An alternative view on the hypocalcaemia of cows

St. George, T.D. and Murphy, G.M.

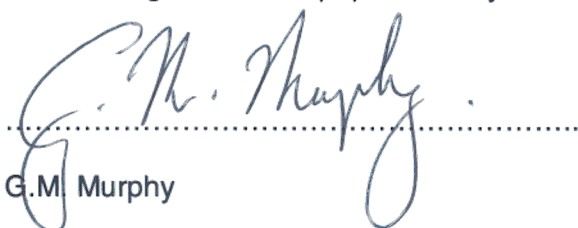Proceedings of The Australian Association of Cattle Veterinarians 2001

Pages 30-39

An invitation was received to present our research on milk fever at the Australian Veterinary Association's Animal Conference in Melbourne 14-18 May 2001   A Powerpoint presentation was developed using the multicolour graphs of the haematology and biochemistry developed for this thesis. It was only possible to publish black and white representations of these illustrations for the proceedings paper, which follows. The data used for the milk fever aspects was drawn from that used for paper 3.28. However, a small amount of additional data was used.

Date: 13/11/01

T.D. St. George

Dr St George wrote the paper with my assistance and technical input.

Date: 13/11/01

G.M Murphy

AN ALTERNATIVE VIEW ON THE HYPOCALCAEMIA OF COWS

TD St.George[1] and GM Murphy[2]

[1]15 Tamarix Street, Chapel Hill, QLD 4069,. [2]3 Cottonwood Crescent, Calamvale, QLD 4116

Abstract

Systemic inflammation induces a characteristic set of biochemical and haematological changes in blood, one of which is hypocalcaemia. Two major diseases of cows, ephemeral fever and milk fever, produce clinical signs which respond similarly to treatment with calcium borogluconate. Blood samples taken from cows hourly or 2 hourly during the febrile period of ephemeral fever and the periparturient period of multiparous cows showed almost the same spectrum of biochemical dyscrasias. Levels of calcium, iron, zinc and inorganic phosphate fell whereas copper and blood pH rose. Plasma glucose rose initially and then fell in a pattern characteristic of stress. In both syndromes there was a neutrophilia and oesinopaenia. In ephemeral fever, the lymphocyte count fell as in most viral infections, but rose near calving in milk fever. These results indicate that there is a common pattern of change which is concurrent with, and not consequential to, a fall in circulating calcium levels. The inflammatory indicators show smaller changes in milk fever than ephemeral fever. The fall in circulating calcium in multiparous cows prior to calving would reduce rumen function and therefore diminish calcium absorption before the precipitating effect of the post-parturient increase in lactation. The fall may also affect uterine muscle during parturition. In ephemeral fever, the clinical signs, including fever and hypocalemia, can be prevented by treatment with non-steroidal anti-inflammatory drugs. This possibility has not been tested in milk fever susceptible cows. We postulate that the cause of the preparturient inflammation that induces a variable hypocalcaemia in multiparous cows is repeated exposure to foetal proteins immediately before or during calving. This would account for the immunity of heifers to milk fever and the increasing risk with increasing parity.

Introduction

In the 1930's, the infusion of calcium salts into the bloodstream of dairy cows with milk fever progressively replaced udder inflation with iodine solutions, or water or air for the treatment of milk fever (1). The transition was prolonged as the older treatment, which reduced the demand for calcium during colostrum secretion, continued to be used for many years. Infused calcium provides a bridging bolus for the period where demand has exceeded input from the diet.

A new name, "post parturient hypocalcaemia", then focussed attention on the period when the clinical signs of hypocalcaemia, especially paresis, were most acute. This name is misleading as our results demonstrate. Various preventive programs have been evolved to reduce prevalence of milk fever or to supplement calcium borogluconate infusions for acute milk fever cases or longer term paralysis of those called "downers".

Clinical signs of hypocalcaemia are not confined to cows with milk fever but occur also in bovine ephemeral fever (mediated through a toxic effect of interleukins) (2). Clinical hypocalcaemia occurs in sheep with cutaneous myiasis (blowfly strike) (3) and in humans with toxic shock (4). However, in ruminants the effect of hypocalcaemia is magnified by the feed back effect of lower calcium levels on rumen motility reducing feed intake (5). In our paper the comparisons will be made between bovine ephemeral fever and milk fever.

Bovine Ephemeral Fever

Paresis is a major clinical sign in bovine ephemeral fever. The causative agent of the disease is an insect borne rhabdovirus. The disease is regularly seen in northern Australia but occasionally reaches the dairy areas of northern Victoria. The clinical signs related to suboptimal plasma calcium are muscle fasciculation, staggery gait, loss of swallowing and other reflexes, bloat and paresis. Paresis often resolves suddenly in the latter part of fever but loss of hindquarter function may persist for days, weeks or months. Milk production diminishes or ceases abruptly (6). Appetite ceases.

Ephemeral fever is a systemic inflammatory disease induced indirectly by the causative virus. Vascular permeability causes local oedema and joint swelling in addition to the hypocalcaemia signs. This is proven by response to anti-inflammatory drugs for prevention and treatment of clinical disease (2,7,8).

A spectrum of biochemistry and haematology has been built up on naturally acquired and experimental ephemeral fever (9,10,11,12,13).

