PHYSIOLOGICAL MECHANISMS CAUSING SICKNESS BEHAVIOUR AND SUFFERING IN DISEASED ANIMALS

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Disease is one of the most important causes of animal suffering. When diseases are treated the aim is to achieve rapid and permanent recovery and this helps to reduce the duration of suffering. It does not, however, alleviate suffering during the fulminant and recovery phases. Greater attention needs to be given to alleviating suffering and the signs of sickness during disease states. In this paper, the role of the cytokines in mediating sickness behaviour and suffering during disease is reviewed. The importance of sickness behaviour in improving the chances of recovery are considered, along with the potential use of anti-cytokine strategies in alleviating suffering in disease states.

Keywords: *animal welfare, cytokines, disease, interleukins, sickness behaviour, suffering*

Introduction

Animal Welfare Science usually focuses on those aspects of animal suffering for which mankind is to blame. This is understandable, but there are situations, which may be unrelated to human activity, in which severe suffering occurs. Infectious disease states are a case in point. Suffering during disease can be recognized from a wide range of signs in the animal, including listlessness, fatigue, reduced social interaction, inappetance, apparent mental confusion, impaired memory, learning deficits and, in some diseases, fever. Animal owners and veterinary practitioners have particular skills (developed through experience) in recognizing these and the many other signs associated with being ill. This paper will explain how some of these sickness behaviours are brought about. Are they inevitable consequences of being ill? Do they serve a purpose in terms of survival – or are they unfortunate side-effects of the disease process and recuperation? It will be shown that there are particular physiological mechanisms which work through the brain and bring about sickness behaviour, and that they are closely associated with the mechanisms which mediate the body's defence during disease. In the future, it is likely that the medical and veterinary professions will be in a position to control the expression of specific aspects of these behaviours by neuro-pharmacological means; and society and the professions will periodically need to review the overall benefits and wisdom of this strategy.

The main body defences occurring during an infection are known, collectively as the 'acute phase response' (Kushner 1988). These responses are initiated – and to a large extent controlled by – a group of chemical mediators known as the cytokines. The cytokines act locally, for

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example by increasing the stickiness of the endothelium to leucocytes and other particles and by increasing capillary permeability. They also act at a distance from the foci of the infection by stimulating the immune system and skeletal muscle catabolism. They are often described as hormone-like mediators that initiate the immune response. A large number of cytokines have now been discovered, and their role in fighting disease is a rapidly expanding field of research. The interleukins are a particularly important group of compounds within the cytokines, and (see Dinarello 1984; Sipe 1985) they mediate the acute phase response by initiating:

i) Fever.
ii) Neutrophilia: through stimulating the bone marrow to produce and release more neutrophils.
iii) Proteolysis; muscle proteins provide amino acids for gluconeogenesis and the synthesis of specific proteins required in the acute phase response. The muscle catabolism may be associated with muscle pain.
iv) Synthesis of acute phase proteins, for example, fibrinogen and proteinases.
v) Immune responses originating in lymphoid tissue.
vi) Collagen synthesis in fibroblasts.

It is increasingly appreciated that the interleukins, and other cytokines, are also directly responsible for initiating specific features of sickness behaviour. They achieve this through their action on the brain, as outlined below.

The benefits associated with feeling ill

There are a number of sickness behaviour patterns which occur in a wide variety of diseases. These include: fever; increased time spent sleeping; reduced food consumption through loss of appetite; social isolation; mental confusion; and impaired memory and learning capacity.

The first four of these sickness behaviours have undoubtedly exerted an evolutionary survival advantage. When an animal is ill it will often stop eating, hide itself, or curl-up in a corner on its own and spend more time sleeping. Intuitively, we would think that rest will help it to recover; social isolation would reduce the risk of spread of the disease; and inappetance would enhance proteolysis and allow the blood supply to be shunted away from the digestive tract to other sites where demands are more important for the body's defence. In these simple terms, there would be survival benefits of sickness behaviour; and presumably for it to occur in the first place, the animal has to feel ill. It is an unfortunate reality that in this instance suffering has probably aided survival.

