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Review:

Acute phase reaction and acute phase proteins*

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Abstract: A review of the systemic acute phase reaction with major cytokines involved, and the hepatic metabolic changes, negative and positive acute phase proteins (APPs) with function and associated pathology is given. It appears that APPs represent appropriate analytes for assessment of animal health. Whereas they represent non-specific markers as biological effect reactants, they can be used for assessing nutritional deficits and reactive processes, especially when positive and negative acute phase variables are combined in an index. When such acute phase index is applied to separate healthy animals from animals with some disease, much better results are obtained than with single analytes and statistically acceptable results for culling individual animals may be reached.

Unfortunately at present no cheap, comprehensive and easy to use system is available for assessing various acute phase proteins in serum or blood samples at the same time. Protein microarray or fluid phase microchip technology may satisfy this need; and permit simultaneous analysis of numerous analytes in the same small volume sample and enable integration of information derived from systemic reactivity and nutrition with disease specific variables. Applying such technology may help to solve health problems in various countries not only in animal husbandry but also in human populations.

Key words: Acute phase protein, Acute phase reaction, Animal health, Assessment, Cytokine, Index, Nutrition
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INTRODUCTION

The first reaction of the body to immunological stress is the innate, non-specific response preceding specific immune reactions. The acute phase response (APR) is a prominent systemic reaction of the organism to local or systemic disturbances in its homeostasis caused by infection, tissue injury, trauma or surgery, neoplastic growth or immunological disorders (Gordon and Koy, 1985; Gruys *et al*., 1999). At the site of invasion by a micro-organism and the place of tissue injury, a number of responses of the tissue itself are initiated. Pro-inflammatory cytokines are released, and the vascular system and inflammatory cells are activated. These responses in turn are associated with production of more cytokines and other inflammatory mediators which diffuse to the extracellular fluid compartment and circulate in the blood.

The cytokines activate receptors on different target cells leading to a systemic reaction resulting in activation of the hypothalamic-pituitary-adrenal axis, reduction of growth hormone secretion (Gruys *et al*., 1999) and a number of physical changes clinically characterised by fever, anorexia, negative nitrogen balance and catabolism of muscle cells (Dinarello, 1983; 1989; Ingenbleek and Carpentier, 1985; Ingenbleek and Young, 1994; Kraft *et al*., 1992; Kushner *et al*., 1981; Langhans, 1996; van Miert, 1995). Furthermore a series of changes can be measured in the laboratory: such as (1) a decrease of blood plasma low and high density lipoprotein-bound cholesterol and leukocyte numbers in blood, (2) increased values of adrenocorticotrophic hormone (ACTH) and

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glucocorticoids, (3) activation of the complement system and blood coagulation system, (4) decreased serum levels of calcium, zinc, iron, vitamin A and of α-tocopherol, and (5) a change in concentration of several plasma proteins, the acute phase proteins (APPs) (Dinarello, 1983; 1989; Gruys *et al*., 1994) largely due to a changed hepatic metabolism. When the receptor triggering has repeated pulses, the acute phase response can become chronic.

Within a few hours after infection the pattern of protein synthesis by the liver is drastically altered resulting in an increase of some blood proteins, the positive APPs (Blackburn, 1994; Dinarello, 1983; 1989; Gruys *et al*., 1994; Ingenbleek and Young, 1994; Kushner *et al*., 1981). Hepatic mRNA upregulation of those APPs is associated with a decrease in synthesis of normal blood proteins, like transthyretin (TTR, formerly called prealbumin), retinol binding protein (RBP), cortisol binding globulin, transferrin and albumin, which represent the negative APPs. The positive APPs are mainly the proteins, C-reactive protein (CRP), serum amyloid A (SAA) and haptoglobin (Hp) which are released by the hepatocytes after cytokine stimulation (Heinrich *et al*., 1990; 1998).

