Lipomobilization Syndrome (Fatty Degeneration Syndrome) in the Dairy Cow

M. Stober
Klinik fur Rinder krankheiten
Tierartschikt Hochshule
D. 3000 Hannover, Fed. Republic of Germany
G. Dirksen
Medizinische Klinik
University of Munich
Fed. Republic of Germany

Introduction

On the basis of information in the literature a summary is presented of the actual problem in modern intensive dairy cow management (operations with a large number of animals, automated, diminished supervision of the individual animal as well as a generous allotment of feed), which may in many ways lead to important economic considerations.

What is meant by "lipomobilization syndrome?"

Definition

This name and other similar terms: fat cow syndrome (38,39,41), fatty liver syndrome (7,44,53), fat mobilization syndrome (46), parturition syndrome, sindrome de la vaca gorda, syndrome de la vache grasse (12), syndrome du part (33), Partus- (50) or Verfettungssyndrome, indicate an exaggerated function of a regulating mechanism of the energy metabolism, peculiar to ruminants, namely the release of fat reserves at the onset of lactation. Origins and effects of such an excessive lipomobilization are more or less closely correlated ("vicious circle") to the feeding at the end of pregnancy, and to milk production as well as to a series of peripartally occurring stresses, illnesses, and production disturbances of the dairy cow. Because of the non-specificity of the clinical picture of massive lipolysis (which is the decisive factor metabolically and pathogenetically, and which is common to all manifestations of the syndrome) it is, in practice, often difficult or impossible to determine whether a certain disturbance observed within the complex mentioned above is to be considered as "releaser" or "maintainer", as "companion" or "successor" of the lipomobilization syndrome. Empirically all illnesses occurring within the framework of this complex have much poorer prognoses than when occurring separately.

How does such a metabolic "derailment" occur?

Pathogenesis

The prerequisite for an excessive lipolysis lies in the peculiarities of ruminant metabolism and the food consumption (1 to 53): As can be seen in Illus. 1 the time of the highest milk production and thus of maximum energy requirement does not coincide with that of the greatest food (energy) intake[a], nor the maximum addition of energy. On the other hand, the appetite of the dairy cow is much greater later, at the time of lower production output, than is required, that is, voluntary food intake lags behind the course of lactation and doesn't diminish at the same rate. As compensation for this temporary "lead" in milk production over the food absorption curve the animal uses from reserves during production peak and later - during the end of the maximum needs - it will again develop reserves, which is reflected in decreases and increases in the body weight. The changes in body weight depicted in the diagram are due not only to growth and expulsion of the fetus but also to deposition and consumption of energy supplies.

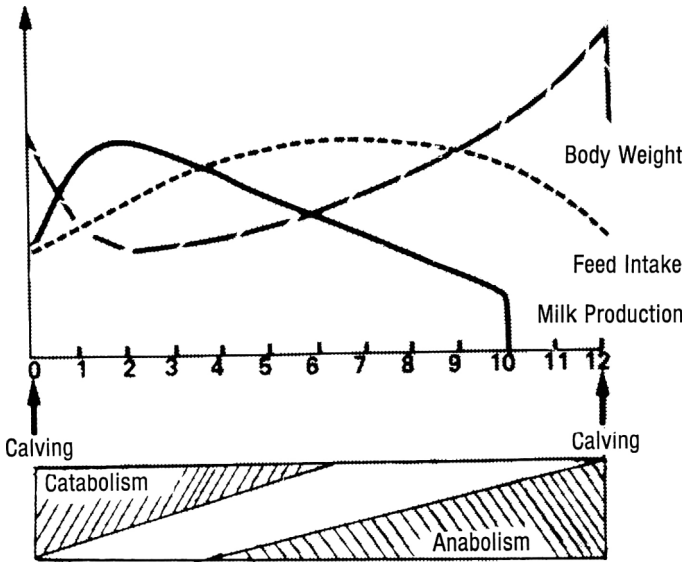
The course of the three curved lines in Illus. 1 shows an abrupt change between the anabolic and catabolic metabolism at the beginning of lactation; at this point the animal must have a stockpile of easily mobilizable energy (see Table 1). For carbohydrates (liver and muscle glucose and glycogen) this holds only partially true since they will mostly be withdrawn with current gluconeogenesis; in times of sharply increased energy demands their supply cannot be raised with equal speed and therefore it will fall short of the needs. In addition, in this connection one must mention the animal's fat deposits as specially significant energy carriers through which normally up to a third of the total energy flow may be provided; at times of higher demand their share may be even higher (up to 80%).

How does the deposition and release of the body fat take place? (See Illus. 2):

The ruminal digestion of carbohydrates (cellulose, starch, sugar) results in volatile fatty acids, of which acetic acid is of most interest in this connection since propionic acid is predominantly used for gluconeogenesis (in the liver). The acetate fractional part arrives via the blood stream at the fatty tissue and serves there as a raw material for the body's fatty acid synthesis (with the help of acetyl-coenzyme-A-carboxylase) and thus liponeogenesis, of which more than 90% occurs here; it is noteworthy that the adipocytes in the

[a] *This is for milk production exceeding 30 to 35 liters per day additionally insufficient (obligated energy deficit).*

Illustration 1. Course of milk production, feed intake capacity and body weight of the dairy cow (12):



——— = milk production (kg/day)
. . . . = feed intake (kg dry matter)
— — — = body weight (kg)
= anabolic metabolism condition with predominance of liponeogenesis or lipodeposition
= catabolic metabolism condition with predominance of lipolysis or lipomobilization

subcutaneous fatty tissue are substantially more active than in the body cavity fat (60, or 30% of the total of the fatty acid formation).

According to the existing energy requirements the newly synthesized fatty acids are either (under the influence of triacylglyceride synthesis) transformed to neutral fats (triglycerides) and embedded in the fat deposits (lipodeposition) or (bound to albumin) conveyed through the blood vessels to the "consumers", especially the liver, for oxidation. The latter pathway is also taken by the higher fatty acids resulting from the intestinal digestion of dietary fats. If the energy requirements exceed the described fatty acid supply, the deposited fat will be "mobilized", that is transformed back into free fatty acids and glycerine (lipolysis) and returned through the blood stream to the liver (lipomobilization).