Over the years these behaviours have presumably had benefits in a predator-prey context as well. The predator, like the veterinarian, has a sharp eye for signs of weakness in animals: if a weakened animal is asleep in a corner on its own it is more likely to escape the attention of the predator. The veterinarian gets round this by knowing or guessing where to look for animals that are hiding when they are sick.

If it is accepted that sickness behaviours have generally given species evolutionary advantages in terms of survival, the next question is, do they have any relevance today? Do most sickness behaviours assist survival in animals that are in our care, or are they undesirable side-effects? If they aid survival, then does this influence how we should nurse and care for sick animals? For example, should we allow and even encourage full expression of these behaviours?

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To start answering these questions we need to consider the ways in which sickness behaviour could directly help to combat disease.

When humans develop a fever we feel discomfort partly from a knowledge of what is to come (learned aversion) but also from the direct effects of the fever. It has been claimed that fever is beneficial in terms of the body's defence in a number of ways (Kluger 1991) and that the elevated temperature could help to: i) enhance leucocyte proliferation; ii) enhance antibody production; iii) increase the rate of neutrophil accumulation at the site of an infection; iv) increase B lymphocyte responsiveness; v) increase the rate of interferon (IFN) production; and vi) induce hypoferraemia, which could help to curtail bacterial growth.

Overall, fever can help to suppress the infectivity of a pathogen. This has been demonstrated circumstantially in a number of ways. For example, when ferrets were infected with a recombinant influenza virus and subsequently treated with sodium salicylate, those animals in which fever was suppressed, had higher levels of viral infection than those in which it was not, irrespective of whether or not they were given salicylate (Figure 1).

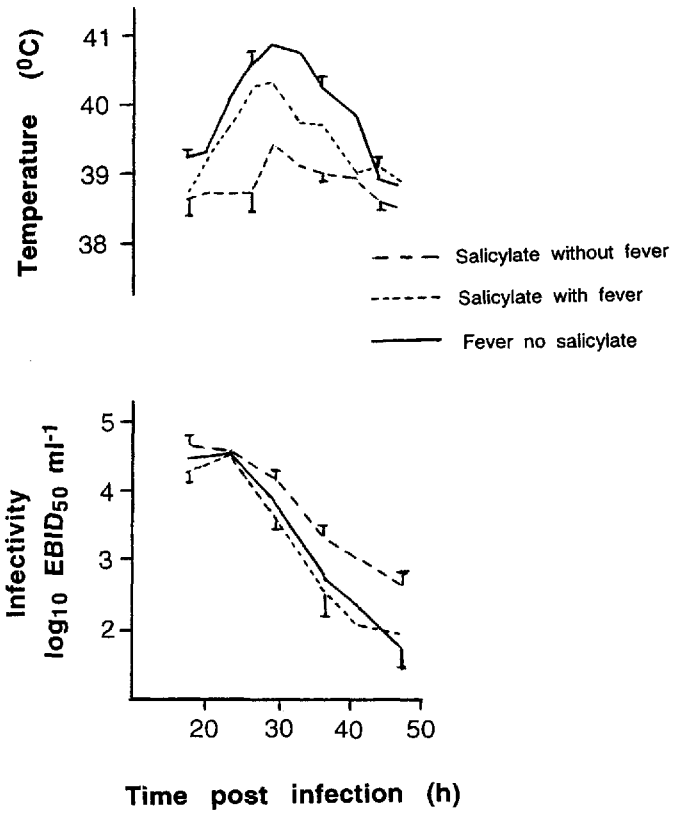

Figure 1 **Association between body temperature and infectivity of an influenza virus in ferrets. (Bars denote SEMs and are shown only for selected data points, for clarity; EBID - Egg-bit infectious dose.) Redrawn from Husseini *et al* (1982) with permission from Chicago University Press.**

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Similarly, when ferrets were shaved to enhance heat loss during fever, those individuals with the lower increments in rectal temperature had the highest viral titres (Husseini *et al* 1982). Evidently the elevated temperature was beneficial in its own right.