During starvation, there is no full positive response, and a general depression of hepatic protein synthesis occurs. Malnutrition and the anorectic effects of pro-inflammatory cytokines in the brain result in a negatively changed hepatic synthesis. The major three of these cytokines (tumor necrosis factor alpha [TNF-α], interleukin-1 [IL-1], and interleukin-6 [IL-6]) have a profound behavioral, neuroendocrine, and metabolic effect (Johnson, 1997; Johnson and Borell, 1994; Johnson *et al*., 1993a; 1993b). Moreover, there is evidence that cytokines and their cognate receptors are present in the neuroendocrine system and brain. In laboratory animal species, IL-1, IL-6, and TNF-α have been found to modulate intermediary metabolism of carbohydrate, fat, and protein substrates, regulate hypothalamic-pituitary outflow, and act in the brain to reduce food intake (Johnson, 1997; Johnson *et al*., 1993a). In addition, induction of the acute phase response and production of pro-inflammatory cytokines may directly affect the process of bone growth (Stephensen, 1999).

Infection burdens often are associated with growth failure. The high prevalence of infections among children living in poor areas of developing countries impairs linear growth in these populations (Stephensen, 1999). Acute, invasive infections which provoke systemic response such as dysentery and those causing pneumonia, and chronic infections which affect the host over a sustained period (e.g., enteric helminth infections), have substantial effect on linear growth. This occurs because the infections may decrease food intake, impair nutrient absorption, cause direct nutrient losses, increase metabolic requirements and catabolic loss of nutrients and may impair transport of nutrients to target tissues.

The acute phase response with its changes in blood plasma composition is thought to be beneficial to the organism by preventing microbial growth and helping to restore homeostasis. Some APPs opsonize microorganisms and activate complement, others scavenge cellular remnants and free radicals, or neutralize proteolytic enzymes.

In this paper the general acute phase changes after interaction of a pathogenic agent with the host are described. The cytokines involved, the hepatocellular reaction, and resulting changes of blood proteins by negative and positive APPs are outlined. Furthermore, the use of APPs as diagnostic tool for assessing health in animals/human patients is discussed.

ACUTE PHASE REACTION

The systemic acute phase reaction

Local inflammation is the major reaction of the body upon tissue injury caused by infection. Infection, however, may occur without inflammation e.g., in immune-compromised individuals. Inflammation may also develop due to non-infectious causes. Any tissue damage during these processes leads to release of pro-inflammatory cytokines (van Miert, 1995). These cytokines, nitric oxide and glucocorticoids trigger and modulate the systemic acute phase reaction and the hepatic acute phase protein response (Gruys *et al*., 1994; Heinrich *et al*., 1990; 1998; van Miert, 1995). Protein-malnutrition and long-term starvation or anorexia, however, can reduce or abrogate a full positive acute phase protein reaction, while reducing the negative acute phase reactants by the starvation process itself. The same holds for hepatic

impairment.

Bacterial infections usually lead to a strong systemic acute phase response (Alsemgeest, 1994; Alsemgeest *et al*., 1994), due to the strong reaction of the mononuclear-phagocytic system's cells. TNF-α and IL-1β are induced in response to endotoxin (Dinarello, 1983; Le and Vilcek, 1989; Monshouwer *et al*., 1996a; 1996b; Schindler *et al*., 1990; Werling *et al*., 1996). In viral infections, generally the APR is milder (Alsemgeest, 1994; Höfner *et al*., 1994; Kimura *et al*., 1995; Nakayama *et al*., 1993). The main cytokines then released by infected cells are primarily interferons (IFNs), especially IFNγ from mononuclear inflammatory cells, although TNF-α and IL-1β from tissue cells may be involved as well. When severe cellular destruction is present, a full APR can be observed (van Reeth *et al*., 1998).

Cytokines and the acute phase response

At least 15 different low molecular weight peptide mediators are known to be secreted by activated leukocytes (interleukines) and other cells. They are collectively termed cytokines and are involved in triggering the acute phase response.