In contrast to the fatty tissue the liver assumes only a limited part of the body's fatty acid synthesis (5 to 10%) and deposits—in times of balanced energy metabolism—only little fat in the hepatocytes. Although the udder does produce a considerable amount of fatty acids (from acetate, lactate, and β-hydroxibutyrate) during lactation, its function during the dry period is to store in the form of fats (mainly triglycerides) a surplus of fatty acids produced elsewhere (namely in adipose tissue).

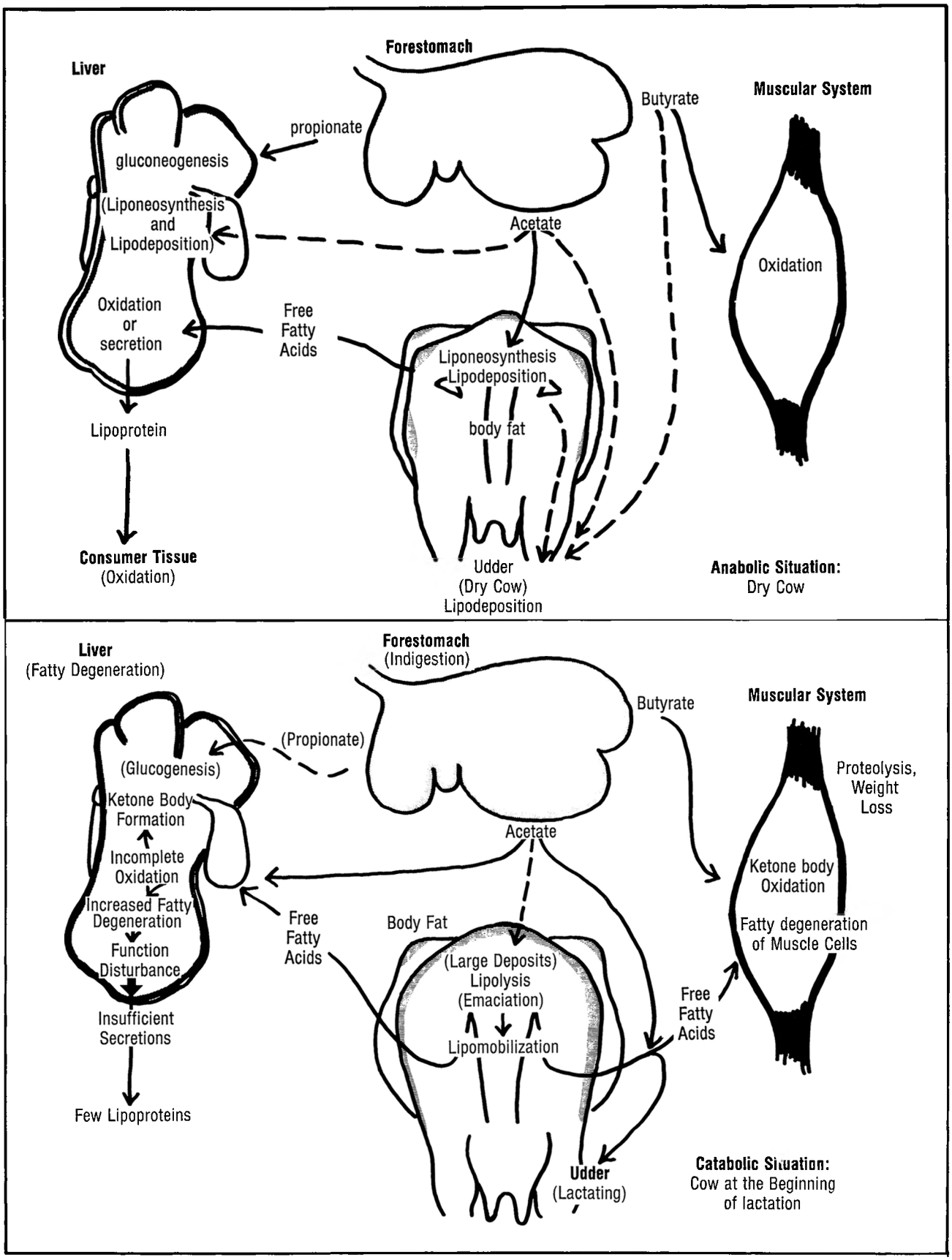
The free fatty acids transported to the liver are normally (in the presence of oxalacetate) more or less completely oxidized (with the aid of the acetylcoenzyme A) (→liberation of energy); the remainder would be resynthesized as triglyceride fat and (bound with apo-lipoprotein) secreted in the blood as lipoprotein. The consumer tissues can get access to free fatty acids and glycerine "on demand" by "in situ" splitting (with the help of lipoprotein lipase which is localized close to the capillaries) of circulating lipoprotein (which to a small part also stems from intestinal absorption) (see Illus. 2). The liver therefore is central to the lipoprotein formation and to the distribution of lipids to the various tissues of the dairy cow.

One of the deciding assumptions for the occurrence of an overwhelming lipolysis after calving is the presence (abnormal) of a large mass of body fat and especially subcutaneous fat deposits (see Illus. 3). These are accumulated when the feed, towards the end of lactation, but particularly during the dry period, contains substantially more energy than is required for the production of the necessary energy reserves. Empirically this is the case when the dry period lasts longer than normal (over 60 days) and the nutrition is composed predominately of fiber-poor, glucide and protein rich fodder (for example finely chopped corn silage, concentrates and especially good, or little to no hay) and allowed to the limit of food intake capacity (Illus.

TABLE 1. Portion of the various body reserves of the energy supplies of the dairy cow

Reserves	Total quantity	Mobilizing ability	Active form	Portion of energy flow
Carbohydrates (glucose and glycogen from blood, liver and muscle)	2-3 kg	+++	glucose	60 percent (including glucogenesis), substantially less with anorexia, hunger or indigestion
Fats (predominately triglycerides but also phospholipids and cholesterol esters, from the fat of the hypo dermis and the body cavities)	40-60 kg	++	free fatty acids, glycerine	= 30 percent (including the neosynthesis of free fatty acids) with an increase energy demand (lactation) or with break-down of glucogenesis up to 80 percent
Protein (muscular substance)	50-75 kg	+	amino acids	< 10 percent

Illustration 2. Schematic presentation of fat exchange in cattle



1).[b] The opportunity for such excessive lipodeposition is presented for example, if all the dry cows of a herd for any reason (technical condition of the barn, shortage of personnel, abundant food supply, ignorance) are not separated from the lactating animals and not fed in proper proportions,[c] e.g. after a change in management from stalls to free stalls (without dividing the animals into feeding groups according to production), or if dry cows are allowed to have leftover feed in addition to their rations. Under such conditions fat deposits can collect that constitute up to 30% of the carcass weight.

