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THE EFFECT OF STRESS ON UDDER HEALTH OF DAIRY COWS

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ABSTRACT

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The appropriate literature has been reviewed for the purpose of defining the phenomenon of stress in lactating dairy cattle, establishing a baseline concept of lactation stress and emphasizing the most significant aspects of the natural mammary defence mechanisms.

Data on the general adaptation syndrome (GAS) make it clear that stress is essentially the rate of wear and tear of the biological system affected by a stressor either eliciting stress of the organism as a whole or partly so. Owing to the variety of stressors which may affect the dairy cow at physiological and pathological levels, a definition of stress in the broad sense is indicated. This is essential from the point of view of the anti-homeostatic effects (metabolic and immunological) of lactation stress, aggravated by anti-homeostatic effects elecited by superimposed other types of stress (e.g. heat stress).

The lactating cow, as a ruminant in a state of sustained stress, requires a special profile of hormonal mediators. In high yielding cows, for example, acute and sustained heat stress promotes increased activities of prolactin, progesterone and catecholamines.

Compared with the mainly glycogenic/glycogenolytic metablolism of non-ruminant mammals, the lipogenic/lipolytic and glycogenic/glycogenolytic metabolism of the dairy cow depends on hormonal mediators which differ from those of the former not so much in their nature but in their magnitude and ratios. Stressors induce the development of GAS reactions in the dairy cow. These enable the cow to create and maintain homeostasis of its integrated 3 main physio-pathological systems and thus to endure the stressor(s). The cow's compensating adjustments to a stressor are therefore the effects of stress. This means that natural lactation is the effect of the lactation stress induced by the cow's progeny (i.e. the natural lactation stressor). Artificial lactation stressors (e.g. removal of milk by hand and machine) may affect the lactation stress in magnitude but not necessarily in nature. Likewise, a range of behavioural, physiological, lactational and lacteal changes related to other stressors are the effects of different types of stress.

Lactation stress, like other types of stress, shows 3 stages of development, i.e., an overcompensating alarm phase (= lactogenesis), resistance phase (= galactopoiesis) and exhaustion phase (= regression). They facilitate adjustments of the cow's homeostasis from the level of involutional homeostasis (= no lactational activity) to that of lactational homeostasis.

Like other tissues in a state of stress, the lactating mammary epithelium requires a greatly increased supply of glucose. This causes the glucose metabolism of the lactating cow to become so precarious that in the secretory mammary epithelium glucose is being reserved for specific key functions, such as balance of energy and electrolytes, and formation of lactose, NADPH and citrate. The secretory epithelium is therefore particularly susceptible to fluctuations of its oxydative glucose metabolism, which, in turn, enables the cow readily to control the number of secretory cells, their level of secretory activities and the integrity of the secretory epithelium. For that reason, mammary regression, unphysiological both in magnitude and timing, if stimulated in dairy cattle by stressful conditions superimposed on normal lactation stress, is of primary importance as a counter-measure to galactopoiesis, and the main predisposing factor to mastitogenic infection. Mammary regression may be considered the cow's inherent, non-specific response to stressors affecting it and/or its lactating udder.

Stressful conditions, superimposed on the lactation stress, promote increased intramammary activities of adrenalin, which contribute to unphysiological mammary regression. Adrenalin also affects the bacterial trapping component, reverse pumping component and other components of the proposed 3 core systems of the natural defence mechanisms of the lactating bovine udder. This unfavourable effect of adrenalin on udder health may be further aggravated by various hormonal mediators in the plasma and milk.

From the data reviewed it is evident that stress may elicit significant lactational and lacteal fluctuations, jeopardize the anti-microbial efficacy of the natural defence mechanisms of the udder and increase the risk of unphysiological mammary regression and subclinical and clinical mastitogenic udder infections. It is clear therefore that stress may be of eminent importance to the 3 major determinants of bovine udder health, namely, intramammary integrity, somatic cellular defence and bacterial challenge.

INTRODUCTION

The effect of stress on udder health of dairy cows may be discussed from different points of view. For decades, investigations on the pathogenesis, pathology, prevalence, diagnosis and therapy of subclinical and clinical mastitis have been the focus of mastitis research with particular reference to cows with mastitogenic infections. One could thus follow that general trend by discussing stress resulting from such infections.

In this presentation, however, I will give a review of those physiological, environmental and managemental stressors which predispose to mastitis.

Such a review is desirable not only because stress in bovine udder health has not been reviewed before. It is also an opportunity to acknowledge the efforts of Drr. S. W. J. van Rensburg and L. W. van den Heever who, during 1940–1965, initiated research on bovine mastitis in South Africa at the Institute.

According to Giesecke & Van den Heever (1974), Giesecke & Viljoen (1974) and Honkanen-Buzalski (1982), bovine udder health usually depends on 3 major determinants, namely, (i) intramammary epithelial integrity, (ii) intramammary somatic cellular defence and (iii) intramammary bacterial challenge. Whether and how stress affects the lactating dairy cow at the level of these 3 major determinants of udder health will be outlined in this paper.

For that purpose it is necessary to define the phenomenon of stress, project the dairy cow into its comparatively stressful environment, appreciate the natural defence mechanisms of the cow's lactating udder and evaluate the effect(s) of stress at the level of the mammary defence systems protecting the secretory parenchyme from infection.

A DEFINITION OF STRESS IN DAIRY CATTLE

The concept of stress and the general adaptation syndrome (GAS) (Selye, 1948) is widely accepted in the veterinary context (Shaw, 1956; Veilleux, 1963; Jahn,

1965; Freeman, 1975; Perry 1975; Jenkins & Kruger, 1973; Johnson & Vanjonack, 1976; Lamb, 1976; Moberg, 1976; Hillman, 1982).

Owing to the multifactorial aetiology of mastitis, several workers have attempted to relate the disease to environmental stress (Schildbach, 1960; Hropot, 1970; Walser, Bieter, Dannerbeck, Gropper, Hropot, Lankenfeld, Mayer, Vergho & Viktor, 1972) and the GAS (Rice, 1965; Tucker, 1969; Jorgensen, 1970; Giesecke & Van den Heever, 1974; Stoevlbaeck-Pedersen, 1975; Carroll, 1977; Giesecke, 1979; Pearson & Greer, 1979; Varner & Johnson, 1983).

As a rule, the workers on mastitis have emphasized interactions between the cow and its stressful external environment, the cow's need and failure to adapt to such external conditions, and the lowering of the cow's resistance which eventually facilitates mastitogenic udder infection. Conversely, the idea has prevailed that to resist mastitogenic udder infections, the cow must adapt to and be in equilibrium with its external environment. For that adaptation the cow presumably depends on the GAS.

However, from the findings of workers like Selye (1948), Hails (1978) and Stephens (1980) it is clear that reactions related to stress and the GAS are indicative of an organism's attempt to establish an equilibrium, not with its external environment, but, rather, at maintaining itself in a state of homeostasis.

Although the former concept on the cow's balance with its external environment may not appear to be different from that on the maintenance of the cow's own homeostasis, more emphasis on the latter nevertheless could be important for a better understanding of mastitis. Mastitis clearly is a dynamic process within the cow's organism, and it affects her homeostasis. This process amounts to a conflict between the mastitogenic micro-organisms and the affected macro-organism, which defends itself by means of adaptive phenomena inherent in its integrated 3 physio-pathological main systems, metabolic, immunological and phlogistic.

Adaptation is conceivably an integral element of mastitis and normal udder health. Mastitic changes such as decreased milk production, altered milk composition, loss of an infected quarter due to necrosis, fibrosis and atrophy, amount to successful adaptations, and death from toxaemic peracute mastitis and others to true failure. One therefore cannot preclude the possiblity that the most common types of mastitis, including the subclinical forms, do not represent an occupational but, rather, an adaptation disease of modern dairy cattle.

Mastitis, as an occupational disease, is a condition which usually depends on a single causative agent. The disease may be regarded, therefore, as an infection problem where the cow has failed to adapt to a specific microbial challenge peculiar to its external environment. Mastitis may thus be regarded as a disease which shows that the infected macro-organism has failed to develop specific adaptive reactions, and/or immunological resistance, to specific mastitogenic micro-organisms. This concept finds support in work on mastitis related to *Streptococcus agalactiae* and *Staphylococcus aureus*, which places particular emphasis on mastitis as an infection problem and its control and prevention by means of measures complementing the cow's natural efforts at ridding itself from infection. Consequently, intramammary treatments with antibiotics and extramammary prophylaxis with teat antiseptics and general disinfectants are widely used, and the possibility of immunizing cows against certain mastitogenic bacteria is being investigated, even though success with any of such measures has been considerably less than satisfactory (Freeman, 1977; Dodd, 1983; Pankey, Boddie & Watts, 1983; Pankey, Duirs, Murray & Twomey, 1983; Smith, 1983). Mastitis is apparently as common as it was before the antibiotic era (Sandholm, 1982; Hug, 1983).

However, mastitis as an adaptation disease, is a condition which usually does not depend on a single causative agent but is due mainly to non-specific stressors and to equally non-specific pathogenic processes associated with the cow's response. This concept finds support in the (i) range of opportunistic micro-organisms associated with mastitis (Heidrich & Renk, 1967; Giesecke, Nel & Van den Heever, 1968; Freeman, 1977; Jain, 1979; Dodd, 1983); (ii) non-specific changes during early stages of mastitis (Heidrich & Renk, 1967; Schalm, Carroll & Jain, 1971; Schalm, 1977); (iii) generally short-lived immunological memory and, consequently, poor immune response of the lactating bovine udder (Norcross, 1977; Lascelles, 1979; Pankey, Boddie & Watts, 1983; Pankey, *et al.* 1983) and (iv) work on mammary regression (Giesecke, 1978), modern therapy of mastitis (Sandholm, 1982) and difficulties in defining a single parameter for genetic determinations (Senft, Meyer & Rudolphi, 1977; Atroshi, Kangasniemi, Honkanen-Buzalski & Sandholm, 1982) on inheritable resistance to mastitis.

Moreover, the term *stress* is being used so widely and with such a variety of meanings that the situation has been critically discussed (Bareham, 1973; Ewbank, 1973; Fraser, Ritchie & Fraser, 1975; Selye, 1976). Fraser *et al.* (1975) have thus proposed a definition of stress in animals which is limited exclusively to "adverse aspects" of environment and management which may become major causes of stress. Such a restrictive definition seems consistent with several definitions of the word syndrome (Hoerr & Osol, 1956; Onions, 1973). However, it is not necessarily consistent with medical definitions of sydrome and general adaptation syndrome (Anonymous, 1981), nor for that matter with data on stress.

Extensive work on the GAS, adaptation syndrome, stress syndrome or simply, stress (Selye, 1948, 1953, 1971, 1976; Jahn, 1965; Guyton, 1971; Freeman, 1975; May, Manoia & Donta, 1975; Perry, 1975; Hails, 1978) has provided a broad base of current knowledge on anatomical, physiological, metabolic, behavioural and other characteristics (Jenkins & Kruger, 1973) of stress. From such data it is apparent that, like the terms *health* and *disease*, that of *stress* is difficult to define in precise terms. However, it is also clear that animals exposed to a variety of different stressors, endogenous and exogenous, real and anticipated, somatic and psychological respond by means of reactions specific to each of such stressors and a general non-specific response superimposed on the specific effects.