Many cattle (>80) with experimental ephemeral fever were observed and sampled hourly or 2 hourly before and during fever. In one experiment, blood samples from eight steers (11) were collected via an indwelling jugular catheter discharging onto the backline to minimise disturbance (14). The pattern of change in one animal is illustrated in Figure 1.

Plasma calcium levels fell in all cases but were below 2 mM/L in four that had hypocalcaemia

signs. Iron and zinc levels fell. Plasma glucose rose initially to a peak of up to 5.1 mM/L then fell. Plasma phosphate fell as low as 0.97 mM/L. In addition, the blood ammonia level rose, as did the pH while the partial pressure of CO_2 fell especially in periods of rapid breathing during fever phases. Plasma fibrinogen levels doubled in the recovery phase. The haematological changes are very characteristic with a neutrophilia overshadowing a lymphopaenia and an oesinopaenia. A fall in lymphocyte numbers that is very characteristic of virus infections occurred. Non esterified fatty acid rose approximately ten-fold during fever [11]. In earlier experiments most enzyme systems assayed showed minor change [15]. Most of the biochemical changes illustrated occur in stress as well as in inflammation [16] (Table 1).

The clinical signs related to hypocalcaemia in ephemeral fever are reversible by calcium borogluconate as they are in milk fever. However, unless anti-inflammatory treatment is also given many relapse [9,17]. The hypocalcaemia is a secondary effect of an underlying inflammation and specific treatment with calcium borogluconate is recommended only as a supplement to treatment with anti-inflammatory drugs as a life saving measure.

Parturition and Milk Fever
The biochemical spectrum accompanying ephemeral fever was developed progressively over a decade. We reached the point where comparison with the biochemistry of milk fever was essential to discover what differences existed from those accompanying milk fever. Very little data was found for normal calving or milk fever [18,19,20]. A comprehensive panel of biochemistry and haematology bracketing normal calving did not exist.

The first attempts were to carry out biochemical tests on the blood taken from milk fever cases before treatment and again 3 to 5 days later [21]. This showed clearly a wide range of calcium levels at the acute stage (0.4 to 2.1 mM/L). Zinc and iron levels were lower than normal. A relative neutrophilia occurred in all cases. Fibrinogen levels were elevated.

In an attempt to establish what pattern occurred in multiparous cows calving normally, blood analyses were carried out on samples taken daily during the period spanning calving for three cows in a dairy herd. The results showed disturbances in zinc, iron, copper as well as in calcium. Again, a relative neutrophilia was noted plus high fibrinogen (two to three times normal in the second sample). However, with once a day sampling the changes

could not be closely related to calving. A heifer sampled in the same herd did not show disturbances in haematology at calving.

A third group of four cows (3rd to 10th calvers) were placed in stalls and were fitted with catheters and allowed to settle down. Feed consumption was monitored daily. An intensive period of blood sampling was started when calving appeared imminent. Three cows did not develop milk fever (Figures 2,3,4). One cow developed characteristic paresis 9 h after calving (Figure 5). The cow with milk fever responded to calcium borogluconate treatment. The general observations [21] on the four cows can be summarised:

- rumination ceased for 2 to 5 h before calving.
- all cows lost some appetite in the 24 h prior to calving but ate avidly within 24 h post calving. The cow with milk fever did not eat until after treatment (Figure 6).
- plasma calcium levels began to fall 1 to 3 days before calving to reach plasma Ca $\leq$ 2.0 mM/L, within the wide range where clinical milk fever can occur.
- plasma fibrinogen levels rose, zinc and inorganic phosphate levels fell.
- plasma glucose rose to a peak at parturition then fell rapidly to below normal.
- plasma iron showed a variable response.
- plasma pH rose.

Neutrophil numbers peaked close to the peak of rectal temperatures. Lymphocyte numbers also rose. Eosinophils disappeared for a 24 h period spanning the calving process.

Taken together, the spectrum of biochemical change that occurred in the group of four multiparous cows in the periparturient period was similar to that found in ephemeral fever with a calcium demand (Figure 1). Neutrophilia and oesinopaenia were similar but lymphocyte numbers rose instead of falling as they do in ephemeral fever. Peaks in body temperature were not as high. The changes from normal occurred earlier in the cow with milk fever and for a more protracted period than in those without milk fever. The variable rectal temperature in milk fever reported by Fenwick [22] during clinical milk fever would depend on when it was measured in relation to the peak above normal.

Implications for Milk Fever
In the periparturient period in multiparous cows:
- there is a wide range of biochemical dyscrasias in multiparous cows in the periparturient period that are concurrent with, not consequential to, a fall in plasma calcium (Table 1).

Table 1 Comparison BEF/milk fever.

	BEF	Milk Fever
Acute paresis responsive to CBG		
Chronic paresis unresponsive to CBG	+	+
Rumen motility	↓	↓
Body temperature	↑↑	↑↓
Neutrophils	↑↑↑	↑↑
Lymphocytes	↓	↑
Oesinophils	↓	↓
Plasma		
Iron	↓	↓
Zinc	↓	↓
Copper	↑	↑
Calcium	↓	↓↓
Phosphate	↓	↓
Glucose	↑↓	↑↓
Fibrinogen	↑	↑
Ammonia	↑	↑
pH	↑↑	↑

- the overall picture near calving is characteristic of a systemic inflammation which is more severe in the cow which developed milk fever.
- periods of mild fever preceded parturition.
- treatment with calcium borogluconate changed only two of the biochemical abnormalities. Overall biochemical normality is therefore not achieved by this treatment.
- a neutrophilia and oesinopaenia occurred consistent with the biochemistry characteristic of inflammation.
- blood pH does not rise as high or for as long as in ephemeral fever with short periods of overbreathing (Figures 7,8).
- a lymphocyte response indicated antigenic stimulus close to calving.
- the clinical picture of milk fever seen by clinicians is only a small part of the syndrome.
- it is possible that the reason that heifers do not experience milk fever or lose appetite (23) is that they have not been sensitised by exposure to foetal proteins during earlier calvings.
- non-steroidal anti-inflammatory drugs should be tried experimentally in prevention and treatment.