How is fat metabolism accomplished?

During the maximum lactation up to 2 kg. of milk fat are produced daily. Up to 40% of this is produced in the udder; the other 60% is taken from the body (see Illus. 2,3). Moreover not only gluco- and liponeogenesis are "geared up" but particularly body fat of the hypodermis is mobilized; that is, split up (under the influence of triazylglyceride-lipase) into fatty acids and glycerine, which are placed partially at the disposal of the energy production (oxidation), and partially of the milk fat production (in the udder). Concurrently, the oxidation of the fatty acids released in increased amounts is in competition with gluconeogenesis, where the use of oxalacetate takes precedence over its share in fatty acid oxidation[d] (see Illus. 4). In some cases, because of a discrepancy between fat mobilization on the one hand and the stress of glucogenesis (through the lactose demand of the udder) on the other hand, there occurs an incomplete oxidation of fatty acids, that is, the formation of ketone bodies and the storage of the unoxidized fatty acids in the liver. The former (beta-hydroxybutarate acid, aceto-acetic acid and acetone) have no pathological significance when present in low concentration detectable only in the urine (subclinical ketosis). The unconsumed remaining fatty acids will be used in triglyceride resynthesis in the hepatocytes; however, as such they can only be "exported" if enough apo-lipoprotein for binding is available.

---

[b] *A feeding method of that kind leads under certain circumstances to a shift of the volatile fatty acid "pattern" in the forestomach in favor of propionic acid and thus to a promotion of gluconeogenesis; as soon as this produces more energy than the animal requires the excess will likewise be retained as stored fat. This kind of feeding is not only dangerous in the sense of lipomobilization syndrome, but also not economical, since the reclamation of the fatty acids stored in the fatty tissue is energy-wise more expendable than their immediate use in the milk fat production.*

[c] *A contribution of Dr. Scholz (Hannover) deals more precisely with this.*

[d] *The liver "sacrifices" its reserve of glycogen in the process.*

The prerequisite for this is a healthy, protein producing liver. The ability of the liver tissue of dry cows to synthesize the necessary proteins is lost in the same measure as they store fat (which results from the nutritional situation described above). Thus the out-sluicing of the triglycerides can lag behind the resynthesizing rate. Sustentation of the described competitive situation between gluconeogenesis and lipo-mobilization may lead to increasing liver degeneration; undoubtedly that is particularly true for such dairy cows, which before calving, have accumulated extreme fat reserves and, moreover, now have very high milk production; this situation is then combined with an abnormally strong and continuous (over 8 weeks long) postpartum weight loss.

Recent research by Roberts, Reid, Rowland and Patterson (1981) indicates that a similar process takes place in the skeletal musculature of severely adipose animals. Muscle tissue will contribute to the coverage of the high energy demand existing at the onset of lactation not only by protein catabolism (release and oxidation of amino acids) but also by oxidation of fatty acids or by deposition of fat (in oxidizing muscle fibers) that is resynthesized from incompletely oxidized fatty acids. Possibly the energy yielding proteolysis is part of the production- and health-limiting regulation mechanism of the dairy cow.

How are the synthesis and catabolism of body fat regulated in the ruminant?

The factors influencing fat metabolism are shown in Table 2. Among these, nutrient supply and food intake capacity seem to be of major importance with respect to lipogenesis and lipodeposition. Lipolysis and lipomobilization are primarily stimulated by declining blood sugar levels (due to increased energy demand), but are inhibited by rising blood levels of free fatty acids or ketone bodies. The short or long term adjustments therefore probably take place through inactivation and reactivation or decomposition and synthesis of the fat metabolism enzymes mentioned above. The correlations between the various distribution processes merit attention in the way of research as to whether they may be influenced prophylactically or therapeutically

We can assert that the metabolism of the dairy cow normally manages to accomplish conversion from the anabolic situation during pregnancy and dry periods, to the catabolic situation at the beginning of lactation by intensifying gluconeogenesis as well as by releasing the fat reserves (and by catabolism of muscle protein - a process which has thus far drawn little attention). This course of events includes a moderate fatty degeneration of the liver (not exceeding 20% of its weight) and subclinical ketosis, i.e. slight ketonuria without further clinical signs.

What causes the failure of this unstable metabolic regulation?

The derailment into an abnormal overwhelming lipolysis or lipomobilization syndrome (and thus transition from latent to clinically manifest ketosis) requires an excessive accumulation of body fat during the dry period (hyper-

NOW for CATTLE a Broader Spectrum Anthelmintic...

PANACUR®

(fenbendazole)

...an anthelmintic with the efficacy you expect, the safety you can trust and the economy you demand: Panacur (fenbendazole) Now for Cattle.

EFFICACY

Effectively removes all common gastrointestinal nematodes and lungworms.

SAFETY

Safe in all beef cattle including breeding stock, pregnant cows and stressed cattle.

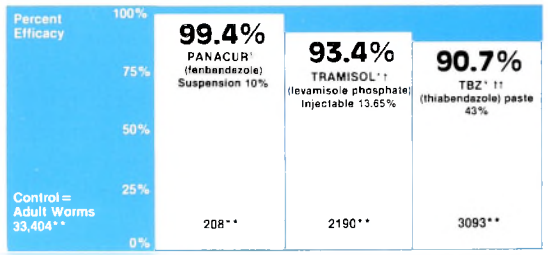
CONVENIENCE

Small volume dosage with "no-waste" gun, not only keeps drug cost per treatment low, but makes administration quick and easy. Saves time too!

Available only to Veterinarians

A Study Comparing Efficacy of Three Anthelmintics in Naturally Infected Cattle

Efficacy results, total adult worm burden*



† TRAMISOL® Injectable, (levamisole phosphate) 13.65% is a registered trademark of Cyanamid Agricultural Division.
†† TBZ®, (thiabendazole) paste is a registered trademark of Merck & Co., Inc.
* Data on file at American Hoechst Corporation, Animal Health Division, Somerville, N.J.
** Average number of adult worms recovered per treatment group.