The term GAS thefore conveys the idea that the non-specific response to a stressor represents the sum of many non-specific but closely integrated responses of several different organs. The term "stress" is meant to cover all such responses, and it has thus been defined as a body state manifested by a specific syndrome consisting of all the non-specifically induced changes in a biological system (Veilleux, 1963). Essentially, stress is the rate of wear and tear of that system affected at any moment by a stressor, either eliciting stress of the organism as a whole (systemic stress) or a portion thereof (local stress).

From modern concepts of stress (Veilleux, 1963; Jenkins & Kruger, 1973) it is evident that stress in dairy cattle should be defined in the broad sense, rather than in the narrow sense proposed by Fraser *et al.* (1975), because stressful natural conditions, such as pregnancy,

birth and lactation, cannot simply be ignored, nor can species-specific and breed-typical pecularities be disregarded. Furthermore, the definition must of necessity provide for variations of behaviour which may precede physiological and pathological changes proper.

The definition of stress proposed by Fraser *et al.* (1975) may therefore be amended to read:

(i) An animal is said to be in a state of stress, in the broad sense, if it is required, naturally or artificially, to make abnormal or extreme adjustments in its physiology or behaviour in order to facilitate its species-specific and breed-typical phenotypic expression and to cope with antihomeostatic aspects of its environment.

(ii) A condition can be said to be stressful if it stresses an animal.

(iii) An individual factor, natural or artificial, endogenous or exogenous, may be called a stressor if it contributes directly or indirectly to the stress of an animal.

Depending on the nature, magnitude and combination of stressors, the responses elicited in the affected animal are modulated in the hypothalamus and other portions of the limbic lobe (Fig. 1).

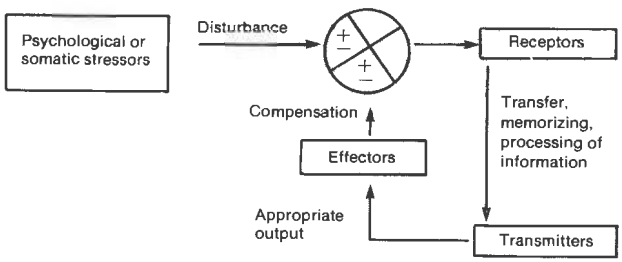

FIG. 1 Schematic presentation of the general control system of stress indicating receptors, transmitters and effectors as basic components of the circuit (from Jenkins & Kruger, 1973)

The above-mentioned definition and general control system of stress (Fig. 1) have important implications in the case of both the cow's physiological and pathological responses to stressors. From the control system (Fig. 1) it is clear that stressors cause a tissue disturbance which is perceived by receptors, i.e., sensors and detectors in tissues that monitor any alteration in the state of the body and its environment. From the receptors the information is then transferred to the central nervous system (CNS) where centres within the brain process the messages received from the receptors, memorize the information and determine both at subcortical and cortical levels the response to be made by the body. Appropriate impulses are then dispatched to the transmitters also localized in the CNS. The output from the transmitters may be either directly mediated by the nervous system or indirectly produced by means of neurohormonal mechanisms (e.g. in the hypothalamus). Whatever output may be involved, it is aimed at certain effectors which are those tissues or organs stimulated by the output. They are capable of compensatory reactions which amount to counteracting the antihomeostatic effects that may result from the disturbances initiated by stressors.

The above indicates how stressors induce the development of the GAS reaction (i.e., stress) which, in turn, facilitates the restoration and maintenance of homeostasis. This enables the animal to resist stressors.

It is therefore evident that the cow's compensating adjustments (Fig. 1) to a stressor are the results of emotional, behavioural, physiological or pathological stress. Consequently, it further stands to reason that lactation is the result of lactation stress induced by the lactation stressor.

A Concept of Lactation Stress

In the light of the above-mentioned definition and general control system of stress (Fig. 1), mammary homeostasis in the mature dairy cow may be considered a physiological state subject to cyclic changes. These changes start at the level of ideal homeostasis, i.e., the state of mammary involution characterized by dormant mammary epithelium (Hollmann, 1974). Advancing pregnancy necessitates gradual re-adjustments of involutional homeostasis similar to those usually associated with mammogenesis (Reynolds & Folley, 1969; Falconer, 1970). Towards the end of pregnancy the bovine foetus induces the maternal organism (Speroff, Glass & Kase, 1983) to respond to it with a distinctly lactogenic alarm reaction (i.e., lactogenesis, as reviewed by Reynolds & Folley, 1969). That alarm phase is followed at the time of calving by galactopoiesis (= maintenance of secretory function, as discussed by Falconer, 1970). Provided galactopoiesis is augmented by the removal of milk, it facilitates the re-adjustment (by means of the GAS) to escalating levels of resistance to the lactation stressor. Depending on the cow's genetic potential and its support from the environment, the escalating resistance eventually helps to create a new level of homeostasis essential for reaching peak lactational response to the stressor. This level of homeostasis is associated with hyperactive lactational activities at levels so extreme that even under ideal conditions they soon commence to exhaust the average cow's natural resources for maintaining peak levels of resistance to the lactational stressor. The cow is forced to re-adjust homeostasis by measures which oppose the galactopoietic activities of its mammary gland. The descending portions of the normal lactation curve suggest that galactopoiesis is initially opposed by gradually escalating mammary regression. The regressive activities continue until involutional homeostasis is restored. The state of mammary involution newly established provides the cow with the opportunity of generally recuperating from the preceding period of sustained lactation stress.

The above indicates that lactogenesis, galactopoiesis and the ascending, persisting and descending stages of the lactation curve (Reynolds & Folley, 1969; Falconer, 1970; Schmidt, 1971) are the direct effects of the cow's degree of resistance to the lactation stressor. This, in turn, means that the volume and composition of milk produced under natural conditions in the healthy udder are also the effects of lactation stress. Conversely, it is clear therefore that complete lack of any lactational activity indicates the complete absence of lactation stress.

Finally, the above definition and control system of stress imply that a lactating cow is always in a state of lactation stress which, in its nature and magnitude, depends on the cow's genetically predetermined capabilities of developing homeostatic resistance, both specific and non-specific (Veilleux, 1963), to the lactation stressor (Fig. 2).

With reference to the development of the different types of homeostatic resistance to stressors suggested by Selye (1948, 1953, 1971, 1976) and Veilleux (1963), it seems conceivable from Fig. 2 that with changing reproduction activities, specific resistance to foetal stressor (A-B) decreases shortly before parturition (C-D). Its complete exhaustion is prevented by the birth of the calf (↑), which neutralizes the foetal stressor. A similar development occurs during the advanced stage of subsequent pregnancies (K-L-↑).

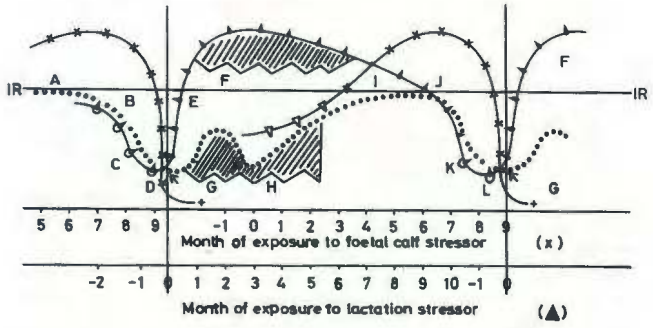

FIG. 2 Schematic presentation of the conceptional development over time of resistance to stressors associated with gravidity and lactation: ▽ ▽ ▽ = embryonic and XXX = foetal stressor; ▲ ▲ ▲ = anticipated and ▲▲▲ = real lactation stressor; ——— = specific and ●●● = non-specific resistance to stressor; shaded area = fluctuating conditions; IR—IR = level of inherent resistance to stressors.

It is proposed that in the mature dairy cow 3 main cyclically interrelated developments of resistance to stressors occur: (i) Specific resistance to reproduction stressors, foetal (A–D), embryonic (H–I, commencing at trophoblast state of embryo) and again foetal (I–L); (ii) specific resistance to lactation stressor, anticipated (C–D and K–L) and real (D–E–F–K); (iii) non-specific resistance to stressors (●●●)

Homeostatic resistance specific to anticipated lactation stressor (C-D) also starts to develop with advancing pregnancy (Fig. 2; A-B). Resistance to real lactation stressor, escalates after calving (↑-E-F) but decreases during further lactation (F-I-J-K). In a heifer pregnant for the first time, however, resistance specific to the anticipated lactation stressor may take longer to develop (B-D) than during a subsequent dry period (K-L).

Subsequent to birth (Fig. 2; ↑) and depending on non-specific resistance associated with the development *post partum* of homeostatic resistance specific to lactation stressor (E-F), resistance to reproduction and other stressors may be low and fluctuating (G) during early lactation (E-F) until the cow is once more affected by embryonic (H) and foetal stressors (I) related to the corresponding development of specific resistance (I-J) similar to A-B.

In the case of renewed pregnancy during lactation (H-J), homeostatic resistance specific to embryonic (H) and foetal (I) stressor may develop concurrent to and dependent on specific (E-F) and non-specific (G-H) resistance to the lactation stressor. The level of inherited homeostatic resistance (IR) also plays a role in these developments. By means of fluctuating maternal and escalating levels of placental hormones (H-J), resistance specific to the lactation stressor is initially reduced gradually (F-I) and then more rapidly (I-J) so that specific resistance to the foetal stressor (I-J) eventually surpasses (I) resistance to the lactation stressor (F-J). The latter is eliminated by cessation of milking at the end of a lactation period (K) to facilitate renewed development of resistance to the next anticipated lactation stressor (K-L) during the dry period. The development of resistance to lactation and concurrent foetal stressors depends on the month when conception occurs *post partum* and the duration of the corresponding dry period.

The base line concept of lactation stress arrived at (Fig. 2) is consistent with the modern concept of stress (Veilleux, 1963), compatible with current knowledge on the general control system of stress (Jenkins & Kruger, 1973) and is supported by a wide range of literature reviewed by us. The concept may thus serve as a general base line for further discussions.

Species-specific and Breed-typical Variations of Stress

It is evident from the above that stress in dairy cattle should be appreciated as stress in the broad sense. Accordingly, interpretations of the GAS in dairy cattle should not be limited, as the word syndrome may imply, to events leading up to certain pathological conditions, unless it has been conclusively shown that such an exclusively pathogenic connotation of the GAS is truly justifiable in different animal species. In the absence of such conclusive evidence, it is preferable to consider the GAS a phenomenon of importance both in the physiology and pathology of animals. This approach to the GAS is especially necessary in lactating dairy cattle.

From investigations on stress conducted in different species it is clear that, like cows in normal lactation stress (Fig. 2), lactating dairy cattle under acute and sustained heat stress, for example (Johnson & Vanjonack, 1976), respond with fluctuations of milk yields consistent with the acknowledged 3 main stages of the GAS (Selye, 1948), namely, (a) the initial alarm phase, (b) the intermediate resistance phase and (c) the final exhaustion phase. However, such similarities between species do not preclude species-specific and even breed-typical variations in the reactions of dairy cattle to stress.