It is often said that one should 'feed a cold', but is this wise for all disease conditions? Empirical evidence from Wing and Young's (1980) study where mice were fasted for varying lengths of time and then injected intravenously with *Listeria monocytogenes*, showed that the longer the mice were fasted the lower the subsequent mortality (Figure 2). Evidently fasting before an infection afforded some protection against the disease. Whether this also applies during the infective stage needs to be tested.

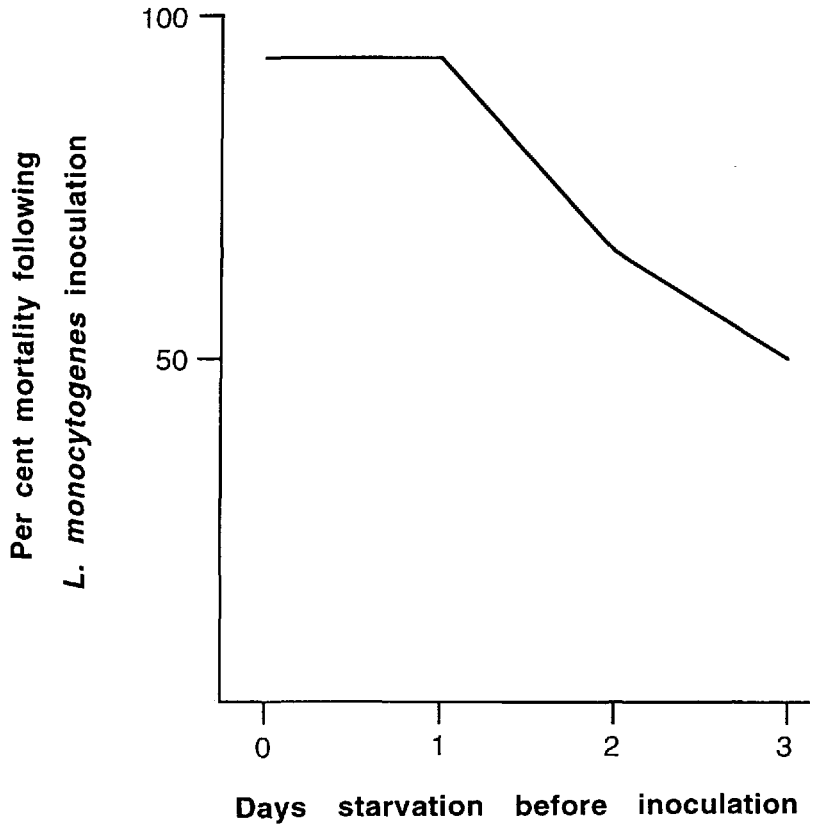

Figure 2 **Effect of fasting on mortality rate in response to intravenous injection of *L. monocytogenes*. After Wing and Young (1980).**

Tiredness and a need for sleep are common features of sickness behaviour. Studies investigating whether these serve a useful role in fighting disease are largely circumstantial as can be seen from the following examples: when rabbits were injected intravenously with *Staphylococcus aureus* those that survived the challenge slept more than those that died (Toth & Kreuger 1988), although whether this was a cause or effect is not clear. When healthy humans

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were subjected to a period of partial sleep deprivation, the natural killer cell activity in their blood was suppressed by about 30 per cent suggesting that they experienced a degree of immune suppression (Irwin *et al* 1994).

These examples for fever, inappetance and sleep imply that allowing expression of sickness behaviours could promote recovery from disease.

Links between the inflammatory response and sickness behaviour

The behavioural survival strategies which have evolved appear to have a physiological basis, and they are strongly linked to the defence reactions in disease. As mentioned (see, *Introduction*), the cytokines are key mediators in both the pathophysiological and behavioural responses. The cytokines assist in: blood clotting; increasing capillary permeability; recruitment of neutrophils; adhesion of leucocytes to the endothelium; increasing the presence of immunoglobulins and B lymphocytes; and in granuloma formation (Table 1). Besides this, they act on the brain and initiate some of the main behavioural effects involved in sickness behaviour (Dinarello 1984; Sipe 1985).

Table 1 Sources and actions of three cytokines that initiate sickness behaviour.