"Downers"

Nerve conduction, causing loss of hindquarter control, can fail due to a lower plasma calcium level, as discussed ,or due to physical interruption at any point in the spinal cord up to the brain. The spinal cords of a few downers have been examined in ephemeral fever. In brief, areas of demyelination were found in the cervical spinal cord (C1 to C3) (24, TD StGeorge, GM Murphy and MWH Hill unpublished data). An interesting point about the unpublished case was that the steer had relatively small falls in plasma calcium (0.3 mM/L) and, when it was killed *in extremis* 3 days after fever had terminated, plasma calcium values were normal. Only one publication recording demyelination in the spinal cord in a milk fever case has been found (25). Two separate causes could also operate in milk fever as spinal cords are seldom examined in chronic milk fever paresis.

Conclusions

Once the value of calcium gluconate treatment for milk fever was established in the 1930s (26) an assumption was made that a fall in plasma calcium was the prime lesion. Our contention is that inflammation can play a role in the initiation of a secondary hypocalcaemia and other biochemical dyscrasias associated with parturition as well as impending lactation. This contention does not invalidate the regimes that have evolved to diminish the prevalence of milk fever (1).

There is much to be done to extend the range of blood parameters measured in the periparturient period. The cows, whose biochemistry and haematology is illustrated here, were multiparous. The close observations should be repeated on first calf heifers which are reputed not to suffer from milk fever.

Paresis has two separate causes in ephemeral fever, one biochemical (hypocalcaemia) and one due to neural changes. "Downer" cows might also not be a direct consequence of low plasma calcium but concurrent loss of myelin.

References

1 Hibbs JW (1950) Milk fever (parturient paresis) in dairy cows - a review. *J Dairy Sci* 33:758-789.

2. StGeorge TD, Uren MF and Zakrzewski H (1986) The pathogenesis and treatment of bovine ephemeral fever. Arbovirus Research in Australia, Proceedings Fourth Symposium May 6-9, 1986, CSIRO/QIMR, Brisbane, Australia. (StGeorge, T.D., Kay, B.H., and Blok, J., Eds) pp.303-307.

3 Murphy GM, StGeorge TD, Guerrini V, Collins RG, Uren MF and Doolan DL (1987) Trace elements and macro electrolyte behaviour during inflammatory diseases in cattle and sheep. Proceedings 6th International symposium on Trace Elements, Asilomar, Monterey, California.

4 Chesney RW, McCarron DM, Haddad JG et al (1983) Pathogenic mechanisms of the hypocalcaemia of the staphlococcal toxic-shock syndrome. *J Lab Clin Med* 101:576-585.

5 Ramberg CF, Johnson EK, Fargo RD, Kronfeld DS (1984) Calcium homeostasis in cows, with special reference to parturient hypocalcaemia. *Am J Physiol* R698-R704.

6 Davis SS, Gibson DS and Clark R (1984) The effect of bovine ephemeral fever on milk production. *Aust Vet J* 61:128-129.

7 Uren MF, StGeorge TD and Zakrzewski H (1989) The effect of anti-inflammatory agents on the clinical expression of bovine ephemeral fever. *Vet Microbiol* 19:99-111.

8 Fenwick DC and Daniel RCW (1996) Evaluation of the effect of ketoprotein on experimentally induced ephemeral fever in dairy heifers. *Aust Vet J* 74:37-41.

9 StGeorge TD, Cybinski DH, Murphy GM and Dimmock CK (1984) Serological and biochemical factors in bovine ephemeral fever. *Aust J Biol Sci* 37:341-349.

10 Uren MF and Murphy GM (1985) Studies on the pathogenesis of bovine ephemeral fever in sentinel cattle. II. Haematological and biochemical data. *Vet Microbiol* 10:505-515.

11 Uren MF, StGeorge TD and Murphy GM (1992) Studies on the pathogenesis of bovine ephemeral fever in experimental cattle. III. Virological and biochemical data. *Vet Microbiol* 30:297-307.

12 Murphy GM, StGeorge TD, Uren MF and Collins RG (1986) The biochemistry of ephemeral fever in cattle. Proceedings Fourth Symposium Arbovirus Research in Australia, May 6-9, 1986 (StGeorge TD, Kay BH and Blok J Eds) pp.307-313.

13 Murphy GM, StGeorge TD and Uren MF (1989) Ephemeral fever - a biochemical model for inflammatory disease in cattle and sheep. Proceedings Fifth Symposium Arbovirus Research in Australia, 28 August - 1 September 1989. (Uren MF, Blok J and Manderson LH, Eds) pp.268-274.

14 Takken A (1984) A long-term venous catheter for cattle. *Proc Aus Soc Anim Prod* 15:756-759.

15 Uren MF (1983) The study of some haematological and biochemical parameters of bovine ephemeral fever. Master of Veterinary Science Thesis, University of Queensland, Brisbane.