Such differences may involve the hormonal mediators related to the GAS. It is apparent from Veilleux (1963), Guyton (1971) and Jenkins & Kruger (1973) that the GAS is a dynamic phenomenon facilitated by various hormones of adaptation, such as adrenocorticotropin (ACTH), a variety of corticosteroids, growth hormone (GH) and catecholamines. More recent data on reproductive and general endocrinology and prostaglandins (Markelonis & Garbus, 1975; Hedge, 1977; Horrobin, 1979; Arthur, Noakes & Pearson, 1982; Speroff *et al.*, 1983) make it clear that both the release of the hypophyseal hormones and their effect(s) at the target tissues, in turn, depend on special hormones, neuro-endocrinological activities, a range of prostaglandins and similar mediators. It is therefore reasonable to assume that the concept of the GAS originally proposed by Selye (1948) and subsequently modernized (Veilleux, 1963; Jenkins & Kruger, 1973) will also be subject in future to modernization.

In comparison with the non-ruminant, in which the metabolism mainly revolves around glycogenesis/glycogenolysis, the lactating cow, as a ruminant, has a metabolism where glycogenesis/glycogenolysis is inseparably combined with lipogenesis/lipolysis as main mechanisms of energy-efficient and glucose-sparing feed conversion (Larson & Smith, 1974 a,b,c; Christie, 1981). Naturally, the latter require hormonal and neuro-endocrinological control mechanisms different from those of non-ruminants. They also predispose the lactating ruminant to unique metabolic disease problems, such as peripartu-rient paresis, ketosis and fatty liver degeneration and low milkfat syndrome (Littledike, 1974; Schultz, 1974; Giesecke, Dirksen & Stangassinger, 1981).

As regards species-specific and breed-typical variations of stress, cattle usually show lower plasma levels of corticosteroid hormones than those of other species (Stephens, 1980). Sustained heat stress tends to favour the development of sub-normal levels of cortisol and elevated ones of prolactin and progesterone. Although thyrotropin-releasing hormone (TRH) releases thyrotropin (TSH), growth hormone (GH) and prolactin in cattle, sheep, man and other species (Turkington, 1974; Johnson & Vanjonack, 1976; Tindal, 1978), sustained heat stress in the rat and dairy cattle is associated with increased plasma levels, particularly of prolactin (Tindal, 1978) but diminishing levels of GH and TSH (Johnson &

Vanjonack, 1976), apparently similar to those in sheep exposed to hot, humid conditions (Guerrini, 1982). Growth hormone, insulin and glucagon are generally considered the 3 most important hormones during galactopoiesis (Bines & Hart, 1982). However, in high yielding cows, insulin in many ways becomes an anti-GH, tending to divert energy from the mammary gland to peripheral tissues (Bines & Hart, 1982). Under such conditions insulin becomes almost incompatible with elevated levels of milk production. The cows, in fact, show insulin deficiency and insulin resistance (Giesecke, Meyer & Veitinger, 1983).

Furthermore, the cow's ruminant digestion, poor regulation of water resources, limited thermo-regulation, precarious glucose and extensive lipid metabolism, exposure to sustained lactation stress, etc., are factors which may affect the cow's response to stressors in ways which differ from those of other species.

Breed differences in lactational (i.e. quantitative) and lacteal (i.e. qualitative) characteristics may also be of importance. Chronic heat stress causes fluctuations in both lactational and lacteal characteristics. However, lactational ones are more readily affected in the Friesian/Holstein than in the Jersey breed. These observations are particularly important from the point of view of the effect of stress on udder health, in so far as the repeatability of milk (M) fat (F) %, the genetic correlation of MF kg/MF % and the genetic correlation of M kg/MF % are concerned. They amount to 0,76; 0,27 and −0,35. These values (Touchberry, 1974) indicate that under conditions affecting the yield of milk, MF more than any of the other components of milk (Touchberry, 1974) can be expected to increase in lacteal concentrations.

Paape & Wergin (1977) have pointed out that milk fat globules may be significant deterrents to phagocytosis and destruction of *S. aureus* by polymorphonuclear (PMN) leucocytes in milk. The ingestion by the latter cells of milk fat globules has been shown *in vitro* to cause loss of cytoplasmic granules associated with reduced bactericidal activity, and leucocyte rounding related to the elimination of pseudopods needed for phagocytic capabilities. Fat globules could be one of the factors responsible for differences of susceptibility to mastitis among cows. Whether their phagocytosis by PMN-leucocytes depends on the numbers, concentration or size of the fat globules (Hassaneyn, 1965) or other factors related to the milk fat globule membrane (MFGM) as such, has not been determined.

It is evident that stress in dairy cattle, as in other species, is part of the continuous effort by the animals to maintain themselves in a state of homeostasis (Selye, 1948; Guyton, 1971; Hails, 1978; Stephens, 1980; Hillman, 1982). In these attempts the animals may respond by means of short-term and medium/long-term reactions. The former are initially accompanied by increased sympathetic-adrenomedullar activity. This emergency response is normally followed by a more medium/long-term adaptive response involving the hypophyseal-adrenocortical system and corresponding secretions of ACTH and corticosteroids.

The importance of both the increased sympathetic-adrenomedullar activity and the secretion of corticosteroids to udder health will be discussed in more detail below. However, to appreciate this it is deemed necessary to first discuss the general importance of lactational stress to udder health and the biological systems involved in the effect of stress on the health of the udder.

General Importance of Lactation Stress to Udder Health

It is clear from Fig. 2 that lactation stress is of significance to the development and maintenance of homeostatic resistance to the lactation stressor and is therefore of particular importance to both general and udder health of dairy cattle. Because lactation stress amounts to the rate of wear and tear in the lactating cow, low and high levels of resistance to the lactation stressor imply correspondingly raised or reduced rates of wear and tear in the cow and its udder.

For example, the decreasing levels of resistance to both the foetal and lactation stressor associated with lactogenesis (Fig. 2), imply correspondingly increasing rates of wear and tear of cow and udder and escalating susceptibility to various health problems. The rates of intramammary wear and tear during lactogenesis are high because of extensive proliferation, functional differentiation and activation of ductular and alveolar epithelium. Concurrently elevated somatic cell counts (SCC) per ml of udder secretion and other characteristics make it clear that during lactogenesis wear and tear in the udder cavity of leucocytic and epithelial cells is increased (Table 1). Furthermore, the elevated values of

TABLE 1 Approximate gross composition and other general characteristics of different normal colostral and lacteal udder secretions*

Characteristics of mammary secretion		Various mammary secretions and composition						
		Colostral secretions relative to days before (−) and after (+) calving						Milk
		Day −14	Day 0	Day +1	Day +2	Day +4	Day +6	
Appearance		Clear, very sticky and viscous, honey coloured	Opaque, sticky viscous to ropy yellow	Changing rapidly from that on Day 0 to that on Day 6			Milk-like	Milk-like
Water	%	63,0–77,0	66,4	84,4	86,3	85,8	87,0	87,6
Total solids (TS)	%	23,0–37,0	33,6	15,6	13,7	14,2	13,0	12,4
Solids non-fat (SNF)	%	19,0–36,0	27,1	12,0	10,0	9,7	9,3	9,0
Fat	%	0,5– 4,2	6,5	3,6	3,7	4,5	3,7	3,4
Total protein	%	16,0–32,0	22,5	6,8	5,1	4,2	3,6	3,5
Casein	%	?**	5,6	4,2	3,9	3,3	2,8	3,0
Whey protein	%	?	16,9	2,6	1,2	0,9	0,8	0,5
Carbohydrate (lactose)	%	0,4– 2,1	2,1	4,2	4,5	4,7	4,8	4,6
Ash	%	0,5– 1,0	1,4	1,0	?	0,9	0,9	0,8
Somatic cells × 10^3 per mℓ		> 1000	> 1000	> 1000	> 1000	Fluctuating		< 1000
Pathogenic bacteria from mastitis		Absent	Absent	Absent	Absent	Absent	Absent	Absent

* Compiled from Heidrich & Renk (1967), Schalm *et al.* (1971) and Kiermeier & Lechner (1973)

** No values found

whey protein in the colostrum indicate that the cow, in anticipation of parturition, has a resistance to the expected lactation stressor sufficiently low to respond during the initial alarm stage of lactation stress with the secretion of its own serum protein (Table 1). Depending on increasing resistance *post partum* to the lactation stressor, SCC and whey protein values decrease and the general nature of the udder secretion changes from that of a serum-like filtrate to that of a lacteal secretion proper (Table 1).

From the above data it is understandable that under the labile peri-parturient circumstances, further aggravated at calving by elevated levels of pro-phlogistic GH (Veilleux, 1963), highly pregnant and freshened heifers and cows tend to be susceptible to clinical types of mastitis. Under practical conditions, acute clinical mastitis is, in fact, an acknowledged major hazard before, at and for a relatively short time after calving, rather than at more advanced stages of lactation during mid-pregnancy (Munch-Petersen, 1934, 1938; Utpott, 1963; Heidrich, Fiebiger & Utpott, 1964; Boge, 1965; Heidrich & Renk, 1967; Grabe, 1969; Grambow, 1970; Schalm *et al.*, 1971; Newbould, 1974; Soerensen, 1974; Eberhart, 1977; Jain, 1979) when all levels of resistance specific and non-specific to the lactation stressor are elevated (Fig. 2).

Intramammary epithelial proliferation, differentiation and activation may also be expected at oestrus and for a few days after (Cowie & Tindal, 1971; Larson & Smith, 1974 a,b,c). Several workers have pointed out that there is a relationship between increased susceptibility to mastitis and the oestrus cycle of lactating cows (Frank & Pounden, 1961; Schalm *et al.*, 1971), feeding cows with oestrogenic feedstuffs (Schalm *et al.*, 1971; Anderson, Smith, Spahr, Gustafsson, Hixon, Weston, Jaster, Shanks & Whitmore, 1983) and the administration of 17-beta-estradiol (Guidry, Paape & Pearson, 1975). Such data imply that episodes of reduced resistance to lactation stressor may also be expected during normal lactation.

Biological Systems Related to the Effect of Stress in Udder Health

The health and welfare of the dairy cow depend on a range of interactive factors (Table 2).

TABLE 2 Descriptions of various interactive factors related to health and welfare of dairy cattle

Class of factors	Description of factors
Veterinary	*Education and specialization, research, field work (curative, preventive, educational), implementation of professional advice
Environmental	*Ecology (soil, surface, climate), feeding (basis, intensity), production techniques, management care and control of animals and labour (disposal of waste, prevention of pollution, animal welfare)
Economic	*Cost of factors related to animal health and production, demand for and marketing of products
Genetic	†Genetic basis (type, origin, breed), selection (charcteristics selected, intensity of selection), breeding (pure and cross breeding)
Productivity	*Quantity and quality of products, rate of production

* Exogenous and † endogenous

These factors may be classified as physical, chemical, biological and composite, depending on their respective natures (Table 3).