Cytokine	Source	Principal Actions	CNS Effects
IL-1	Macrophages, fibroblasts, endothelial cells, monocytes	Increased circulating neutrophils Secretion of colony stimulating factors Increased capillary permeability Increased prostaglandin synthesis Increased leucocyte adhesion Increased endothelial adhesion	Fever Sleep CRF secretion Inappetance Memory impairment Learning disability
IL-6	Fibroblasts, tumour cells, macrophages, endothelial cells	Increased synthesis and secretion of immunoglobulins by B lymphocytes	Fever
TNF	Macrophages, monocytes, T-lymphocytes	Haemorrhagic necrosis in tumours Lysis of bone Increased leucocyte adhesion Increased endothelial adhesion Induces granuloma formation Aids blood coagulation	Fever

Cytokine production is initiated by other cytokines and by chemical components present in bacterial cells. For example, the outer membrane component of Gram-negative bacteria lipopolysaccharide (LPS) stimulates macrophages to synthesize interleukin-1beta (IL-1β) and tumour necrosis factor (TNF). See van Deuren *et al* (1992). These cytokines in turn initiate the macrophage synthesis of IL-1, IL-6 and IL-8, while IL-6 acts on the macrophages inhibiting the further synthesis of IL-1β and TNF (Figure 3). In this way, cytokines have autocrine as well as paracrine and endocrine effects.

Normally, cytokines are unable to pass through the blood-brain barrier. Instead, the cytokines that are released peripherally bypass the blood-brain barrier and initiate sickness behaviours through at least two specialized routes: i) activation of afferent neurones which pass to the brain,

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eg vagal afferents activated by IL-1β (Fleshner *et al* 1995); and ii) activation of the organum vasculosum of the laminal terminalis (OVLT) alongside the third ventricle (Gottschall *et al* 1992). This region acts as a bypass around the blood-brain barrier, and operates in part by converting cytokine stimulation into Prostaglandin E_2 (PGE_2) synthesis. The prostaglandins synthesized in the OVLT then activate neurones in the brain and, in particular, neurones in the preoptic area (POA) of the hypothalamus. It is also suspected that cytokines acting on the OVLT stimulate cytokine synthesis within the brain (Gottschall *et al* 1992), but this has not yet been validated.

