings of concern, anxiety, heightened awareness, and stress. If an animal does not adapt within a relatively short period of time, prolonging those feelings may lead to distress. An animal that feels fear transiently is different from one that is in persistent fear. Both duration and intensity are important aspects. Such circumstances derive from both internal feelings, experienced through internal homeostatic neural and hormonal mechanisms, as well as external stressors that an animal perceives through its senses. Some environmental changes or stimuli can be advantageous e.g. stressors an animal can cope with (so-called 'eustress' - Greek 'eu' having a sense of goodness) and make it 'fitter' for survival in that ecological niche). In the future, that animal may habituate and so no longer experience that stressful feeling having adapted to the stressor.

### **Dystress**

The word is derived from the Greek word '*dus*' having a connotation of bad (i.e. bad stress) and is caused when an animal can no longer adapt to the stressors imposed upon it. Examples might include: temperatures outside the thermal neutral range and outside the lower and higher critical temperatures, excessive humidity, transport for long distances, restraint, and inadequate or irregular food supply. The body is maintained within a range of physiological parameters (homeostasis) e.g. blood glucose, and will adapt to, or cope with, its 'new' environment. However, stressors that are severe, prolonged or repeated may eventually erode an animal's ability to cope and so cause dystress. Dystress can be increased when the animal is unable to predict or control the stressor (Wiepkemea & Koolhaus, 1993).

Dystress, will primarily activate the hypothalamic/ pituitary/ adrenal cortical axis, ultimately leading to an increase in corticosteroid levels. Non-steroidal hormones may also be raised and these include prolactin, tumor necrosis factor (TNF), and interleukins, which in turn can affect other body systems and predispose animals to disease through reduced effectiveness of the immune system (see Dantzer & Kelley, 1989). Dystress may lead to poor growth, altered reproductive cycles leading to a reduction in breeding capacity (even short term stressors such as noise and vibration are known to affect breeding), as well as affecting other systems controlled by the anterior pituitary gland (thyroid, parathyroid). Dystress is measurable from circulating hormone levels, hormone receptor density binding studies, and end organ responses. Circulating hormone levels are the easiest to measure but are the most dubious, as unless hormone molecules are taken up by the cell through binding to a cell surface receptor, they can have no effect on that organ. It is debatable what proportion of blood hormones is simply destined for excretion and what proportion is destined to bind to target organ receptors to elicit an effective response.

### **Mental distress**

Mental distress I use to describe adverse psychological (mental) states often measurable by abnormal behavioral parameters, so-called stereotypic behaviors. Distress is often associated

with the other adverse states described above but can occur in a more restricted sense when animals elaborate abnormal behaviors because they are unable to meet their mental (psychological as opposed to physiological) needs.

Stereotypic behaviors are, by definition, repetitive, have seemingly no obvious function, and may be novel to that animal species or be an exaggerated form of a natural behavior (in terms of the amount of effort or time spent carrying it out). Stereotypic behaviors vary in style and with species according to the environmental conditions. Broadly, these behaviors reflect mental states such as boredom, frustration, torment, social isolation. Mental distress seems to result in an involvement of serotonin, nor-adrenaline and dopamine receptors as drugs classified as Re-uptake Inhibitors have been found to reverse such stereotypies in both humans and animals. It is important that humans are able to separate the behavioral 'needs' of animals from their 'desires' and to provide them with the freedom to carry out many behaviors. It seems intuitively obvious that some behavior patterns i.e. those that damage the ability of that animal to survive ('fitness' in the Darwinian sense), e.g. self-mutilations are particularly unacceptable (chewing digits in monkeys, repeated gnawing leading to damage to the mouth and teeth - often called 'vices' in the past as if they were the fault of the animal!). Other behaviors seem less self-destructive in a physical sense but may be mentally 'destructive' (weaving, inactivity, pacing) and be irreversible even though the original cause has been removed. Such behaviors are seen in many mammals in zoos and laboratories and occur in nearly all species. Any behavior not seen in the wild counterpart of a species should be treated as an indicator of poor welfare.

It is not easy to determine the behavioral needs of animals but Dawkins and others have attempted to address these issues in two ways (Dawkins, 1990). Behaviors can be measured through choice experiments to determine what animals prefer by giving them a choice of two environments (e.g. two types of cages or bedding). These experiments have limitations in that an animal may like or dislike both but is forced to choose one; it may also not know what is good for it in the long or short term; and it may change its mind with time, experience, or physiological states e.g. pregnancy and age. The second method is to measure how hard animals will work (e.g. lever pressing or pecking) in order to gain access to a particular environment or enrichment. Such quantitative estimates enable one to rank environmental behaviors. We are under an obligation to meet those behavioral needs that appear to be important for that species in so far as is practicable in the laboratory and within any scientific objective. In my view, we should strive to meet any such 'needs' in its normal husbandry, and only when the scientific objective cannot be achieved, should we not do so.