Three main groups of cytokines corresponding to effect pathways can be distinguished (van Miert, 1995): (1) cytokines that primarily act as positive or negative growth factors for a variety of cells (IL-2, IL-3, IL-4, IL-7, IL-10, IL-11, IL-12 and granulocyte-macrophage colony stimulating factor), (2) cytokines with pro-inflammatory properties (TNF-α/β, IL-1α/β, IL-6, IFN-α/γ, IL-8, and macrophage inhibitory protein-1), and (3) factors with anti-inflammatory activity (IL-1 receptor antagonists, soluble IL-1 receptors, TNF-α binding protein and IL-1 binding protein).

The pro-inflammatory cytokines (those of the second group) are responsible for induction of the mentioned fever and muscle catabolism, and they activate white blood cell precursors in the bone marrow, growth of inflammatory tissue fibroblasts and macrophages (Dinarello, 1983; 1989; Heinrich *et al*., 1990; Sehgal *et al*., 1989; van Miert, 1995). They are responsible for a broad spectrum of synergistic or antagonistic effects that influence the specific immune response of the stressed organism against foreign antigens and invading microorganisms (Pinelli, 1996; van Miert, 1995). TNF-α, IL-1β and IFNγ are crucial for the induction of other cytokines (IL-6 and IL-8) and agents such as platelet activating factor, prostaglandins, leukotrienes and nitric oxide (van Miert, 1995).

In the hepatic APR, TNF-α, IL-1 and IL-6 play a key role (Heinrich *et al*., 1990; 1998; Ingenbleek and Young, 1994; Le and Vilcek, 1989; Sehgal *et al*., 1989). They activate hepatocytic receptors, and synthesis of varying APPs starts. IL-6 is the major mediator for the hepatocytic secretion of most of the APPs (Heinrich *et al*., 1998; Le and Vilcek, 1989; Sehgal *et al*., 1989). Furthermore, TNF-α causes muscle catabolism that is also mediated by glucocorticoids, as well as glucagon-induced hyperglycemia and amino acid uptake by the liver. IL-1 stimulates an increase in whole body amino-acid flux, and activation of the pituitary-adrenal system. It has been shown that Kupffer cells play an intermediate role (Knolle *et al*., 1995). After stimulation by the pro-inflammatory cytokines the Kupffer cells form IL-6 and present it to the hepatocytes. IL-6 depresses mononuclear phagocytic production of IL-1 and TNF-α (Schindler *et al*., 1990) thus mitigating the whole cascade reaction. Down-regulation of the hepatocytic APR is achieved by rapid hepatic removal of circulating cytokines (Heinrich *et al*., 1998), release of IL-10 by the Kupffer cells which results in suppression of the local IL-6 production (Knolle *et al*., 1995) and by gene suppression pathways coactivated on receptor binding (Heinrich *et al*., 1990; 1998). Receptors for the pro-inflammatory cytokines may induce a janus-kinase effect resulting in activation of the APP formation pathway as well as several receptor inhibiting pathways (Heinrich *et al*., 1998). Moreover, parts of the hepatic APR are suppressed by IL-1 and IL-4 (Loyer *et al*., 1993) and some acute phase proteins can modulate monocyte cytokine production (Pue *et al*., 1996).

The glucocorticosteroids have a double function: (1) glucocorticosteroid dependent (Heinrich *et al*., 1990) hepatic stimulation of hepatocytes by IL-6; (2) the steroids down-regulate cytokine production by monocytes and macrophages (Baybutt and Holsboer, 1990). The APR observed is the resultant of all these complex interactions. It is important to realise that the APP-response-inducing cytokines represent small molecules with very short half-life. Therefore, cytokines are not very useful for most general diagnostic

purposes, in contrast to the APPs (Blackburn, 1994; Gruys *et al*., 1994; 1999).