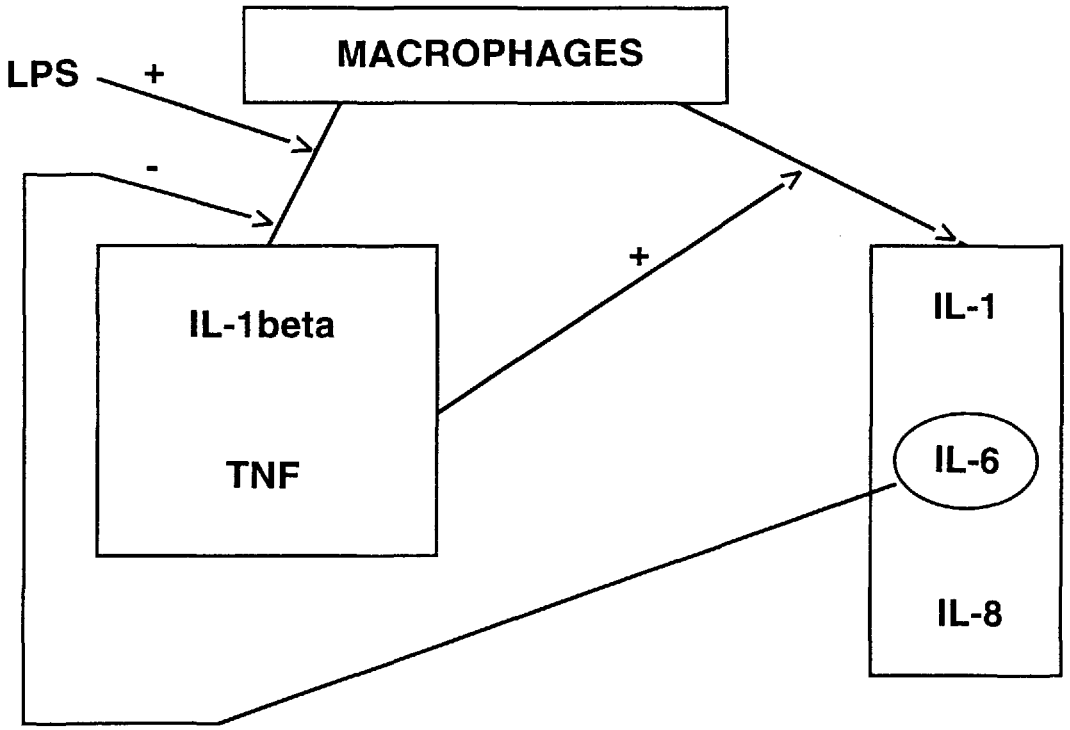

Figure 3 **Feedback mechanisms that operate in the production of cytokines by macrophages.**

Fever

The POA of the hypothalamus is the region in the brain which controls the set-point about which body temperature is regulated. In other words, it acts as the thermostat in the control of core body temperature. When a cytokine surge initiates activation of the POA, there is an increase in the set-point and this results in fever. Unlike many of the other behavioural effects of cytokines, this particular response is not necessarily mediated by prostaglandins in the OVLT.

The expression and severity of a fever is controlled and modified in a complex manner by a variety of interacting influences (Blatteis 1992). The following list of observations demonstrates how complex this subject is:

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i) There are thought to be about 12 endogenous pyrogens: IL-1α, IL-1β, IL-2, IL-6, IL-8, TNFα,TNFβ, IFNα $_2$ IFNβ, IFNγ, Macrophage Inflammatory Protein-1 (M1p-1), and Granulocyte-Macrophage Colony-Stimulating Factor (GM-CSF). Their potency varies between species. For example, IL-1α is less potent than IL-1β in the rat but it is more potent in the rabbit (Blatteis 1992).

ii) The duration of a fever varies according to the pyrogenic cytokine (eg interferons in general elicit long-lasting fevers, whereas with IL-1β they are short). See Blatteis (1992).

iii) Different infectious stimuli provoke the production of different pyrogenic cytokines (eg bacteria activate IL-1β, IL-6 and TNF, whereas viruses activate interferons). See Blatteis (1992).

iv) Different pyrogenic cytokines are active at different stages of a fever (eg TNFα is only present at the start of a fever). See Roth *et al* (1993).

v) Some pyrogenic cytokines promote the production of other pyrogens (eg IL-1β stimulates IL-6 production). See van Deuren *et al* (1992).

vi) The thermogenic action of lipopolysaccharide-induced IL-1β is reduced by a simultaneous stress, such as restraint (Blatteis *et al* 1991).

vii) Other factors released peripherally during the inflammatory response can reduce cytokine production and fever (eg corticosteroids, PGE_2). See Coelho *et al* (1995).

viii) Other factors released during the inflammatory response can prevent pyrogenic cytokines from interacting with their receptors (eg interleukin-1 receptor antagonist, IL-1ra). See Opp and Krueger (1991).

ix) Cytokines initiate feedback mechanisms involving arginine vasopressin and αMSH (melanocyte-stimulating hormone) which limit fever (Blatteis 1992).

x) With the exception of IL-8, the pyrogenic action of cytokines is inhibited by peripheral injection of cyclo-oxygenase inhibitors.

xi) IL-1β is pyrogenic in both the anaesthetized and unanaesthetized states, and fever occurs independently of any effects on physical activity. When IL-1β is administered centrally, it exerts its pyrogenic effect through the release of corticotropin releasing factor (CRF) in the paraventricular nucleus (PVN) of the hypothalamus. The pyrogenic response to CRF is an acute response, and it is subsequently reversed by the action of glucocorticoids which are released during activation of the hypothalamic-pituitary-adrenal axis (Figure 4). The glucocorticoids also serve to control the inflammatory response locally, by reducing the formation of leukotrienes, thromboxanes, prostaglandins and prostacyclin at the site of infection.

In the future, it is quite likely that the different febrile responses occurring in different diseases will be explained (at least in part) by the way in which particular micro-organisms provoke a cytokine response.

