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Animal Feed Science and Technology
126 (2006) 175–213
ANIMAL FEED SCIENCE AND TECHNOLOGY
www.elsevier.com/locate/anifeedsci

Feeding- and management-related diseases in the transition cow Physiological adaptations around calving and strategies to reduce feeding-related diseases☆

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Abstract

The objective of this review was to address the basis for and prevention of selected diseases (fatty liver, ketosis, rumen acidosis and displaced abomasums) that are feeding- and management-related and frequent in periparturient cows. The focus has been to discuss (1) the general physiological regulation and adaptations that are believed to be important for a successful transition to lactation, (2) for each disease the disease incidence rate, risk factors, aetiology and pathophysiology and (3) feeding and management strategies to prevent diseases. Unfortunately, few studies have documented prevention strategies and they consequently need to be developed based on risk factors and knowledge of the aetiology of the diseases. Strategies to prevent these diseases are therefore based on major factors directly or indirectly increasing the risk of fatty liver, ketosis, acidosis and displaced abomasum—factors such as over-conditioning at calving, excessive mobilisation of body fat, low nutrient intake, nutrient or diet specific factors and management and environmental stress. Finally, thoughts are presented on how prevention potentially could be improved in the future. It is suggested that there should be greater focus on individual animals in order to identify "risk animals". Status-oriented strategies for optimising dairy cow health, reproduction and production are suggested that aims at securing a desirable status of epithelia, metabolism and immune function in different cells, tissues or organs through surveillance and health and production management based on indicators.

☆ This paper is part of the special issue entitled Feed and Animal Health, Guest Edited by Professor Kjell Holtenius.

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doi:10.1016/j.anifeedsci.2005.08.003

Keywords: Transition cows; Physiological adaptation; Fatty liver; Ketosis; Rumen acidosis; Displaced abomasum; Disease prevention

1. Introduction

A successful lactation with high productivity and low incidence of production diseases is essential to farmers in order to compete and have a production taking into account food safety and ethical aspects, which are of major concern to consumers. Generally, attempts by dairy farmers to maintain profits have focussed on maximising milk output and making rations as cheap as possible, with little consideration of other costs, such as health and reproduction. Consequently, milk yields have increased substantially over recent decades. The increase in milk yield is the result of intense genetic selection as well as improved nutrition and management. However, there is mounting concern about a concomitant increase in health and fertility problems. The increase in health and reproductive problems may, at least to some extent, decrease the benefits of increased yield through reductions in the amount and quality of saleable milk and increased costs associated with veterinary treatments and replacement animals.

A majority of the health problems in the dairy cow occur during the periparturient period. To a large extent these health problems relate to cows having difficulty in adapting to lactation which results in physiological imbalance, a situation where the regulating mechanisms are insufficient for the animals to function optimally leading to a high risk of a complex of digestive, metabolic and infectious problems. It is believed that these health problems can be reduced in particular by new concepts and strategies in feeding and management (Ingvartsen et al., 2003a,b). The focus of this paper will consequently be: (i) to discuss the general physiological regulation and adaptations that are believed to be important for a successful transition to lactation, (ii) to discuss the disease incidences, risk factors, aetiology and pathophysiology of selected feeding- and management-related diseases and finally, (iii) to address feeding and management strategies to prevent diseases.

2. General physiological regulation and adaptations around calving

2.1. Key processes and tissues

Late in pregnancy and in early lactation, the nutrient demand increases quite considerably. In late pregnancy it increases as a result of foetal development, *i.e.*, the foetus, foetal membranes and supplementary tissue (Jakobsen, 1957; Bell et al., 1995). The energy demand for foetal development late in pregnancy (day 250; foetal weight of 35 kg) is calculated at 2.3 Mcal NE_l/day in Holstein cows (Bell, 1995). Especially glucose and amino acids are used for foetal development as they constitute 35–40% and 55% of the energy demand, respectively, while the remaining 5–10% is chiefly made up of acetate (Bell et al., 1995; Bell and Ehrhardt, 2000).

Table 1
A list of the most important biological processes or metabolic changes associated with transition to lactation in ruminants regulated by the animals (modified from Bauman and Currie, 1980; Bauman, 2000)

Process or metabolism	Response	Involved tissue
Milk synthesis	↑ Number of secretory cells	Udder
	↑ Blood flow	
	↑ Nutrient consumption	
Fat metabolism	↓ *De novo* fat synthesis	Adipose tissue
	↓ Absorption of fatty acids	
	↓ Esterification of fatty acids	
	↑ Lipolysis	
	↑ Use of lipid as energy	Other body tissues
Glucose metabolism	↑ Size of the liver	Liver
	↑ Blood flow	
	↑ Rate of gluconeogenesis	
	↓ Use of glucose as energy	Other body tissues
Protein metabolism	↓ Protein synthesis	Muscular tissue
	↑ Proteolysis	
	↑ Protein synthesis	Other body tissues
Mineral metabolism	↑ Absorption	Gut
	↑ Mobilisation	Bones
Feed intake	↑ Feed intake	Central nervous system
Digestion	↑ Hypertrophy of the digestive tract	Digestive tract
	↑ Absorption rate and capacity	
	↑ Metabolical activity	
Blood flow	↑ Output of blood from the heart	Heart
	↑ Part to the udder	
	↑ Part to the gastrointestinal tract, including the liver	

At the onset of lactation the nutrient demand increases dramatically. A cow with a maximum milk yield of 50 kg secretes approximately 2 kg of milk fat daily, 1.6 kg of milk protein, 2.5 kg of lactose, 65 g of Ca, 50 g of P and 8 g of Mg, which, of course, increases the demand for energy, protein and minerals. The nutrient requirement in late pregnancy, and particularly the nutrient demand for lactation, call for a coordination of the biological processes in different tissues resulting in metabolic changes (see Table 1) that try to ensure that the cow's genetic potential for milk yield is exploited concurrently with maintenance of the homeostasis physiological parameters.

2.2. Hormonal regulation

The endocrine system plays an important role in the metabolic regulation and nutrient partitioning, but the nervous system and immune system are also involved. The endocrine regulation comprises both homeostasis and homeorhesis. Bauman and Currie (1980) defined homeorhesis as 'the orchestrated or coordinated changes in the metabolism necessary to support a physiological state", an adaptation to a new equilibrium that takes place over days or weeks. Homeostasis can be defined as the regulation that maintains the equilibrium of

the organism with the environment; a regulation that takes place from minute to minute. The homeorhetic regulation that makes it possible for the cows to maintain homeostasis is believed to be of major importance for disease resistance in cows, particularly metabolically related production diseases.

The regulation of the biological processes described in Table 1 is very complex and involves a large number of hormones, and the nervous system. A number of reviews have described in detail the metabolic regulation and feed intake around calving (Bauman and Elliot, 1983; Bell, 1995; McNamara, 1995; Bell and Bauman, 1997; Vernon and Pond, 1997; Chilliard, 1999; Herdt, 2000; Ingvartsen and Andersen, 2000; Ingvartsen and Boisclair, 2001), and the reader is referred to these for further information on regulation of the adaptation to a new lactation. In Table 2, a summary is given of changes in selected homeorhetic and homeostatic hormones and their probable effect on tissue sensitivity and response, as well as changes in hepatic, adipose and muscular tissues.

To simplify the above, the ratio of growth hormone to insulin in blood is high in cows in early lactation, which stimulates mobilisation of long-chain fatty acids from adipose tissue in support of lactation. Fatty acids released from adipose tissue circulate as non-esterified fatty acids (NEFA), which are a major source of energy to the cow during this period. The concentration of NEFA in blood reflects the degree of adipose tissue mobilisation (Pullen et al., 1989).

Adipose tissue in the cow is oriented towards mobilisation of NEFA in early lactation rather than lipid deposition (McNamara, 1991). Adipose lipogenesis is essentially shut down, and the sensitivity to lipolytic signals (epinephrine and norepinephrine) is greatly enhanced. In a study including a large number of cows, we have demonstrated that the increase in blood NEFA in response to an intravenous epinephrine challenge was significantly greater in early lactation compared to any other stages in lactation (Theilgaard et al., 2002), results that are confirmed in a recent American study (Underwood et al., 2003). Consequently, stressors and poor nutritional management causing decreases in voluntary DMI will result in large increases in NEFA immediately after calving (Bertoni et al., 1998; Drackley, 1999; Ingvartsen and Andersen, 2000).

2.3. *Variation in physiological parameters*

Already before calving, the homeorhetic changes (Table 2) will cause great changes in the udder tissue *via* the mammogenesis, lactogenesis and galactopoesis. These mechanisms develop the alveolar system, increase the synthetic capacity of the udder cells, increase blood flow and nutrient intake, activate lactation and maintain the milk synthesis.

The large nutrient requirements for the galactopoesis are coordinated with changes in the peripheral tissue and results in mobilisation or formation of nutrients in these tissues to support the production of milk in the udder. This mobilisation of nutrients implies that the animals are in negative nutrient balance in early lactation and in particular negative energy balance. Negative nutrient balance at parturition and during early lactation is quite normal for both ruminants and monogastrics and is a result of the homeorhetic regulation. This regulation includes changes in the plasma concentration of homeorhetic hormones and changes in tissue sensitivity and tissue response to homeostatic hormones, like insulin and catecholamines, in, *e.g.*, adipose tissue, muscular tissue and hepatic tissue (Table 2). Further,

Table 2
Changes in selected homeorhetic and homeostatic hormones, tissue sensitivity and tissue response and effect on selected tissue and organs during pregnancy and in early lactation (modified from Ingvartsen and Andersen, 2000)

	Mid-pregnancy	Late pregnancy	Lactogenesis[a], early lactation
Homeorhetic hormones			
Progesterone	↑	(↓)	↓
Placental lactogen		↑	↓
Estrogen		↑	↓
Prolactin	–	(↑)	↑
Somatotropin	–	(↑)	↑
Glucocorticoids (cortisol)	–	–/↑	↑
Leptin	↑	↑↓	↓
Homeostatic hormones			
Insulin		↑↓	↓
Glucagon	–	–	↑?
CCK and somatostatin	?	?	?
Parathyroidea hormone	–	–/↑	↑
1,25-dihydroxyvitamin D_3	–	–/↑	↑
Calcitonin	–	–/↓	↓
Tissue sensitivity (except udder tissue)			
Insulin	↑	↓	↓
Catecolamines		↑	↑
Tissue response (except udder tissue)			
Insulin		↓	↓
Catecolamines	↓	↑	↑
Udder tissue			
Lactose synthesis			↑
Milk-fat synthesis			↑
Milk-protein synthesis			↑
Liver tissue			
Gluconeogenesis (glucose formation)		(↑)	↑
Ketogenesis (ketone body formation)		(↑)	↑
Adipose tissue			
De novo fat synthesis	↑	↓	↓
Fatty acid esterification (lipogenesis)	↑	↓	↓
Lipolysis		↑	↑
Muscular tissue			
Protein synthesis	–	↓	↓
Proteolysis	–	↑	↑
Glucose consumption	–	↓	↓
Fatty acid and ketone body consumption	–	↑	↑
Bone tissue			
Osteogenesis (bone formation)	–	–	?
Osteolysis (bone disintegration)			↑

[a] Lactogenesis is the onset of lactation.

