Physiology and Behaviour of Animal Suffering
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12 Sickness and Disease

Disease is one of the most important causes of animal suffering, and yet it is one that is often given the least recognition. To understand the suffering in disease one has to appreciate its pathophysiology and the feelings experienced by humans in comparable situations. Some forms of suffering are peculiar to particular diseases, but there are a number of sensations that are common to a wide range of diseases (Table 12.1).

Ascites is a good example of a specific disorder with fairly precise forms of suffering. This condition is common in broiler chickens, and is associated with congestive heart failure or kidney failure in other species. From experience in humans we know that the raised intraperitoneal pressure from ascitic fluid can cause pain and a sense of dyspnoea, especially during exercise. Pressure on the viscera causes a sense of nausea and suppresses the appetite. Observing the animal's behaviour may tell us whether a particular animal is experiencing these or similar forms of suffering. In people the suffering can be quickly relieved by draining the fluid with a hypodermic needle, and if this procedure improves an animal's behaviour it adds to the evidence that it was indeed suffering.

12.1 Is Suffering an Inevitable Consequence of Being Ill?

There are specific centres in the brain that control general sickness behaviours and some immune responses. This common link makes it difficult to divorce immune responses from sickness behaviour, and presumably sickness perception. This section summarises the evidence behind this dual role for the CNS.

Lesioning the hypothalamus and reticular formation reduces cellular immune system responses in rats, and ablation of the *locus coeruleus* diminishes the ability to mount an antibody response. These three regions also regulate sleep, attentiveness, hunger and body temperature, which are some of the key elements of sickness behaviour. Corticotrophin releasing hormone (CRH) released by these centres

Table 12.1 Some behavioural abnormalities and forms of suffering associated with sickness and disease.

General disturbances	Specific diseases
Loss of appetite	Sore throat
Impaired concentration and memory	Pain in lymph nodes
Fatigue	Fever
Depression	Generalised muscle weakness
Anxiety	Myalgia
Weight loss	Sore sinuses or respiratory tract
Reduced activity	Arthralgia
Anhedonia	Headache
Somnolence	Dyspnoea

activates the hypothalamic-pituitary-adrenal cortex (HPA) axis, and this provides a further link to the metabolic responses that occur in disease states.

Some immune responses can be recruited without involving the brain, but they are associated with sickness behaviours. This peripheral immunity operates through the release of cytokines from infected cells, endothelial cells, fibroblasts, mononuclear phagocytes and lymphocytes in response to toxins produced by the infective micro-organism. The cytokines that are released peripherally act locally, and they can also stimulate the release of cytokines from glial cells within the brain. The CNS response depends on special mechanisms that allow cytokines to bypass the blood–brain barrier, and within the brain they provoke five key sickness behaviours or signs. They are:

(1) fever;
(2) loss of appetite;
(3) impaired memory and learning;
(4) social isolation;
(5) tiredness (Gregory, 1998b).

Cytokines are key agents which recruit both the immune and behavioural responses in sickness.

Feelings of sickness probably depend on activation of the immune system rather than the mere presence of a pathogen or disease condition. Sickness sensation can develop when there is no disease, for example when the immune system is challenged during a vaccination procedure. When people have been vaccinated with attenuated rubella vaccine they have experienced a sickness phase which included depression, social and attention problems and delinquent behaviour (Morag *et al.*, 1998). They did not develop German measles, but their immune system was activated.

12.2 Do the Behaviours Expressed During Sickness Serve a Purpose?

When we develop a **fever** we feel discomfort partly from a knowledge of what is to come but also from the direct effects of the fever. Fever serves some useful purposes. The temperature-raising effect assists body defences by enhancing leucocyte proliferation, promoting antibody production, increasing the rate of neutrophil accumulation at the site of an infection and improving B-lymphocyte responsiveness, all of which help curtail micro-organism growth. In terms of overall outcome, mild to moderate fevers have assisted survival in rabbits that were infected with *Pastuerella multocida* (Kluger & Vaughn, 1978), and allowing a fever to express itself has reduced the severity of influenza infection in ferrets (Husseini *et al.*, 1982).