Building on the 'choices test' paradigm it may be possible to decide what animals prefer to avoid as opposed to work hard for what they prefer. This has been well demonstrated recently with respect to the use of carbon dioxide (CO<sub>2</sub>). Various tests have shown that animals will not stay in certain concentrations of CO<sub>2</sub> if they have the chance to escape and that they will pay a high price to do so; e.g. not take food when they are very hungry. Such experiments may help us decide what situations animals find mentally distressing and to what degree.

### **Measurement of distressing situations by their impact on the animals**

Recognition and assessment of adverse states in animals will vary according to the species, the system of husbandry and, of course, the individual response of the animal (biological variation is such that animals will inevitably differ even though what is being done to them appears to be the same (e.g. lethal dose tests where at the LD50 dose, 50% of the animals die and 50% survive). Nevertheless, systems for recognizing and scoring animal distress in a controlled laboratory environment, in the context of good husbandry systems that impose a minimum of stress, and in

developing reliable scientific and humane endpoints can be made and these are described below. Evaluation of clinical signs such as whether an animal is eating and drinking, its bodyweight, its appearance, its physiological state, posture and behavior become crucial for underpinning the scientific assessment of the well-being of that individual animal.

### **Interpretation of clinical signs, behavior and physiological measures**

There is a mistaken impression that physiological measures, because they are often quantitative are better or more reliable than behavioral or qualitative measures. It is important to separate the reliability of data collection and its accuracy from that of *interpreting* any data collected. Observer variation and confidence limits for data collection are important and any variance should be minimized. Whether it is scoring the time spent carrying out stereotypic behavior, the EEG pattern, the bodyweight, the presence of diarrhea; all such data should be recorded as accurately as possible. However, it is how that data is interpreted that is the key to the overall assessment of wellbeing, and is no different between quantitative and qualitative data measures.

Some see assessment of clinical signs as not being objective and a matter of subjectivity; nothing could be further from the truth. What is true is that some clinical signs are metric and can be quantified (like body weight, body temperature, respiration and heart rates, behavior) whereas others are parametric and cannot. These would include signs like quality of respiration (deep, shallow, labored), posture, appearance (such as closed eyes), disturbed pelage as with ruffled fur or feathers, diarrhea, coughing, and convulsions. Such parametric signs tend to be either present or absent, but can also be present to varying degrees, and it is often possible to grade them in some way or another. For example, pain in the foot as a result of a broken metatarsal bone causing an animal (or human) to limp is a repeatable clinical observation, backed up in this case from verbal evidence in humans that limping is painful as it hurts to bear weight on the foot. An animal may be hopping lame, bear some weight and be obviously limping, or bear more weight and be only slightly lame. All these signs are objective observations in exactly the same way that one can observe the stars or that oil floats on water. The cause of the lameness may indeed vary but the impact on the animal is what matters in this context, and if that pain affects the animal's appetite and it loses bodyweight, or its body temperature is raised, we then can start to get an idea of the overall impact of the experimental or clinical condition on that animal and its ability to cope.

### **Situations where distress might occur**

When considering distress in situations where pain is not involved, such as social isolation or barren environments, the clinical signs may be very different. The potential for distress is far wider and less predictable than for pain. With pain, we would routinely predict it occurring as a sequel to a surgical procedure, but the range of stressors to cause potential distress is far greater. Non-pain induced distress may be caused through social isolation (separating aggressive animals, studies involving metabolic cages, indwelling cannulae that prevent grouping animals for fear of interference through allogrooming); barren environments for all species so that animals become bored or frustrated (e.g. caging animals); maternal separation studies; studies on infection or studies that cause immunosuppression and a range of adverse pathophysiological states (e.g. persistent diarrhea, coughing, nausea, dizziness and affecting balance and social interactions), studies on organic diseases such as diabetes (e.g. polydipsia to the point of drinking their bodyweight in water daily, cancer (e.g. space occupying lesions in the cranium, or abdomen with ascites, or that interfere with mobility), lesions that affect the motor system (e.g. studies on spinal lesions and nerve regeneration, stroke models, and other

models of neurodegenerative disease such as Parkinson's), food and water withdrawal, restraint for long periods, sexual frustration when housed near receptive females, and so on.