Panacur® (fenbendazole) Cattle Dewormer
Suspension 10% (100 mg/ml)

DIRECTIONS: Determine the proper dose according to estimated body weight. Administer orally.

DOSAGE: Cattle - 5 mg/kg (2.3 mg/lb) for the removal and control of—Lungworm: *(Dictyocaulus viviparus)*.; Stomach worms: Barberpole worm *(Haemonchus contortus)*, Brown stomach worm *(Ostertagia ostertagi)*, Small stomach worm *(Trichostrongylus axei)*; Intestinal worms: Hookworm *(Bunostomum phlebotomum)*, Thread-necked intestinal worm *(Nematodirus helvetianus)*, Small intestinal worms, *(Cooperia punctata & C. oncophora)*, Bankrupt worm (Trichostrongylus colubriformis), Nodular worm *(Oesophagostomum radiatum)*.

The recommended dose of 5 mg/kg is achieved when 2.3 mL of the drug is given for each 100 lb. body weight.

EXAMPLES:

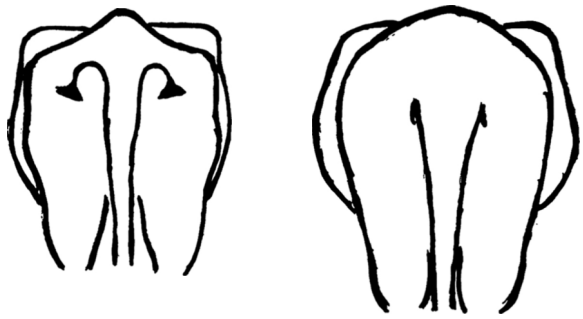
Dose	Cattle Weight
2.5 mL	109 lb.
5.0 mL	217 lb.
10.0 mL	435 lb.
15.0 mL	652 lb.
23.0 mL	1,000 lb.

Under conditions of continued exposure to parasites, retreatment may be needed after 4-6 weeks. There are no known contraindications to the use of the drug in cattle.
WARNING: Cattle must not be slaughtered within 8 days following last treatment. Because a withdrawal time in milk has not been established, do not use in dairy cattle of breeding age.
CAUTION: Consult your veterinarian for assistance in the diagnosis, treatment and control of parasitism.
Sales to licensed veterinarians only.
Keep this and all medication out of the reach of children.

American Hoechst Corporation
Animal Health Division
Somerville, New Jersey 08876

Hoechst

Illustration 3. Interpretation of the subcutaneous fat deposits in the dairy cow.



lipodeposition), an above-average milk yield (high energy demand) as well as an additional periparturient disturbance which causes a depression of the food intake and/or ruminal digestion of the affected animal that is more pronounced and lasts longer than the depression usually occurring during the peripartal period (9). Empirically the following factors and diseases are particularly frequent "releasers" of the lipomobilization syndrome, and therefore they should be considered when taking the history, or looked for by appropriate examinations:

- stall or feed changes, lack of proper water or feed, stressful shipment, severe climate fluctuations, change in the number of animals per barn, or -- through redistribution -- the social position within the herd;
- difficult calving with long persistent labor, retained placenta, puerpural uterine inflammation, and recumbency due to various causes (including hypocalcemic parturient paresis), abomasal displacement, rumen acidosis, foreign body disease, mastitis and basically also any other condition which disturbs the general health of the animal e.g. a hoof lameness which can be observed not infrequently during the dry period because of the increased body weight (due to fat deposition) and the fact that claw trimming is postponed with respect to the advanced pregnancy [vicious circle].

How does a releaser-dependent derailment proceed?

As an immediate result of the events listed above (several of which may occur at the same time, and which depress food intake or cause a downright indigestion) gluconeogenesis is inhibited (insufficient supply of propionic acid). Thus, the organism must now draw on its reserves to an even higher degree than before. It has already been explained that to this end, the subcutaneous fat deposits in particular are available, and so is - to a certain extent - muscle protein. From such an additional periparturient strain, accordingly, a "hyper"-lipomobilization may arise with excessive hepatosteatosis, and with a restriction in the functional efficiency of the liver (over 30% of its tissue volume involved). This "liver injury" is based on a reduction in the metabolically active surfaces within and between hepatocytes by increasing fatty degeneration;[e] there is also a shift in balance between lipostabilizing (antiautoperidoxydative) substances and deposited fat. Thus again the risk of protein membrane injury increases ("vicious circle"). In addition the overburdened liver parenchyma produces less protein; this then causes a decrease in the serum albumin and the absence of adequate amounts of apo-lipoprotein for the outpouring of resynthesized triglycerides from the liver, and thus a further increase of hepatosteatosis ("vicious circle"). Over and above it reduces the ability of the damaged liver to remove the metabolic debris, and elsewhere, for example, harmful material originating from the diseased uterus (=detoxification function), that contributes to autointoxication with such products and thus also stresses the hepatocytes ("vicious circle"). Ultimately it is true that because of the performance of the liver within the defense mechanisms of the animal's body, such patients exhibit an increased tendency to local and general septic infections, which then in their turn lead to the aggravation of the disease ("vicious circle").

The illnesses listed as "releasers" of the lipomobilization syndrome often continue to operate as "maintainers" because they have -- (owing to the generally weakening and immunosuppressing effects of the hepatsteatosis) -- a poorer prognosis for recovery than when occurring unassociated with this vicious circle. They contribute by their prolonged existence to continued indigestion and to an increase in toxic endogenous metabolites - in summary to a more severe liver damage. Thus they remain as integral parts of the syndrome, closely joined to its metabolic nucleus; under these conditions they should, therefore, not be seen isolated, but rather as important component parts of the described pathogenesis.

The authors feel that certain connections attributed to the lipomobilization syndrome require still further corroboration. That is true for the magnesium- and calcium-lowering effect of a massive lipolysis and of the vitamin D metabolism disturbance on the basis of pronounced hepatosteatosis as well as for the effect of the observed intramuscular fat deposition on the functional efficiency of the locomotor system (tendency for recumbency), perhaps also of the gastrointestinal tract (periparturient gastrointestinal atony, tendency to abomasal displacement).