TABLE 3 Factors related to normality and stress in dairy cattle

Nature of factors	Descriptions of factors
Physical	Ambient temperature (18 °C = thermoneutrality in European dairy breeds), humidity, rain, wind, solar radiation, light, altitude, atmospheric pressure
Chemical	Air composition (O_2, CO_2< 3,5 ℓ/m³, N, SO_2, PbO_2, CO, H_2S<0,0 1ℓ/m³, NH_3<0,05 ℓ/m³), odour, particles, other pollutants, minerals and trace elements in feeds and water
Biological	Behaviour (social hierarchy, butting, crowding, isolation, separation, fear), parasites, insects, micro-organisms, other animals (predators, snakes)
Composite	Feed and water quantity and quality, soil, housing, shelter, husbandry and management, disease, removal of milk, calving

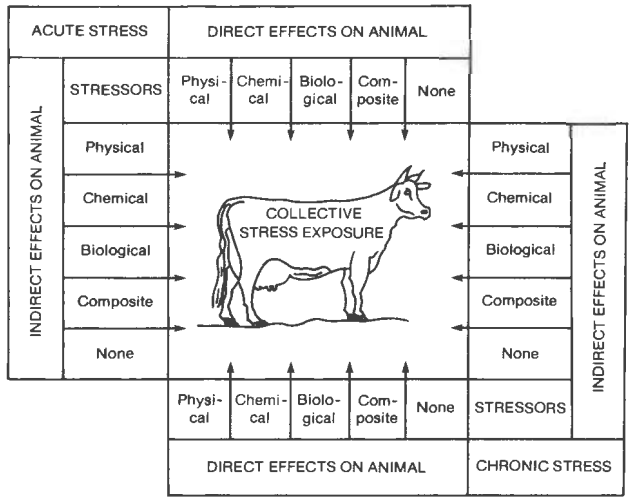

FIG. 3 Schematic presentation of matrix of different stressors and corresponding types of stress affecting the cow singly and in different combinations including superimposed ones (e.g. acute stress superimposed on chronic stress)

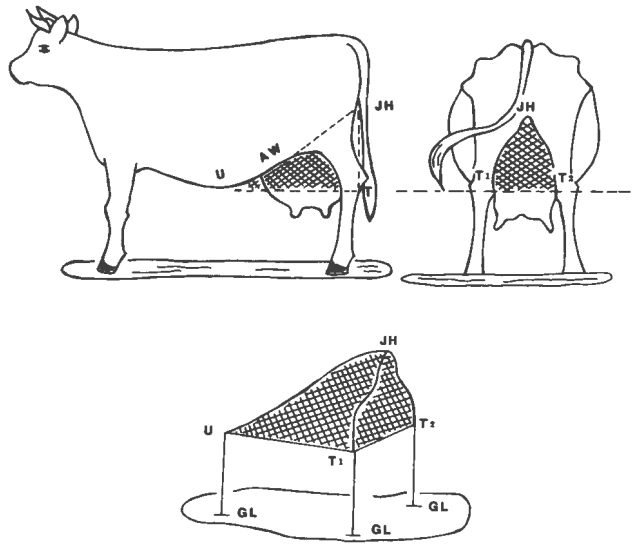

FIG. 4 Schematic presentation of the cow's udder shelter (Giesecke, 1983).

The natural shelter of the udder (shaded) is an umbrella-like space bordered by the inclining abdominal wall (AW), a vertical plane with its tip where the hind legs join (JH) and its horizontal base line between the medial aspects of the 2 tarsal joints (T1,2), and the plane reaching from the medial aspects of the tarsal joints to the umbilicus (U). The shelter is raised off the ground level (GL) by the legs. The protective efficacy of the udder shelter depends on the size of the udder and the distance between GL and U-T1-T2

The modern dairy cow may thus be seen as living in an environment which affects it and its udder by means of various stressors. Through direct and indirect effects on the animal, they initiate different types of acute and chronic stress of a somatic, psychological, actual and anticipated nature (Fig. 3).

Dairy cattle, and especially the Friesian/Holstein breeds, under South African conditions are frequently subjected to chronic nutritional and heat stress (Bonsma, 1943; Bonsma & Joubert, 1957). Efficient water and thermo-regulation are therefore indispensable for the cow's response to heat stress, and are both involved during lactation because of the removal of lacteal water during milking, the additional heat generated during biosynthesis and secretion of milk, and heat generated during the digestion of concentrate rations. Dairy cattle living in warm climates therefore require particularly careful feeding, sufficient drinking water and very efficient shade management. Unless such requirements are met, acute stress, related to parturition, lactation, febrile disease, fluctuating ambient temperatures and elevated humidity, etc., will add to chronic stress.

The response of dairy cattle to stressful exposures is modified by breed, sex, physiological, metabolic and other factors.

In the afore-mentioned environment (Fig. 3), the mammary gland is protected from different stressors by means of the udder shelter (Fig. 4).

The udder shelter's action is augmented by an extramammary and an intramammary master system of defence (Fig. 5). The proposed model of the latter is portrayed as a lattice-like system with backups consisting of immunologically specific and non-specific sub-systems. The latter may be subdivided into sub-systems of lesser significance (= peripheral systems) and sub-systems of key significance (= core systems), as outlined in Fig. 5.

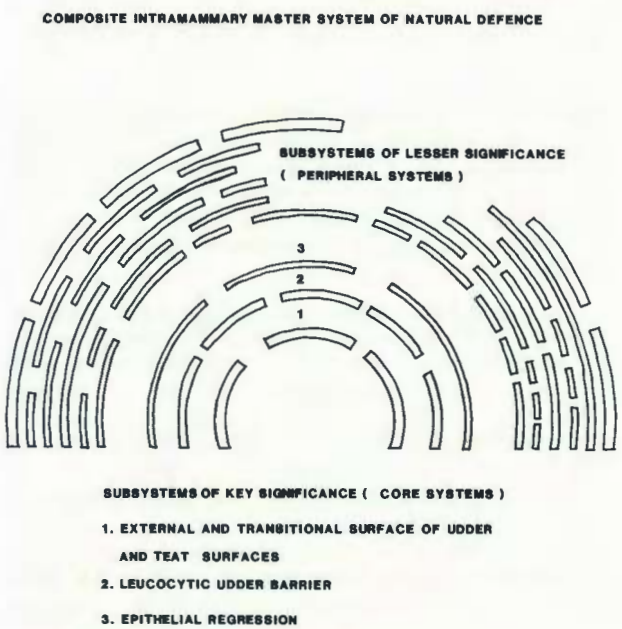

FIG. 5 Schematic presentation of the proposed model of natural defence mechanisms of the lactating bovine udder. Each of the block areas indicates one of the different over-lapping and inter-locking systems or portions thereof involved in protecting the udder from infection

The 3 core systems are augmented by the peripheral systems and function as an integrated unit of intramammary defence. This unit has several functional components:

- The teat canal, teat cistern and gland cistern. They provide the morphological boundaries, capture, immobilize and also kill bacteria on their surfaces, normally limit bacterial invasion and may thus be considered the bacterial trapping component.
- The smooth musculature of the internal orifice of the teat canal and the teat wall, which, by means of rhythmic contractions, reduces milk pressure at the internal orifice of the teat canal, effectively closes it, augments the bacterial trapping component and also provides the reverse pumping component.
- The lacteal secretion, which acts as the environment for reactions between bacteria and PMN-leucocytes of the leucocyte udder barrier (LUB) (Schalm *et al.*, 1971), for the suspension of milk fat globules, disposal of metabolic and cellular waste, dilution of anions and cations, and storing and conveying to the calf of nutrients.
- The PMN-leucocytes, which are readily available, and disposable cells with specialized defensive capabilities amount to the LUB component.
- Mammary regression (Giesecke, 1978).

Mammary Regression—A Single Response to Various Stressors

Mammary regression, if physiological, is probably the cow's most effective means of maintaining normal udder health. However, mammary regression, if unphysiological and suddenly developing during lactation, may seriously jeopardize the normal functioning of the LUB. Because stress in lactating cows promotes premature regression, the key role in udder health of this phenomenon must be pointed out.

The bovine udder is an organ genetically programmed to produce a range of compounds which are of vital importance to the well-being of a series of calves born during the normal life-span of a cow. Functioning of the udder depends on 4 extensively reviewed (Reynolds & Folley, 1969; Falconer, 1970; Cowie & Tindal, 1971; Schmidt, 1971; Larson & Smith, 1974 a,b,c) main stages of development, namely: (i) Structural development and differentiation (i.e. mammogenesis); (ii) induction of secretory functioning and differentiation (i.e. lactogenesis); (iii) maintenance of secretory function (i.e. galactopoiesis) and (iv) termination of secretory function and discarding of secretory epithelium (i.e. regression).

The stages of galactopoiesis and regression are of greater or lesser importance in the context of lactation stress according to the cow's production. A lactating cow may lose energy at a rate of some 3,054 MJ per kg of 4 % fat corrected milk (plus increased amounts of protein, lipid, carbohydrates, minerals, vitamins, etc.), whereas at any stage during lactation it can control the loss of energy and matter by regression. Naturally, these losses only occur if galactopoiesis is augmented by the actual removal of milk from the udder. This removal stimulates lactation, i.e. the secretion of milk proper.

Briefly, the secretion of milk amounts to the passive movement of H_2O along an osmotic gradient (Linzell & Peaker, 1971; Peaker, 1974, 1977, 1978; Mepham, 1976) which depends on active transportation of various solutes essential for establishing and maintaining that gradient. That work is performed by the secretory epithelium, a tissue partition which also protects the metabolic and immunological homeostasis of the mammary interstitium from the anti-homeostatic effects of the lacteal secretion.

TABLE 4 Special features of the bovine mammary gland relevant to inducing regression of the secretory alveolar epithelium during and/or at the end of lactation*

Features of mammary regression	Significance of features of regression	Features promoting regression
Teat canal, cisterns, lactiferous ducts and alveoli	Intramammary retention of milk, development of milk stasis and escalating milk pressure which eventually affect the secretory epithelium through end-product inhibition, occlusion of blood capillaries, metabolic waste, breakdown products from milk	Partial and complete cessation of milking and similar conditions promoting intramammary retention of milk
Lobular and alveolar morphology of secretory tissue	Adaptable regression depending on localized and generalized retention of milk, fluctuating blood circulation and changed susceptibility to oxytocin of myoepithelial alveolar cells	Intra-alveolar and intra-lobular stasis of milk; different types of stressors
High metabolic activity and requirements of secretory epithelium	Functional changes and complete destruction of cells by means of circulatory adjustments of peri-alveolar blood supply, waste- and end-product inhibition	Elevated secretion of adrenalin (= intralobular/peri-alveolar vasoconstriction; blocking of oxytocin at myoepithelium), waste- and end-product inhibition (= autolysis) and increased intramammary milk pressure (= vaso-occlusion)
Incomplete junctional complexes of lactating epithelium	Lack (at least in mice) of desmosomes between secretory epithelial cells and presence of fragile gap junctions between secretory and myoepithelial cells of alveoli, easy discarding of secretory cells, whereas typical ductular epithelium has a complete junctional complex, lacks myoepithelium and is thus more firmly attached to the basal membrane	Metabolic changes (glucose, calcium) reducing the efficacy of the incomplete junctional complexes of the secretory alveolar epithelium
Extensive lysosomal and autophagic activity in normally functioning lactating epithelium	Secretory cells susceptible to necrobiosis under normal conditions	Any of the above features
Balance in lactating epithelium of Na^+, K^+ and Ca^{2+}	Secretory cells highly dependent on the normal glucose metabolism required for maintaining physiological levels of Na^+, K^+ and Ca^{2+}	Gluco-corticosteroids and/or any of the above features affecting glucose metabolism in secretory epithelium
Intra-alveolar availability of chemotactic agents of epithelial and leucocytic origin	Epithelial agents such as casein micelles, milk fat globules and lysosomes released into the alveolar lumen attract phagocytes, are phagocytized and thus affect liberation of leucocytic chemotactic agents (e.g. lysosomes, superoxide radicals) and early deterioration of the phagocytes. Depending on further escalation of autocatalytically controlled leucocytic invasion, intra-alveolar concentrations of lysosomal enzymes and cytotoxic agents (e.g. H_2O_2, O_2^-, OH°) facilitate further epithelial regression	Any of the features above which promote epithelial deterioration and leucocytic invasion of secretory alveoli

* Compiled from Cowie & Tindal (1971), Schalm *et al.* (1971), Larson & Smith (1974 a,b,c), Lück, Giesecke, De Villiers & Mackie (1976), Mackie, Giesecke, Lück & De Villiers (1977) and Larson (1978)

The secretory epithelium, in the broad sense, may thus be regarded as a biologically extremely active cellular membrane which separates the elevated H^+ concentrations of the lacteal environment from the much lower H^+ concentrations of the interstitial environment. The main object of the H^+ gradient is the re-absorption from normal milk of Na^+ in exchange for H^+ and K^+. Owing to the close correlation between Na and Cl, the conservation of Na^+ also facilitates that of Cl^-. In contrast K^+ is secreted in preference to Na^+ and Cl^- for making up the balance between the osmolality of lactose and isosmotic conditions in normal milk (Palmiter, 1969).