Table 3
Disease incidence measured as treatment frequency of cows in tie-stall barns and loose-housing systems (modified from Trinderup et al., 2001)

Disease	Treatment frequency, % of annual yield of a cow	
	Tie-stall	Cubicle
Milk fever	5.0	3.6*
Ketosis	1.7	0.9*
Digestive disorders[a]	4.6	3.5*
Foot/leg disorders[b]	5.7	8.2*
Calving assistance	1.3	1.0*
Retained placenta	6.7	6.4
Reproduction disorders[c]	2.2	3.4*
Clinical mastitis	37.1	33.9*

Treatment frequencies within row marked with * show significant differences between tie-stall and cubicle ($P<0.05$).

[a] Displaced abomasum, rumen acidosis, foreign bodies, intestinal infection, tympanites, hypomagnesemia and intestinal infection.

[b] Laminitis, sole ulcer, interdigital dermatitis, heel erosion, foul-in-the-foot, *etc.*

[c] Uterine infection, cysts and inactive ovaries.

changes take place in a number of physiological processes in hepatic, adipose, muscular and bone tissues. The energy used for *de novo* fatty acid synthesis and esterification to triglycerides is reduced in adipose tissue while the lipolysis increases considerably (Table 2). The consequence is a mobilisation of fat deposited during gestation, which results in a rise in free fatty acids (NEFA) and glycerol in plasma. An example of a change in NEFA is shown in Fig. 1. Similar changes take place in the muscular tissues where proteolysis is increased (Table 3), and the mobilised amino acids contribute as substrates in the gluconeogenesis and milk protein synthesis. Measurement of 3-methylhistidine in plasma indicates, however, that the proteolysis is only substantially increased in the first 1–2 weeks postpartum (Blum et al., 1985; Ndibualonji et al., 1997; Plaizier et al., 2000; Doepel et al., 2002). In adipose tissue as well as muscular tissue, the glucose intake is reduced, and instead the use of fatty acids and ketone bodies is increased. Despite the reduced use of glucose in these tissues and a quite considerable increase in the gluconeogenesis in liver tissue and kidney tissue (Table 2), the glucose concentration normally drops postpartum (see Fig. 1), particularly in multiparous cows. The increased ketogenesis in hepatic tissue generally increases the level of ketone bodies, especially in second lactation and older cows (Fig. 1). For all the above-mentioned metabolites, there is, however, a very considerable individual variation between cows (Ingvartsen et al., 2003a,c) illustrating that some cows have a higher risk of developing production diseases such as, *e.g.*, fatty liver and ketosis.

As mentioned earlier, quite considerable amounts of minerals are secreted in the milk, especially Ca and P. In support of lactation, an increased absorption of minerals from the intestines generally takes place (Van't-Klooster, 1976), just as minerals are resorbed from the bones through osteolysis (Horst et al., 1994), processes that are central in maintaining, *e.g.*, the calcium homeostasis. The resorption of minerals from bones is under precise hormonal regulation of the parathyroid hormone, 1,25-dihydroxyvitamin D_3 and calcitonin (Table 2) (Goff, 2000).

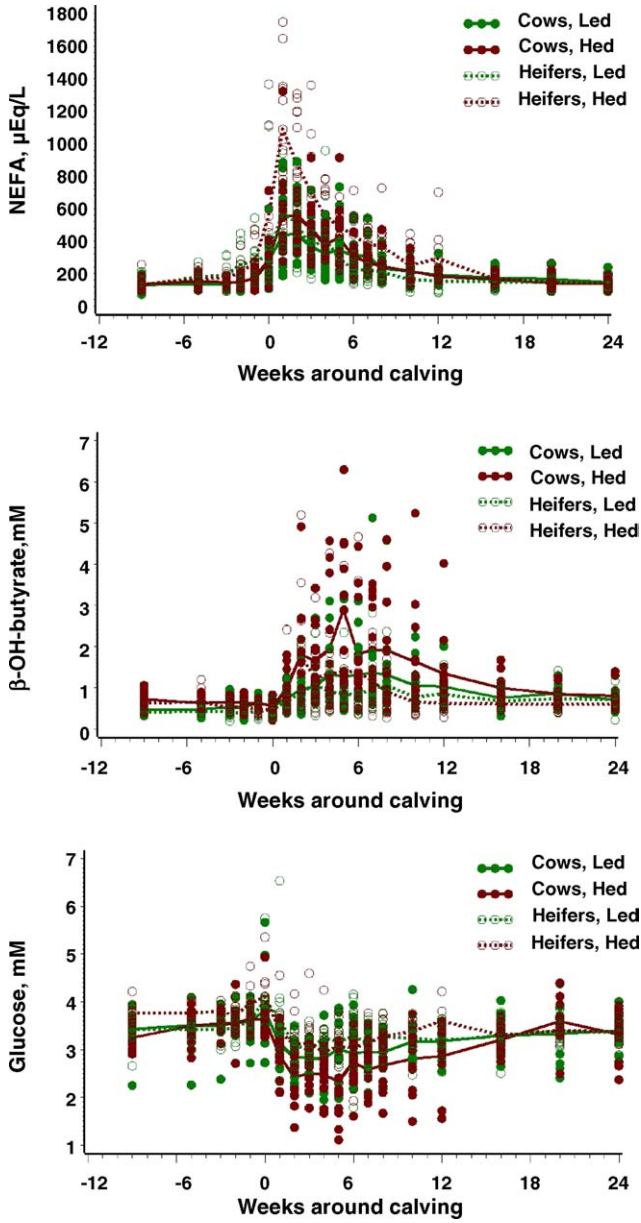

Fig. 1. Group averages and variation for plasma insulin, non-esterified fatty acids, β-hydroxybutyrate and glucose in heifers and cows fed *ad libitum* with diets low (Led) or high (Hed) in energy density prepartum; all cows were fed the same diet (Hed) postpartum (Ingvartsen et al., 2003a).

Late in pregnancy, the feed intake in ruminants is reduced (Ingvartsen et al., 1992) despite an increased nutrient requirement for foetal development and mammogenesis/lactogenesis. This down-regulation of the appetite is probably caused by an increased concentration of sex hormones, an incipient mobilisation of lipid from body deposits and maybe also a reduced rumen capacity as a result of the growing foetus (Ingvartsen et al., 1999; Ingvartsen and Andersen, 2000). In early lactation, the feed intake increases considerably (Ingvartsen and Andersen, 2000) as a result of a greater sensation of hunger caused by the rapidly increasing nutrient demand. The sensation of hunger occurs in the central nervous system based on signals from metabolites and hormones as well as cytokines, and is thus an integrated response to the metabolic and nutrient state of the animal (Ingvartsen and Andersen, 2000; Ingvartsen and Boisclair, 2001). The increased feed intake stimulates the digestive tract causing hypertrophy and increased absorption capacity. The main message of the existing literature and the present paragraph is that the physiological regulation is very complex, and that great changes and adaptations in feed intake, digestion and metabolism take place particularly in the periparturient period. These changes are normal and occur in both monogastrics and ruminants and result in relatively large amounts of nutrients and minerals being mobilised in the periparturient period and especially in early lactation. The periparturient period is, however, also the period when the risk of production diseases is highest. This is partly due to the fact that some cows have difficulty in adapting to lactation and consequently suffer from physiological imbalance—a situation where the homeorhetic and homeostatic regulating mechanisms are insufficient for the animal to function optimally. Cows in physiological imbalance are therefore defined as cows whose parameters (reflecting the function of the digestive tract, metabolic state and immune state) deviate from the normal, and who consequently have an increased risk of developing production diseases (clinical or subclinical) and reduced production and/or reproduction.

3. Feeding- and metabolic-related diseases

3.1. Disease incidences

Based on veterinary recordings of disease treatment in a national database, incidence rates of some of the important diseases have been estimated (Table 3).

Compared to earlier estimations of disease incidences in Denmark (Jørgensen and Nielsen, 1977; Andersen, 1991), there seems to be a reduction in the frequency of ketosis, digestive disorders and reproduction disorders. Comparisons over time are difficult, however, as there will be differences in definitions, registrations and statistical methods. The treatment frequency depends on, *e.g.*, the housing system (Table 3). However, it does not seem likely that the number of reproduction problems have declined (Friggens, 2003). The reduced frequency of, *e.g.*, milk fever and ketosis may probably be due to the fact that farmers, to a greater extent than earlier, perform preventive treatments themselves.

The vast majority of production diseases occur very early in lactation (Fig. 2) before the cows reach their maximum milk yield. However, the high risk of disease occurs concurrently with a high rate of acceleration in milk yield (Fig. 3).

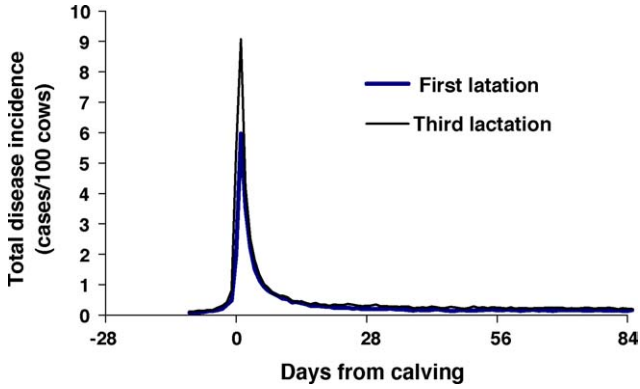

Fig. 2. Total disease incidence relative to days from calving for first and third lactation cows. Total disease incidence was the sum of mastitis, ketosis, digestive disorders and laminitis from national records for the Danish dairy herds for cows that calved in 1998 ($n = 93{,}347$ and 58,459 for first and third lactation cows, respectively; *source:* Danish Advisory Centre).

Acceleration, the change in milk yield per day, is highest immediately after calving (Fig. 3). The similarities between the acceleration pattern and the incidence of disease over time are striking. As there is little or no difference in time of peak yield between genetically high and low yielding cows (Congleton and Everett, 1980; Ferris et al., 1985), the acceleration of the high yielder will be substantially greater than that of the low yielder as illustrated in Fig. 3. It is not yet clear to what extent the acceleration in the physiological machinery caused by the onset of lactation constitutes a stressor. Studies which have tried to moderate the acceleration in milk yield by omitting the dry period (Remond et al., 1997a,b), reducing the milking frequency (Remond and Boit, 1997; Røntved and Ingvartsen, unpublished), or by prepartum milking (Grummer et al., 2000) are based on too few cows to address health issues.

