Chapter 1b

Stressors and vitamin C metabolism in animals: a brief review
Summary
This brief review is an account of stressful conditions in relation to vitamin C metabolism in animals. It considers the effects of various stressors on vitamin C blood status and consequently the immune response. It is aimed to describe the immune system-vitamin C interrelationship, different stressors and the beneficial effect of vitamin C supplements.

Introduction
Stress in animals results in a wide range of physiological changes in order to maintain their homeostasis (34). The response to stressors comprises the activation of the sympathetic-adreno medullary system, which involves the immediate release of catecholamines, or the hypothalamic-pituitary-adrenocortical system, which involves a more gradual system release of glucocorticoids (34, 37).

One of the major roles of the water-soluble vitamin C (ascorbic acid), is its antioxidant property. This function is accomplished by inactivating harmful free radicals produced through normal cellular activity and mediated through various stressors (10). Mammals and poultry have evolved the ability to synthesize ascorbic acid in the liver and kidneys, respectively. Under normal conditions, the requirement of vitamin C is met endogenously and there is no need for exogenous supplementation. However, under stress conditions, the status of vitamin C is greatly reduced. Therefore, this review was performed in an attempt to investigate the effect of different types of stress on vitamin C status.

Vitamin C and the Immune system
Ascorbic acid is the most important antioxidant extracellular fluids (50). It is thought to be important in optimum functioning of the immune system through enhancement of neutrophil production and also through protection against free radical damage (6, 3). Vitamin C is found in high concentrations in blood leukocytes (35). The protective effect of vitamin C may in part be mediated through its ability to reduce circulating glucocorticoids (17). It has been reported that vitamin C stimulates either humoral or cell-mediated immunity of mice (32), guinea pigs and humans (40), rabbits (49) and calves (31). The favorable effect of ascorbic acid appears to occur only in the presence of sufficient quantities of the antioxidant, vitamin E (41).

Ascorbic acid acts as a scavenging or neutralizing substance of free radicals. The antioxidant function of ascorbic acid could, at least in part, enhance immunity by maintaining the functional and structural integrity of important immune cells. Nutrients involved in the antioxidant function are used at a greater rate in infected animals. Participation of vitamin C in augmenting the white blood cells function takes several ways. Indeed, ascorbic acid is involved in the immunological and antibacterial functions of white blood cells by several factors: increasing their mobility (42); stimulating the energy producing monophosphate shunt within the cell (2) and consequently is coupled with their phagocytic processes (42). Secondly, vitamin C protects leukocytes from auto-oxidation (2, 28). Thirdly, vitamin C increases serum immunoglobulins concentrations and antibody functions (28).
Vitamin C has been shown to be important in complement activity (46), antibody responses, and a variety of other immune functions in higher vertebrates (38). Vitamin C also stimulates the phagocytic capacity of neutrophils in the peripheral blood. It is suggested that vitamin C can be used with other immunomodulators to adapt the defence by organisms (11).

Types of stressors affecting vitamin C concentrations
Vitamin C plays a potential role as a stress-relieving nutrient as it has recently been characterized as one of the anti-stress substances (4, 1). The synthesis of ascorbic by farm animals is reduced or may cease during stress caused by disease, vaccination, higher temperature, overcrowding or physical activity (22, 53). Fasting increased mean buffy coat ascorbic acid concentration and decreased mean plasma ascorbic acid concentration (30). It was proved that glutathione and ascorbic acid could significantly reduce ceftriaxone-sodium-induced lipid peroxidation, and they appear to be promising candidates for further investigation in this regard (45). Stress increases the demand for ascorbic acid (36).

Housing
The stress associated with confinement of calves decreased the immune response to a specific antigen and decreased concentrations of ascorbic in plasma (16). There was also a decrease of adrenal ascorbic in mice (47) and a drop in blood and adrenal levels in rats as well as increased urinary excretion (51). A correlation was found between temperature and the decrease in plasma ascorbic acid (43). Under these types of conditions, higher doses of ascorbic, amounting to 1.25-2.5 g/animal and day, have a positive effect on the immune system and health of calves (7, 26).

Under heat stress, supplementary vitamin C can support the bird’s performance in modern poultry operations. The utilization of ascorbic acid usually is, under such conditions, elevated in individual organs and tissues, and high vitamin C applications can distinctly improve the immune response. Obviously, high producing poultry breeds under heat stress cannot synthesize sufficient vitamin C to cope with their requirements (19).