### **Assessing distress: the role of the score sheet**

A score sheet is simply a list of those clinical signs likely to be seen in a particular scientific procedure for an individual species, or even for a particular strain or breed of that species. It is not possible to prepare a generalized list of clinical signs that will occur in all experiments (compare the predictable side effects for a failed skin graft with a failed liver or heterotopic heart graft in a dog, compare also with a mouse dying of rabies infection). Consequently, score sheets have to be drawn up specifically for each scientific procedure.

Moreover, some of these feelings occur only at specific physiological times in life e.g. close to parturition for nest building in sows, dogs, cats. For other feelings, humans may be able to better adapt to some basic instincts e.g. sex drive, paralysis, social isolation, because of their 'higher' cognitive ability, but may also feel distress in other ways e.g. not being able to exercise, write letters, meet friends, play golf, etc. Humans may show the same instincts in different ways e.g. nest building being the equivalent of preparing a nursery. The variety of possible behaviors that humans carry out gives them greater scope for distress than nonhuman animals.

### **A word on 'critical anthropomorphism'**

In many of these situations the assumption of distress rests on analogy with humans with a similar condition or in the same circumstances. In such circumstances one has to try to separate 'primitive basic feelings' from those that are of a 'higher' order. That is, basic feelings such as hunger, thirst, social isolation, and nest building are very likely to be shared between all mammals (and probably all vertebrates), including humans, whereas others may not be for various reasons. The use of language by humans is very important for conveying feelings to each other, but may also give some insight into what animals might feel in certain situations. It might not, of course, hence it is important that any anthropomorphism takes into account the different biological attributes of the species and is used only as a guide and not an absolute rule. Interestingly we do this for other humans that cannot communicate, or when we learn about the predicament of others and we empathize with their plight. We also do it for pre-verbal humans i.e. babies which may be the closest analogous group.

### **Measuring mental distress**

When measuring distress in barren environments, one is likely to see stereotypic behaviors or even self-mutilation. In those cases one would be scoring the presence of that behavior, and if possible quantifying it. That may raise some difficulties in that some of these behaviors are diurnal and such behavior may be present only at night in nocturnal species (i.e. their daytime) like rodents, at dawn and dusk in crepuscular species, and at 'our normal human' times for other animals. It may be possible to overcome this by the use of reversed lighting in laboratories. The second problem lies in quantification, as it either has to be continuous or some form of snapshot (focal sampling). Nevertheless, as some stereotypic behaviors may take up a substantial part of the day, this data collection need not be over burdensome. Furthermore, small-scale studies may be sufficiently representative to form the basis for a judgment or treatment. When the impact on an animal is severe, such as with a lethal infection, the signs may be very easy to score and would be very similar to those seen when animals are in pain. As far as self-mutilation is concerned the degree of physical damage may reflect the severity in that chewing the off the end of a digit is different to its complete removal. However, care has to

be exercised as it is not a linear progression in any way. Losing a digit(s) may cause less lasting harm than losing a limb, but that does not necessarily mean it causes less pain? Moreover the mental distress caused by not being able to manipulate objects is different from not being able to walk? Who can say which is perceived as more important by an animal?

When an animal is unable to cope with stressors, several clinical signs may be noted depending on the degree of dystress and its duration, as well as the type of exposure. Several categories of stressors can be recognized:

- a) single stressor of short duration;
- b) repeated single stressor of short duration;
- c) multiple stressors of short duration;
- d) repeated multiple stressors of short duration; and
- e) prolonged exposure to a single stressor.

All of these occur in research laboratories on an almost daily basis. Examples of: a) could be withdrawal of food and water pre-surgery; b) restraint, multiple anesthetics, daily exposure in inhalation studies; c) single intraperitoneal injection with restraint followed by a period of separation from cage mates and subsequent re-grouping; d) multiple daily injections with or without restraint, or removal from the cage to assess responsiveness in some apparatus e.g. von Frey tests and other analgesiometric tests; e) maternal separation, being placed in a metabolic cage for several weeks.

It is obvious that it is virtually impossible to remove all stress in a laboratory setting but we can focus on how to reduce it to the lowest level, as that is likely to be good for the science as well as for the animals. Sometimes habituation or training to a procedure may help e.g. training dogs to sit still for an injection, or acclimation to an environment by making sure the animals are used to going into that room for a procedure to be carried out. This may sometimes reduce the impact of the procedure but on other occasions it may not, and this requires some research to be carried out. Thus mice do not seem to habituate to restraint, and it is likely that non-human primates will not adapt to being caught in a squeeze back cage, but positive training strategies by reward may well be more welfare effective.