Sleep

The sleep-inducing properties of the cytokines can be related to their fever-inducing properties. Some of the pyrogenic cytokines also have a somnogenic effect. In addition, the time-response patterns for the fever and sleep responses are similar. Typically, it is the non-REM type of sleep pattern that is increased during disease states, and in particular slow wave sleep (Toth & Krueger 1988). Slow wave sleep is a deep form of sleep. One distinction between the fever- and sleep-inducing effects is that non-REM sleep cannot be conditioned behaviourally, whereas fever can

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be conditioned, for example when using intraperitoneal LPS as the unconditioned stimulus (Bull *et al* 1994). Different mechanisms may initiate sleep and fever. For example, CRF can initiate fever in the short term whereas CRF either reverses, or has no effect on, sleep or investigatory behaviour (Dantzer et al 1992).

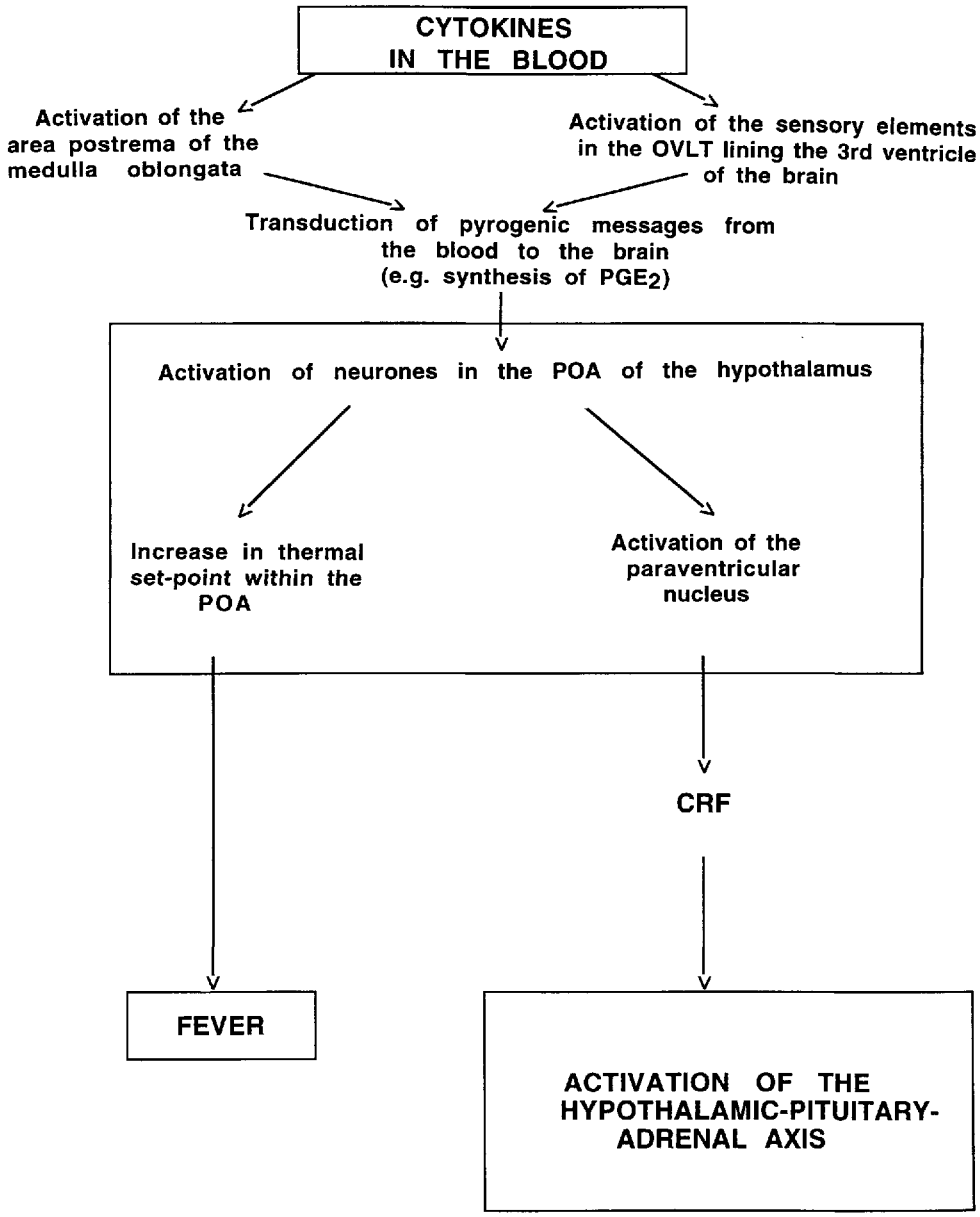

Figure 4 **Initiation of fever and adrenocortical activation by cytokines.**

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Inappetance and discomfort

A curious feature of the cytokines' action is that they do not pass the blood-brain barrier, yet the same behavioural effects can be produced when the cytokines are administered directly into the brain as when they are administered peripherally. One example of this is the effect of cytokines on appetite. Feeding can be suppressed by intracerebroventricular administration of IL-1, by intrahypothalamic IL-1, and by intraperitoneal IL-1 (Plata-Salamán & Ffrench-Mullen 1992).

The hypophagic response to interleukins can be suppressed with indomethacin, suggesting it is probably mediated through activation of prostaglandins; it can also be suppressed by intracerebroventricular administration of IL-1ra. It is thought that peripherally administered cytokines activate cytokine release within the brain (Plata-Salamán & Ffrench-Mullen 1992).

In rats, eating rate, meal size and meal duration are all suppressed by IL-1β, and water intake may also be reduced (Plata-Salamán 1994). When given a free choice of dietary components, rats will increase the proportion of carbohydrate they consume and reduce their protein intake while undergoing IL-1β-induced hypophagia (Aubert *et al* 1995; Table 2).

Table 2 **Diet selection in rats treated with IL-1β in comparison with a cold exposure.**

	Caloric intake	% of Diet (mean[1] ± SEM)		
	kcal	Carbohydrate	Protein	Fat
Control	97±6	55.2[a]±4.1	29.7[a]±3.4	15.0[a]±2.2
*IL-1*β	42±5	68.7[b]±4.2	14.8[b]±2.9	16.5[a]±3.6