The variation in morbidity measured in different studies or herds is generally large. Table 4 shows the average incidence across different studies and the variation (lowest and

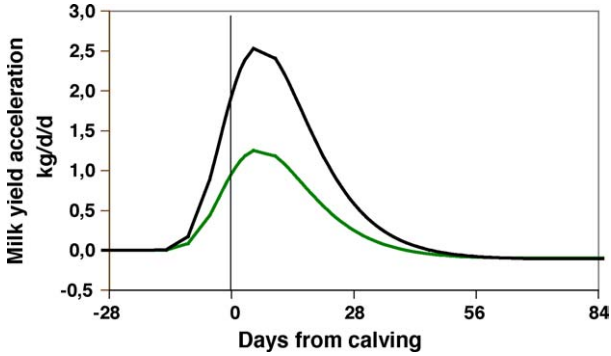

Fig. 3. Acceleration in milk yield through lactation for cows peaking at 30 kg (normal line) and 60 kg (bold line) milk daily (Ingvartsen et al., 2003a).

Table 4
Average and variation in incidence risk of production diseases in dairy cows in normal-yielding herds (Kelton et al., 1998; Ingvartsen et al., 2003a) and in very high-yielding herds (average 11,000 kg of milk per cow per year) (Jordan and Fourdraine, 1993)

Disease	Ingvartsen et al. (2003a)[a]	Kelton et al. (1998)	Jordan and Fourdraine (1993)
Milk fever	4.6% (0.2–8.9%), $n = 17$	6.5% (0.03–22.3%), $n = 33$	7.2% (0–44.1%), $n = 61$
Ketosis	4.1% (1.6–10.0%), $n = 17$	4.8% (1.3–18.3%), $n = 36$	3.7% (0–20%), $n = 61$
Displaced abomasum	2.1% (0.6–6.3%), $n = 10$	1.7% (0.3–6.3%), $n = 22$	3.3% (0–14%), $n = 61$
Foot/leg disorders	14.7% (1.8–60%), $n = 7$	7.0% (1.8–30%), $n = 39$	
Retained placenta	7.8% (3.1–13%), $n = 13$	8.6% (1.3–39.2%), $n = 50$	9.0% (0–22.6%), $n = 61$
Ovarian cysts	8.9% (3.1–12.4%), $n = 14$	8.0% (1.0–16.1%), $n = 44$	13.5% (0–58.8%), $n = 61$
Uterine infection	10.8% (2.2–43.8%), $n = 16$	10.1% (2.2–37.3%), $n = 43$	12.8% (0–66%), $n = 61$
Mastitis	17.6% (2.8–39%), $n = 25$	14.2% (1.7–54.6%), $n = 62$	

[a] Studies selected for examining the relationship between yield and incidence of production diseases.

highest incidence). The data in the table originate from reviews based on the international literature focusing on registration and calculation of disease incidence (Kelton et al., 1998), correlations between yield and the risk of production diseases (Ingvartsen et al., 2003a) and disease incidence in very high-yielding herds (Jordan and Fourdraine, 1993).

Table 4 shows that there is a very large variation in the risk of contracting different diseases, including diseases frequent in transition cows (milk fever, ketosis, displaced abomasum, retained placenta and uterine infection). Discounting a few very high incidence risks of milk fever reported by Kelton et al. (1998) and the incidence risk of 60% for foot/leg disorders reported by Van-Dorp et al. (1998), the average incidence risks and variations of the individual production diseases reported by Ingvartsen et al. (2003a) and Kelton et al. (1998) are at approximately the same level. It has often been speculated whether high-yielding cows are at greater risk of contracting production diseases, and whether this could partially explain the variation in disease frequency. This is not necessarily the case. Firstly, the literature only shows that there is an increased risk of mastitis with increased phenotypical and genetic milk yield, and that selection for increased milk yield may be positively correlated with the risk of ketosis and foot/leg disorders (Ingvartsen et al., 2003a). Secondly, the highest risk of production diseases occurs before the cows reach their maximum daily yield. Therefore, Ingvartsen et al. (2003a) concluded that it is hardly the yield as such that is the cause of the high incidence risk of production disease around calving. A study of disease incidence in 61 of the highest-yielding herds in the USA in 1991 (Jordan and Fourdraine, 1993) seems to confirm this as they had similar incidence risks to those reported by Ingvartsen et al. (2003a) and Kelton et al. (1998) (Table 4). It is also interesting that herd variation was very large among the very high-yielding herds (Table 4). More interesting, however, is the large variation between cows for certain physiological indicators, *e.g.*, free fatty acids, β-hydroxybutyrate (BHB) and glucose, which are also important indicators of certain production diseases, such as ketosis (Ingvartsen et al., 2003a,c; Friggens and Chagunda, 2005). The between-cow variation within a herd may be due to the cows' inability to maintain homeostasis for central physiological and immunological parameters, which may be related to the acceleration in yield in early lactation (Ingvartsen et al., 2003a).

The above paragraphs focus on treatment frequency. It is not only the treatment frequency of production diseases that is important—the treatments reflect only the "tip of the iceberg". Many of the production diseases may also occur subclinically—characterised by the lack of clinical symptoms, but the production may be reduced and the animals are at greater risk of developing clinical symptoms.

3.2. Fatty liver

Fatty liver (also called "fat cow syndrome") is a metabolic disorder characterised by a high content of lipids and triglycerides (TG) in the liver. This disease occurs especially subclinically, but in some cows with moderate fatty liver and in cows with severe fatty liver, the disease also occurs clinically. The clinical symptoms comprise depression, lack of appetite and weight loss, and the cows may seem weak and apathetic (Radostits et al., 2000). Most cows will suffer from non-specific clinical signs such as reduced rumen motility and decreased milk yield. Other clinical signs may relate to concomitant production diseases that may provoke the fatty liver situation, *e.g.*, cytokines down-regulating appetite and stimulating the mobilisation of lipid from body reserves (Ingvartsen and Andersen, 2000). Predisposing production diseases include in particular retained placenta, uterine infection, milk fever, displaced abomasum and mastitis.

3.2.1. Incidence and risk factors

Fatty liver is a multifactorial metabolic disorder that occurs around parturition and as a secondary disease of other production diseases that depresses appetite or increases mobilisation of body lipids. Since the lipid content of the liver can only be determined with reasonable certainty by taking liver biopsies (Gerloff et al., 1986; Young et al., 1991), the knowledge of the extent of this disease in practice is very limited. A number of studies, however, show changes in liver lipid content around calving in England (Reid, 1980; Gaal et al., 1983), Holland (Van-den-Top et al., 1996; Jorritsma et al., 2001), France (Mazur et al., 1988), the USA (Bertics et al., 1992; Studer et al., 1993; Vazques-Añon et al., 1994; Grum et al., 2002), and Denmark (Ingvartsen et al., 1995; Andersen, 2001). English as well as Dutch studies indicate that subclinical fatty liver can be a substantial problem for up to 50% of the cows in early lactation (Reid, 1980; Jorritsma et al., 2001).

Among the risk factors of fatty liver is a high rate of mobilisation of body lipids around calving as a result of high body condition score caused by overfeeding in late lactation and the dry period (Fronk et al., 1980; Reid, 1980; Reid et al., 1986; Ingvartsen et al., 1995; Van-den-Top et al., 1996) or low feed intake around calving (Gerloff and Herdt, 1984; Bertics et al., 1992). Cows fed rations low in protein have a higher risk of developing fatty liver compared with cows offered plenty of protein, independent of the energy content of the feed (Holtenius and Hjort, 1990; VanSaun and Sniffen, 1996). There are most likely other risk factors, but due to a lack of non-invasive methods of quantifying liver lipid content, the existing knowledge of risk factors is limited.

3.2.2. Aetiology and pathophysiology

The aetiology and pathophysiology of fatty liver have been discussed in a number of reviews (Emery et al., 1992; Grummer, 1993; Bauchart et al., 1996; Drackley, 1999;

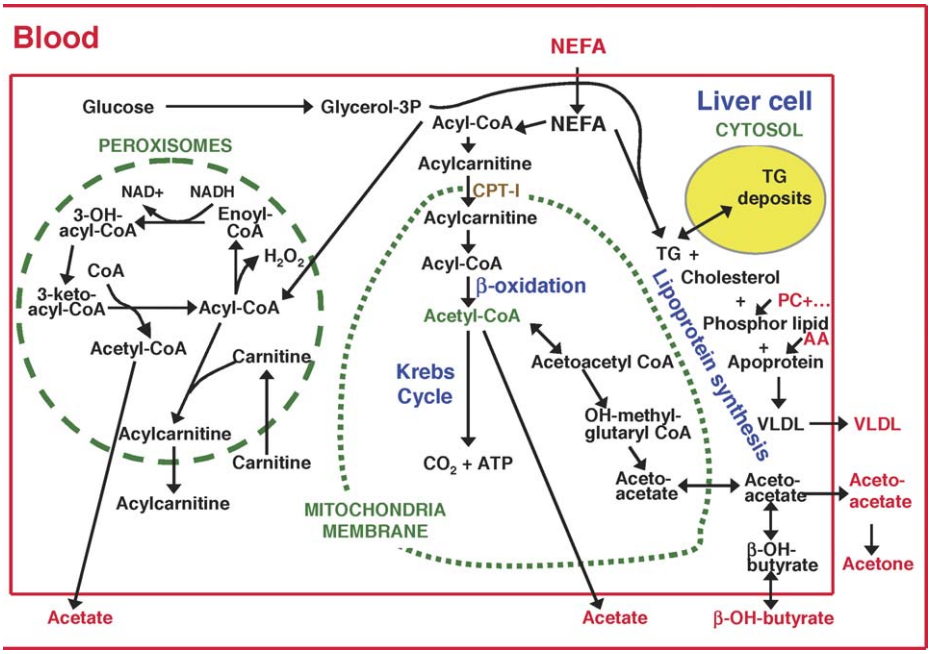

Fig. 4. Overview of important intermediary processes in the liver of importance to the development of fatty liver. *Abbreviations:* AA, amino acids; CPT-I, carnitine palmityl transferase I; PC + . . ., phosphatidylcholin and other components producing phosphor lipid; TG, triglyceride; VLDL, very low density lipoproteins.

Hocquette and Bauchart, 1999; Drackley et al., 2001) to which the reader is referred. Here, an outline of the major metabolic processes of importance for the development of fatty liver will be discussed based on the simplified Fig. 4.

In short, fatty liver develops when the synthesis of triacylglycol exceeds the export of triacylglycerol (TG). The central elements of the development are high NEFA concentrations in plasma, turnover of fatty acids in peroxisomes and mitochondria, and the production and export of lipoproteins.

The most dramatic increase in NEFA occurs in the periparturient period as a result of homeorhetic adaptations to the increased nutrient requirement in lactation (see Table 2). As NEFA are absorbed into the liver in proportion to the plasma concentration (Bell, 1979), the absorption of NEFA in the liver increases dramatically around calving (Emery et al., 1992). Hormones regulate the mobilisation of body reserves as illustrated in Table 2. The low plasma concentration of insulin is particularly important for the flux of NEFA from the adipose tissues (Mashek et al., 2001) and consequently the amount of fatty acids entering the liver. The blood flow through the liver has been reported to be proportional to energy intake and is consequently considerably higher in early lactation than in the dry period (Lomax and Baird, 1983), which may also increase the absorption of NEFA. In the liver, NEFA can be (1) completely oxidized to carbon dioxide to provide energy for the liver, (2) partially oxidized to produce ketone bodies that are released into the blood and serve as fuels for other tissues or (3) reconverted to triglycerides (TG). If NEFA uptake by the

liver becomes excessive, fatty liver may develop. Negative energy balance and carbohydrate insufficiency in the liver after calving also lead to increased production of ketone bodies, which can result in clinical or subclinical ketosis.

