

## Why is it getting more difficult to successfully artificially inseminate dairy cows?\*

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*Successfully using artificial insemination (AI) is defined as getting cows pregnant when the farmer wants them in-calf and making the best use of appropriate genetic potential. Over the past 30 to 50 years, the percentage of animals in oestrus that stand-to-be-mounted (STBM) has declined from 80% to 50%, and the duration of STBM from 15 h to 5 h; both in parallel with a reduction in first-service-pregnancy-rate from 70% to 40%. Meanwhile, the incidence of lameness and mastitis has not decreased; and it takes more than an extra 40 and 18 days, respectively, to get a lame or mastitic cow in-calf compared to healthy herd-mates. The intensity of oestrus is 50% lower in severely lame cows, and fewer lame cows ovulate. Luteal phase milk progesterone concentrations are also 50% lower in lame cows, and follicular phase oestradiol is also lower in non-ovulating lame cows compared to ovulating animals. Furthermore, lame cows that do not ovulate do not have an LH surge, and the LH pulse frequency in their late follicular phase is lower (0.53 v. 0.76 pulses/h). Thus, we suggest that the stress of lameness reduces LH pulsatility required to drive oestradiol production by the dominant follicle. The consequent low oestradiol results in less-intense oestrus behaviour and failure to initiate an LH surge; hence there is no ovulation. A series of experimental studies substantiate our hypothesis that events activating the hypothalamus–pituitary–adrenal axis interfere at both the hypothalamus and the pituitary level to disrupt LH and oestradiol secretion, and thus the expression of oestrus behaviour. Our inability to keep stress at a minimum by appropriately feeding and housing high-production cows is leading to a failure to meet genetic potential for yield and fertility. We must provide realistic solutions soon, if we want to successfully use AI to maintain a sustainable dairy industry for the future.*

**Keywords:** oestrus, oestradiol, progesterone, LH, stress, lameness, mastitis

### Background

The keyword in the title is 'successfully' – partially defined as getting cows pregnant when the farmer wants them pregnant, i.e. voluntarily, not because he could not get them pregnant at any other time. The other part of the definition refers to the appropriate use of genetic potential. A bull can successfully inseminate cows but there are few on-farm bulls available with the desired genes, and many adult bulls can be dangerous when running with a herd. Some farmers use a hand-mating bull system by which cows are selected by the herdsman to be introduced into the bull pen but this entails the many disadvantages involved in oestrus detection by humans.

There is substantial evidence that fertility of the modern dairy cow is getting lower with increasing milk yields (Royal

*et al.*, 2000; Butler, 2003). Along with this documented decline, the literature over the recent past reveals a parallel decrease in the percentage of cows standing-to-be-mounted (STBM; Figure 1; Hall *et al.*, 1959; Williamson *et al.*, 1972; Esslemont and Bryant, 1976; Glencross *et al.*, 1981; Fonseca *et al.*, 1983; Stevenson *et al.*, 1983; Hackett and McAllister, 1984; Britt *et al.*, 1986; Pennington *et al.*, 1986; Van Vliet and Van Eerdenburg, 1996; LeBlanc *et al.*, 1998; Lyimo *et al.*, 2000; Van Eerdenburg *et al.*, 2002; Roelofs *et al.*, 2004 and 2005a; Walker *et al.*, 2008).

Thus, in research studies, although the duration of total primary and secondary signs of oestrus has not changed significantly over the past 30 to 50 years, the percentage of animals STBM (Figure 1) and the duration of STBM have both declined (Table 1). Furthermore, there is evidence that high milk production increases the number of silent heats (averages of 0.7 v. 1.6 silent heats for 28 and 36 kg/day, respectively; Harrison *et al.*, 1990). So, in practical terms, it is not surprising that fewer herdsmen are seeing cows in oestrus. These observations have, of course, been associated