Other effects during the acute phase response

Other effects of pro-inflammatory cytokines on the liver are suppression of the cytochrome P-450 enzyme system (Monshouwer *et al*., 1995a; 1995b; 1996a; 1996b; Morgan, 1997; Morgan *et al*., 1994) and induction of heat shock proteins (Jacquier-Sarlin *et al*., 1994) and of metallothionein synthesis (Disilvestro and Carlson, 1992; Dowton and Colten, 1988; Hallquist and Klasing, 1994). The first has large impact on the metabolism and toxicity of various chemical compounds and drugs (Alcorn *et al*., 1992; Disilvestro and Carlson, 1992; Langhans, 1996; Monshouwer *et al*., 1996b; Morgan, 1997). Heat shock proteins, or stress proteins, are beneficial compounds chaperoning damaged cellular molecules. The metallothionein synthesis induced increases the hepatic resistance against metal toxicity and may enhance intracellular metal ion binding capacity. Together with decreased hepatocytic secretion of albumin (transporting zinc) and of transferrin and lactoferrin, this causes decreased serum zinc and iron values. The latter is regarded as beneficial for the infected organism, since iron is essential for microbial growth. As less beneficial blood reaction during the acute phase response associated with infection, calcium values decrease as well (Gruys *et al*., 1994).

Sickness behavior with decreased appetite or anorexia is mediated by the pro-inflammatory cytokines. The cytokines induce formation of prostaglandins and the prostaglandin-dependent induction of fever (Johnson, 1997; Johnson and Borell, 1994; Johnson *et al*., 1993a; 1993b; van Miert, 1995). Furthermore, the immunological stress induces adrenal gland medullary hormone release with catecholamines causing re-distribution of the blood flow to brain and muscles instead of to the splanchnic system. Intestinal villus atrophy and reduced enteric absorption may develop and result in diarrhoea (Kraft *et al*., 1992; Nabuurs, 1995). The changed metabolism results in negative energy balance and growth retardation is ameliorated.

During the acute phase response, plasma viscosity increases as a result of the total changes in total blood protein concentration, among which is an increase of fibrinogen which influences the erythrocyte sedimentation rate (ESR) (Majno and Joris, 1996) used in many western hospitals as non-specific marker for disease activity (Magnus *et al*., 1994). Because fibrinogen is a slow reacting positive acute phase reactant with a possible delay of some days after infection, the ESR increases and then reflects the activity of the acute phase response. The ESR was found to be useful for monitoring pigs with abscesses (Odink *et al*., 1990). In cows fibrinogen and the ESR are not reliable indicators of activity of the acute phase response.

ACUTE PHASE PROTEINS

Negative acute phase proteins

In addition to the decrease of serum zinc, iron and albumin, a decrease of transferrin, cortisol-binding globulin, transthyretin (TTR) and retinol-binding protein (retinol=vitamin A) have been described (Ingenbleek and Young, 1994). Their decrease indicates a temporarily increased availability of free hormones bound to these proteins. The negative acute phase proteins are therefore described by some authors as ‘acute booster reactants’ (Ingenbleek and Young, 1994).

In malnutrition and chronic infections the response of positive acute phase variables may be less evident (Morlese *et al*., 1998; Stephensen, 1999). Changes in blood protein profiles partly depend on starvation and muscle catabolism (Reeds *et al*., 1994). In chronic infestation and inflammatory states of children and during pregnancy in developing countries in addition to malnutrition, vitamin A deficiency is worsened (Stephensen, 2001; Stephensen and Gildengorin, 2000). The latter has a well-known negative feedback effect on immunity (Baeten *et al*., 2004; El Beitune *et al*., 2003; Stephensen, 2001; West, 2004).

Positive acute phase proteins

Although species-differences exist for separate proteins and especially are known between mammals and birds (Table 1), the positive APPs of man and domestic animals (Dowton and Colten, 1988; Kushner *et al*., 1981; Lannergard *et al*., 2003; McGuire *et al*., 1996) can generally be listed in three major groups: (1) with an increase of about 50%: ceruloplasmin and complement factor-3 (C3), (2)

with an increase of two-three fold: haptoglobin, fibrinogen, α-globulins with antiprotease-activity and lipopolysaccharide binding protein, and (3) with a rapid increase of up to 5-fold to 1000-fold: CRP and SAA. For the pig, a kallikrein-related 'major acute phase protein' (pigMAP) has to be added to this latter group (Alava *et al*., 1997).