Cold	102±7	52.3[a]±4.3	24.6[a]±3.0	23.1[b]±2.8

[1] Means within columns with different superscript letters were significantly different at $P < 0.05$. (After Aubert *et al* 1995.)

It is not entirely clear whether interleukin- and sickness-induced hypophagia are secondary to discomfort, or, whether they are brought about by discrete centrally mediated mechanisms. Rats show distinct aversion to cues which forewarn them that they are about to receive LPS (Exton *et al* 1995) and this could affect overall feed intake. Other effects of IL-1β which could be due to discomfort include reduced locomotory activity, learning disabilities and increased sensitivity to pain. The learning disability takes the form of poor acquisition and retention of memory and it is independent of the expression of fever (Gibertini *et al* 1995). The increased sensitivity to pain is both prostaglandin- and bradykinin-mediated (Perkins *et al* 1994).

Inflammatory mediators of pain

The pain which occurs during an infection serves as a physiological warning and it provokes responses which encourage the animal to protect the affected regions. It arises from tissue swelling, direct activation of nociceptors (which respond to tissue injury) and from enhanced excitability or responsiveness of sensory neurones. A number of substances are released from the damaged region which provoke inflammation which leads to pain. One which is attracting particular interest among research scientists is nitric oxide (NO). Nitric oxide is synthesized from arginine in a variety of cells by NO synthase, particularly when there is nerve injury. It can

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induce a delayed, burning pain when it is present in sufficient concentrations. This is achieved in various ways, including the production of pro-inflammatory prostanoids, and increasing the responsiveness of sensory neurones to inflammatory agents such as bradykinin (Dray1995).

The kinins (such as bradykinin, kallidin) promote inflammation by stimulating the release or synthesis of prostanoids, cytokines and free radicals. They also degranulate mast cells causing the release of histamine which increases capillary permeability. Through mediators, they can help to bring about the acute phase response and the inflammatory response. They also provoke pain by directly activating the nociceptors and by inducing hyperalgaesia (Dray 1995). The kinins are formed in the pathway that allows blood clotting. New opportunities in kinin analgaesia are being opened by B2 bradykinin receptor antagonists (Perkins *et al* 1993).