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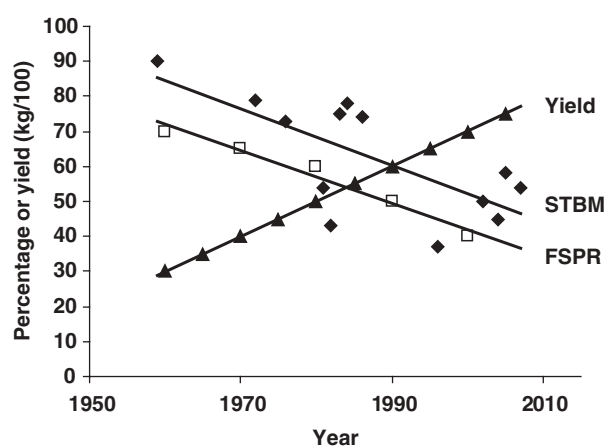
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with a marked decline in first-service-pregnancy-rate (FSPR; Figure 1). Coupled with the decline in farm labour on dairy units, it is no wonder that it is getting more difficult to successfully artificially inseminate (AI) dairy cows to get them pregnant when required.

### Factors predisposing to lower fertility and disrupted oestrus

There are several (clinical) 'production diseases' associated with lower fertility. We know that low BCS in the early *post partum* period results in >10 extra days to establish a pregnancy (Lopez-Gatius *et al.*, 2003; Garnsworthy, 2006), whereas cows that have had hypocalcaemia take 13 days longer to get pregnant (Parker, 1992). The calving-to-pregnancy



**Figure 1** Percentage of animals standing-to-be-mounted (STBM; ◆), first-service-pregnancy-rate (FSPR; □) and average milk yield (▲) in Holstein Friesian dairy cows reported over the last 50 years (references in text).

interval is at least 18, 25 and 31 days longer in cows treated for mastitis, retained foetal membranes or endometritis, respectively, compared to healthy herd-mates (Borsberry and Dobson, 1989; Schrick *et al.*, 2001). Lame cows are even less fertile, as it takes them up to an extra 40 days to get pregnant even after treatment (Collick *et al.*, 1989; Melendez *et al.*, 2003; Hernandez *et al.*, 2005; Figure 2). Reviewing studies of milk progesterone profiles, but without detailed acknowledgement of production diseases, the percentage of atypical profiles tends to increase with time ( $P = 0.08$ ), and also possibly the percentage of cows with delayed onset of luteal activity or with prolonged luteal phases (Figure 3; the observations are too few for rigorous statistical analysis; Bulman and Wood, 1980; Etherington *et al.*, 1991; Opsomer *et al.*, 1998; Royal *et al.*, 2000; Veerkamp *et al.*, 2000; Fulkerson *et al.*, 2001; Horan *et al.*, 2005; Shrestha *et al.*, 2005; McCoy *et al.*, 2006; Petersson *et al.*, 2006a; Patton *et al.*, 2007). A delay in the resumption of ovarian cyclicity after calving certainly contributes to the increased calving–pregnancy interval in diseased animals, for example, an extra 7 days in cows with mastitis and 17 days for lame cows (Huszenicza *et al.*, 2005; Petersson *et al.*, 2006b). However, this does not account for all the delay in getting mastitic or lame cows pregnant again. Once ovarian cyclicity has resumed, the ability to express oestrus is also important.

### Oestrus, follicles and hormones in diseased cows

In view of our early observations that lame cows are less fertile than clinically 'normal' cows, we have been assessing the effects of this particular production disease on oestrous behaviour. Increasing severities of lameness (defined in

**Table 1** Summary of the literature regarding the first and last sign (duration) of behavioural oestrus, or stood-to-be-mounted (STBM) event, within one oestrus period