### **Measuring dystress**

Recognition of the impact of a stressor can be made from measuring circulating hormone levels such as corticosteroids of the appropriate type, catecholamines, and end organ responses such as heart rate, blood pressure, dilatation of the pupil. Some studies have also looked at adrenal cortex responsiveness by injecting a dose of ACTH (Adreno-Cortico-Trophic Hormone) to elicit a maximal response by measuring corticosteroid levels. A high level response may be interpreted as adrenal cortical hypertrophy and a low level as exhaustion, both indicating a prolonged exposure to varying degrees of stress. More recently target cell receptor binding studies have been carried out and would seem to be an important feature as up-regulation of such receptors would indicate a stress response.

It may be worth noting that the level of corticosteroids may have important repercussion in immunological research, as they could affect scientific outcome measures and it would be important to minimize all such sources of variance.



## Drawing up a score sheet

Score sheets are usually specific for the experiment, the species and even the strain. By closely following the first few animals, the most relevant and important clinical signs can be identified. In this regard the opinion of the animal care staff is invaluable; thus, it is critical that they are made aware of what the study involves, what specific signs should be looked for, and so on. The laboratory animal veterinarian and/or ethologist should also be skilled in identifying objective clinical signs. From their knowledge of the biology of the species it should be possible to include the range of an animal's relevant behavioral and physiological responses. Regularly observing animals throughout a pilot study will help identify those critical periods during the experiment where animal wellbeing is particularly at risk (e.g. in the immediate post-operative period; or in a study on infection after the incubation period, or at the predicted time of tumor growth or organ graft failure).

One should first look for those signs that can be observed from a distance in a relatively undisturbed animal, in that way one can score its natural, unprovoked behavior (e.g. appearance, behavior, posture, respiratory rate and pattern). The animal is then observed more closely by handling and examination of the animal itself (to measure signs such as body weight, body condition and temperature, heart rate, dehydration). Clinical signs are scored as being present (+) or absent (-) or, if unsure, then that too can be indicated (+/-). Clinical signs are reduced to an observation that can only be scored in this binary way, otherwise misinterpretation and subjective evaluation may creep in. This is one of the strengths of the scheme as it leaves little room for observer error (such 'errors' when they have occurred have been at low levels of severity). The convention is that negative signs indicate normality, i.e. within the normal range, and that positive signs indicate the animal is outside the normal range. However, this does result in some contorted descriptors as an animal showing convulsions would be a sign of poor wellbeing and be scored a (-), but if an animal was eating then this is a good sign and could be scored also as a (+). In this latter case the descriptor is changed to "Not eating" so that if an animal is not eating it is then scored as a (-), and the convention maintained. Using this convention it is possible to scan a score sheet to gain an overall impression of animal well-being: the more plusses, the more an animal has deviated from normality with the inference that the scientific procedure is having more impact than before.

It is also not unreasonable to assume, and this would be born out by human experience, that the greater the deviation from normality, the greater has been the impact. Thus an animal may lose 5, 10, 20 or even 40% of its bodyweight, or its temperature may be several degrees above or below normal. In these cases the assessment can give some idea of the impact that the experiment is having on that animal at that time. The degree of deviation from normality can be used to grade the degree of distress or whatever form of adverse effect it is considered to be. An understanding of the type of suffering and why and how it is caused may help us prevent it in the first place. The type of suffering is also important from a therapeutic viewpoint as giving an analgesic will be good for pain, but not for boredom, frustration or distress if pain itself is not involved. In fact one of the most important aspects of recognizing the type of suffering is how to alleviate it, unless it is part of the scientific objective. Not causing avoidable suffering to animals is an important objective in producing good science.

Score sheets can also be used to see if any therapy being applied is working. A bodyweight loss because of pain or feeling unwell due to an infection can lead to an animal not eating, and this weight loss reflects one impact of the experiment on that animal. If this weight loss can be reversed through the provision of analgesics then it provides some evidence that the anorexia was due to pain, and that the therapy is being effective. Moreover, through the provision of

such treatment, severity can be reduced and the wellbeing of the animal, as well as the science, can be improved.. With distress, however, few treatments are available and it is more likely that prevention, training, habituation and acclimation will be successful.

At the bottom of the score sheet there are guidance notes on what should be provided for the animals in terms of husbandry and care. There are also guidelines on how to record qualitative clinical signs (such as lameness, diarrhea, respiration), as well as criteria at which to implement humane endpoints (see below). Finally, if an animal has to be killed, there are instructions about what other actions should be taken, such as a blood sample before killing, so that the maximum amount of information is always obtained from a study.

While these sheets take time to fill in it is relatively easy for an experienced person to see if an animal is unwell, so the NAD box (Nothing Abnormal Diagnosed) is simply ticked. However, if an animal is not normal, it does take time to score it and to make judgments over what actions should be taken; that is the price for practicing humane science.

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