Table 1 Major positive and negative acute phase reactants in mammals and birds*

Mammals	Birds
Positive reactants	
TNF-α, IL-1, IL-6, cortisol	TNF-α, IL-1, IL-6, cortisol
SAA, CRP, Hp, AGP, etc.	SAA, CRP, hemopexin, AGP, etc.
Fibrinogen, Ceruloplasmin	Fibrinogen, Transferrin, Ceruloplasmin
Cu	Cu, Ca
Negative reactants	
TTR, RBP	Hp
Albumin, Transferrin	Albumin
Fe, Zn, Ca	Unbound serum iron, Zn

TNF: Tumour necrosis factor; IL: Interleukin; SAA: Serum amyloid A; CRP: C-reactive protein; Hp: Haptoglobin; AGP: α1-acid glycoprotein; Cu: Copper; Ca: Calcium; TTR: Transthyretin; RBP: Retinol binding protein; Fe: Iron; Zn: Zinc

*Major positive and negative acute phase reactants in mammals (Gruys *et al*., 1994; 1999) and birds after lipopolysaccharide (LPS), turpentine and croton oil studies in domestic fowl (Patterson and Mora, 1964; 1965; Hallquist and Klasing, 1994; Tohjo *et al*., 1995; 1996; Takahashi *et al*., 1997; Nakamura *et al*., 1998; Chamanza *et al*., 1999a; 1999b; Adler *et al*., 2001; Xie *et al*., 2002; Upragarin, 2005) and LPS and haemorrhagic enteritis virus investigations in turkey (Mazur-Gonkowska *et al*., 2004). For avian cytokines the reader is referred to (Lynagh *et al*., 2000; Sijben *et al*., 2003; Leshchinsky and Klasing, 2003; Abdalla *et al*., 2004; Kaiser *et al*., 2004; 2005)

Some of the APPs are fetal proteins normally not found in large quantities in sera of adult subjects, e.g., α-macrofoetoprotein in the rat (van Gool *et al*., 1984) and α1-acid glycoprotein (AGP) in most animal species.

Positive acute phase proteins are formed during the acute phase response associated with anorexia and changed metabolism. This indicates that rather than the role of protein absorption in the digestive tract, muscle protein functions as major storage for the amino acids required for APP synthesis. Since the amino acid composition of the APPs differs from that of muscle protein, the demands for phenylalanine, tryptophan and tyrosine together necessitate the mobilization of an amount of muscle protein that is considerably in exceeding (thrice) the quantity of the APP synthesized (Reeds *et al*., 1994). To minimalize muscular catabolism, for hospitalized acute phase patients protein diets have been recommended (Alexander *et al*., 1980) which are now beginning to be given to pigs and chickens as well.

It is important to realise that physiologically, APPs may react at pregnancy (Eckersall *et al*., 1993) and parturition in the adult animal (Alsemgeest *et al*., 1993; Goff and Stabel, 1990; Koets *et al*., 1998; Sordillo *et al*., 1995; Uchida *et al*., 1993) like man (de Villiers *et al*., 1990). Distinct positive APPs from some species do not react in the same way in other species; serum amyloid P-component (SAP) is an APP in the mouse, but not in man, and CRP reacts as APP in several monogastric species, but not very well in small ruminants (Gruys *et al*., 1994). Transferrin, which is a negative APP of most mammalian species, reacts as positive APP in chicken (Hallquist and Klasing, 1994; Tohjo *et al*., 1995).

The plasma concentration of APP measured, is the resultant of production and catabolism. The APP of the above mentioned rapidly reacting group (C), SAA and CRP, become measurable within 4~5 h after a single inflammatory stimulus. The APP of the second group (B) like lipopolysaccharide-binding protein, show increases from about 8 h onward. After a single stimulus the levels of these proteins remain elevated for a minimum of 24 h and decrease after about 48 h. Permanent infusion of endotoxin in cows causes plasma SAA quantities to remain on a plateau (Werling *et al*., 1996). During permanent stimulation (chronic infection) positive acute phase protein levels remain elevated in comparison to normal values, and can be used for diagnostic purposes.