16 Van Miert ASJPAM (1985) Fever and associated clinical haematologic and blood biochemical changes in the goat and other animal species. *Vet Q* 7:200-216.

17 StGeorge TD (1997) Effective treatment of bovine ephemeral fever. *Aust Vet J* 75:221-222.

18 Marr A, Moodie EW and Robertson A (1955) Some biochemical and clinical aspects of milk fever. *J Comp Path* 65:347-365.

19 Guidry AJ, Paape MJ and Pearson RE (1976) Effects of parturition and lactation on blood and milk cell concentrations, corticosteroids and neutrophile phagocytosis in the cow. *Am J Vet Research* 37:1195-1200.

20 Dufty JH, Bingely JB and Cove LY (1977) The plasma zinc concentrations of non-pregnant and parturient Hereford cattle. *Aust Vet J* 53:519-522.

21 StGeorge TD, Murphy GM, Burren B and Uren MF (1995) Studies on the pathogenesis of bovine ephemeral fever. IV: A comparison with the inflammatory events in milk fever of cattle. *Vet Microbiol* 46:131-142.

22 Fenwick DC (1969) Parturient paresis (milk fever) of cows. 4. Rectal temperature. *Aust Vet J* 45:123-126.

23 Moodie EW and Robertson A (1961) Dietary intake of the parturient cow. *Res. Vet.Sci* 2:217-226.

24 Hill MWH and Schultz K (1977) Ataxia and paralysis associated with bovine ephemeral fever. *Aust Vet J* 53:217-221.

25 Unger M (1964) Microscopic findings in the spinal cord in bovine postparturient paresis. *Vet Med* 59:484-489.

26 Greig JR (1930) Calcium gluconate as a specific in milk fever. *Vet Rec* 10:115-120.
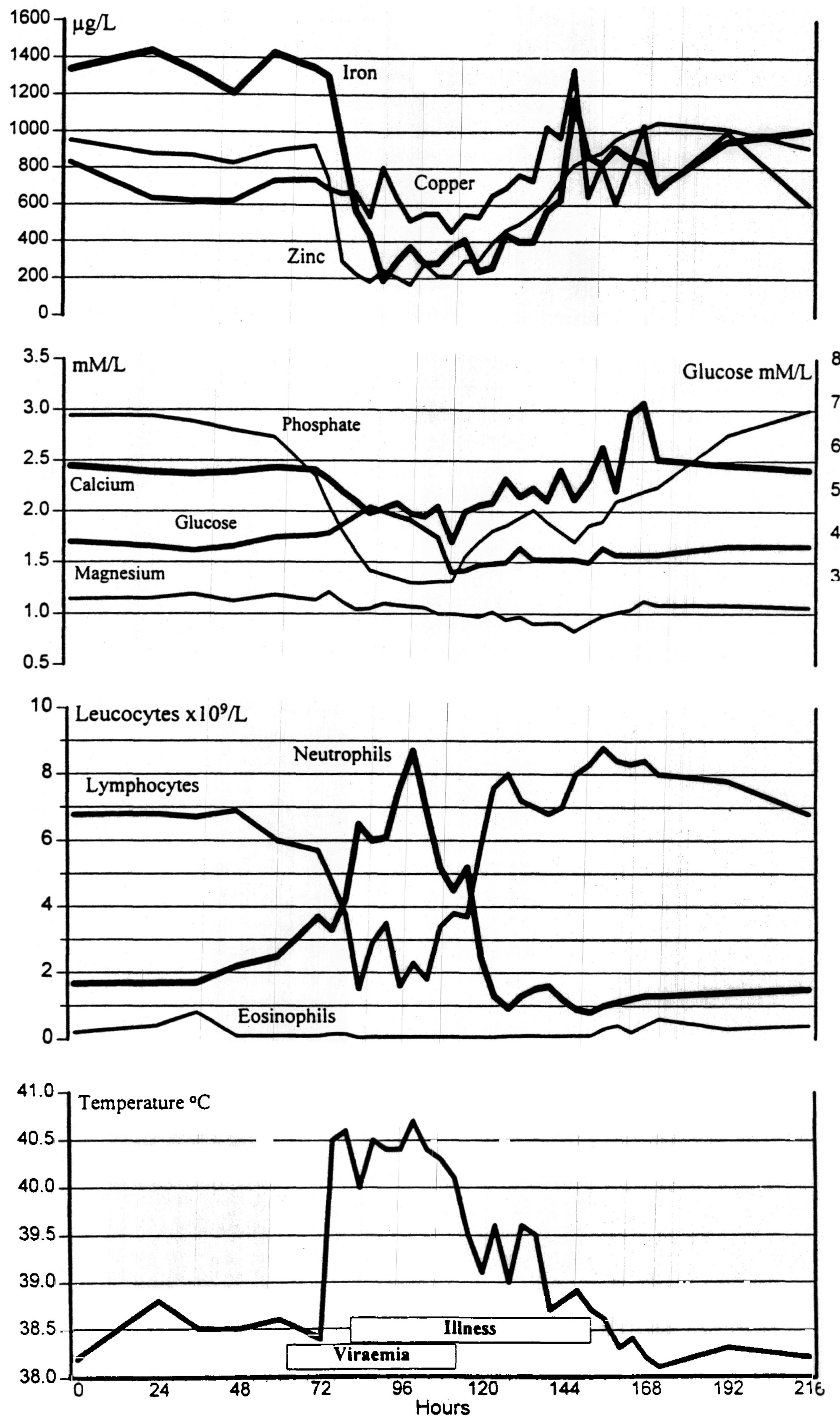
Bovine Ephemeral Fever