Reference	Method	Mean (h)	Range (h)
Wishart, 1972	Visual	14.7 ± 1.6	10 to 18
Hurnik <i>et al.</i> , 1975	Visual (24 h/day)	7.5 to 10.1	
Esslemont and Bryant, 1976	Visual (24 h/day)	14.9 ± 4.7 (s.d.)	
Britt <i>et al.</i> , 1986	Visual (8 h intervals)	13.8 ± 0.6 (s.e.)	
Coe and Allrich, 1989	Visual (24 h/day)	14.9 ± 0.7 (s.e.)	2 to 27
Lyimo <i>et al.</i> , 2000	Visual (30 min every 3 h)	20.3 ± 10.4 (s.d.)	6 to 33
Stevenson <i>et al.</i> , 1996	HeatWatch	14 ± 0.8 (s.e.)	2.5 to 26
Walker <i>et al.</i> , 1996	HeatWatch	9.5 ± 6.9 (s.d.)	
Dransfield <i>et al.</i> , 1998	HeatWatch	7.1 ± 5.4 (s.d.)	0.5 to 36
Xu <i>et al.</i> , 1998	HeatWatch	8.6 ± 0.46 (s.e.)	1 to 21
At-Taras and Spahr, 2001	HeatWatch	5.83 ± 0.78 (s.e.)	
Lopez <i>et al.</i> , 2002	HeatWatch	3.6 ± 0.8	0.2 to 12
Cavaliere <i>et al.</i> , 2003	HeatWatch	10.9	10 to 12
	Visual (30 min every 3 h)	14.4	13 to 16
Roelofs <i>et al.</i> , 2005b	Visual (30 min every 3 h)	11.8 ± 4.4 (s.e.)	
	STBM only	5.0 ± 3.0 (s.e.)	
Roelofs <i>et al.</i> , 2005a	Pedometers	10.0 ± 4.2	
Walker <i>et al.</i> , 2008	Visual (30 min every 3 h)	15.2 ± 1.3 (s.e.)	3 to 24
	STBM only	10.0 ± 1.1 (s.e.)	3 to 18

HeatWatch refers to an electronic pressure recording device placed on the sacrolumbar region of cows to record STBM.

Table 2) have no impact on the incidence of oestrus once ovarian cyclicity has been spontaneously resumed (oestrus observed per period of low progesterone: 20/32, 11/18, 12/17 for not lame, moderately lame and severely lame cows, respectively; Walker *et al.*, 2008). However, the intensity of oestrus was lower in severely lame cows using a weighted scoring system to quantify the intensity of all signs (Van Eerdenburg *et al.*, 2002; scoring system summarised in Table 3; normal  $n = 18$ :  $583.1 \pm 64.9$  points; moderately lame  $n = 9$ :  $657.8 \pm 96.8$  points; severely lame  $n = 9$ :  $284.4 \pm 42.7$ ;  $P < 0.05$ ).

This prompted a more careful evaluation of oestrus behaviour by looking at the frequency of each component

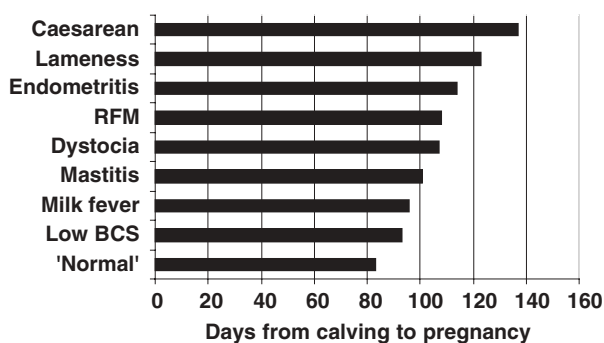


Figure 2 Days from calving to pregnancy in cows with different clinical production diseases (RFM retained foetal membranes; BCS body condition score; references in text).