Infections also induce **sleepiness**, but whether the individual spends more time sleeping depends on circumstances. Sleep is considered beneficial during illness because it may hasten recovery by improving morale and promoting immune function. The evidence that supports this is largely circumstantial. Rabbits that have died following inoculation with live *Staphylococcus aureus* showed reduced neutrophil responses during the infection and spent substantially less time sleeping in comparison with rabbits that overcame the infection (Toth & Kreuger, 1988). In humans, sleep deprivation has been associated with impaired immune function, including natural killer (NK) cell activity, lymphokine-activated killer cell activity, and interleukin-2 (IL-2) production in response to antigen challenge (Irwin *et al.*, 1994, 1996). In rats, fatigue reduced survival after inoculation with bacilli which included anthrax spores, in comparison with animals allowed to rest.

It is often said that one should feed a cold. In other words, do not stop eating when there is a respiratory infection even though **appetite** is suppressed. This axiom may not apply to all disease states. When mice were fasted for varying lengths of time and then injected intravenously with *Listeria monocytogenes* it was found that those that were fasted longest had the lowest subsequent mortality. Similarly, limiting feed intake during the early stages of cancer can help to delay the rate at which it develops (Shields *et al.*, 1991). Evidently, fasting before a disease sets in can afford some protection against the disease. However, other studies have shown that the immune system can be compromised by fasting. For example, feed and water deprivation for two days suppressed the antibody response to inoculation with killed *E. coli* in chickens. We do not have a clear picture of when it is best to stop or start eating, but sickness-induced suppression of eating can be beneficial in some conditions.

In herding species, the urge for **social isolation** during sickness reduces the opportunity for cross-infection. Social isolation may be linked to activity of the *locus coeruleus* in the brain, which is thought to enhance or mediate the sense of nausea, photophobia, phonophobia and headaches during illness.

12.3 Cytokines and Sickness Behaviours

In bacterial infections, cytokine production is induced by cell wall components present in the bacteria, such as lipopolysaccharide (LPS). LPS endotoxin induces a broad range of flu-like sensations, including depression, anhedonia, headache, muscle aches, short-lasting chills and nausea, through the release of cytokines. The psychological effects seem to be correlated with particular cytokines, and they can be reduced by treatment with antidepressants. Part of this effect could be due to suppression of the release of cytokines. For example, antidepressants can suppress the release of IL-1β and IL-6 from monocytes and IL-2 and interferon-γ (IFN-γ) from activated T-cells (Maes *et al*., 1999).

Cytokines can be either pro-inflammatory or anti-inflammatory. The **pro-inflammatory cytokines** mediate the following:

- fever;
- leukocytosis;
- increased synthesis of acute-phase proteins;
- muscle catabolism;
- stimulation of the HPA;
- activation of leukocytes and endothelial cells.

The precise response depends on the individual cytokines that are present. For example:

- IL-2 produces anhedonia.
- IL-1 and IL-6 promote fever.
- IL-1 and tumour necrosis factor-α (TNF-α) cause an increase in non-REM sleep.
- Interferons cause psychiatric morbidity and flu-like symptoms, including fever, tachycardia, headache, arthralgia, myalgia, and sometimes nausea and vomiting. IL-2 produces similar symptoms, but is more likely to cause peripheral oedema and diarrhoea and less likely to result in myalgia, arthralgia and loss of appetite (Fent & Zbinden, 1987).
- IL-1 can be neurotoxic.

Excessive release of IL-1β, IL-6, TNF-α, IFN-γ and adenosine can promote diffuse intravascular coagulation, and increase the synthesis of nitric oxide in endothelial cells. Nitric oxide promotes vasodilatation, and in extreme situations it exacerbates septic shock reactions.

The pro-inflammatory proliferative cytokines (granulocyte–macrophage colony-stimulating factor (GMCSF), platelet-derived growth factor BB (PDGF-BB) and transforming growth factor β2 (TGF-β2)) also accelerate wound healing.

The **anti-inflammatory cytokines** control inflammatory reactions through autocrine inhibition of pro-inflammatory cytokine production, and some of them promote antibody and allergic responses instead. They include IL-4, IL-10 and TGF-β, and their effects can be beneficial. For example they help to control septic shock.

Several cytokines can activate the HPA, but the pathways vary between the individual cytokines. IL-1α, IL-1β, IL-2, IL-6 and TNF-α stimulate the release of CRH from the hypothalamus. This response is mediated by the induction of nitric oxide, and it leads to activation of the HPA axis through stimulating the release of ACTH.