A proportion of the fatty acids absorbed by the liver are either oxidized in the mitochondria or the peroxisomes, which are subcellular organelles present in most cells. As shown in Fig. 4, the oxidation in the peroxisomes is incomplete. In the last step, 3-ketoacyl-CoA is transformed into acetyl-CoA and a molecule acyl-CoA is regenerated. Carnitine acyltransferases probably make it possible to export acyl-CoA or acetyl-CoA out of the peroxisomes for further metabolisation in, *e.g.*, the mitochondria. The processes in the peroxisomes deviate from those of the mitochondria by not being regulated in relation to the energy status of the cells. This is due to the peroxide being produced in the first step instead of reduced NAD and the peroxisomes lacking the respiration chain and the ability to produce ATP. The peroxisomes consequently only oxidize the substrates partially and pick up less energy in cofactors and more energy is emitted in the form of heat compared with the mitochondria. The peroxisomes are adapted to oxidize fatty acids and foreign substances that can only be metabolised in the mitochondria with difficulty. Beta-oxidation in the peroxisomes may play a role as an "overflow" route for the oxidation of fatty acids in situations where there is an excess of fatty acids. *In vitro* studies report a considerable capacity for β-oxidation in the peroxisomes in liver tissue of cows (Grum et al., 1994, 1996b; Drackley et al., 2001), and that β-oxidation in peroxisomes can possibly be induced by feeding fat (Grum et al., 1996a). Our quantitative knowledge of β-oxidation in peroxisomes *in vivo* and how this can be manipulated is very limited, however.

The oxidation of fatty acids in the mitochondria takes place either completely (CO_2 + energy equivalents) or incompletely to ketone bodies. Before these reactions can take place the fatty acids have to be transported over the mitochondria membrane. This requires that the free fatty acids in the cytosol are activated to acyl-CoA that can be transported over the external membrane, whereupon CPT-I transforms acyl-CoA to acylcarnitine that can be transported over the internal mitochondria membrane. CPT-II in the internal membrane then transforms acylcarnitine to acyl-CoA that is oxidized to acetyl-CoA in the β-oxidation. Acetyl-CoA is either oxidized completely in Krebs cycle or incompletely to acetoacetyl-CoA in ketogenesis (see Fig. 4). The regulation of CPT-I activity and other conditions of importance for the oxidation and the distribution between complete oxidation in the TCA-cycle and incomplete oxidation to ketone bodies are dealt with in the paragraph concerning ketosis. It suffices to mention here that CPT-I activity is hampered by malonyl-CoA, and that this, as a result of hormonal and metabolic changes, is reduced in the periparturient period and early lactation.

The part of the fatty acids that is not oxidized completely or incompletely to ketone bodies and exported out of the liver is esterified to triglyceride. The rate of triglyceride production in liver tissue in ruminants is similar to the rate found in other species (Pullen et al., 1990; Emmison et al., 1991). A part of the triglyceride produced is exported out of the cells in the form of lipoproteins, of which very low density lipoproteins (VLDL) constitutes the largest part. Together with the oxidation of fatty acids, the lipoprotein synthesis plays a central role in the development of fatty liver. The secretion of VLDL from liver is very small in ruminants compared with other species (Kleppe et al., 1988; Rayssiguier et al., 1988; Pullen et al., 1990), which is probably partly the reason why triglyceride is generally

stored in the liver around calving. It has been found that apolipoprotein B and A are reduced in serum around calving and in early lactation (Marcos et al., 1990b), and that cows with the highest lipid concentrations in the liver have the lowest concentrations of lipoprotein in plasma (Rayssiguier et al., 1988; Marcos et al., 1990a).

Triglyceride, which is not exported as VLDL, is stored in the cytosol as fat droplets. The capacity of cows to incorporate NEFA into TG is similar to other species (Kleppe et al., 1988; Graulet et al., 1998) and the hepatic tissue capacity to esterify NEFA to TG is increased at the time of parturition (Grum et al., 1996b). Consequently, cows during the dry period and periparturient period have an increased concentration of TG in the liver 1 day after calving (Skaar et al., 1989; Grum et al., 1996b). Factors important for the level of fatty liver in the periparturient period are thus the mobilisation of free fatty acids from body reserves, how large a proportion of the fatty acids absorbed by the liver are oxidized completely, and how large a proportion of the free fatty acids that enter into the ketogenesis or the lipoprotein synthesis is exported as ketone bodies or VLDL. Finally, it should be mentioned that fatty acids are secreted *via* bile salts. It is unclear, however, why a given level of negative energy balance or plasma concentration of NEFA results in fatty liver in some cows but not in others. Due to the limited secretion of VLDL from the liver, it takes some time before an established fatty liver disappears again. Fatty liver is often a reversible condition and does not necessarily cause lasting pathological changes. Fatty liver predisposes to reduced liver function, however, and to a number of other production diseases (Grummer, 1993; Bruss, 1993; Drackley, 1999; Rukkwamsuk et al., 1999; Drackley et al., 2001).

3.3. Ketosis and hyperketonaemia

Ketosis is a metabolic disorder characterised by relatively high concentrations of the ketone bodies acetoacetate, β-hydroxybutyrate, and acetone, and a low to normal concentration of glucose in the blood. This disorder occurs both subclinically and clinically. For this disease to be manifested clinically, the cows normally have a low glucose level (hypoglycemia).

3.3.1. Incidence, risk factors and ketosis types

In Denmark, clinical ketosis only occurs in approximately 1–5% of the cows (Andersen, 1991; Trinderup et al., 2001), but in reports from Europe and the USA, the incidence risk varies from 2 to 20% (Baird, 1982; Lean et al., 1991; Jordan and Fourdraine, 1993; Kelton et al., 1998; Ingvartsen et al., 2003a). Ketosis is primarily seen in the first month of lactation, less frequently in the second month, and only rarely later in lactation in cows (Lean et al., 1991; Bigras-Poulin et al., 1992). Often ketosis is a herd problem with herd incidence risks up to as high as 70% (Simensen et al., 1988).

The incidence of subclinical ketosis depends on the limits applied for the different ketone bodies, but subclinical ketosis occurs much more often than clinical ketosis and can be found in up to 34% of the cows—primarily in the period from 2 to 7 weeks postpartum (Dohoo and Martin, 1984; Andersson and Emanuelson, 1985; Mills et al., 1986; Nielen et al., 1994; Duffield et al., 1997).

Risk factors: The incidence risk of ketosis increases with parity until the fifth or sixth lactation (Kauppinen, 1983; Gröhn et al., 1984). Cows that have suffered from ketosis

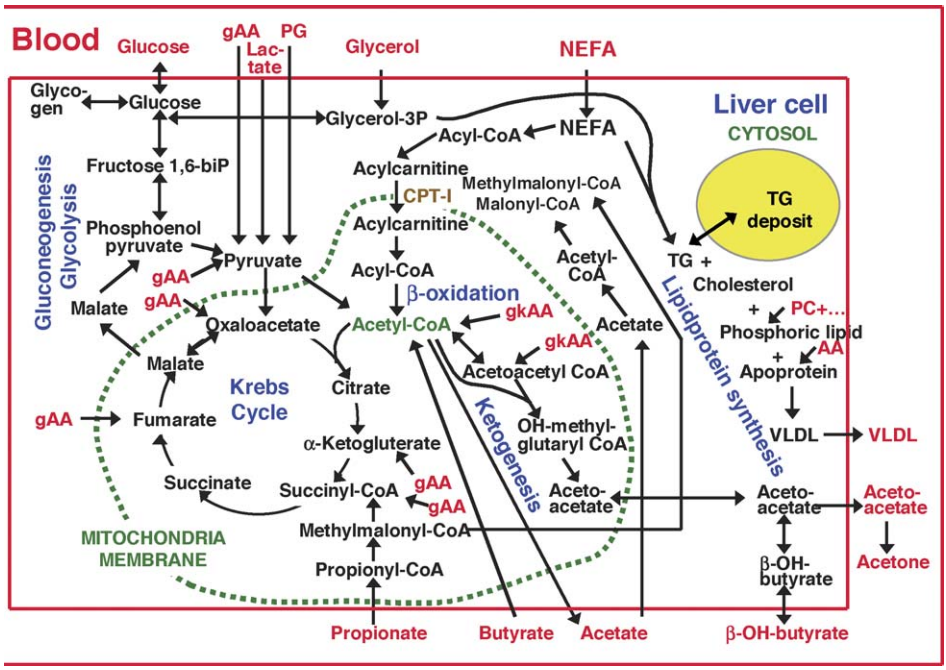

Fig. 5. Overview of substrates to and products from significant intermediary processes in the liver of importance to the development of ketosis and fatty liver. *Abbreviations:* AA, amino acids, gAA, glucogenic amino acids, CPT-I, carnitine palmityl transferase I; kAA, ketogenic amino acids; PC + . . ., phosphatidylcholin and other components for the production of phosphoric lipid; PG, propylene glycol; TG, triglyceride; VLDL, very low density lipoproteins. The glucogenic amino acids are included *via* pyruvate (Ala, Cys, Gly, Hyp, Ser, Thr), α-ketogluterat (Arg, His, Gln, Pro), Succinyl-CoA (Ile, Met, Val), Fumarate (Tyr, Phe) and oxaloacetate (Asp). Amino acids that are both ketogenic and glucogenic are included *via* acetoacetyl-CoA (Leu, Lys, Phe, Trp, Tyr) and *via* Acetyl-CoA (Ile, Trp), where also the only purely ketogenic amino acid (Leu) is included.

have a higher risk of ketosis in the following lactation (Andersson and Emanuelson, 1985; Bendixen et al., 1987). Body condition scores of 3.5 or more at calving increase the risk of ketosis considerably (Markusfeld and Adler, 1986; Gillund et al., 2001).

Ketosis types: Based on different risk factors for the development of ketosis, Lean et al. (1992) have suggested the following classification of ketosis: primary ketosis (also called spontaneous or production ketosis), secondary ketosis, butyric acid ketosis and finally underfeeding ketosis.

Primary ketosis occurs mainly 3–6 weeks after calving. Supposedly, primary ketosis normally occurs when the glucose demand exceeds the gluconeogenesis capacity of the liver. In such situations, glucose and insulin concentrations are generally low resulting in a low insulin/glucagon ratio that may lead to a high activity of CPT-I in the mitochondria membranes of the liver (see Fig. 5). This will stimulate mobilisation of lipid from body reserves and the absorption of fatty acids in the mitochondria of the liver cells. The supply of glucogenic substrates being low, results in increased ketogenesis, and thus high concentrations of ketone bodies in blood, milk, and urine. This agrees with the fact that this

disorder is mainly seen in fat cows and cows that have had a long dry period (Markusfeld et al., 1997).