Apart from being the solvent for a range of solutes, the lacteal H_2O acts as the vehicle of choice for the transportation to the calf of a wide range of nutrients and other matter as well as the removal from the udder cavity of waste products, not removed from the mammary metabolism through the blood but through the lacteal secretion. This mixture of compounds normally removed from the lactating udder is commonly known as milk. The rate of secretion depends on the number and activity of secretory cells of the mammary epithelium. The number of cells is controlled by cell division and cell loss. Their activity is subject to the control of metabolically active intracellular units at ultrastructural levels. Collectively, units such as mitochondria, RER, Golgi's apparatus and transportation vesicles, lysosomes, etc., amount to a metabolic machinery which is essentially used to establish and maintain the osmotic gradient mentioned above. Although normally the organism of the cow is not particularly susceptible to deficiencies and fluctuations of Na, Cl and other elements related to the intramammary osmotic gradient (Coppock, Grant, Portzer, Escobosa & Wehrly, 1982), such tolerance does not necessarily apply to the secretory mammary epithelium and its junctional complex.

To function as a barrier that ensures the maintenance of interstitial homeostasis, the secretory epithelium must be intact. It is also involved in the establishment of the H^+ gradient and conservation of Na^+ and Cl^- (Peaker, 1974, 1977, 1978). Moreover, it produces nutrients for the calf and in particular lacteal calcium and phosphorus. The secretory epithelium indeed concentrates Ca^{2+} by means of a process necessitating increased synthesis of citrate, as a buffer system and chelating agent for Ca^{2+} and Mg^{2+}. The above-mentioned depends on one hand on unimpeded glucose metabolism, and on the other hand on the equally unimpeded removal of its end-products, CO_2 and H_2O, associated with the balancing of bases and acids on both sides of and within the epithelial membrane (Larson & Smith, 1974 a,b,c).

Glucose is essential at the intracellular level, for synthesis in the Golgi vesicles of lactose, which, in turn, determines the secretion of the aqueous phase of milk. Glucose is also essential for the production in the mitochondria of adenosine triphosphate (ATP) and citrate. Furthermore, it is necessary for the action at different

TABLE 5 Mean concentrations of different components in bovine mammary secretion during normal lactation and after suspension of milking*

Components of mammary secretion		Periods of normal lactation and suspended milking, and mean values			
		Normal lactation	Suspension of milking		
			Day 1	Days 7/8	Day 14
Lactate	mM	0,15	0,26	2,92	3,85
Pyruvate	mM	0,05	0,08	0,10	0,11
Glucose	mM	1,03	0,68	0,13	0,12
Lactose	mM	126,8	118,3	36,9	51,4
Na^+	mM	19,0	27,5	93,2	80,5
K^+	mM	43,4	40,5	17,8	21,0
Whey-proteins (mg/mℓ)					
Total		8,92	8,73	29,04	20,75
Serum albumin		0,38	0,48	3,57	4,89
Immunoglobulin		1,43	1,51	13,53	8,91
beta-Lactoglobulin		5,41	5,24	7,14	4,95
alpha-Lactalbumin		1,7	1,5	4,8	2,0
Somatic cell count (log of number per mℓ)					
Polymorphonuclear leucocytes		3,53	4,87	6,03	5,95
Lymphocytes		2,36	4,26	5,93	5,99
Epithelial cells		4,73	4,92	4,90	4,58
Estimated redox potential (mV)		−218	−220	−248	−252

* Compiled from Lück *et al.* (1976) and Mackie *et al.* (1977)

TABLE 6 Correlation during induced premature regression between mean concentrations of different components of bovine mammary secretion*

Components correlated	Co-efficients of correlation(r)
Glucose/log PMN-leucocytes	−0,89***
Lactate/log PMN-leucocytes	0,78***
Lectate/redox potential	0,69***
Lectate/glucose	−0,78***
Lactate/Na^+	0,86***
Lactate/K^+	−0,88***
Lactate/serum albumin	0,94***
Lactate/lactose	−0,91***

* From Mackie *et al.* (1977)
*** = P <0,001

TABLE 7 General trends of most consistent lactational and lacteal changes in dairy cattle affected with chronic heat stress, induced regression and mastitis*

	Conditions and changes		
	Induced regression	Chronic heat stress	Mastitis
Lactation (yields)			
Milk	Down	Down	Down
TS	Down	Down	Down
SNF	Down	Down	Down
Lacteal (concentrations)			
TS %	Down	Down	Variable
SNF %	Down	Down	Variable
Butterfat %	Down	Up	Down
Lactose %	Down	Down	Down
K^+, Ca^{2+}	Down	Down	Down
Na^+, Cl^-	Up	Up	Up
Lacteal (other values)			
pH-values	Up	Up	Up
Freezing point	Up	Up	Up
Fatty acids	More long-chained, unsaturated	More long-chained, unsaturated	More long-chained, unsaturated
Somatic cells	Up	Up	Up

* Compiled from Heidrich & Rink (1967), Schalm *et al.* (1971), Kiermeier & Lechner (1973), Lück *et al.* (1976), Mackie *et al.* (1977) and Giesecke (1978)

cellular membranes of various ion-activated ATP-ases, which determine homocellular active transportation of certain monovalent (e.g. Na^+, K^+, H^+ and Cl^-) and bivalent (e.g. Ca^{2+}, Mg^{2+}) ions (Mepham, 1976; Linzell, Mepham & Peaker, 1976).

Because of its high metabolic requirement and corresponding production of metabolic waste, the secretory epithelium is particularly susceptible to adverse conditions which affected its electrolyte and energy balances. The latter, in turn, depend on a blood supply which is extremely sensitive to any fluctation in adrenalin concentration (Linzell, 1974) as well as the regular complete removal of milk. It is therefore evident that the intact existence of the secretory epithelium is precarious indeed.

The major portions of secretory epithelium line those mammary tissues which are metabolically most active, namely, the secretory alveoli. If they are regularly emptied by complete milking, the development of milk stasis in their lumens is prevented. Milk stasis in the alveoli is a potentially dangerous condition, because it results in intra-alveolar accumulation and decomposition of secretory products, trapping of cytotoxic metabolic waste products, increasing availability of agents which stimulate positive chemotaxis of leucocytes, and persistence of milk pressure at levels high enough to adversely affect normal extra- and intra-epithelial circulation.

The above-mentioned changes may be simulated experimentally by temporarily suspending (e.g. for 24–36 h) the removal of milk. The lactating cow usually responds to this exogenous stressor with a slight reduction, after resumption of milking, in the yield of milk and with slightly elevated MF %. At the microscopic level one finds alveoli that are distended with milk and milk fat globules, the epithelium containing large amounts of manufactured protein granules and milk fat droplets (Hollmann, 1974). Although extrusion of fat droplets and exopinocytosis of protein granules at the apical aspects of the epithelium are impeded, neither their production nor that of metabolic waste products within the cells are initially affected. Eventually the function, integrity and location of cellular organelles such as microtubules and mitochondria are affected.

Intracellular changes associated with milk stasis may escalate to those of initial regression (e.g. the formation of autophagic vacuoles) and regression proper (Cowie & Tindal, 1971; Hollmann, 1974; Lascelles & Lee, 1978), which is an irreversible degeneration, especially of the secretory alveolar epithelium. This degeneration may be regarded as a physiologically programmed cellular deterioration (necrobiosis). Normal mammary regression

apparently does not cause irreparable damage to the basal membrane and other tissues supporting the mammary epithelium. It is thus essentially a non-inflammatory type of cellular degradation which may occur either prematurely, i.e., during lactation, or normally, i.e., at the end.

Mammary regression is also closely associated with various stressors such as fright, pain, strain, fever and exertion (Giesecke & Van den Heever, 1974, 1981; Giesecke, 1978, 1979), the udder being equipped with several special features for the initiation of regression on the slightest provocation (Table 4).

The fact that some 20 % of alveoli in normal udders, even at the peak of lactation, are completely involuted, suggests that physiologically-induced regression is an integral aspect of normal lactation. It follows a stereotyped pattern of progressive changes from oxydative to anaerobic glycolytic metabolism in the secretory epithelium. The udder secretion changes concurrently from lacteal to a more serum-like composition (Lück *et al.*, 1976; Mackie *et al.*, 1977) (Table 5).

The development (Table 5) of premature regression is apparently associated with the epithelial metabolism of glucose, as suggested by the highly significant correlation of glucose with lactate and leucocytic cells during artificially induced regression (Mackie *et al.*, 1977) (Table 6).

From the point of view of stress in bovine udder health premature regression is a very important phenomenon because it is associated with loss of integrity of the mammary epithelium. Tables 5 and 6 indicate that the tight junctions are becoming "leaky", i.e., changes similar to those also observed on regressive udders of goats (Faulkner, Blatchford, White & Peaker, 1982).

Data in Tables 4 and 5 indicate that the development of regression depends on exogenous factors, such as incorrect feeding, insufficient water for drinking, milk not regularly removed from the alveolar lumen and endogenous ones, such as vasoconstriction, electrolyte and energy balance and related haemotogenous and endocrinological factors. Different combinations of these main factors seem conceivable. The most important exogenous factor in the lactating dairy cow is bacterial udder infection which is usually associated with mastitis.

There is evidence (Giesecke, 1978) that udder inflammation coincides but is by no means synonymous with normal mammary regression. Regression is obvious during the chronic stage of the disease (Heidrich & Renk, 1967; Schalm *et al.*, 1971), but it is not readily detected during the more acute phase when both production and composition of milk begin to change dramatically.