FIGURE 1. Haematological and biochemical dyscrasias related to fever and clinical disease in a steer with bovine ephemeral fever.
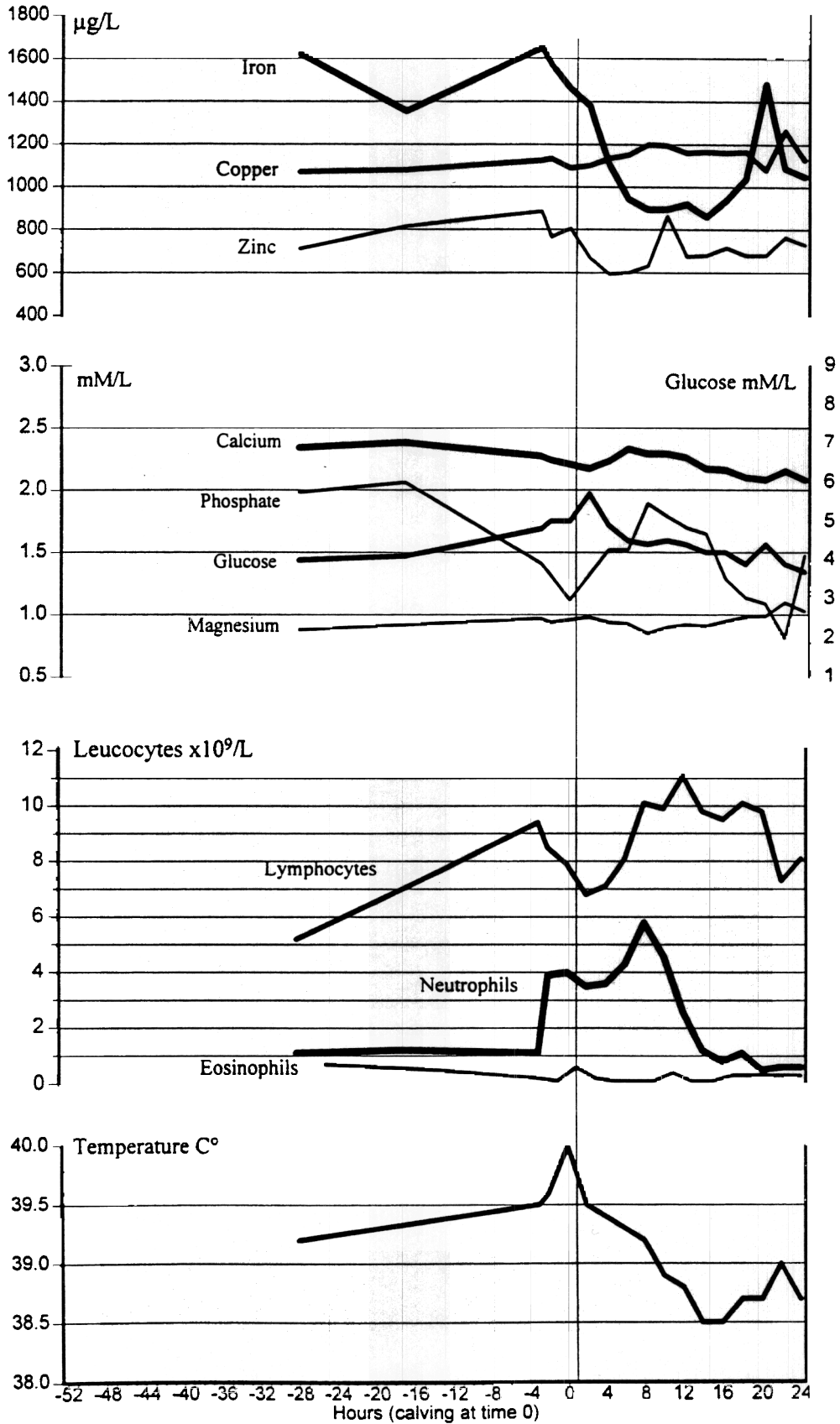
Calving cow