Secondary ketosis is defined as ketosis resulting from another disease. The typical aetiology will be that a disease causes depressed feed intake and increased mobilisation, which will reduce the plasma glucose concentration and increase the concentration of NEFA and ketone bodies. In cows, an increased risk of ketosis has been found in connection with milk fever and grass tetany (Curtis et al., 1985; Bendixen et al., 1987; Gröhn et al., 1989; Bigras-Poulin et al., 1992), displaced abomasum (Curtis et al., 1985; Gröhn et al., 1989), retained placenta, and uterine infection (Dohoo et al., 1984; Markusfeld, 1985; Bendixen et al., 1987; Correa et al., 1993), foot/leg disorders (Gröhn et al., 1989) and mastitis (Dohoo et al., 1984; Syvajarvi et al., 1986; Gröhn et al., 1989; Rajala and Gröhn, 1998). A few epidemiological studies, however, have found no effect of any given production disease on the risk of ketosis—for example, no effect of mastitis on ketosis (Bigras-Poulin et al., 1990; van Dorp et al., 1999).

Butyric acid ketosis is especially caused by large amounts of butyrate in the feed and probably also by a related depressed feed intake. Thus, silage with high butyrate concentrations results in an increased concentration of β-hydroxybutyrate in the blood (Adler et al., 1958; Andersson and Lundstrom, 1985; Tveit et al., 1987, 1992). This rise in ketone body levels may partly be due to an increased absorption of butyrate from the reticulorumen, but probably particularly to depressed feed intake (Ingvartsen, 1994a). The level of ketone bodies in blood and milk may also increase by feeding with large amounts of ketogenic feedstuffs such as sugar beets and molasses which increase rumen butyrate concentration (Aaes, 1988). When determining the level of ketosis, the prandial variation in ketone bodies should be considered (Mashek et al., 2001), the ketone body levels being highest 3–4 h after feeding at twice-a-day concentrate feeding (Andersson and Lundstrom, 1984). Feeding complete diets show no significant prandial or diurnal variation in ketone bodies (Nielsen et al., 2003).

Underfeeding ketosis occurs especially in cows that are fed insufficiently or with feed rations having a high fill-value. The cause of underfeeding ketosis is supposedly that the underfeeding results in a deficiency of glucogenic precursors (Danfær et al., 1995), and this condition then leads to increased ketogenesis.

Type I and Type II ketosis: An alternative to the above-mentioned classifications of ketosis was suggested in 1996, namely Type I and Type II ketosis (Holtenius and Holtenius, 1996). These designations are parallel to those used for diabetes (Type I = insulin-dependent diabetes mellitus; Type II = non-insulin-dependent diabetes mellitus). Type I ketosis is characterised by low plasma concentrations of glucose and insulin and high concentrations of NEFA and ketone bodies. The response in glucose and insulin to a glucagon injection is very limited in Type I cows (Holtenius, 1992). Type I ketosis fits the classic description of primary ketosis. It is believed that the extensive use of NEFA in the production of ketone bodies means that only relatively modest amounts are esterified to triglycerides and that consequently the risk of fatty liver is small.

According to Holtenius and Holtenius (1996), Type II ketosis primarily occurs in early lactation, and in the majority of situations in combination with other disorders. These cows have relatively high concentrations of glucose (hyperglucosaemia) and insulin (hyperinsulinemia) and the response to glucagon is strong. The cows show signs of insulin resistance,

glucose intolerance, and in certain cases non-insulin-dependent diabetes. There has been some disagreement on whether ketotic cows can have high concentrations of glucose and insulin, and on the etiological background and response to different treatments.

3.3.2. Aetiology and pathophysiology

Ketosis and fatty liver are diseases associated with excessively negative energy balance for long periods of time. Increased ketogenesis is, however, also a metabolic adaptation to a hunger situation—a condition that is comparable with the negative energy balance in early lactation. The primary function of ketogenesis is consequently to transform excessive fatty acid carbon in the liver to an easily oxidizable form for extra-hepatic tissues, which can be used instead of glucose. In this context, the role of the liver is central, and indeed, comprehensive reviews dealing with energy metabolism with focus on liver metabolism and the correlations with ketosis and fatty liver have been published (Zammit, 1990; Emery et al., 1992; Grummer, 1993; Holtenius and Holtenius, 1996; Bauchart et al., 1996; Drackley, 1999; Hocquette and Bauchart, 1999; Herdt, 2000; Drackley et al., 2001), to which the reader is referred for further details. In relation to the aetiology of ketosis, it is essential to understand the physiological regulation and adaptation of the metabolism in the periparturient period and in early lactation, as previously discussed, which explains the increased ketone body concentration and the low glucose concentration that are the primary causes of ketosis in situations of physiological imbalance.

Ketosis occurs if the amount of glucogenic substrates is limited. In the case of excessive lipid mobilisation in early lactation, *e.g.*, as a result of the cows being over-conditioned at parturition, poor feed quality, diminished appetite, *etc.*, ketogenesis will be highly increased thus involving a risk of ketosis. In Section 3.2, the importance of CPT-I for the transport of fatty acids through the mitochondria membrane was briefly mentioned (see also Fig. 5). The two metabolites malonyl-CoA and methylmalonyl-CoA are important inhibitors in the regulation of CPT-I activity (Reid and Husbands, 1985; Brindle et al., 1985b; Jesse et al., 1986a; Knapp and Baldwin, 1990). The regulating effect of methylmalonyl-CoA on CPT-I could be a link coordinating the supply of rumen propionate with the need for free fatty acids as substrate in ketogenesis (see Fig. 5). It has been shown that glucagon decreased and insulin increased the concentration of malonyl-CoA in liver cells (Brindle et al., 1985a,b) indicating a coordinated regulation between the liver and the peripheral tissues. In late lactation or the dry period, for example, when the energy supply is plentiful, the concentrations of insulin and nutrients are normally relatively high leading to a comparatively high concentration of malonyl-CoA (see Fig. 5), which will result in a modest absorption of NEFA for oxidation in liver mitochondria.

The periparturient period and early lactation are characterised by the cows being in negative energy balance and having low plasma glucose and insulin concentrations, but high glucagon concentrations, especially in high-yielding cows. In such situations, the concentration of malonyl-CoA in the cytosol is low. A low concentration of malonyl-CoA leads to a high CPT-I activity stimulating the transport of NEFA over the outer mitochondria membrane. This is in accordance with *in vitro* studies of liver tissue showing that high concentrations of propionate, acetate and insulin inhibit fatty acid oxidation (Jesse et al., 1986b; Whay et al., 1997). The inhibitory effect of propionate and acetate on the oxidation is probably due to increased concentrations of methylmalonyl-CoA and malonyl-CoA,

which inhibit CPT-I and consequently the transport of fatty acids over the mitochondria membrane. Insulin inhibits the transcription of CPT-I and modifies CPT-I sensitivity towards malonyl-CoA (Zammit, 1983; Chow and Jesse, 1992; Beylot, 1996). Further, it has been shown that NEFA inhibit acetyl-CoA carboxylase activity and consequently malonyl-CoA activity.

When NEFA have been absorbed in the mitochondria, what determines whether fatty acids are oxidized completely to CO_2 and water to produce ATP or only partially oxidized while producing ATP and ketone bodies? In the 1970s, the most widespread hypothesis was that acetyl-CoA was directed towards the incomplete oxidation (ketogenesis) as a result of low accessibility of oxaloacetate in the mitochondria (Krebs, 1966). Already in 1969, this theory was criticized as it had already been documented that the activity of phosphoenolpyruvate carboxykinase in the mitochondria and cytosol was unchanged in ketogenic situations, and that the gluconeogenic flux was diminished in fasted animals (Kronfeld, 1969). Zammit (1990) concludes that Krebs' theory of maintaining a low level of oxaloacetate is the cause for ketogenesis is probably correct—but the reasoning for it is wrong. The low concentration of oxaloacetate is achieved by the much higher $NADH/NAD^+$ ratio in the mitochondria. This should result in a minimal rate of intramitochondrial phosphoenolpyruvate formation under ketogenic conditions accounting for the lower rate of gluconeogenesis during ketotic periods with inappetance (Zammit, 1990). The enzyme β-hydroxybutyratdehydrogenase is not present in the mitochondria and the concentration is low in the cytosol, which limits the transformation of β-hydroxybutyrate to acetoacetate (Zammit, 1990).

The production of lactose rises dramatically in early lactation thus increasing the glucose requirement significantly. To meet this demand, gluconeogenesis increases (see Tables 1 and 2), and the glucose consumption in other tissues than the udder decreases as a result of hormonal adaptations (Table 2), but in spite of this, the glucose concentration drops, especially in older high-yielding cows (Ingvartsen et al., 1995). As shown in Fig. 5, the substrates for gluconeogenesis are propionate, glucogenic amino acids (included *via* pyruvate or *via* Krebs cycle), lactate and glycerol. The quantitatively most important substrates are propionate and glucogenic amino acids (Danfær et al., 1995). Suboptimal supply of glucogenic substrates will contribute to hypoglycemia and increase the risk of ketosis.

The concentration of circulatory ketone bodies is generally increased in support of lactation in early lactation as illustrated for instance in Fig. 1. Ketone bodies originate from two sources, an exogenous (from the feed) and an endogenous (from the mobilisation of body lipids). *The endogenous source of ketogenic substrates* in ruminants is principally made up of long-chained fatty acids. As a result of the increased nutrient demand and the hormonal regulation, the glucose concentration is reduced and consequently also the insulin concentration. Fatty acids will be mobilised in this situation, for instance as a result of a low insulin/glucagon ratio and a high growth hormone level (Table 2). In situations where the energy supply of the hepatocytes is low, *i.e.*, when the concentration of malonyl-CoA in the cytosol is supposed to be low, the uptake of free fatty acids will be high, and because the concentration of oxaloacetate will be relatively low due to the consumption of substrates in gluconeogenesis, the ketogenesis will be stimulated (see Fig. 5). Factors stimulating the mobilisation of free fatty acids and the resulting ketogenesis in early lactation are over conditioned cows, high yield and feeding low energy rations which lead to low absorption of

glucogenic nutrients (Markusfeld et al., 1984; Andersson and Emanuelson, 1985; Riemann et al., 1985; Bendixen et al., 1987).

Exogenous sources of ketogenic substrates originate from the feed, including butyrate (butyric acid) in silage or butyrate produced microbiologically in the reticulorumen. Half or more of the butyrate absorbed from the rumen is transformed to β-hydroxybutyrate in the rumen epithelium (Hird and Symons, 1961). The rest is absorbed and transformed effectively in the liver where butyrate can either be oxidized in Krebs cycle or enter into the ketone body formation (see Fig. 5). Cows fed silage with high concentrations of butyrate thus have an increased concentration of β-hydroxybutyrate in the blood (Adler et al., 1958; Andersson and Lundstrom, 1985; Tveit et al., 1987, 1992). The effect can also be indirect, however, *via* reduced feed intake which, especially in early lactation, can increase the mobilisation of fat depots as feed intake is negatively correlated with silage butyrate content. This may be due to an increased content of biogenic amines such as putrescine, tryptamine, cadaverine and histamine (Lingaas and Tveit, 1992; Tveit et al., 1992; Ingvartsen, 1992). Likewise, other ketogenic feeds such as sugar beets and molasses may increase rumen butyrate concentration, and thus the ketone body level in blood and milk (Aaes, 1988).