During the first 10–12 hours of mastitis, the usually gradual course of regression becomes accelerated and changes to an acute inflammatory condition, apparently due to the early release from damaged cells of different classes of biochemical mediators such as lytic, coagulative, kininogenic and phlogistic (Honkanen-Buzalski, 1982). They even may affect the apparently normal adjacent quarters of an acutely mastitic udder (Giesecke & Van den Heever, 1981). The concurrent development of oedema, milk stasis, increased intra- and extracellular lysosomal activity and extensive destruction of leucocytes in milk (Schalm *et al.*, 1971) all contribute to the mastitogenic effect of the infection and its toxic bacterial metabolites. Hence, considerable parts of the mammary epithelium may show rapidly advancing necrosis, sometimes aggravated by lesions of the basal membrane and supporting interstitial tissue. This pathologically provoked destruction of portions of udder tissue is inflammatory in nature. It eventually leads to fibrosis and the mammary tissue becomes unproductive from the economic point of view.

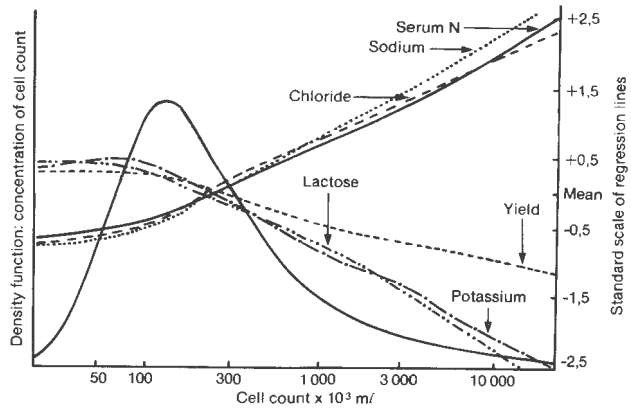

FIG. 6 The standardized frequency curve of the log values of the somatic cell counts in 2310 milk samples in relation to regression lines of corresponding yields of milk and lacteal levels of chloride, serum N, sodium, lactose and potassium (Reichmuth, 1975)

Such pathological changes are related to changes in the composition of the milk secreted (Giesecke, Van den Heever, Hope & Van Staden, 1968; Giesecke & Van den Heever, 1974, 1975, 1981; Giesecke & Viljoen, 1974; Giesecke, 1978, 1979; Honkanen-Buzalski, 1982). In subclinical mastitis increased values of SCC, Na, Cl, BSA, immunoglobulin, lactoferrin, catalase and antitrypsin, and decreased ones of Ca, K, lactose, casein, H^+, citrate and others have been recorded (Randolph & Sharma, 1974; Randolph & Erwin, 1974; Kitchen, Middleton, Durward, Andrews & Salmon, 1980; Honkanen-Buzalski & Sandholm, 1981 a,b; Honkanen-Buzalski, Katila & Sandholm, 1981; Honkanen-Buzalski, Kangasniemi, Atroshi & Sandholm, 1981; Honkanen-Buzalski, 1982) (Fig. 6).

It is clear that lacteal changes in mastitic udder secretions are similar to those associated with regression (Table 5). If they are associated with clinical rather than with subclinical mastitis, the lacteal changes develop more rapidly, become more pronounced, and are associated with more mastitogenic micro-organisms, inflammatory exudate and severe tissue damage (Heidrich & Renk, 1967; Schalm *et al.*, 1971; Newbould, 1974; Schalm, 1977; Van den Heever & Giesecke, 1980). However, the regressive changes are common to all types of deterioration of the mammary epithelium irrespective of whether they are mastitic or non-mastitic in origin. Lactating dairy cattle tend to respond with lactational and lacteal changes which are generally similar in nature (Table 7), irrespective of whether the stressor is mastitis, febrile disease (Heidrich & Renk, 1967; Theodoridis, Giesecke & Du Toit, 1973), heat (Bianca, 1965; Thompson, 1973; Johnson & Vanjonack, 1976) or another stressful condition (Giesecke & Van den Heever, 1974; Giesecke, 1979).

Mammary regression is always associated with the deterioration of secretory epithelial cells discarded for the purpose of restoring and maintaining involutional mammary homeostasis. Complete restoration of metabolic and immunological homeostasis is feasible only by discarding all lactogenic cells so that the udder can completely involute. Unless the udder ceases to synthesize any lacteal product, mammary regression is incomplete and homeostasis is not at its ideal involutional level because low level lactation stress prevails. Complete

mammary regression, therefore, may be considered the lactating cow's most powerful non-specific, inherent defence mechanism against the variety of stressors common to its stressful environment.

Regression is a physiological phenomenon, provided it develops at a time and rate physiological in terms of the cow's lactation. However, in the stressed cow, both the timing and rate of mammary regression becomes unphysiological. They may further coincide with events such as erosion, infection or patency of teat canals, and other conditions which favour potentially mastitogenic contaminations of the lacteal environment and/or cause other components of the natural intramammary defence to become deficient. In the stressed lactating cow mammary regression has the following adverse effects: accelerated deterioration of epithelial integrity and mammary homeostasis; provision, at elevated levels, of chemotactic agents and phagocytyzable matter which causes premature and more rapid ageing of leucocytes.

The leucocytic defence of the lactating udder of the stressed cow thus may become deficient before being challenged by bacteria invading the udder cavity. A deficiency of the LUB is more important in the lactating udder because its local immunological defence depends mainly on non-lymphocytic cellular elements in milk. It has a limited immunological memory, and little diffuse lymphoid tissue. In contrast, during involutional homeostasis the udder secretion contains mainly monocytic/macrophagic and lymphocytic cells, and the tissue a well-developed immunological memory and fairly extensive diffuse lymphoid tissue (Derbyshire, 1962; Butler, 1974; Giesecke & Van den Heever, 1974; Watson & Lascelles, 1975; Lascelles & Lee, 1978; Lascelles, 1979; Chang, Winter & Norcross, 1981; Nickerson & Pankey, 1983; Nickerson, Pankey, Watts & Boddie, 1983).

This implies that the immunological defence of the mammary cavity shifts from mainly humoral during involutional homeostasis to primarily cellular during lactational homeostasis. This indicates further that monocytes/macrophages and PMN-leucocytes may be in milk not only as phagocytes but also in relation to hypersensitivity reactions. In fact, investigations on sensitized guinea-pigs have shown that antigen-elicited emigration into the milk of leucocytes appeared to be a local expression of a general state of lymphocyte-dependent hypersensitivity (De Cueninck, 1982). Such findings may have considerable implications for a more complete understanding of the LUB.

In this respect it is important that fat globules, once secreted into the lacteal environment, cease to be self in the immunological sense. Milk fat globule membranes (MFGM) have been shown to carry certain immunoglo-

TABLE 8 Changes of cortisol, progesterone, lactational, lacteal and physiological determinations on 9 Holstein dairy cows subjected at about 90 days of their 2nd lactation to escalating temperatures at a constant relative humidity of 65 %†

Level of exposure to heat during periods of 7 days each °C	Parameters‡ monitored × mean values						
	Plasma levels (ng/mℓ)		Lactational	Lacteal		Physiologic	
	Cortisol (C)	Progesterone (PG)	Milk yield (MY) kg	Milk fat (MF) %	Solids-not-fat (SNF) %	Rectal temperature (RT) °C	Respiration rate (RR) counts/min
18,5	21,2	4,3	27,5	2,0	8,9	39,1	44,1
21,2	25,4	3,2	27,4	1,4	8,5	39,6	62,9
24,0	16,7	4,2	26,0	1,4	8,1	40,0	70,9
26,8	19,6	3,2	22,4	2,2	8,6	40,2	76,0
29,5	16,4	4,7	18,3	2,4	8,9	40,9	85,0
29,5	7,0	4,2	15,4	2,4	8,0	41,5	75,7
29,5	3,0	3,9	17,1	2,2	8,1	40,7	78,3

‡ Coefficients of correlation (r) significant (*) and highly significant (**): SNF/RT = −0,27*; SNF/C = 0,37**; MF/MY = −0,44**; MY/RT = −0,67**; MY/RR = −0,49**; MY/C = 0,36**; RT-RR = 0,64**; RT/C = −0,34**

† Compiled from Lee, Beatty & Roussel (1971)

TABLE 9 General trends of most consistent physiological changes in chronically heat stressed dairy cattle*

	Parameters monitored	Trend of changes
Temperatures	Rectal, skin	Up
Sweating	Rate, H_2O, $KHCO_3$, KCl, $NaHCO_3$, all ions (Na, K, Mg, Ca, Cl) except P	Up
Behaviour	(a) Drinking frequency, water intake and consumption/kg of roughage, standing time;	Up
	(b) frequency of changing from lying to standing.	Down
Respiration	Frequency/min	Up
Circulation	(a) Cardiac frequency [1], peripheral resistance, blood pressure;	Down
	(b) Cardiac output	Up
Digestion	Body mass, roughage intake, rumination, rumen contents (osmotic pressure, acetate, acetate/propionate ratio, pH, Na^+, K^+) except H_2O.	Down
Kidneys	(a) Urine volume, Na^+ and $NaHCO_3$ secretion;	Up
	(b) K^+ secretion	Down
Hormones (plasma levels)	(a) Progesterone, prolactin, adrenalin, noradrenalin;	Up
	(b) thyroxine, growth hormone[1], aldosterone[1], insulin, glucocorticosteroids[1]	Down
Blood	(a) Haematocrit, haemoglobin, glucose[1] O_2 (venous blood);	Up
	(b) volume, plasma volume, pH, free fatty acids, CO_2 (venous blood), Zn	Down

* Compiled from Manresa, Reyes, Gomez, Zialcita & Falcon (1940), Dale, Brody & Burge (1956), Bianca (1965), Schleger & Turner (1965), Paape, Schultze, Miller & Smith (1973), Thompson (1973), Wegner, Ray, Lox & Stott (1973), Johnson & Vanjonack (1976), Lee, Roussel & Beatty (1976), Terui, Ishino, Matsuda, Shoji, Ambo & Tsuda (1980), Bünger (1981), Moreau (1981), Colliers, Beede, Thatcher, Israel & Wilcox (1982), Grossman (1983) and Zöldag (1983a,b).

[1] Elevated during acute heat stress.

bulins (e.g. IgA, IgM) (Honkanen-Buzalski, 1982). Normal secretion of milk is associated with phagocytosis of fat globules by PMN-leucocytes (Paape, Wergin, Guidry & Pearson, 1979). Increased secretion of fat globules occurs during regression, and these globules are attractive to PMN-leucocytes and especially monocyte/macrophages (Lascelles & Lee, 1978). The PMN-leucocytes and monocyte/macrophages therefore seem involved in the disposal of fat globules which are apparently non-self and coated with antibody, a process which is similar to phagocytosis of other opsonized antigens. The question arises whether, under certain circumstances, this phagocytosis can be further directed towards fat globules not yet secreted but bulging from the apical surfaces of secretory cells.

Regression is characterized by major metabolic and structural changes of, especially, secretory epithelial cells which show increased levels of autophagocytosis (Hollmann, 1974; Lascelles & Lee, 1978) and the presence of fat globules distending their apical portions.

Although the available evidence suggests that epithelial regression is initiated by a metabolic process (Tables 4 & 5), hypersensitivity reactions may be involved in the extension thereof. During lactation limited epithelial regression is an ongoing process and it is conceivable that non-phlogistic and phlogistic hypersensitivity reactions are important in normal and abnormal udder health during lactation.