On the basis of comprehensive investigations a number of additional disturbances concerning reproductive function must be viewed as obligatory consequences of the lipomobilization syndrome of the dairy cow, and they contribute greatly to the economic impact of the disease complex (7,12, 16,23,33,34,35,36,38,39,40,41,44,50,53):

- increased tendency to uterine inertia, placental retention and/or metritis

[e] *The respiratory quotient of fatty degenerated liver tissue is smaller than that of the normal liver cell.*

Illustration 4. Schematic presentation of the linkage of gluconeogenesis (⟶) and fat catabolism (⟵⟶) in the energy metabolism in cattle: with raised glucose requirements the appropriation of oxalacetate in gluconeogenesis has priority over its use in the condensation of acetylcoenzyme A and the ensuing channelling of the fat catabolism metabolism into the tricarbonic acid cycle; if fat catabolism increases at the same time, increased ketone formation results (⟵···⟶).

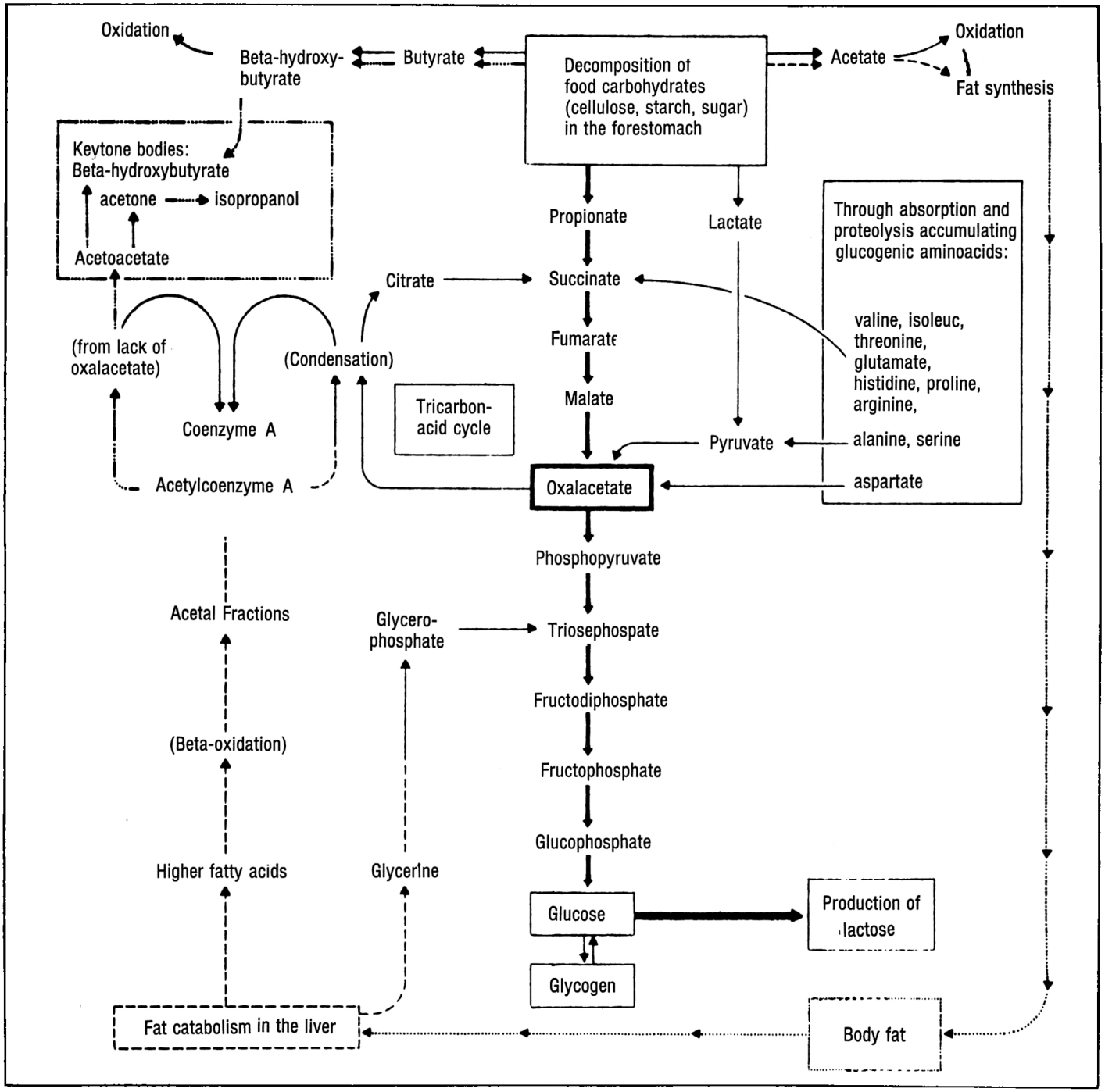


TABLE 2. Pathogenesis of the lipomobilization syndrome of the dairy cow (schematic)

Normal balance between anabolic and catabolic phases	Derailment of energy metabolism in the lipomobilization syndrome
Controlled, "restricted" feeding during the dry period (moderate exercise)	Uncontrolled, high energy ration during the (extended!) dry period (lack of exercise)
Accumulation of moderate body fat reserves prior to calving	Accumulation of excessive body fat reserve prior to calving
Healthy, undisturbed periparturition	Periparturent stress and/or illness
Moderate to good milk yield	Extremely high milk production
Good, gradually increasing appetite	Decline of appetite
Stimulation of gluconeogenesis	Disturbed gluconeogenesis
Normal lipomobilization rate	Excessive lipomobilization
Light to moderate fatty degeneration of the liver (without functional disorder)	Moderate to severe fatty degeneration and functional disorder of the liver
No or at most subclinical ketosis	Clinically manifest secondary ketosis (with more or less distinct symptoms of the "triggering" or "accompanying" illness)
Normal weight loss postpartum (the result of calving and lactation)	Excessive and longer lasting loss of weight due to additional lipomobilization and protein catabolism in the (fatty degenerated) muscles
Normal return of the heat cycle after calving	Delayed and poor reinstatement of the heat cycle postpartum
Normal fertility	Decreased fertility
Normal calving interval	Prolonged calving interval

- late appearance and a tendency to a quiet first heat after calving
- elevated insemination index (>2.0); and
- prolonged time between calving (>380 days)

These fertility disorders are seen as the result of a delayed replacement of the body weight loss (owing to lactation demands); due to an overwhelming lipolysis this loss of body weight is usually particularly severe and persistent (Illus. 1). Moreover, it is found that the ovarian function is disturbed as a result of steatosic liver insufficiency, particularly since lipogenesis stimulating estrogens are inactivated. In the correlation between fat metabolism and fertility of the dairy cow another especially significant "vicious circle" exists, since the delay of the beginning of the next pregnancy results

in longer dry periods and offers an opportunity for renewed overfeeding and thus leads to an excessive deposit of body fat. Thus the lipomobilization syndrome may occur more frequently in a herd one year after the "overcoming of a fertility problem".