FIGURE 2. Haematological and biochemical changes in a cow having its 3rd calf.
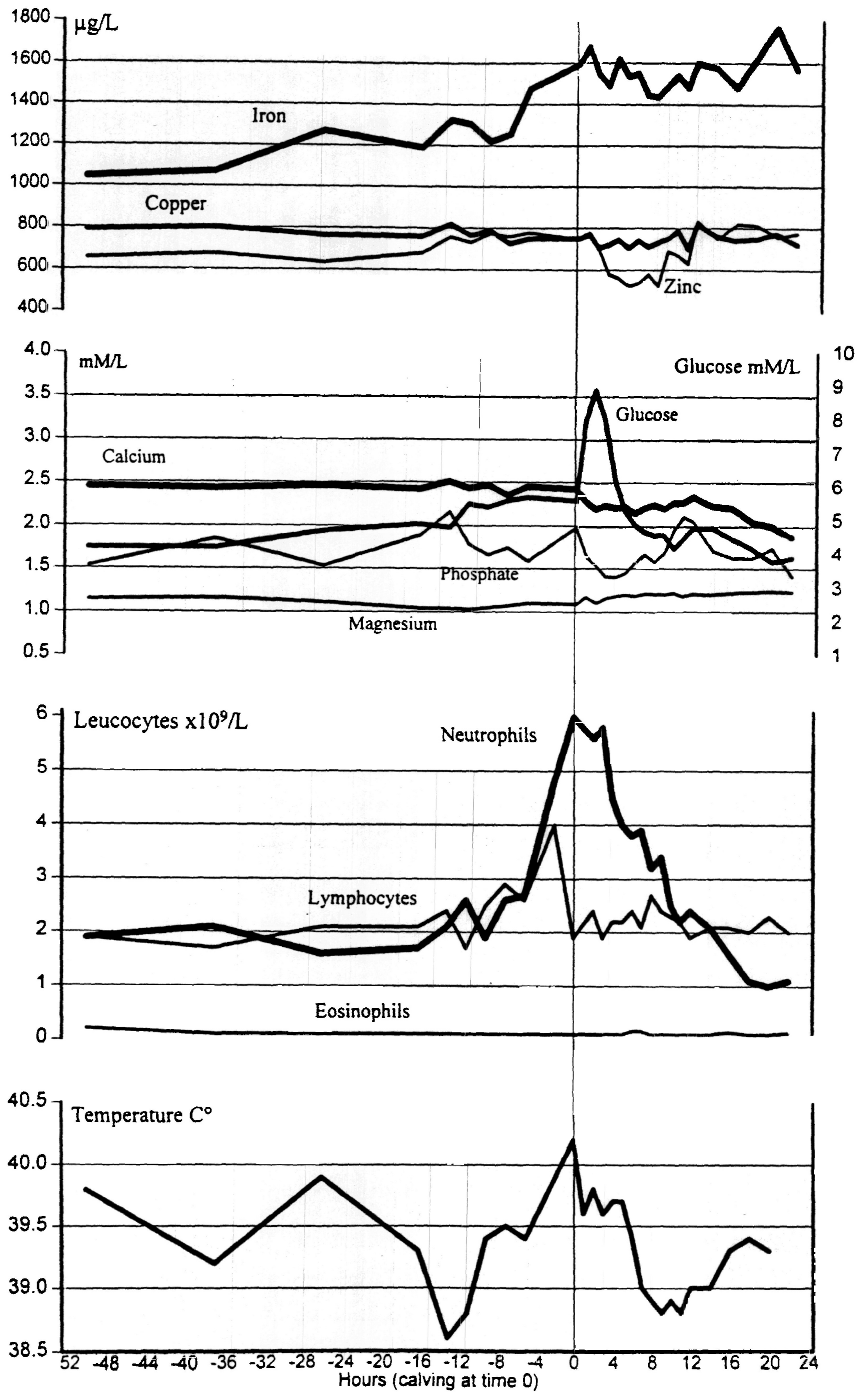
Calving cow

FIGURE 3. Haematological and biochemical changes in a cow having its 8th calf.
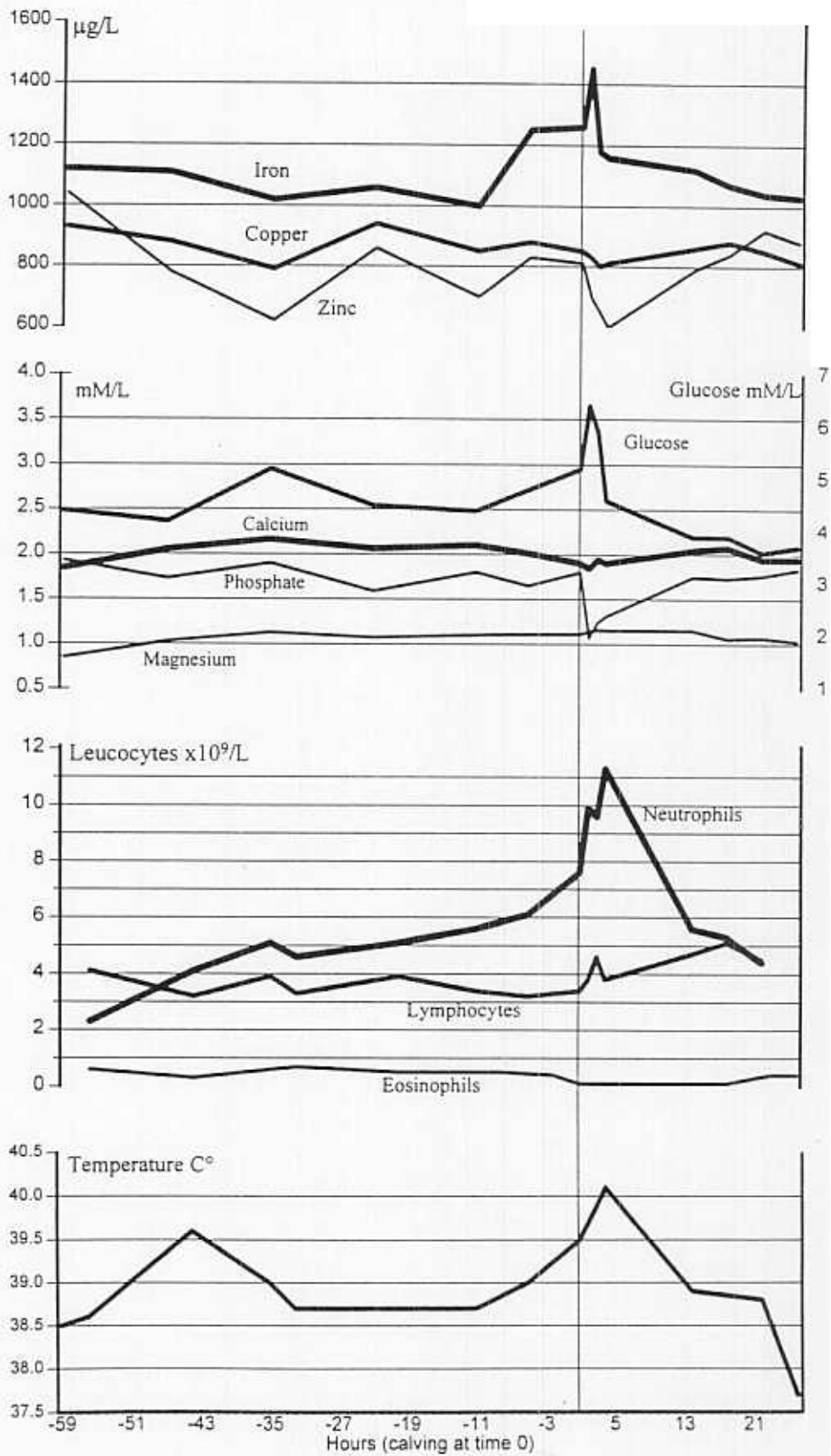
Calving Cow