Mammary regression stimulated by stressful conditions superimposed on the stress of normal lactation is therefore of importance, not only as a compensatory response to stressors, but probably also predisposes to mastitis. This is accentuated by the inflow into the regressive portions of mammary glands of serum proteins, such as complement and immunoglobulins, enzymes such as catalase, lipase and protease and other haematogenous agents. These could seriously affect the peripheral and core systems of mammary defence (Fig. 5) by, for example, deficient binding of iron by lactoferrin, and inactivation of H_2O_2 by catalase (Shahani, 1966; Schanbacher & Smith, 1975; Senft, Klobosa, Meyer & Pfleiderer, 1976; Reiter, 1978; Poutrel, 1982; Maisi, Mattila & Sandholm, 1983).

Responses to Stressors of Biological Systems Involved

During stress due to prolonged exposure to ambient temperatures higher than 21 °C, dairy cows show several distinct physiological, lactational and lacteal changes (Table 8).

Particularly noteworthy are fluctuating plasma levels of cortisol (Table 8), stable levels of progesterone, decreasing values of SNF % and milk produced, and increasing values of MF %, body temperature and respiration rate.

More detailed parameters indicate (Table 9) that sustained heat stress affects dairy cattle at behavioural, physiological, endocrinological and neuro-endocrinological levels. As was already mentioned above in Table 7, stress promotes mammary regression and is therefore related to major changes in the secretion and composition of milk.

In the light of the above it is reasonable to suggest that stress may affect udder health in 3 ways:

1. Milk stasis and regression, suspension of reverse milk pumping and deficient muscular teat canal closure in acute stress due to elevated secretion of adrenalin.
2. Mammary regression in chronic stress due to sustained increased secretion of prolactin, progesterone and adrenalin.

TABLE 10 Main factors associated with stress and elevated intramammary sympathetic-adrenal activity and their importance to bovine udder health

Factors	Significance of factors
Stressors affecting dairy cattle	Increased sympathetic-adrenomedullar activity in animal
Efferent innervation of udder	Exclusively sympathetic adrenergic; under conditions of stimulation, of particular importance at the level of the secretory alveoli, blood supply and teat contractions
Increased sympathetic/adrenalin activity in mammary tissue initiating several changes	Stimulates vasoconstriction, prevents oxytocin from reaching alveolar myoepithelium and smooth muscle fibres, raises the myoepithelial threshold to oxytocin; promotes, therefore, the development of milk stasis and regression which, in turn, have major implications on udder health
	Acts on *alpha*-receptors of blood vessels, stimulates marked vasoconstriction which can temporarily decrease mammary blood flow. Affects, therefore, transportation of (i) oxytocin to myoepithelial cells of alveoli, and (ii) nutrients to and metabolic waste from highly active secretory epithelium which, in turn, promote regressive changes on the level of the epithelial metabolism
	Acts on *beta*-receptors of smooth muscle fibres in teat and around teat canal; causes them to relax, thus (i) inhibiting contractions of teat wall and teat canal, (ii) promoting the intracisternal accumulation of milk and corresponding increases of milk pressure at internal orifice of teat canal, which, in turn, may affect the closure of the teat canal
Increased sympathetic/adrenalin activity in mammary tissue synchronizes multiple effects on udder tissue and secretion	Depending on epithelial regression initiated by milk stasis and/or circulatory/metabolic changes, limited and more extensive degradation of secretory mammary epithelium stimulates positive chemotaxis of leucocytes, especially PMN-leucocytes, promotes escalating leucocyte counts per mℓ of milk and increases, therefore, the leucocytic udder barrier in magnitude
	PMN-leucocytes entering the regressive udder secretion (i) gorge on cellular debris and other phagocytizable matter (e.g. fat globules, casein micceller) and (ii) commence, to gradually deteriorate, become less viable and less competent to protect the mammary cavity from infection
	Depending on (i) the morphological characteristics of the teat canal and its epithelium, especially at the internal orifice, (ii) effective length and strength of the teat canal, as a physical barrier, (iii) the antimicrobial efficacy of its epithelium, (iv) characteristics of micro-organisms inhabiting the teat canal epithelium, as a potential sources of udder infections, the intracisternal accumulation of milk pointed out above (3) promotes intracisternal and further spreading of mastitogenic micro-organisms at a time when the leucocytic udder barrier is increased in magnitude but very limited in defensive responsiveness and efficacy
Hormones and other factors	Fluctuating levels/activities in blood, udder tissue and mammary secretion of certain hormones (e.g. glucocorticosteroids) and changes of physiological (e.g. elevated general metabolism) and environmental (e.g. unhygienic conditions), factors aggravate the above-mentioned conditions and accentuate their significance to udder health during stress

* Compiled from Mackie *et al.* (1977), Sambraus (1971), Grosvenor & Mena (1974), Linzell (1974), Tucker (1974), Peeters & De Bruycker (1975), Paape & Wergin (1977) and Paape *et al.* (1979)

TABLE 11 Approximate ranges of mean plasma levels of corticosteroids in dairy cows under various stressful conditions*

Stressors of the dairy cows investigated	Corticosteroids × ranges of mean plasma levels (ng/mℓ)			
	Corticosteroids	Glucocorticosteroids	Cortisol	Corticosterone
Healthy but at different stages of lactation, e.g.	10,93	8,24	7,76	4,02
—at calving	25,30	8,88	19,20	
—at oestrus			8,90	4,30
—not at oestrus			7,60	4,00
Milk fever			4,8–11,3	
Mastitis	10,6–22,9			
Herd relocation, e.g.				
—before	8,8–9,4	10,4–11,3		
—during	9,1–25,3	13,0–27,0		
—after	21,3–22,0			
Ambient temperatures				
—intermediate	36,3		21,2–25,4	
—elevated	22,8		3,0–19,6	

* Compiled from Paterson (1957), Venkataseshu & Estergreen (1970), Lee *et al.* (1971, 1976), Paape, Schultze & Smith (1971); Paape, Schultze, Desjardins & Miller (1974), Christison & Johnson (1972), Wagner & Oxenreider (1972), Willett & Erb (1972), Edgerton & Hafs (1973), Hudson, Mullford, Whittlestone & Payne (1974), Arave, Walters & Lamb (1978), Schwalm & Tucker (1978), Hayashi, Ono, Sato & Miyake (1979), Ingraham, Stanley & Wagner (1979), Brendler (1980), Pope & Swinburne (1980), Adeyemo, Heath, Adedevoh & Steinbach (1981), Varner & Johnson (1983) and Varner, Johnson, Britt, McDaniel & Mochrie (1983)

TABLE 12 Approximate ranges of mean levels of corticosteroids, glucocorticosteroids, cortisol and corticosterone in bovine plasma and milk after administration of 150 i.u. ACTH on average*

Conditions applicable to values indicated	Corticosteroids × ranges of mean plasma levels (ng/mℓ)			
	Corticosteroid	Glucocorticosteroid	Cortisol	Corticosterone
Plasma values under various normal/abnormal conditions:				
(i) Range of mean values (normal/abnormal)	4–42	2–21	3–31	3–5
(ii) Range of normal values	4–11	2–13	6–10	3–4
(iii) Normal mean values	7,19	7,9	6,0	4,0
Lacteal values under various normal/abnormal conditions:				
(i) Range of mean values prior to systemic ACTH admin.		0,2–1,4	0,2–2,0	2,5–3,5
(ii) Mean values prior to systemic ACTH administrations		0,6	0,5	3,0
(iii) Range of mean values after systemic ACTH admin.		3–24	0,8–3,1	
(iv) Mean values after systemic ACTH administrations		14,0	1,8	

* Compiled from references applicable to Table 11 and Gwazdauskas, Paape & McGilliard (1977), Bremel & Gangwer (1978), Fox, Butler, Everett & Natzke (1981) and Termeulen, Butler & Natzke (1981)

3. Inhibition of the defence core systems in sustained acute stress alone, or acute stress superimposed on more chronic types of stress due to increased production of adrenalin, glucocorticosteroids, prolactin and progesterone.

From the available information it is clear that of all the hormonal mediators possibly related to stress in lactating dairy cattle, adrenalin, glucocorticosteroids and progesterone are of particular significance to udder health.

Effects of Hormonal Mediators on the Natural Intramammary Defence

Adrenalin, in particular, affects the secretory alveoli, their blood supply, and the teat canal and cistern of the lactating udder, as outlined in Table 10.

Adrenalin probably plays a part in the natural defence of the udder by its effects on the bacterial trapping, reverse pumping, general lacteal environmental and LUB components, as well as in mammary regression.

Since adrenalin stimulates glycogenolysis and the rate of intracellular use of glucose in PMN-leucocytes, increased adrenomedullar activity may affect the glycogen reserves of the PMN-leucocytes prior to them entering the general lacteal environment.

It also seems fairly certain that adrenalin promotes deficiencies of the 3 core systems of mammary defence (Fig. 5), or may even synchronize their defensive weaknesses. By its effects on teat canal closure, teat contractions, mammary regression and the LUB, adrenalin therefore promotes intramammary conditions which favour bacterial invasion of and survival in the mammary cavity.

The plasma levels of various corticosteroids determined under different conditions are listed in Tables 11 and 12.

Judging from mean values of cortisol alone, heat stress at about 24 °C (Table 8) may be considerably more stressful than milk fever and other stressors (Table 11). Plasma and lacteal levels of cortisol show positive correlations although lacteal concentrations are usually much lower (Table 12).

The elevated glucocorticosteroid plasma levels during acute sustained stress, may inhibit the core systems of intramammary defence in the following ways:

- The circulating leucocytes are inhibited by reduction of the intake of glucose and intracellular glycogen reserves, increased stability of cellular and lysosomal membranes, and correspondingly decreased activities of phospholipase A2 and lysosomal enzymes.

- The mammary gland is inhibited by reduced availability of lacteal glucose as a source of energy for leucocytes in the milk, decreased uptake of glucose by epithelium and increased secretion of milk fat globules. These developments, in turn, results in loss of energy and accelerated ageing of PMN-leucocytes, and an increased ratio of cortisol:corticosterone in milk which depresses the uptake of glucose by PMN-leucocytes.

THE COMBINED EFFECT OF ADRENALIN AND GLUCOCORTICOSTEROIDS ON THE NATURAL INTRAMAMMARY DEFENCE

From the above it is evident that adrenalin may be of major significance to bovine udder health depending on sympathetic stimulation during acute sustained and chronic stress. Through its effects on PMN-leucocytes, milk stasis, mammary regression, teat contractions and teat canal closure, adrenalin probably promotes intramammary conditions favourable to invasion, survival, spreading and proliferation of bacteria.

Glucocorticosteroid levels which increase to physiological limits of not more than 30 ng/mℓ plasma or to higher levels during therapeutic administrations, apparently supplenent or aggravate the intramammary changes elicited during stress by adrenalin. Under such conditions glucocorticosteroids probably affect udder health by inhibiting the following: Glucose metabolism of secretory mammary epithelium; intracellular transportation of calcium of the secretory mammary epithelium; glucose metabolism, phagocytic activity and iodination reaction of PMN-leucocytes in milk.

It is clear therefore that elevated levels of adrenalin and glucocorticosteroids may singly and in combination directly affect the main functional components of intramammary defence. Further, it is conceivable that the effects of adrenalin and glucocorticosteroids are augmented by those of progesterone, prolactin and other hormones.