The observations on pathogenesis can be summarized in the following way: the extent of fatty liver degeneration occurring in the periparturient dairy cow and thus the danger of a "derailment" of normal lipomobilization in the complex lipomobilization syndrome is dependent on:

- feeding during the dry period (→hyperlipodeposition),
- high milk production (→great, uncoverable energy demands) at the onset of lactation, and
- the occurrence of health disturbances or illnesses occurring in the interval from about two to four weeks after calving (→detrimental to gluconeogenesis → hyperlipomobilization)

The pathogenetic conditions listed above often concern only certain individual "particularly valuable" animals in a dairy herd, which differ in some way or another from the otherwise normal herd average, thus leading to sporadic cases of the syndrome. Due to certain errors by management in maintenance or feeding (or heat observation!) the lipomobilization syndrome can also appear as a "herd problem", whereby a greater part of the freshening cows become ill one after the other.

(In beef breeds a similar disease may afflict well fed cows at the end of a twin pregnancy, who at this time are already affected by a disturbance in food intake or whose health otherwise suffers; the disease is then discribed as "pregnancy toxicosis". Cows and heifers around the end of gestation and, rarely, beef bulls of all breeds, in extremely good nutritive condition, can likewise fall ill of fatty degeneration of the liver characteristic of the lipomobilization syndrome when subjected to unaccustomed transport stress (long journey, severe climatic changes, lack of food or water, overcrowded vehicles).

What are the symptoms of lipomobilization syndrome?

Clinical Signs

The history often reveals that the affected animals are valuable breeding stock, for whom the owner allowed prolonged calving intervals, or, in other cases, allowed to reach parturition in especially well fed "blocklike" appearance. Frequently the excessive fatty deposition is clearly recognizable upon presentation of the animal, but after a lengthy illness, it may have turned into emaciation due to lipomobilization. Therefore it is important to ask about an exceptional weight loss when taking the history. To estimate the extent of the subcutaneous fat deposits the lumbar and croup region of the patient should be inspected and palpated, special attention being paid to the lumbar vertebral transverse processes, the tubera coxae and ischial tuberiosites, and the sacrococcygeal region. Illus. 3 presents a schematic key from the National Institute for Research in Dairying in Reading (43) with levels (0-5) from "very imaciated" to "very fat". A cow evaluated as 4 or 5 or with a history of recent severe loss of weight may be considered as overfat or susceptible to lipomobilization. (The weight of such patients should be ascertained and observed during the disease).

Veterinary assistance is usually sought because of a periparturient decline in food intake or complete anorexia ("indigestion") and fallen-off milk production; moreover retained placenta, fetid lochial discharge, or any other illness (e.g. lameness) may be present which affects the cow's appetite or forestomach digestion and this sets off the lipomobilization syndrome. Often the clinical signs of this "releaser" or "companion" illness are so in the foreground of the clinical picture that the metabolic background is "overlooked", that is, it is not even considered.

The examination of the patient reveals a series of unspecific signs, as a decreased interest in the surroundings, depression, "rigid" stare, lack of activity, frequent lying down, diminished appetite (where first the concentrates, then the silage, and finally even hay would be refused), decreased rumen activity and scanty (frequently also fairly dark colored and mucous covered feces) and more solid feces than normal. In addition, the manifestations of the "releaser" or "companion" disease are present.

More solid indications for involvement of the liver in the course of the disease (1,3,7,11,12,14,17,21,26,36,38,38,40, 41,46,53) can be found in the ketone body odor of the breath and skin perspiration, as well as from positive results of the ketone body test of the urine and milk. In more severe cases the liver percussion field is enlarged, and is occasionally also sensitive to percussion; yet, as a rule, there is no icterus. None too rarely it turns out only, after repeated unsuccessful treatment, that the ketosis present is secondary in nature; therefore, such a possibility should always be checked for when a fat cow is first presented by a thorough examination of all organs which are notorious sites of "releasers" of excessive lipomobilization: to this end, particularly the vagina and perivaginal connective tissue, the uterus, udder, forestomach and abomasum as well as the locomotor system should be scrutinized for any disturbances that may maintain this pathological process.

Unfortunately, the biochemical changes associated with fatty degeneration of the liver thus far offer only very little that is "diagnostically available" for the practitioner, because the values observed are frequently in the border area between the normal and abnormal. Besides more or less elaborate laboratory procedures are required (see Table 4). Thus the most important signs are the establishment of ketone bodies in the urine and milk, the lowered serum albumin as well as the raised values of bilirubin in the blood serum, free fatty acids and pyruvate.

In severe cases of lipomobilization syndrome sooner or later complete anorexia will occur—independent of any releaser or "maintainer". Finally, no doubt as a result of the general muscle weakness, recumbency will set in. These cases

TABLE 3. Summary of factors influencing fat metabolism in the ruminant

Lipogenesis and lipodeposition

are promoted through: acetylcoenzyme-A-carboxylase, triazylglycenide synthetases, high energy (over) feeding, lengthy dry periods, estrogens

are retarded through: body movement, cold

Lipolysis and lipomobilization

are prompted through: fatty acid mobilizing lipases, high milk production, low blood sugar level, hunger/food refusal, stress/illness, catecholamines (adrenaline, noradrenaline), growth hormone, prolactine, adrenocorticotropic hormone and glucocorticosteroids, glucagon.

are retarded through: high blood level of free fatty acids or of betahydroxbutyratic acid, intravenous glucose administration, insulin, adrenergic alpha- and beta-blockers, nicotinic acids.