FIGURE 4 Haematological and biochemical changes in a cow having its 10th calf.
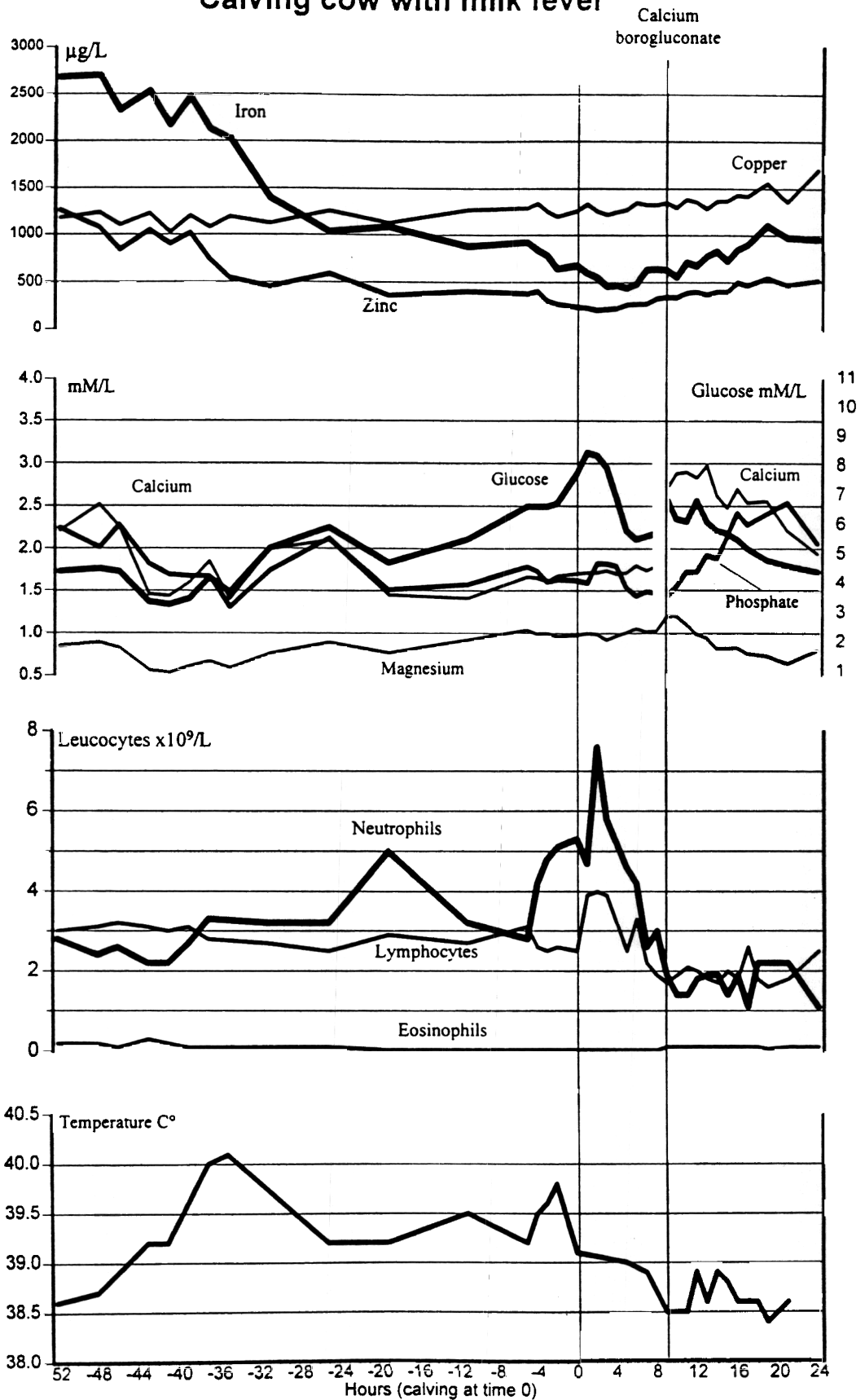
Calving cow with milk fever