Function of positive acute phase proteins

The function of most APPs has not been totally elucidated. The positive APPs are regarded as having general functions in opsonization and trapping of micro-organisms and their products, in activating complement, in binding cellular remnants like nuclear fractions, in neutralizing enzymes, scavenging free haemoglobin and radicals, and in modulating the host's immune response.

CRP (Pepys, 1981), a ring consisting of five 23000 Da units (pentraxin), is the first described acute phase protein (Tillett and Francis, 1930). It was discovered due to its binding to the C-polysaccharide of

pneumococci. It binds directly to several microorganisms, degenerating cells and cell remnants, and activates complement by the classical C_{1q} pathway, and acts as opsonin.

SAA (Gruys *et al*., 1994; Husby *et al*., 1994; Nakayama *et al*., 1993) is an apolipoprotein of high-density lipoprotein (apoSAA). As acute phase protein it is thought to influence high-density lipoprotein-cholesterol transport. In tissues it attracts inflammatory cells and inhibits the respiratory burst of leukocytes (Linke *et al*., 1991) and modulates the immune response (Gruys *et al*., 1994). It is described to bind lipopolysaccharide, comparable to lipopolysaccharide binding protein (LBP) (Schroedl *et al*., 2001). Several isotypes of SAA are found; types 1 and 2 represent positive APPs. In the bovine, also a negative protein cross-reacting with anti-SAA serum has been described (Yamamoto *et al*., 1998).

Besides the acute phase SAAs, constitutive variants are described (Husby *et al*., 1994). Human SAA4 is normally present in serum (Husby *et al*., 1994; Yamada *et al*., 1994). Rabbit SAA3 (Mitchell *et al*., 1993) is formed by synoviocytes, fibroblasts and macrophages, and is not a blood protein. The mammary gland is a well known source of a SAA3 variant (Eckersall *et al*., 2001; McDonald *et al*., 2001; Larson *et al*., 2005) occurring in colostrum and in mastitis milk, that should have beneficial functions for the gut mucosa of the offspring (Larson *et al*., 2003a; 2003b; Mack *et al*., 2003).

Haptoglobin (Hp) strongly binds haemoglobin, has anti-inflammatory capabilities and binds to CD_{11b}/CD_{18} integrines (El Ghmati *et al*., 1996) representing major receptors on the cell membranes of leukocytes. Although representing a positive acute phase protein, its quantity may decrease on massive erythrolysis (Smith and Roberts, 1994), and when blood is haemolytic, determination by haemoglobin binding assays may give unreliable results.

Ceruloplasmin (Cp) (Cooper and Ward, 1979) contains copper, has histaminase- and ferroxidase-activity, and scavenges Fe^{2+} and free radicals, while α2-macroglobulin (α2MG) binds proteolytic enzymes (Alsemgeest, 1994). The function of fibrinogen is clot-formation and C3 has complement function; α1-acid glycoprotein (α1AGP), formerly called orosomucoid (Cooper and Ward, 1979) and which has been found not to react as a major (group C) acute phase protein in most domestic animal species except the cat (Duthie *et al*., 1997), is reported to influence T-cell function and to bind steroids such as progesterone. The functions of α1-proteinase inhibitor which is also called α1-antitrypsin, a serine protease inhibitor or serpin, and α1-antichymotrypsin are inhibitors of leukocyte and lysosomal proteolytic enzymes (Cooper and Ward, 1979).