TABLE 4. Biochemical findings in lipomobilization syndrome

Blood:
Ketone bodies 10 mg/dl
Glucose 40 - 50 mg/dl (can be normal or raised, however, in situations of stress, as long as liver glycogen is still available)
Pyruvate 2.0 mg/dl
(Leucocyte count 4000/ with left shift)
(PCV terminally 40%)
Serum/Plasma:
Albumin 3.0 g/dl
Free fatty acids 10 mg/dl
Triglycerides 7 mg/dl
(β-hydroxi-butyric acid 1.0 mmol/1)
(Total cholesterol mg/dl [?])
Total bilirubin 0.5 mg/dl
(AST, SGOT 40 U/l, is also influenced by muscle damage)
SDH 7 U/l
OCT 20 U/l
BSP Retention (25 min) 5 — 10%
(Ca sometimes 8.0 mg/dl)
(terminally urea 40 mg/dl)
Urine:
Ketone bodies 50 mg/dl (+ to +++)
Urochrome methylene blue test — to +
Milk:
Ketone bodies 10 mg/dl (+ to +++)
Liver: (Biopsy specimens)
Glycogen content 1 g/100 g wet weight
Fat content 20% V/V

Antibody Responses of Heigers Vaccinated with Reduced Doses of **Brucella abortus** Strain 19

almost always ending fatally, usually involve cows that were extremely fat initially and had unrecognized or untreated or incurable "releaser" diseases. Provided the syndrome exhibits no local (uterus, udder, intestine) or general infection (sepsis), respiration, circulation and body temperature often, but not always, remain normal. In the terminal stage retention icterus ("puerperal hepatic coma") and/or blackish diarrhea like feces (hemorrhagic to ulcerating abomasal inflammation) may occur; agonal failure of the main functions is heralded by recumbency and gradually increasing dyspnea with regular expirational groans (interstitial emphysema of the lungs).

Post Mortem Findings

Post mortem examinations of cows that died or were around parturition slaughtered (7,12,14,21,24,26,38,41,45, 46,49,52,53) reveals large fat deposits as well as fatty deposition in the liver as indications of the lipomobilization syndrome. In this connection one finds distinct fat layers in the hypodermis, in the great body cavities (subserous), in the coronary grooves as well as perirenally and in the mesentery; in a lengthy illness the subcutaneous fat reserves tend to disappear more rapidly than that of the other before mentioned deposits. The hepatic manifest: (from one and half times or even double the norm), the ocher is saffron colored and strikingly round-edged liver is enlarged, its surface is smooth; it is friable so that moderate finger pressure may perforate the parenchyma. On dissection of the liver distinct fat traces stick to the knife; pieces of liver tissue placed in water frequently float because of the high fat content. The fatty liver degeneration (7,12,14,21,24,26,44, 45,46,49,52) is considered moderate, if up to 20% of the microscopic picture (that is of the liver cell volume), and as extreme if more than 30% (up to 70%) is occupied by fat droplets (46). The fatty degeneration is centro-lobular at the onset and progresses peripherally, fine droplets appearing at first; in more severe cases, there are larger drops, at last, the hepatocytes may be completely filled with fat. This process is accompanied by a corresponding depletion of liver glycogens (from an average of 3 to less than 1 g of glycogen per 100 g wet weight of liver) (26). This fatty degeneration constitutes a uniform reaction of the liver tissue to any disturbance of gluconeogenesis and acceleration of lipomobilization (hypoxia and lack of lipotropic factors); therefore it permits no conclusions about the "releaser" illness, at best only about the degree and duration of the action of the primary noxae (which have to be identified by other means). As a rule, the course of the disease is not long enough to permit an appreciable degree of cirrhosis. The gall bladder is often rather large and full of more or less inspissated gall. The kidneys appear pale and contain in their tubular epithelia histologically recognizable fatty deposits. In protracted and especially severe cases retention icterus ("puerperal liver failure") subserous and submucosal bleeding (the latter particularly in the gastro-intestinal canal, occasionally in combination with ulcers) as well as resulting agonal pulmonary emphysema can also occur.

Further postmortem findings give indications of the "releasers" or "supporters" of the lipomobilization syndrome, like retained placenta, supperative endometritis, or delayed involution of the puerperal uterus, muscle fiber laceration or advanced muscle necrosis, mastitis, and local or general septic infection elsewhere, abomasal displacement, and so forth.

Diagnosis and Prognosis

The diagnosis of lipomobilization syndrome is supported by the simultaneous findings of excessive fat deposits in the hypodermis (or a history of a recent weight loss on one hand, and continuing anorexia, decreased or absent forestomach activity as well as ketonuria and ketolactia on the other hand. Closer examination usually reveals the latter to be secondary and very refractory to therapy. The search for the actual "releaser" and "companion" disease is of special importance, since from the onset it must be jointly treated, particularly in those high producing cows that reached parturition in a very fat condition. Conversely with all periparturiently ill dairy cows—independent of the clinical picture of the individual case the possibility of an overwhelming lipolysis should be borne in mind, and it should be considered in any therapeutic regimen if the patient is fat and thus prone to lipomobilization.

The prognosis of the lipomobilization syndrome depends on the nature and degree of the "releaser" and "companion"-illness as well as the extent of fatty liver degeneration; the latter, however, is difficult to assess under present practice and clinic conditions. Consequently one should strive to improve the available laboratory methods. In this connection it would indeed be interesting to use liver biopsy more than has been previously done in the diagnosis and prognosis of the periparturiently occurring illness in the dairy cow; however, this procedure involves a considerable amount of work and time, and there is also, in these patients, an increased risk of post biopsy hemorrhage because a manifest disturbance of hepatic function includes decreased prothrombin synthesis.

Clinical experience shows that the close interrelations (or vicious circles) between the different factors of the causal complex of the syndrome (as discussed in the section on pathogenesis) always lead to poorer chances of recovery in fat animals (which "stew in their own fat") than in animals subjected to the same stresses or illnesses, but in normal nutritional state. In the latter case, with prompt attention and appropriate treatment, one can count on normalization of the histologic appearance of the liver (retrogression of the fat deposition and accumulation of new glycogen reserves) within four weeks. On the other hand in patients who become recumbent within the framework of lipomobilization syndrome one can expect no improvement.