3.4. Rumen acidosis

Acidosis is an imbalance in the acid–base system of the animal. Acidic conditions may occur in blood (metabolic acidosis), rumen (rumen acidosis) or both in rumen and blood. Blood pH is normally around 7.4 and varies relatively little whereas rumen fluid pH may vary considerably. Subclinical rumen acidosis is defined as a condition where rumen fluid pH is below 6. Rumen acidosis is defined as conditions where rumen fluid pH is below 5.5, and where rumen motility is weak or has ceased. Rumen acidosis and metabolic acidosis can be acute (<few hours), of long duration (>few hours) or chronic (weeks and months). For details on rumen acidosis se elsewhere in this issue.

3.5. Displaced abomasum

Displaced abomasum is a multifactorial disease where the abomasum is dilated as a result of gas and dislocated to the left (left-displaced abomasum) or to the right (right-displaced abomasum) in the stomach in relation to the normal placing in the right side of the abdominal cavity just below the rumen. In case of displaced abomasum, the passage of feed to the intestines is partly or totally blocked. Approximately 85% of the incidences are left-displaced abomasum (Geishauser, 1995). Norwegian studies have found that 88% are left-displaced while 12% are right-displaced abomasums (quoted from Radostits et al., 2000). Similarly, an American study found 86% left-displaced and 14% right-displaced abomasums (Constable et al., 1992).

3.5.1. Incidence and risk factors

Displaced abomasum occurs in all types of cattle but is most frequent in high-yielding dairy cows in early lactation and especially in 4–7-year-old cows (Constable et al., 1992). The disease may occur prior to calving, but 80–90% of the cases are seen in the first 4 weeks postpartum (Erb et al., 1984; Pehrson and Shaver, 1992; Constable et al., 1992). In

an earlier Danish study, incidence risks of left-sided displaced abomasum of 0.6% have been found with a variation of 0.2–1.6% (Hesselholt and Grymer, 1979). Later reports show an incidence risk of 1.3% based on results from the Danish Cattle Database (Blom, 1993). North American studies report somewhat higher incidence risks in systems with intensive feeding. Incidence risks of 2% have been found in a Canadian study (Geishauser et al., 1997), while average incidence risks of 3.3% (Jordan and Fourdraine, 1993) and 5% (Pehrson and Shaver, 1992) have been reported for very high-yielding herds in the USA. The variation in the between-herd incidence risk can be very large and has been from 0 to 14% (Jordan and Fourdraine, 1993) and from 0 to 21.7% (Pehrson and Shaver, 1992) in two American studies illustrating that displaced abomasum is very much a herd problem.

Displaced abomasum occurs more frequently in dairy breeds than in beef cattle (Constable et al., 1992), and there seems to be differences in breed, the risk increasing from Guernsey to Holstein to Brown Swiss cattle (Constable et al., 1992; Geishauser, 1995). The effect of yield on the risk of displaced abomasum is unclear as varying results have been found in different studies (Geishauser, 1995).

Among the most important risk factors are a number of nutritional and management conditions (Geishauser, 1995; Shaver, 1997). A dip in feed intake occurs around calving (Ingvartsen and Andersen, 2000). This is natural, but low feed intake just before calving has been found to increase the risk of displaced abomasum (Constable et al., 1992). An increased negative energy balance prepartum, expressed by increased plasma NEFA concentration, increases the risk of left-displaced abomasum (Cameron et al., 1998). Cameron et al. (1998) found that a high BCS, poor feed bunk management, dry cow rations with high energy concentration (>1.65 Mcal NE_l/kg dry matter) and high genetic potential for milk yield were important risk factors for displaced abomasum.

A rise in the concentrate/roughage ratio of the feed in late pregnancy and early lactation increases the risk of displaced abomasum considerably (Coppock et al., 1972). In the study of Coppock et al. (1972), the cows changed suddenly to a complete diet containing a higher amount of concentrates 4 weeks prior to parturition. This sudden change to a diet more rich in energy can probably also be a risk factor for displaced abomasum.

Increasing the nutrient supply in the last 2–3 weeks prepartum is generally recommended to ensure the nutrient demand of the cows and to adapt the cows to lactation feed. Increasing energy and protein supply reduced the risk of left-displaced abomasum considerably in a study by Curtis et al. (1985) while an increased allocation of concentrates intensified the risk of displaced abomasum in another study (Correa et al., 1990). Differences in the risk can possibly be explained by escalating to different feeding levels and different nutrient supply. As the feed intake is relatively low in the periparturient period (Ingvartsen and Andersen, 2000), the concentrate/roughage ratio can get relatively high in herds not fed complete diets. Rapid increase in concentrate feeding in early lactation can reduce the intake of roughage considerably as the substitution rate in early lactation is very high (Ingvartsen et al., 2001).

Some feeds increase the risk of displaced abomasum compared to others. Thus, a two to three times higher risk of displaced abomasum has been found for silage compared with hay (Zamet et al., 1979; Nocek et al., 1983). The reason for the differences between silage and hay is probably partly that silage is finely chopped. The importance of silage length for the risk of displaced abomasum has not been investigated, but grinding of lucerne hay increases the risk of displaced abomasum significantly (Dawson et al., 1992). Danish

experience shows that feeding very finely chopped maize silage as the only fibrous feed to cows in early lactation constitutes a significant risk of displaced abomasum and that this risk can be almost eliminated if every cow eats a kilogram of straw daily.

Lack of feeding space and consequently much competition will reduce roughage intake and probably result in too variable feed intake in low-ranking cows and will likewise be a risk factor for displaced abomasum (Constable et al., 1992). The above-mentioned conditions are clearly a problem in the periparturient period and early lactation when the animals are often moved from one group to another.

Other production diseases have also been reported to be risk factors for displaced abomasum (Geishauser, 1995; Guard, 1996; Radostits et al., 2000). Displaced abomasum occurs simultaneously with fatty liver (Herdt et al., 1982; Holtenius and Niskanen, 1985; Taguchi et al., 1992), but the relationship between the diseases are not clear. Similarly, displaced abomasum occurs concurrently with ketosis (Pehrson and Shaver, 1992; Constable et al., 1992), which has been reported as a risk factor for displaced abomasum (Curtis et al., 1985; Markusfeld, 1987; Erb and Gröhn, 1988; Gröhn et al., 1995). Displaced abomasum is also seen in connection with milk fever, which is also presumed to be a risk factor for displaced abomasum (Willeberg et al., 1982; Markusfeld, 1986; Pehrson and Shaver, 1992; Massey et al., 1993). Further, it has been reported that preventive treatment with calcium chloride gels reduces the risk of displaced abomasum (Oetzel, 1996).

3.5.2. Aetiology and pathophysiology

The precise cause of left- and right-displaced abomasum is still unclear despite the efforts to clarify the aetiology and pathophysiology in reviews (Svendsen, 1969; Geishauser, 1995). Various factors are thought to be prerequisites for the development of displaced abomasum. One factor is reduced contractility and atony (slackness) and gas-dilated abomasum (Constable et al., 1992). Gas is partly produced in the abomasum when rumen bicarbonate reacts with HCl, but the gas also partly originates from the rumen (Sarashina et al., 1990). Another factor is that the mesentery shall stretch for the abomasum to be able to dislocate. A third factor is the space in the abdominal cavity. The amount of space changes considerably around calving as a result of delivery of the calf and decrease in feed intake (Ingvartsen and Andersen, 2000). If the rumen does not resume its normal place on the left abdominal floor, the abomasum will be able to slide under the rumen and result in a displaced abomasum. Gas and a dilated abomasum where the mesentery has stretched in combination with more free space within the abdomen are thus supposed to be prerequisites of developing left- or right-displaced abomasum.

The conditions leading to atony and reduced motility are still unclear. Hypocalcaemia around calving is a possible factor. Reduction in the calcium concentration around calving results in a reduction in abomasal contractility, which is presumed to lead to atony and dilatation of the abomasum (Daniel, 1983; Massey et al., 1993). Likewise, volatile fatty acids (VFA) in the abomasum have been reported to reduce abomasal motility (Breukink, 2003). However, normally there is a poor correlation between VFA concentration in the rumen and the abomasum (Breukink and Deruyter, 1976) when the rumen has a well-functioning floating fibre matt. A high percentage of concentrates and very finely chopped roughage reduce the floating fibre matt (Nørgaard, 1989; Shaver, 1997). Shaver (1997) states the following mechanism in the development of displaced abomasum: in cows with

insufficient floating fibre matt, the concentrate particles fall into the ventral part of the rumen and the reticulum where they ferment or pass on to the abomasum. VFA produced in the ventral part of the rumen can pass on to the abomasum before they are absorbed by the rumen, and thus restrain abomasal motility.

Surprisingly good possibilities have been found for predicting displaced abomasum based on plasma analyses for high activity of aspartate aminotransferase, high concentration of β-hydroxybutyrate and a high fat/protein ratio in the milk (Geishauser et al., 2000), the latter being the mechanistic reason why animals with displaced abomasum have diminished appetite and increased mobilisation.

4. Feeding and management strategies to prevent diseases

As discussed above fatty liver, ketosis, rumen acidosis and displaced abomasum are multifactorial diseases that, to a large extent, relate to problems in feeding and management. Despite this very few studies have documented prevention strategies primarily because a large number of animals are needed to have enough statistical power to prove differences in disease incidence rates between different strategies. Due to the limited data available on prevention strategies these need to be developed based on risk factors and knowledge on the aetiology of the diseases in question. Some of the major factors directly or indirectly increasing the risk of fatty liver, ketosis, acidosis and displaced abomasum are over-conditioning at calving, excessive mobilisation, low nutrient intake, nutrient or diet specific factors and management and environmental stress. It is not the intention of this paper to review all aspects of feeding and management strategies, to prevent diseases or to develop prevention strategies, but rather to point out selected important aspects in relation to preventing the periparturient diseases discussed above.

4.1. Avoid overconditioning

Over-conditioned cows (≥4.0 on a five-point scale) have a greater risk of developing periparturient health problems than normal cows as described in previous sections and in reviews (*e.g.*, Morrow, 1976; Grummer, 1993; Ingvartsen et al., 1996, 2003a). In our review (Ingvartsen et al., 1996), we gathered information about the effects of prepartum feeding of heifers, lactating and dry cows on, *e.g.*, body weight or body condition scores, body reserve, mobilisation and health. Based on the available literature it was concluded that there is a positive relationship between prepartum weight gain and extent of mobilisation. It was also concluded that postpartum feeding and differences in prepartum feeding causing mobilisation of less than 30–40 kg body weight do not appear to influence voluntary feed intake, milk yield and milk composition. Differences in prepartum feeding causing mobilisation of more than 40 kg body weight seem to depress feed intake and milk yield and to increase milk fat content during the mobilisation period. Finally, it was concluded that increased prepartum body weight gain or body condition increase liver fat content and indicate increased risk of fatty liver and related disorders.