During fever, the point about which body temperature is regulated is set at a higher level. This readjustment is controlled from the pre-optic area (POA) of the anterior hypothalamus and this centre also mediates sleep. Endogenous agents that reverse the fever include α-melanocyte stimulating hormone (α-MSH), arginine vasopressin, glucocorticoids and IL-10. Although virus infections are often associated with a fever, some small mammals such as mice often show a reduced body temperature. This is probably due to the antipyretic effect of TNF (Conn *et al.*, 1995). The mice try to minimise the fall in their body temperature through behavioural responses.

12.4 Cancer

The most common forms of suffering in subjects dying of cancer are fatigue, pain and dyspnoea. **Fatigue** is often the most distressing symptom. It can be due to the natural progression of the disease and dysfunction of organs, poor feeding, muscle wasting, depression and sleep disorders. In some forms of cancer, the general malaise is made worse by hypercalcaemia and anaemia. Weakness from anaemia can be due to overexpression of IL-1, IL-6 and TNF-α by cancer cells, and suppression of erythropoiesis by these cytokines. Wasting develops from loss of appetite and enhanced hydrolysis of body protein, and TNF, IFN-γ and leukaemia inhibitory factor can mediate this response.

Stress can increase the risk of tumour-cell proliferation. In humans, cancer mortality tends to be high in individuals who have a driving, impatient and sometimes hostile personality. Such people go through states of repeated frustration because of unachieved goals. They alternate between a sense of being able to cope to one of being unable to cope. This pattern is thought to cause repeated episodes of suppression and recovery of the immune system, and to increase the growth of transformed cells (Fox *et al.*, 1987). Some of the ways this occurs are:

- increased β-adrenergic-induced suppression of NK cell activity, and reduced recruitment of spleen cells as anti-tumour cells;

- reduced function of tumour-specific cluster designation 4^+ ($CD4^+$), and inhibition of IL-12 production by adenosine accumulation where large tumours cause localised hypoxic conditions;
- potentiation of capillary growth (angiogenesis) in tumours by glucocorticoids making nutrients more readily available for tumour growth.

In mice infected with mammary tumour virus, handling stress increased the prevalence of mammary tumours from 7% to 92% (Riley, 1975). Stress also reduces the effectiveness of chemotherapy against this form of cancer.

The prevalence of **pain** among patients with newly-diagnosed cancer is about 28%, and this rises as the disease advances and as therapy becomes more aggressive. Unrelieved cancer pain is debilitating, interferes with the ability to eat and sleep and leads to fatigue. Bone metastases are the most common cause of chronic pain in cancer patients. They are often associated with direct invasion of bone marrow with a tumour that has metastasised from soft tissue. The tumour cells adhere to endothelial surfaces within the bone marrow, and the cancer develops through marrow sinusoids to the endosteal bone surface where it causes remodelling of bone. The thoracic vertebrae are a common site where the metastases lodge, and they inflict pain by compressing the spinal cord, stretching the periosteum as the tumour expands, putting pressure on regions where the bone is weakened and collapsing the bone in regions where it has been resorbed (Mercadente, 1997). The pain is often dull, intermittent in nature and occurs as breakthrough pain associated with physical movement or weight bearing. Stabbing pains may be felt when there is nerve compression.

It is well recognised that bone cancer causes pain and discomfort in animals as well as humans (Plate 10). In one of the mouse experimental models for bone cancer, murine osteolytic sarcoma cells are injected into the intramedullary space of the animal's femur (Schwei *et al.*, 1999). Light palpation of the distal femur produces a nocifensive response, including withdrawal of the limb, fighting, vocalising and biting. There is also guarding of the affected limb. This model is being used in designing pain therapies.

12.5 Stress and Immune Function

It is well known that stress can suppress immune function. Stress-induced immune suppression helps to limit and delay inflammatory pain until the immediate danger from the stressor has passed. It also helps prevent abnormal overactivity and exhaustion of the immune system that might otherwise occur during the acute-phase response. In the short term this has benefits, but if the stress-induced suppression persists, there can be unfortunate consequences. In general, chronic stress is immunosuppressive and acute stress is immunoenhancing (Table 12.2). During

Table 12.2 Common effects of acute and chronic stress on immune function.

Acute stress	Chronic stress
↑ leukocyte redeployment	↓ leukocyte proliferation
↑ effector-cell function	↓ effector-cell function
↑ cell-mediated immunity	↓ cell-mediated immunity
↑ humoral immunity	↓ humoral immunity

acute stress, adrenaline and noradrenaline mobilise leukocytes which are distributed through the blood to other organs. Leukocyte uptake during acute stress is usually raised and so there can be a decrease in circulating leukocyte numbers.