Acute phase proteins and pathology

Some disease states are associated with, or are causally related to APPs. The pathogenic role of fibrin in thrombosis is well known. Similarly, CRP-mediated complement activation has a key role in some forms of tissue alteration such as cardiac infarction. Elevated serum values are known to be associated with increased risk of human atherosclerosis. Many studies had been conducted on the relationship between SAA and deposition of reactive (AA) amyloid (Gruys and Snel, 1994) in patients with chronic arthritis, tuberculosis or Familial Mediterranean Fever. AA-amyloid is the most frequently found type of amyloid in animal species like horse, cow, dog, cat, *anatidae* and domestic fowl (Gruys and Snel, 1994; Landman *et al.*, 1996). The causal relationship between the acute phase protein, SAA, and the extracellular deposition of amyloid fibrils has been proven (Husebekk *et al*., 1985; Tape *et al*., 1987). In some species (mouse, mink and horse) a special amyloidogenic SAA-isotype has been recognised (SAA_2). The mechanism of amyloid formation from the acute phase protein, however, has not totally been elucidated. Sustained high plasma levels of SAA, amyloid enhancing factor (Kisilevsky *et al*., 1994), impairment of SAA-degrading proteases (Yamada *et al*., 1996), apolipoprotein-E4 (Gruys *et al*., 1996), and many other factors such as proteoglycans (Magnus *et al*., 1994), have been implicated.

ACUTE PHASE RESPONSE IN (ANIMAL) MEDICINE

CRP, SAA, Hp and some other APPs, have been described as useful for assessing health in human patients (Blackburn, 1994; Counotte *et al*., 2002; Ferard *et al*., 2002; Ingenbleek and Carpentier, 1985; Sipe, 1995) and in various domestic animals (Gruys *et*

al., 1994; Petersen *et al*., 2004; Pyorala, 2000; Toussaint, 2000; Toussaint *et al*., 1997; 2000a; 2000b) and wildlife animal species (Duffy *et al*., 1996; Funke *et al*., 1997). They are more sensitive than the above mentioned ESR, which is used in most western human hospitals. The significance of APPs as non-specific variables for monitoring inflammatory activity has been adopted in veterinary clinical chemistry. Cytokines and the acute phase reaction elicited have been published for ruminants, horse, pig and several other species (Gruys *et al*., 1994). APPs are used with conditions varying from cows with mastitis (Eckersall *et al*., 2001), to cattle with tropical theileriosis (Glass *et al*., 2003), and horses with influenza (Hulten *et al*., 1999).

When APPs are used to assess unhealthy animals versus healthy ones, values of single reactants are often not sensitive enough to detect a special subject in a population of livestock. However, the acute phase signal/starvation situation obtained for an individual animal can be enhanced when the values of positive APPs (rapid and slow) are combined with those of rapid and slow negative APPs in an index (acute phase index (API) (Toussaint *et al*., 1995) or nutritional and acute phase indicator, NAPI) (Gruys, 2002). NAPI=(value of a rapid positive APP×value of a slow positive APP)/(value of rapid negative APP×value of a slow negative APP).

The index has been used as prognostic inflammatory and nutritional index (PINI) for human patients (Bonnefoy *et al*., 1998; Ingenbleek and Bernstein, 1999a; 1999b) and as acute phase index (API) for cattle (Toussaint *et al*., 1995). Such index enhances sensitivity and specificity remarkably in comparison to single APPs in the detection of unhealthy subjects among populations of normal animals, as was shown for cattle and finishing pigs at slaughter (Toussaint *et al*., 1995; 2000a; 2000b) and was favoured by findings in experimental pigs with *Streptococcus suis* infection (Toussaint *et al*., 2000b). In human patients a simple quotient of the values of CRP/TTR already proved its usefulness in monitoring bone fracture patients (Ferard *et al*., 2002).

CONCLUSION

The acute phase reaction can be used for assessment of general health, including starvation and growth. Pro-inflammatory cytokines and blood proteins of hepatic origin are potential variables for monitoring the changes induced. APPs are more useful for monitoring health than the cytokines, because the latter are cleared from the circulation within a few hours, whereas APP levels after a single stimulus remain unchanged for 48 h or longer.

Determination of APPs can help in monitoring health of individual subjects especially when several acute phase variables are combined in an index. Well-chosen combinations of variables (which may differ for various species) result in a nutritional and acute phase indicator (NAPI). The acute phase reaction offers a biological effect mechanism appropriate to include in future systems for assessing health in animals and human patients.

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