A marked decrease of L-ascorbic level was seen in purebred Friesian cattle as compared with 62.5% crossbred (Butana X Frıesan) and Butana cattle during the summer season (33). The noticeable decrease in ascorbic acid levels may be attributed to the influence of high environmental temperature. This means that the metabolic need for ascorbic is increased under stressful conditions. It has been proved that conditions, such as extreme temperature, led to a higher metabolic requirement for vitamin C (18, 8, 15).

Vitamin C can reduce the negative effect of corticosterone by regulating their concentration. It is not yet fully understood whether this is achieved by reducing the synthesis and/or secretion of corticosterone, or by breaking it down. It was suggested that the administration of ascorbate could nullify the oxidative stress produced by exercise in thoroughbred racehorses, but it could not prevent muscular damage (55).
Transportation

Transportation is an acute stressor for ruminants and can elevate serum cortisol concentrations for 4 to 7 days post transportation. As a consequence of transportation, cortisol and other glucocorticoids suppress the immune response in cattle and other species (44). Ascorbic acid, pyridoxine and riboflavine when given to male Black Pied German cattle and before and after transportation helped them to adapt and increase their resistance to stress (54). These results may give a clue to the importance of supplementing transported sheep with vitamin C. However, it was found that plasma ascorbic acid in transported mares increased (5).

Weaning

Weaning is regarded as stress to young animals. To reduce the effect of post weaning in young guinea pigs it was considered necessary to add ascorbic acid before weaning (48). It is recommended that imported rhesus monkeys should be given ascorbic acid during the period of acclimatization. To study the effect of acute stress by dog barking, ewes were infused with oxytocin, prolactin and ascorbic acid with a resultant suppressed cortisol responsiveness to stress (12). For the horse, it was found that plasma ascorbate concentrations were low in weaned foals (24).

The beneficial effects of vitamin C supplementation

The vitamin C requirement of the calf is determined by the conditions under which it is kept. Ascorbic acid supplementation increased the concentrations of IgG in plasma of calves that were deprived of colostrum (7, 15). The levels of IgM in calves supplemented with vitamin E and C generally tended to be higher than those of control calves (23). However, dietary ascorbate was not immunostimulatory in dairy calves up to 56 days of age and appeared to inhibit antibody synthesis. At 14 day of age there was an interaction of ascorbic supplementation and colostrum feeding: plasma IgM concentrations were higher in colostrum-deprived calves fed ascorbate than in colostrums-deprived calves not fed ascorbate (15). However, attempts to stimulate immune function with dietary supplements of ascorbic acid had mixed success (14).

Dietary ascorbic acid was shown to increase antibody response to sheep red blood cells (34). Chickens fed an ascorbic acid supplemented-diet had lower heterophil to lymphocytes ratios than did untreated controls indicating that ascorbic acid may help chickens in coping with stress by improving humoral immune response to pathogens. Presently, the mechanism by which resistance occurs is not clear. Calves supplemented with vitamin C had a lower incidence of scouring (15). Similarly, vitamin C supplemented at 330 mg/kg reduced mortality and pericarditis in chicks infected with E. coli (21). The amount of vitamin C needed for this protective effect increased with a higher environmental stress level. In rabbits, the supplementation of ascorbic acid reduced the oxidative damage of erythrocytes, liver and kidney caused by T. brucei (52).
Under unfavorable conditions, dietary supplements of ascorbic acid often help to reduce the effects of stress (20) by alleviating the suppressive effect of corticoids on neutrophil function in cattle (44).

Adaptation

Vitamin C plays a central role in the bird’s ability to cope with stress as its involved in the synthesis of adrenaline and corticosterone. These hormones are responsible for the mobilization of energy for the so-called essential functions such as blood flow, heat dissipation, maintenance of body temperature, respiration, etc. As long as vitamin C is not depleted, adrenaline, and later corticosterone, can be synthesized and released. This allows the bird to survive and remain productive. However, the greater the depletion of vitamin C, the smaller is the ability of the birds to synthesize these hormones. Vitamin C has yet another role to play in stress management. During stress, corticosterone is released in such large amounts that it became cytotoxic and suppress the immune functions (49). Further research is needed to explore this area.

Concluding remarks

Recent studies revealed that under stress conditions, supplementation of ascorbic acid could support the animal. The low ascorbic status resulted in depression of growth, increased susceptibility to infections and eventually death of the animal. The great advantage of vitamin C supplementation is that it is safe and easy to use. Furthermore, since vitamin C can be added to the feed or drinking water, it is a cost-effective tool to counteract heat stress in non-ruminants.

References
17. Degkwitz, E. 1987. Some effects of vitamin C may be indirect, since it affects the blood levels of cortisol and thyroid hormones. Ann. NY. Acad. Sci.