FIGURE 5. Haematological and biochemical changes in a cow having its 3rd calf and affected by milk fever treated with calcium borogluconate nine hours after calving
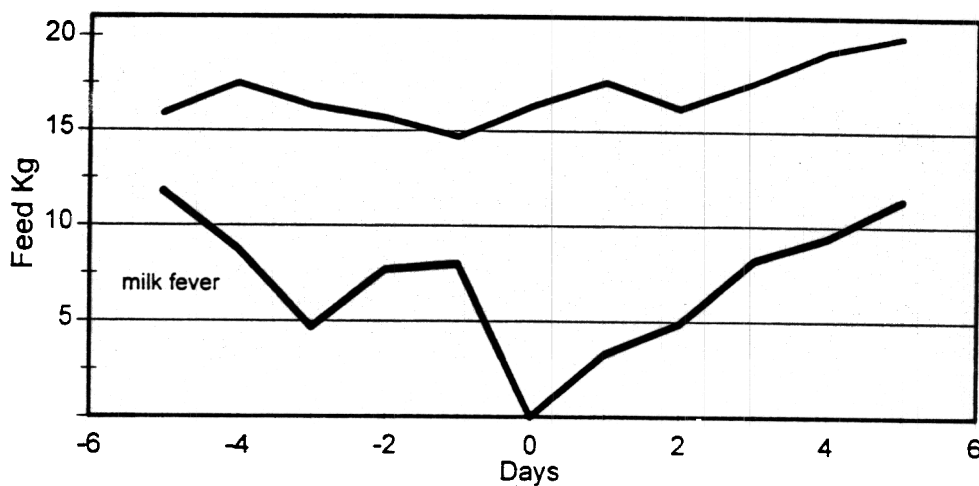
Feed consumption before & after calving

Figure 6. Daily feed consumption in a multiparous cow that developed milk fever compared with one that did not.
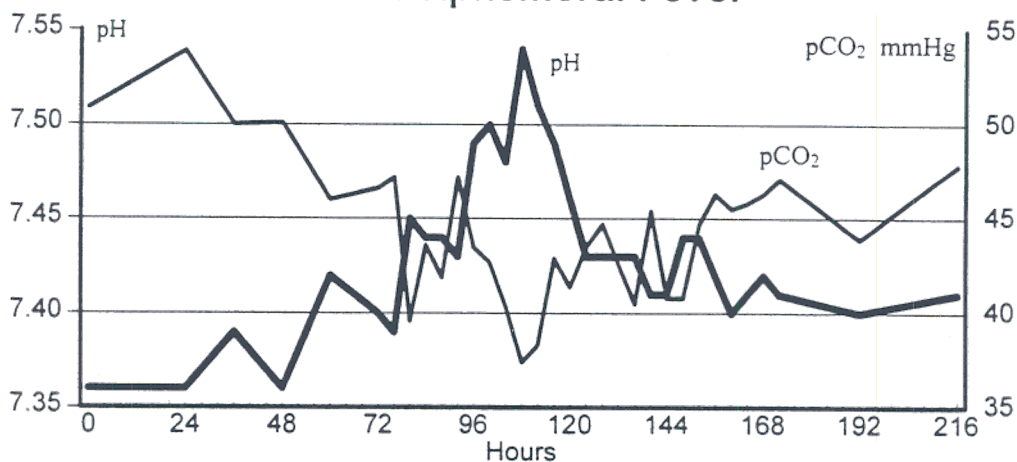
Bovine Ephemeral Fever

Figure 7. Partial pressure of carbon dioxide in blood and effect on pH in an ephemeral fever
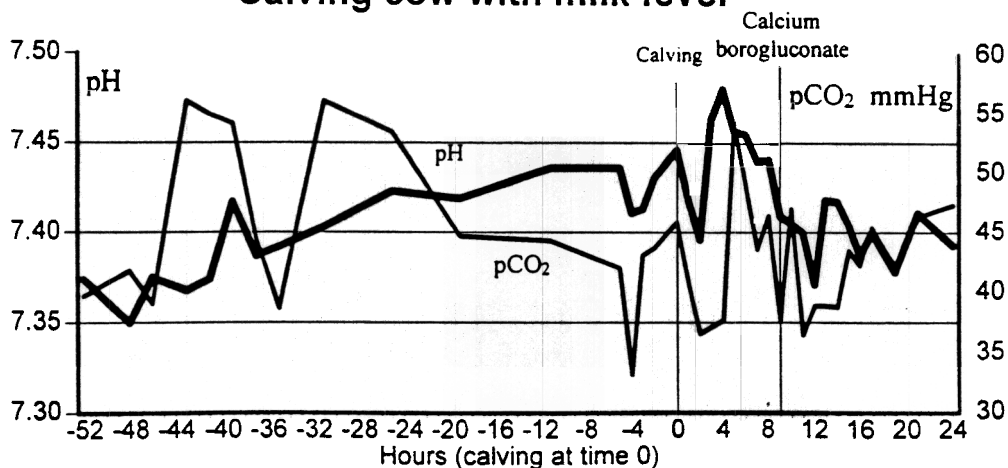
Calving cow with milk fever

Figure 8. Partial pressure of carbon dioxide in blood and effect on pH in a milk fever case.