The ways in which **chronic stress** suppresses the immune system are highly specific, and only particular types of defence against disease are affected. One of the main inhibitory mechanisms is mediated through T-helper cells (Th). T-helper cells are lymphocytes that enable the destruction of pathogens by interacting with phagocytes.

Stresses that involve the release of glucocorticoids, adrenaline or noradrenaline, and inflammatory responses that provoke histamine or adenosine release, can all result in suppression of IL-12 production. IL-12 is one of the key regulators of the balance between Th1 and Th2 cells. IL-12 encourages a shift away from a Th2 immune response towards a Th1 response. Th1 and Th2 cells have quite distinct cytokine profiles. Th1 cytokines are IFN-γ, TNF-β and IL-2, whilst Th2 cytokines include IL-4, IL-5, IL-6, IL-9, IL-10 and IL-13. The Th2 cytokines are involved in humoral immune responses such as antibody and allergic responses, whereas the Th1 cytokines activate cellular immune responses including cytotoxic, inflammatory and delayed hypersensitivity reactions (Elenkor *et al*., 2000). Thus, when stress suppresses IL-12 production, the capacity of cellular immune mechanisms is reduced. Th2 responses are still effective, but these are less organ specific than the Th1 responses.

In practical terms, this means that some disorders are more likely to be precipitated by chronic stress than others. These include respiratory disease, toxoplasmosis, *Salmonella* infection and cancer. Infection of an existing gastric ulcer is also likely to be increased, because defence against this happening is largely mediated by Th1 responses. Similarly, traumatic injury, including burns, which provoke intense sympathoadrenomedullary and HPA axis activation, leads to diminished IL-12 and IFN-γ production, and this will promote a Th2 shift which could lead to infection (Molloy *et al*., 1995). Wound healing is also likely to be delayed. Ischaemia leads to localised build-up of adenosine, which in turn inhibits IL-12 and TNF-α production and potentiation of IL-10, which together produce a Th2 shift and suppression of cellular immune responses.

Another way in which stress can lead to immune suppression is through increasing the release of natural opioids. Endogenous opioids can suppress immune responses by reducing antibody production and NK cell activity through κ-opioid receptors (Rogers *et al*., 2000). Met-enkephalin, on the other hand, enhances immune reactions.

There is one positive outcome of the immune-suppressing effects of chronic stress. Chronic stress can help to reduce the incidence and severity of autoimmune diseases, and this has been demonstrated in rats using an experimental model for allergic encephalomyelitis.

Some of the stressors that compromise immune function are inevitable aspects of life, whilst others are quite subtle. In humans, psychological stressors such as bereavement, preparing for examinations, marital strife, looking after a spouse with dementia and depressive illness, have been shown to adversely affect immune function. In mice, social disruption, through transferring dominant mice between cages of subordinate mice, increased subsequent mortality to an influenza virus challenge from 11% in unmixed controls to 86% in the mixed dominant mice (Sheridan *et al*., 2000). In monkeys, low social status has been linked to a greater probability of being infected with an upper respiratory tract infection and gastrointestinal infection with an adenovirus.

Susceptibility to infection is greatest in young, old and immunocompromised individuals. Weaning in very young animals can be a high risk period. During **segregated early weaning** (SEW), piglets are weaned at 5–21 days of age into a low-pathogen environment. The stated purposes with SEW are to eliminate or avoid respiratory diseases in a herd by weaning piglets at a time when immunity to those particular diseases is provided by colostrum-derived immunoglobulins, and to encourage high growth performance. Normally, the piglets' immunity is low at three to four weeks of age. This is because the maternally-derived passive immunity is declining and the piglet's own ability to produce an active immune response has not completely developed. This period of reduced immune protection is known as the **immunity gap**. Weaning during the immunity gap is thought to pose a particular risk for piglet health, and current thinking amongst veterinarians is that this can be avoided by either using SEW or by weaning later, when the piglet can mount its own immune responses.

Early weaning is the least sensible of these two strategies as it is likely to lead to some serious health risks after weaning. It is not always realistic to wean piglets into a pathogen-free environment, and so the weaning ration is usually medicated with antibiotics. These help to control enteric disease and they promote growth rate, but there is growing evidence that such indiscriminate use of antibiotics by the pig industry is leading to antibiotic-resistant strains of bacteria. Weaning at four to five weeks of age would be a more sensible strategy, as it would avoid the immunity gap and it would not require the widespread use of feed antibiotics.