Given the link between body fatness at calving, subsequent degree of mobilisation and risk to the complex of digestive and metabolic disorders and infectious diseases, it is clearly

important to manage cows to calve at the optimum body fatness. The optimum body condition at calving is around 3.25 on a 1–5 scale (Skidmore et al., 2001). This level of body reserves allows the cow to meet any forthcoming dietary inadequacies without incurring excessive rates of postpartum mobilisation in support of a potential production. Obtaining the recommended body condition is relatively easy in heifers when feeding the recommended energy levels. However, in dairy cows it is a bit more complicated—feeding in the dry period cannot be used to markedly change body condition. There is generally only small differences between body condition at drying off and at calving in practice, the difference being within ±0.5 units for the majority of cows (Markusfeld et al., 1997). Due to the limited time frame in the dry period (approximately 7 weeks) and the reduced intake capacity during late pregnancy (Ingvartsen et al., 1992), it is difficult to change body condition markedly by feeding unless extreme diets are used. Attempting to drastically reduce the fatness of over-conditioned cows by severely restricting nutrient intake is not advisable as inclusion of barley straw (at 400 g/kg DM intake) in silage-based dry cow diets has led to mobilisation of maternal body lipid and protein and reduced milk yields in the subsequent lactation (Dewhurst et al., 2000; Moorby et al., 2000). Managing cows to obtain a desired level of body condition at calving should be considered early in the previous lactation, as they may be resistant to dietary manipulation of their body reserves in the late part of lactation (Ingvartsen et al., 1996). To study this we fed cows *ad libitum* during late lactation and the dry period (the last 24 weeks prepartum) with complete diets varying in energy density to reach different body weight and BCS at calving. The total body weight gains were 134, 134 and 117 kg in cows fed complete diets with high, medium or low energy density, respectively. The small difference in weight gain during late lactation was related to changes in both energy intake and milk yield. Cows fed high, medium and low energy density diets consumed 14.5, 13.9 and 13.0 kg DM per day and produced 20.7, 16.3 and 12.9 kg ECM daily, respectively. These results illustrate that varying energy intake in late lactation may not necessarily change body weight significantly at calving due to changes in nutrient partitioning (milk yield). If the problem is too thin cows, a useful strategy would be to dry off the cows a week or two earlier to allow them more time to replenish reserves before the next lactation.

4.2. Prevent excessive lipid mobilisation

Physiological and pathological changes associated with negative energy balance are important factors in, *e.g.*, fatty liver, ketosis and displaced abomasums as discussed in previous sections. Avoiding excessive mobilisation in the periparturient period is therefore important in preventing these feeding- and management-related diseases. By excessive mobilisation of body reserves is meant mobilisation that exceeds the normal mobilisation in cows managed so that they are not compromised by environmental factors (Ingvartsen et al., 2003a). Cows, like other mammals, have developed a strategy to build up body reserves in anticipation of lactation and to use these reserves in support of lactation (Friggens, 2003) and these changes in body reserves are hormonally regulated as discussed in Section 2.2.

As illustrated by the plasma NEFA concentrations in Fig. 1, dry cows usually start to mobilise body fat towards the end of the dry period and reach a peak in early lactation. The plasma NEFA concentration is negatively correlated with dry matter intake

(Ingvartsen and Andersen, 2000). Pregnancy decreases intake capacity by approximately 20–25% (Ingvartsen et al., 1992) and as energy requirements for pregnancy and mammary development increase, it has been assumed that increased nutrient density may allow maintenance of the same intake of key nutrients despite lower total DMI. Such an increase in nutrient density during the last 2–3 weeks prepartum, generally by increasing the non-fibrous content of the ration, has been referred to as steaming-up or close up diet. More generous prepartum grain feeding or higher feeding levels have resulted in higher NEFA levels in plasma (Kunz and Blum, 1985; Ingvartsen et al., 1995; Minor et al., 1998; Dann et al., 1999; Vandehaar et al., 1999; Rabelo et al., 2001; Holcomb et al., 2001; Holtenius et al., 2003). Above diet changes also increase plasma insulin (Fronk et al., 1980; Kunz and Blum, 1985; Ingvartsen et al., 1995; Vandehaar et al., 1999; Holcomb et al., 2001; Holtenius et al., 2003), which plays a pivotal role in the regulation of lipolysis and lipogenesis, thereby affecting plasma NEFA. We have shown that insulin infusion (hyperinsulinemic–euglycemic clamp) significantly reduces both NEFA and BOHB in both early and mid-lactation (Mashek et al., 2001).

While it may seem sensible to use close-up diets to limit mobilisation, overfeeding and feeding of high-starch diets should not be extended for too long as this will increase the risk of disease as discussed earlier. Holtenius et al. (2003) have recently reported that cows fed a higher energy level during the dry period had a greater degree of insulin resistance before and after calving, which allowed higher plasma NEFA concentrations compared to those in cows fed below requirements. Insulin resistance may be the reason why we observed no difference in NEFA concentration during early lactation in cows fed diets differing considerably in starch despite significant differences in plasma insulin (Andersen et al., 2004). We also found no effect of different roughage/concentrate ratio on plasma NEFA concentration which is in accordance with other studies (Dhiman et al., 1991; Kokkonen et al., 2000).

4.3. Strategies to improve feed intake

The dip in intake in periparturient cows has been found to be negatively correlated with plasma NEFA (Ingvartsen et al., 1995), and consequently much interest has been directed towards avoiding too severe drops in dry matter intake (Ingvartsen and Andersen, 2000). Many factors, both animal factors, diet factors and management, are involved in regulating dry matter intake (Allen, 2000; Ingvartsen and Andersen, 2000; Mertens, 1994; Ingvartsen, 1994b). Clearly, it is beyond the scope of this paper to review or even mention all the factors influencing intake. I will merely address a few points concerning adaptation of the gastrointestinal system to changes in physiological stage, intake in periparturient cows and potential relationships to diseases.

It has been speculated that intake capacity in early lactation could be improved by increasing VFA absorption capacity in the rumen, thereby reducing VFA accumulation and increasing rumen pH (Dirksen et al., 1985; Mayer et al., 1986). A low energy diet in the dry period can cause a degeneration of the rumen epithelium and thereby a reduced VFA absorption capacity (Liebich et al., 1982; Mayer et al., 1986). These authors also observed that feeding a high level of concentrates in the last 2 weeks before calving stimulated the proliferation of the rumen epithelium and increased the epithelial area during the first

1–2 months of lactation. The most important factor stimulating epithelium growth is the concentration of VFA in the rumen liquid, in particular butyrate and propionate (Flatt et al., 1958; Hinders and Owen, 1965; Kauffold et al., 1977; Galfi et al., 1991). Furthermore, daily fluctuations in propionate and butyrate concentration had a pronounced positive effect on the proliferation of sheep rumen epithelium *in vitro* (Sakata and Tamate, 1978). However, stimulating rumen epithelium by increasing the feeding levels during the dry period may have negative effects on periparturient health due to increased fatness at calving, which should be avoided. To improve the absorption capacity of VFA in the rumen in early lactation, and subsequently feed intake, a dry cow feeding strategy ("VFA-load") consisting of feeding barley (4 kg) as the sole feedstuff in the morning and forage (3.5–4.7 kg silage DM) as the sole feedstuff in the afternoon was suggested. The VFA-load strategy clearly resulted in increased propionate and butyrate concentrations and created a within-day variation in rumen pH, but no indications of an improved rumen environment (Andersen et al., 1999). We have investigated the VFA-load feeding strategy in the dry period on a large number of animals (Ingvartsen et al., 2001) and found no effects of the VFA-load treatment on postpartum feed intake and performance, which indicates that the feeding strategy used does not contribute significantly to a better rumen epithelium absorption capacity or rumen environment. These conclusions have later been supported in an American study (Rabelo et al., 2001).

Generally, dry matter intake may be increased by increasing diet digestibility and rate of passage. To accommodate the increased nutrient need for foetus development and milk production transition cows and cows in early lactation are generally offered diets consisting of chopped roughage and increasing amounts of non-fibre carbohydrates. We compared three feeding strategies in early lactation: separate feeding of silage *ad libitum* and restricted feeding of concentrate with a daily increase in allowance of 0.3 kg (C-0.3) or 0.5 kg (C-0.5) up to a total of 10.2 kg/day, and a complete diet (Complete diet) (Ingvartsen et al., 2001). The postpartum diets were designed to contain 500 g concentrates DM/kg. Group C-0.5 ate less silage DM during weeks 2–4 than group C-0.3. The substitution rate between concentrate and silage was 0.94 during lactation weeks 2–4, with a higher concentrate to roughage ratio in group C-0.5. Daily milk yield did not differ between C-0.5 and C-0.3 but group C-0.5 had a depressed milk fat percentage during lactation weeks 4 and 5. Consequently, our recommendation is not to increase concentrate allowance by more than 0.3 kg daily during early lactation—too rapid an increase may reduce roughage intake inappropriately and potentially increase the risk of rumen acidosis.

Cows fed the complete diet had a significantly higher feed intake compared to cows fed concentrate and forages separately, particularly during the first 3 weeks of lactation. During the first 3 weeks, cows fed the complete diet ate 24, 17 and 12% more DM than cows fed concentrates and silage separately. From week 4 of lactation, DM intake of the complete diet was approximately 6% higher than in cows fed concentrates and silage separately. Differences are even bigger if energy intake is considered due to the lower percentage of concentrate in the diet during the first 15–26 days of lactation (Ingvartsen et al., 2001). The improved DM intake of between 12 and 24% during the first 3 weeks has previously only been observed in studies using a high level of concentrates, and under such circumstances DM intake has been improved by between 13 and 17% (Phipps et al., 1984; Istasse et al., 1986; Aaes, 1993). Cows fed complete diets appear to have a lower frequency of

metabolic and digestive diseases compared to cows fed concentrate and silage separately (Ingvartsen et al., 2001), and therefore complete diets are recommended over separate feeding.

4.4. Nutrient or diet specific factors

Numerous feed factors potentially affecting intake are generally considered in diets for dairy cows (Mertens, 1994; Ingvartsen, 1994b) but only a few aspects relating to the periparturient disease complex will be covered here.

The physical form of the diet is essential in maintaining an optimal rumen environment that secures animal health. The lack of physical form reduces chewing activity, ruminal fill, motility, fibre matt formation and increases rumen VFA concentration (Wyburn, 1980; Welch, 1982; Shaver et al., 1986).

As a general rule abrupt changes in the diet should be avoided and instead animals should be allowed gradual changes in diet.

Poor feed quality, such as silage with elevated levels of butyrate, should be avoided as it is linked with poor intake capacity (Ingvartsen, 1992) and may increase ketone body levels and the risk of ketosis in periparturient cows (see Section 3.3).