The prostanoids (prostaglandins, leukotrienes, hydroxy acids) are particularly important mediators of inflammatory hyperalgaesia. They are produced from arachidonic acid by cyclo-oxygenases and lipoxygenases. They do not usually provoke pain directly, but they do sensitize nociceptors and the pain can be prevented with cyclo-oxygenase inhibitors (Bonica *et al* 1990).

Sensitization can also occur through the effects of serotonin. Serotonin is released from platelets and mast cells during injury and inflammation, and it lowers the pain threshold to heat and pressure. Histamine is also released from the mast cells and provokes pain at high concentrations or itching at lower levels (Simone *et al* 1991).

Substance P[1] provokes pain both locally and by secondary hyperalgaesia through increasing excitability in the dorsal horn. The cytokines provoke pain indirectly by increasing prostanoid release and by increasing responsiveness of the bradykinin receptors.

This brief overview summarizes the great variety of mediators that are involved in inflammatory pain, and it highlights two things. Firstly, that there should be a number of opportunities for manipulating inflammatory pain by pharmacological means. Secondly, because a given inflammatory response could provoke more than one pain-producing mechanism, it may be difficult to alleviate inflammatory pain completely by using only one analgaesic.

Opportunities for anti-cytokine strategies

The discovery of an interleukin receptor antagonist (IL-ra) has opened up the possibility of manipulating the expression of sickness behaviour (Arend 1993) – and of recovering from a disease without having to feel ill. Whether this is desirable depends on the circumstances, on which behaviours are being manipulated, and whether their manipulation will compromise a subject's ability to combat the disease. Table 3 lists some circumstances in which high cytokine concentrations exert undesirable effects, or where, for other reasons, an anti-cytokine strategy might be appropriate. For certain endotoxaemias (eg *Escherichia coli, Staphylococcus epidermidis, Borrelia burgdorferi*), there is growing evidence that anti-cytokine strategies can reduce mortality – as well as presumably alleviating suffering (Dinarello *et al* 1993).

[1] Substance P is an undecapeptide, first described in 1931 by von Uller and Gaddum (*J. Physiology[London] 72:* 74-87). Released from the terminals of certain neurosensory cells, it acts as a neurotransmitter or modulator in the pain response.

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Table 3 Opportunities for anti-cytokine strategies.

Treating shock, due to vascular leakage and vasodilation
Alleviating respiratory distress syndrome due to adhesion and sequestration of leucocytes in the lungs
Preventing DIC due to procoagulant activity
Alleviating excessive fever
Treating cachexia
Alleviating mental confusion
Managing fever during pregnancy
Managing fever in patients with a heart condition
Reducing mortality during septicaemia

IL-1ra is a protein with 152 amino acids which is synthesized in the same cells (monocytes) that make IL-1. Normally, only a few IL-1 receptors need to be occupied by IL-1 to induce a biological response (Arend 1993). This implies that an excess of IL-1ra has to be present to block a substantial part of the effects of IL-1. Nevertheless, IL-1ra has been found to be effective in inhibiting the inflammatory response and a number of the behavioural effects that are produced by IL-1β including: reduced food and water intake; reduced social interaction; fever; and sleep (Plata-Salamán & Ffrench-Mullen 1992). No doubt other IL-ras will be discovered in the future, and high potency analogues will be synthesized. This is an exciting area of scientific endeavour which could lead to alleviation of some of the suffering associated with particular diseases.

Animal welfare implications

The sickness behaviours associated with an infectious disease are an integral part of the mechanisms that help an animal recover from that disease. Without them, survival could be jeopardized. Immune responses and some sickness behaviours are closely linked through the cytokines that are produced during the response to a disease. In these situations, animal suffering may inevitably be linked with immune defence and survival. Appropriate strategies which reduce suffering in disease states without compromising an animal's ability to recover need to be explored. However, for the present, it is proposed that clinical manipulation of sickness behaviours using anti-cytokine strategies should only be undertaken where there is a good understanding of the possible side-effects.

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