The work by Jones, Hillhouse & Burden (1977) on hypothalamic corticosteroid feedback suggests that preexposure of dairy cattle to high levels of progesterone, cortisol and corticosterone, either singly or in combinations, might indirectly condition lactating cows for a limited period to deficient GAS reactions during a stressful exposure. This may partially explain why clinical mastitis, other than that at the start of lactation, tends to be more frequent during oestrus (Anderson *et al.*, 1983) and during the 3rd to 9th day following oestrus (Frank & Pounden, 1961), when high concentrations of progesterone, estradiol and cortisol overlap (Roth, Kaeberle, Appell & Nachreiner, 1983). Progesterone and cortisol may also affect the phagocytic activities of PMN-leucocytes (Nicol, Bilbey, Charles, Cordingley & Vernon-Roberts, 1964; Guidry, Paape & Pearson, 1976; Crabtree, Munck & Smith, 1979; Paape, Gwazdauskas, Guidry & Weinland, 1981; Roth & Kaeberle, 1983) which, as LUB, protect the mammary gland from infection (Schalm *et al.*, 1971; Paape *et al.*, 1979).

There is evidence that estradiol stimulates leucocytic random migration during the oestrus cycle (Nicol *et al.*, 1964; Roth *et al.*, 1983). Progesterone enhances not only random migration but also antibody-dependent cell-mediated cytotoxicity, whereas it reduces the iodination reaction and superoxide production of leucocytes (Roth *et al.*, 1983). The effects of progesterone, estradiol and cortisol (with peak blood levels on days 13–14, 19–20 and 19-1 of the oestrus cycle) on udder health may further be augmented by that of aldosterone. The latter peaks on days 7–9 and reaches lowest activities on days 19–20 of the cycle and is associated with correspondingly high and low retentions of Na^+ and Cl^- in exchange for K^+ (Roussel, Clement & Aranas, 1983).

Furthermore, cortisol and progesterone, thyroid hormones and insulin may modulate the effect(s) of prolactin at the epithelial level (Horrobin, 1979).

Prolactin is very important during growth and lobuloalveolar differentiation of the mammary parenchyme. In the lactating udder, prolactin acts exclusively on epithelial cells with rough endoplasmic reticulum, where it stimulates intracellular synthesis of all types of RNA, milk protein (e.g. casein, *alpha*-lactalbumin) and several enzymes (e.g. galactosyl-transferase, lactose synthetase). However, data obtained from small laboratory animals indicate that prolactin does not affect cellular function directly, but acts by stimulating the formation in the cell membrane of prostaglandin PGE_1. Cortisol may block this synthesis of PGE_1, but it does not prevent PGE_1 from acting upon cellular functions. In contrast, progesterone does not block the prolactin-induced formation of PGE_1, but prevents prostaglandin from acting on the cell (Horrobin, 1979). Sharply decreasing plasma levels of progesterone in dairy cattle are related *ante partum* to increased synthesis of alpha-lactalbumin (Saacke & Heald, 1974; Flint, 1982), whereas *post partum* the early reduction of cortisol levels, usually raised at calving, co-incides with steeply escalating secretion of milk. Thyroid hormones enhance the effects of prolactin (e.g. on phospholipase) but not of PGE_1. The effect(s) of prolactin on cells depends on a chain of events involving the activation of adenylate cyclase, conversion of adenosine triphosphate (ATP) to cyclic adenosine monophosphate (cAMP), and the activation of protein kinase. Furthermore, the prostaglandin and cyclic guanisine monophosphate (cGMP) may participate in a negative feedback system. Cellular function is therefore determined by the interaction of PGE_1, cAMP and cGMP (Rillema, Linebaugh & Mulder, 1977; Horrobin, 1979; Rillema, 1980. Rillema, Wing & Cameron, 1981; Speroff *et al.*, 1983).

The effects of prolactin are only possible in the presence of Ca^{2+} and intracellular proteins which are known as calcium-dependent regulators (CDRs) (Horrobin, 1979). Functioning of many important enzymes, such as adenyl cyclase, protein kinase, phosphodiesterase, ATPases, is determined by the combination of these CDRs with the enzyme in the presence of Ca^{2+}. Likewise, many hormone receptors also require Ca^{2+} for normal functioning which is also essential for the synthesis of casein and the maintenance of the epithelial junctional complex, integrity of the mammary epithelium and mammary homeostasis (Pitelka, 1978; Neville & Watters, 1983). It is thus evident that calcium is a critical ion for cellular regulation, epithelial integrity and mammary homeostasis. Prolactin and PGE_1 at low concentrations raise cytoplasmatic calcium levels by enhancing its release from intracellular stores. High concentrations tend to have the opposite effect (Horrobin, 1979). This would explain the low cytoplasmatic values of Ca found in normal secretory mammary epithelium (Neville & Watters, 1983).

The effects of prolactin on milk protein synthesis, milk secretion and epithelial integrity can therefore be ascribed to PGE_1 synthesis (Horrobin, 1979). The data suggest that these effects might be enhanced by thyroid hormones and inhibited by thyroid deficiency, progesterone and cortisol. Thyroid hormones and zinc also facilitate the synthesis of PGE_1, whereas, in the presence of magnesium, adrenalin, noradrenalin and glucagon stimulate the activity of adenylate cyclase, which forms cAMP from ATP (Diem & Lentner, 1971). In terms of the model of casein synthesis proposed by Rillema

(1980), such interaction between hormonal mediators suggest that, under conditions of sustained acute heat stress alone (Table 8) raised levels of cortisol, progesterone and adrenalin might well inhibit synthesis of casein. Low casein concentrations in milk have been observed occasionally under South African conditions.

To summarize, the above deliberations indicate that stress may have a deleterious effect on each of the 3 major determinants of udder health, namely, intramammary epithelial integrity, somatic cellular defence and bacterial challenge. Depending on the nature and magnitude of stressors affecting the cow, stress may significantly affect the yield and composition of milk secreted.

Conclusion

It may be concluded from the available evidence that different classes of stressors, which may be endogenous or exogenous, anticipated or real, somatic or psychological, physiological and pathological, systemic or local, may affect the metabolic and immunological homeostasis of the dairy cow and its mammary gland. The animal attempts to restore and maintain homeostasis by means of compensating GAS reactions, i.e., stress, which usually develops through an alarm, resistance and exhaustion phase controlled by sympathetic-adrenomedullar and hypophyseal-adrenocortical activities.

Stress can be defined, in the broad sense, as follows: "An animal is in a state of stress, if it is required to make abnormal or extreme adjustments in its physiology or behaviour in order to facilitate its species-specific and breed-typical phenotypic expression and to cope with antihomeostatic aspects of its environment. A condition can be said to be stressful if it stresses an animal. An individual factor, natural or artificial, endogenous or exogenous, may be called a stressor if it contributes directly or indirectly to the stress of an animal".

It may be concluded that lactation is the result of lactation stress, i.e., a compensatory adjustment to the lactation stressor. Because of its ruminant physiology based on lipogenesis/lipolysis, which is integrated with and supplements the glycogenesis/glycogenolysis of non-ruminants, the dairy cow in lactation stress depends on a central control system of stress similar in principle to but different in function from that of the non-ruminant. The adaptation hormones of importance in the cow tend to promote the lipogenic/lipolytic metabolic processes, sparing the glycogenetic/glycogenolytic ones, mainly for transient adjustments that require sudden increases of metabolism during acute types of stress. This concept is consistent with the observation of raised plasma levels, during chronic heat stress, of prolactin, progesterone, adrenalin and noradrenalin and decreased ones of glucocorticosteroids, thyroid hormones and growth hormone. It is also supported by the transient increases of cortisol observed during acute heat stress, at calving and on other occasions. Moreover, high milk yields are usually associated with reduced levels of insulin and cortisol, whose sustained increases seem almost incompatible with the highly elevated requirements by the secretory mammary epithelium for glucose, which is the pivot of normal bovine lactation.

Most of the glucose required by the lactating udder for specific functions, such as the synthesis of lactose, glyceride-glycerol, glycero-phosphate, pyruvate, ATP and NADPH, is supplied by the liver by gluconeogenesis. This places glucose at a premium. Acetate and, to a lesser extent, beta-hydroxybutyrate are the predominant sources for fatty acid synthesis in the udder and other lipogenic tissues, which accentuate the glucose sparing implications of the lipid metabolism of the cow.

Because of the key role of glucose in the physiology of the lactating mammary epithelium, the latter is particularly susceptible to any factor affecting its glucose metabolism and events related to it, such as circulation, energy and electrolyte balance, osmotic gradient essential for secretion of water, synthesis of lactose and citrate, dissipation of heat, and removal of milk from secretory alveoli. However, for the same reasons, changes in the epithelial glucose metabolism become the method by which the cow can regulate secretion of milk, depending on its needs for maintaining homeostasis during stressful conditions. This depends on the cow's inherent ability to initiate mammary regression by discarding secretory epithelium.

The udder is equipped with a range of special features for fine adjustments of mammary regression, a phenomenon which may be regarded as the lactating cow's most important mammary response to various stressors. Contrary to galactopoiesis as a means to create and maintain a state of lactational homeostasis during lactation stress, complete mammary regression facilitates the maintenance of involutional homeostasis. Involutional homeostasis affords the cow the highest level of resistance to the stressors of its comparatively hostile environment.

Mammary regression is readily induced because of special features of the udder, including the exclusively sympathetic efferent innervation. Elevated sympathetic-adrenomedullar activities are normally related to the alarm phase of the GAS, but they become persistent during chronic heat stress. They may, directly and indirectly, affect at various levels the cow's natural defence mechanisms, such as the udder shelter and portions of the intramammary master system of natural defence, and are therefore of vital importance.

Udder health depends on 3 major determinants, namely, intramammary epithelial integrity, somatic cellular defence and bacterial challenge. The 3 core systems of mammary defence protect the udder parenchyme from infection. Raised levels of adrenalin may have inhibitory effects on the anti-microbial efficacy of each of the core systems individually as well as on their ability to function as an integrated unit which consists of various components, including mammary regression. The latter may become the main predisposing factor for mastitogenic udder infections because of its association with important metabolic, structural, secretory and possibly also immunological fluctuations. Changes similar to regressive ones occur in subclinical and clinical mastitis. In such circumstances, however, the regressive changes may be augmented with or even obscured by various phlogistic lesions and the presence of mastitogenic bacteria.

The effects of adrenalin on the lactating udder may be supplemented by the concurrent effects of stress on the general health of the animal and those of various hormonal and physio-pathological mediators. It is also apparent that stress may elicit significant fluctuations in the yield and composition of the milk. It further jeopardizes the anti-microbial efficacy of the natural defence mechanisms of the lactating udder. The main effects of stress on udder health are therefore an increased risk of unphysiological mammary regression and subclinical or clinical mastitis.

A considerable range of genetic factors may also play a part in mammary defence mechanisms. Further research therefore seems necessary to investigate, under South African conditions, the effects of stress on udder health, production and composition of milk. It is also necessary to develop better measures in the disciplines of

preventive veterinary medicine, animal husbandry and farm management to protect dairy cattle from undesirable stressful exposures.

However, finally it must be emphasized that more determined efforts should be made in the immediate future to promote the co-ordinated and effective practical application of knowledge already available on the improvement of health and welfare of dairy cows. This is essential for their highest productivity.

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