We recently reviewed how propylene glycol (PG) is metabolised in the rumen and liver and how it affects metabolites, hormones, liver composition, feed intake and milk production, in order to evaluate whether PG is likely to prevent excessive fat mobilisation and imbalances in carbohydrate and fat metabolism and thereby reduce the risk of ketosis (Nielsen and Ingvartsen, 2004). PG is partly metabolised to propionate in the rumen and the remaining PG is absorbed from the rumen without alteration, and subsequently enters gluconeogenesis *via* pyruvate. Oral administration of PG increases insulin by 200–400% within 30 min after drenching, indicating that PG is absorbed rather quickly. Allocation of PG also increases plasma glucose, although the response is limited, probably because of the large increase in insulin. PG decreases plasma concentrations of non-esterified fatty acids and β-hydroxybutyrate, especially in early lactating cows with relatively high levels of NEFA. PG also reduces the triacylglycerol content of the liver and the concentrations of ketone bodies in milk, and hence has anti-ketogenic properties. Factors such as metabolic status of the animals, time of blood sampling in relation to time of feeding PG, supplementation method and dose of PG influence the magnitude of the response in blood parameters. PG has no effect on energy corrected milk yield (ECM) and does in general not affect feed intake. However, due to its low palatability it may reduce feed intake if not mixed thoroughly with other feed components or drenched. The reducing effect of PG on NEFA, hepatic TG concentrations and milk fat content indicates that PG improves the energy balance of cows in early lactation. Together with the anti-ketogenic properties of PG, this suggests that PG may reduce the risk of subclinical and clinical ketosis. It should be mentioned though that PG may show some side effects including ataxia, salivation, hyperventilation, and depression. Later studies have confirmed the beneficial effects of PG in periparturient cows (Juchem et al., 2004). However, although indicators of metabolic status were improved by peripartal use of PG-enriched concentrate, economic benefits are questionable for dairy farms with good nutritional programs as economically important factors such as milk production, animal health and fertility were not influenced (Hoedemaker et al., 2004).

Glycerol has also shown promising glucogenic effects when given as an oral drench (Goff and Horst, 2005) but no beneficial effects of feeding glycerol-supplemented diets have been found (DeFrain et al., 2004). Other glucogenic precursors may be propionate salts (not reviewed).

4.5. Avoid management and environmental stress

Based on the risk factors and aetiology of the diseases discussed in previous sections, it is clear that stressors relating to management and environmental conditions are major determinants of periparturient diseases. Among management factors it is important to reduce stress relating to grouping and space allowance. Heifers housed in separate groups have been found to have a 14 and 9% higher dry matter intake and milk yield, respectively (Konggaard and Krohn, 1978), probably through reduced social stress. Also, regrouping cows from one group to another may increase aggression that may affect the eating behaviour and performance of low ranking cows in particular (Hasegawa et al., 1997), stress that potentially may increase disease risks. Also, sufficient space should be available at the feed bunk. From the experiments reviewed (Friend and Polan, 1974; Friend et al., 1977; Manson and Appleby, 1990; Albright, 1993; Menzi and Chase, 1994) it may be concluded: (1) >0.5 m per cow has no effect on feeding behaviour and intake, (2) 0.2–0.5 m per cow shows variable effects on intake and increased competition at the feed bunk and (3) $\leq$0.2 m per cow causes reduced eating time and intake. Management strategies increasing aggression between animals should be avoided, not only because of its negative effect on eating behaviour and intake, but also because such stress may potentially increase mobilisation of body fat and thereby increase disease risks in periparturient cows.

Environmental stress such as heat and humidity stress should be prevented as it may have negative effects on dry matter intake, the immune system, health, reproduction and production (Davis, 1998; Kadzere et al., 2002; West, 2003). For dairy cows, the upper critical temperature is 25–26 °C (Berman et al., 1985) but the upper critical temperature probably depends on physiological state and other environmental conditions. High producing dairy cows are assumed to be at higher risk of heat stress than low yielding cows (Collier et al., 1982) due to a high correlation between milk yield and heat increment (Kadzere et al., 2002). This is supported by the finding that cows with high (31.6 kg/day) and medium (18.5 kg/day) milk production generated 48.5 and 27.5% more heat, respectively, than dry cows (Purwanto et al., 1990). However, not only temperature determines the decrease in intake—*e.g.*, humidity and ventilation also modify heat stress (West et al., 2003). Heat stress reduces feed intake slightly at 25 °C but at temperatures of 30 °C or above the reduction is significant (Young, 1987). Heat stress or other types of environmental stress also influence the immune system and potentially the disease risk (Davis, 1998). Heat stress may be prevented through shade or cooling (fan, sprinkler, evaporative cooling) of the cows (West et al., 2003). Further, heat stress may be reduced nutritionally by using feed ingredients with a relatively low heat increment, such as concentrates and fats. However, improved dietary energy density and the lower heat increment associated with the inclusion of dietary fat must be coupled with limitations in fat feeding to avoid ruminal and metabolic disorders. Numerous nutritional modifications are used for hot weather feeding; however, many need further investigation to achieve specific recommendations (West, 1999).

4.6. Other preventive measures

Among other aspects that may be important in preventing diseases in the periparturient cow would be a good hygiene and a good claw and leg status, *e.g.*, through regular claw trimming. Also, it is important to prevent hypocalcemia as this may lead to other periparturient diseases.

5. Concluding remarks—towards status-oriented strategies

Prevention of production diseases has been in focus for many decades, but in spite of that, the incidence risk of the feeding-related diseases is still substantial (see Tables 3 and 4); not because the preventive measures up till now have been useless, but probably because of a dynamic development in the risk of production diseases as a result of, *e.g.*, selection for higher production and changed production conditions. Further, the preventive measures have previously focused on implementing changes at herd level, for instance in feeding. These measures have improved the health in many problem herds. However, this is hardly the way to reduce morbidity in ordinary herds with an "average" morbidity. A greater focus on more homogeneous groups of animals or possibly the individual animal, is necessary in order to identify "risk animals", *i.e.*, animals with an increased risk of disease, reproduction problems and suboptimal production as a result of poor status of their external and internal epithelia (*e.g.*, internal epithelia in rumen, intestines, lungs, udder, external epithelia in teat canal, hoofs), metabolism or immune system as illustrated in Fig. 6.

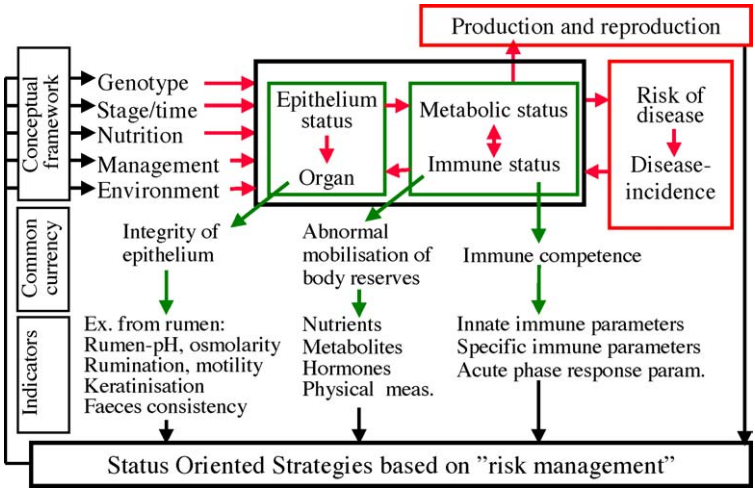

Fig. 6. Status-oriented strategies for optimising dairy cow health, reproduction and production. Status-oriented strategies aim at securing a desirable status of epithelia, metabolism and immune function in different cells, tissues or organs through surveillance and health and production management based on indicators (Modified from Ingvartsen et al., 2003b).

Fig. 6 illustrates how genotype, stage of production, nutrition, management and environment may influence the risk of disease through effects on the epithelial, metabolic and immune status; epithelial status meaning the ability of the epithelia to resist, *e.g.*, physical stress, pathogen load and transmission of for instance endotoxins from rumen to the circulation, as for example, during rumen acidosis. Ingvartsen et al. (2003a) argued, among other things, that disease risk could be reduced by minimizing physiological imbalance, and that such a reduction would at the same time improve the production and reproduction of the cows. Fig. 6 further illustrates that the condition of the epithelium of the rumen is of importance for the metabolic and immune status, but also that metabolic and immune status are important for the organ function, *e.g.*, the function of the alimentary tract. Fig. 6 moreover illustrates that the metabolism and the immune system communicate, and that the animals' immune status plays a central role in their disease resistance. There are many examples of interactions between the physiological and immunological system, as well as the influence of nutritional factors on the immunocompetence (Ingvartsen et al., 2003a). A number of production diseases, including the feeding-related diseases, have "common currencies" that can be recognized by measuring indicators. Some insight into disease aetiology has been gained through the research up till now, but the knowledge of the disease aetiology and pathophysiology of many diseases remains scarce. A continuous effort in this field is very important in order to uncover the multifactorial complexity of the diseases and identify indicators that can be used in early diagnosis and identifying the causal factors of production diseases, *i.e.*, in the subclinical phase.

The prevention of certain diseases is problematic as it may be difficult to diagnose the diseases, in particular in the subclinical phase. If recognition of subclinical diseases is difficult, the condition may be confirmed by analysing blood, milk or urine (*e.g.*, hyperketonaemia, hypocalcaemia, hypomagnaesia), while other subclinical conditions are more difficult to diagnose in practice (*e.g.*, rumen acidosis and fatty liver). On-line systems for analysing milk parameters have been developed which most likely can be used for diagnosing, for example, subclinical ketosis. Other non-invasive methods, *e.g.*, ultrasound, will probably improve the insight into the extent of fatty liver, and furthermore render it possible to recognize and document risk factors. It is vital to recognize the problems at an early stage before the disease, *e.g.*, rumen acidosis, causes permanent damage and manifests itself clinically. Since there are now fewer persons attending to an increasing number of animals, new technology is needed to contribute to monitoring and early identification of "risk animals" with an increased risk of developing production diseases and reproduction problems.

It is essential to understand the interaction between different factors involved in disease risk. An example is the interaction between the physiological and immunological systems and how feeding, management and environment in different genotypes affect these systems. It would be desirable if future research could contribute to establishing the risk of an animal (value between 0 and 1) developing a certain disease at a given time, and to use these values in health management programmes instead of the descriptive terms healthy, subclinical and clinical. Fig. 6 suggests that future prevention of production diseases should take place by status-oriented strategies, *i.e.*, feeding and management, taking into consideration not only the production but also the condition of the animal. Status-oriented strategies based on "risk management", continuously adjusting feeding and management on the basis of the status of individual cows or a group of cows (indicators, production and reproduction), and

herd information on production system, economic conditions (prices, cost/benefit), *etc.*, are expected to be able to reduce morbidity and at the same time improve reproduction and production. Developing such systems for prevention of production diseases requires a considerable knowledge of the symptoms of the diseases, their incidences and risk factors, the aetiology and pathology of the diseases as well as the value of different indicators for predicting the disease risk.

Acknowledgements

I wish to thank Karin V. Østergaard for her skilled assistance in preparing the manuscript and the staff at our library for providing me with the large number of articles used for this paper. This work was funded by a grant financed by the Directorate for Food, Agriculture and Fisheries, the Danish Cattle Association, Lattec I/S, and the Danish Institute of Agricultural Sciences.

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