Treatment

One must consider in the treatment of the lipomobilization syndrome—and each case may be different —the "releaser" or "companion" diseases and the resulting ketosis together with fatty liver degeneration; the causal excessive accumulation of body fat deposits is, of course, no longer accessible to therapy. The breaking of the "vicious circle" between secondary ketosis and primary illness can be recognized by the reappearance of an appetite, increase of the milk yield as well as the decline of ketonuria and ketolactia. To attain this goal, as many as possible of the following objectives should be pursued simultaneously, and treatment can be expected to continue for at least one week.*

- Diagnosis and consequent etiotropic treatment of all illness that contribute to the maintenance of ketosis (as retained placenta, endometritis, mastitis, abomasal displacement, disorders of the locomotor system, etc.); while on the other hand with a hopeless appearing "supporter" illness only the punctual termination of obviously ineffective unprofitable therapeutic treatment and advice to disposal remains.
- To promote the outsluicing of the triglycerides from the liver: administration of "lipotropic" substances, although the therapeutic use in cattle has yet to be proved (choline chloride: 25 g per animal b.i.d. orally or 25 g daily in a 10 percent solution s.c. for 3 or 4 days (32); "liver protection" preparations, such as Amynin® (IFFA-Mérieux) or Hepasteril® (Fresenius), in moderate doses, given slowly IV and not at the same time as other drugs [17,18]; B-complex vitamins) give no calcium preparations IV!
- To promote gluconeogenesis, and thus the decrease of the triglyceride deposit in the liver:
  - stimulation of the appetite: offer palatable food (green fodder, especially good hay, dried beet leaves, etc.) 3 or 4 times a day, or pasture; discontinue ketogenic rations (such as silage containing butyric acid or concentrates with high fat content); application of appetite stimulating or "orexigenic" substances (these substances, however, are still in the trial stage); forced feeding (green alfalfa or alfalfa pellets in 10 to 20 liter electrolyte solutions administered with a stomach tube.
  - promotion of forestomach digestion: transfer of 5 to 10 liters of rumen fluid from clinically healthy donor animals receiving the same ration; administration of "rumen stimulators" per os or with a stomach tube; ashering to a ruminant-suitable feeding schedule (8).
  - oral doses of gluco-plastic substances (sodium propionate: 100 g. per animal twice a day, (if administered via the appetite; propylene glycol: 100 to 150 g. per animal twice a day; 1 to 2 kg steamed potatoes or dried chopped sugar beets, or 0.5 to 1.0 kg of molasses per day) or increasing the propionates in the rumen contents (monensin-sodium: 250 mg per animal per day added to concentrates).
  - parenteral doses of glucocorticoids (prednisilone: 100 to 150 mg; dexamethasone: 10 to 30 mg; flumethasone: 2 to 5 mg), but take care with a patient with a local or generalized infection (in these cases antibiotic protection is mandatory!)

** In contrast to the often obstinate course of secondary ketosis, which is bound to the underlying disease, primary ketosis may heal spontaneously within seven days in about 50% of the cases (28).*

Decrease of glycogen catabolism in the liver:

— raising the blood sugar: intravenous dextrose (150 to 200 g. per day of 5 to 10% solution; in stubborn cases it is better to use drip solutions of 10% glucose (up to 10 liters) in from two to three days (dissolving the dextrose in pyrogen free electrolyte solution; glucose solution prepared fresh daily to prevent fungal contamination!)
— promotion of glucogenesis: see above.
— promotion of glycogen formation: intramuscular dose of depoinsulin (see below)
— lowering of milk production: temporary (incomplete milking); parenteral application of glucocorticoids (see above) or depo-insulin (see below).

Applying the brakes to lipomobilization:

— lowering of milk production (see above)
— parenteral antilipolytic substances: 200 I.E. protamine zinc insulin suspension IM (4,5,25,30,37,47,53) usually in combination with glucocorticoids and dextrose (see above); 6 g. nicotinic acid twice a day for 5 to 7 days with the feed concentrate (15); 2 to 4 mg/kg body weight of dimethylisoxasole s.c. or 1 to 2 mg/kg body weight dimethylprazole (48).Promotion of ketone body—as well as the fatty acid oxidation in the muscle tissue: moderate exercise (1 hour per day); depo-insulin IM (see above).

Protection of the fatty degenerated muscle cells from autoperoxidative processes: parenteral doses of vitamin E and selenium. Experience teaches that the treatment of manifest lipomobilization syndrome is both costly and almost ineffective and that the economic impact of the disease is almost always significant. Therefore more effort than in the past should be directed toward the prevention of this disease complex.

Preventive Measures

To successfully prevent the lipomobilization syndrome one must consider the causes. Above all the first consideration is "restraint"; feeding during the dry period which brings about the deposit of excessive fat reserves should be avoided. The dry period should not be longer than 50 to 55 days. Therefore one should strive to attain a body weight during the dry period no more than 10% higher than that during highest lactation; at the calving period it should not be more than 20% of the above, and the condition score should never exceed 3 to 4 (c.f. Illus. 3). With the absence of abnormal fat deposits an overwhelming lipomobilization cannot occur, thus this objective (proper nourishment) has considerable significance. It is discussed in Prof. Dr. Scholz's (Hannover) contribution.

Further important prophylactic measures concern the prevention of all peripartal stresses that may have a detrimental effect on food intake and forestomach activity. This includes the creation of calmer and more hygienic calving conditions, the security of a normal parturition, the avoidance of sudden quali- or quantitative changes in feed or water supply as well as other stress situations (as changes in the number of animals per stall, changes in the division of the herd, fluctuating microclimate). To support a "healthy" metabolism—with "trained" gluconeogenesis and lipolysis—regular exercise for the high producing cow (1.5 km. per day) is recommended. It is also very useful to check the urine and milk of the freshly lactating cow for the presence of ketone bodies.

Finally it should be considered that the susceptibility to the lipomobilization syndrome under comparable conditions varies between individuals and is therefore possibly genetically determined. For this reason breeding stock should be recruited preferentially from those cows that are not affected by the disease despite equal ration, housing, and level of production (8,9,31).

With regard to the pathogenesis of the lipomobilization syndrome discussed above it appears impossible to the authors of this report, however, to effectively influence the accumulations of excessive bodily fat reserves, the occurrence, or the course of the disease complex through single or repeated pro-or meta- phylactic parenteral administration of drugs (stimulatory, assimilatory or tonic), the lipotropic or catabolic effect of which has not been sufficiently confirmed. These convictions are particularly true for herds or experimental set-ups, where the feeding of the dry cows, the "degree of fatty degeneration" at the time of calving, as well as the periparturient burden of the animals is not taken into consideration.

English translation by Mrs. Laverne Jones, Librarian, College of Veterinary Medicine, Oklahoma State University, Stillwater, OK 74078 and Dr. Franklyn Garry, Munich, W. Germany.