12.6 Corticosteroid Therapy

Corticosteroids are used routinely in veterinary and human medicine to control inflammation, provide relief from pain that is caused by inflammation, induce parturition and, in conjunction with antineoplastic drugs, in treating cancer. Injudicious use of corticosteroids at pharmacological doses can increase the risk of infection through suppression of:

- T-lymphocyte numbers;
- Th cells;
- immunoglobulin levels;
- NK cell activity;
- macrophage antigen expression;
- cytokine production.

These are normal effects of this group of drugs, and one of the implications of inducing calving in dairy cows with long-acting corticosteroids as a routine measure for controlling the calving pattern, is the increased risk of infections. Similarly, hyperactivity of the HPA during depression or chronic stress, leading to high circulating levels of glucocorticoids, causes immune suppression and increased susceptibility to infectious disease (Falaschi *et al.*, 1994). Lower (physiological) concentrations of corticosteroids are more likely to be immunoenhancing.

12.7 Anaemia

Anaemia is associated with a sense of fatigue, dizziness or headaches, and dyspnoea during exertion. In the human being these feelings develop when haemoglobin levels are less than 7 g/100 ml of blood. The heart compensates by increasing stroke volume, and, in severe cases, circulatory congestion similar to that seen in congestive heart failure can develop. In animals, anaemia has been a problem in calves used for white veal production, because of the iron deficient milk diet they receive. Iron deficiency anaemia also occurs in piglets and lambs that are reared indoors without access to iron supplementation.

12.8 Hazards of Improving Disease Control

Some of the tests that are used for genetically-selecting animals for resistance to particular diseases have been criticised because they are very unpleasant for the animals. They involve producing either the clinical or the subclinical condition, and its associated suffering. An example is the facial-eczema test used in sheep in

New Zealand. Facial eczema occurs in cattle, sheep and deer (Plate 11). It is caused by a fungal toxin (sporodesmin) in dead pasture and results in liver damage and photosensitisation when eaten.

The test sheep are dosed with sporodesmin, and liver damage is assessed from the serum gamma glutamyl transferase (sGGT) response. Animals with a high sGGT response are susceptible to the disease. In severely-affected animals there would be photosensitisation, skin soreness and jaundice, but this can be minimised by using subclinical doses of sporodesmin. The adverse welfare consequences with this type of test in susceptible animals are almost inevitable, but the overall saving in suffering through genetic selection helps justify the procedure.

Sometimes the cure is almost as unpleasant as the disease itself. In the past, the gapes in chickens was treated by forcing the birds to breathe in carbolic-acid fumes. Great care was needed to ensure the birds were not overdosed. Nowadays, this parasitic worm is eliminated from the airways of the lungs in a kinder way, with anthelmintic drugs.

12.9 Diseases Used for Controlling Pests

The advantage of using a disease for pest control is that it can be effective against large numbers of the pest species with little expenditure of effort. In some cases it can also be species specific.

Myxomatosis has been used to control rabbits in many countries. The time to death following infection with the myxoma virus varies with the virulence of the strain of virus. It ranges from 10–50 days. With virulent strains, skin swellings appear over the body after four or five days. Conjunctival swellings emerge on the fifth or sixth day and the eyes are completely closed a day or two later (Ross, 1972). Death is often from secondary infection of the respiratory tract. Rabbits that recover from an infection have difficulty seeing, because their eyes are glued together by a tenacious purulent exudate, and their breathing is restricted.

Rabbit calicivirus has been introduced as an alternative to myxomatosis. This virus is thought to cause liver damage which results in the release of clotting factors such as thromboplastin, which causes disseminated intravascular coagulopathy (DIC). This in turn results in a stroke if the clot lodges in the brain, or cardiac irregularities if there is an infarct in the heart, which should be relatively benign ways to die. Unfortunately, this is not always the case. Sometimes there are signs of sickness including anorexia, rapid respiration, cyanosis, ataxia, paddling movements of the limbs and, finally, frenetic behaviour with squealing before death (Chasey, 1997). About 20% of affected rabbits discharge foamy blood from the nostrils. When death is quick, following the stroke or cardiac arrest, it should provide a more humane death than that from myxomatosis.