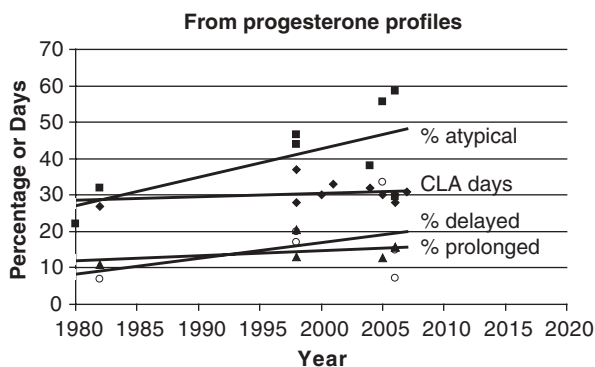


Figure 3 Days from calving to commencement of luteal activity (CLA; ◆), and percentage of atypical profiles (■), of delayed onset of luteal activity (▲) and prolonged luteal phases (○) reported from milk progesterone studies over the past 30 years (references in text).

Table 2 Lameness scoring scale<sup>a</sup>

Lameness score	Description	While standing	While walking	Gait
1	Non-lame	Level back posture	Level back posture	Normal
2	Moderately lame	Level back posture	Arched back	Normal to short striding
3	Severely lame	Arched posture	Arched back	Takes one step at a time; reluctant to bear weight on one or more limbs/feet

<sup>a</sup>Modified after a previously described 5-point scale (Sprecher *et al.*, 1997) in which the above scores of 1, 2 and 3 are comparable to the scores of 1, 2 and  $\geq 3$  on the Sprecher 5-point scale, respectively.

of behaviour in groups of eight to 12 cows that had been synchronized with GnRH, followed 7 days later with prostaglandin (GnRH + PG; to increase the number of cows simultaneously in oestrus; adapted from Pursley *et al.*, 1995). Table 4 shows that lame cows (score 1 v. 2 + 3) had a less-intense oestrus than non-lame cows (fewer total points), because the frequencies and duration of certain behaviours were lower in lame cows. Mounting the rear of another cow is an appetitive (courtship) behaviour and chin-resting plus being-mounted-but-not-standing can be construed as 'testing' behaviours to determine if cows will STBM. Daily milk progesterone concentrations 4 to 9 days before these oestrus observations were lower in lame cows but surprisingly oestradiol values in the same daily milk samples were not different between lameness groups (Walker *et al.*, 2008). It is well known that prior progesterone exposure in ruminants has a marked effect on the intensity of oestrous behaviour (Fabre-Nys and Martin, 1991).

In a subsequent study of ovarian follicular growth and ovulation after GnRH + PG synchronisation, we have recently established that fewer lame cows ovulate compared to non-lame animals (26/37 v. 17/18), although dominant follicles grow to a similar size (15 to 20 mm pre-ovulation). Milk progesterone profiles prior to the follicular phase were lower in lame cows, thus confirming our earlier observations, and oestradiol concentrations in plasma samples every 4 h were lower in non-ovulating lame cows compared to ovulating non-lame cows. In addition, all the lame cows that did not ovulate did not have a surge of luteinising hormone (LH; analysed in 2-hourly blood samples) and the LH pulse frequency in the late follicular phase was lower in non-ovulating lame cows than in ovulating cows (0.53 v. 0.76 pulses/h;  $P = 0.012$ ). Thus, we suggest that the stress of lameness reduces LH pulsatility to drive oestradiol production by the dominant follicle; the consequent low oestradiol fails to initiate an LH surge and hence there is no oestrus behaviour and no ovulation.

During on-going studies, the ovaries of 52 cows treated by farmers for mastitis were scanned weekly by ultrasound and had dominant ovarian follicles on average 2 mm smaller than in paired healthy herd-mates (G Lloyd, personal communication). Furthermore, cows prone to mastitis, i.e. those with  $>100\,000$  somatic cells per ml milk (SCC), appeared to ovulate after GnRH + PG 1 day later than herd-mates with  $<100\,000$  SCC ( $5.5 \pm 2.4$  v.  $4.6 \pm 2.2$  days,  $n = 16$  and 15, respectively; K Kaneko and S Uppal, personal communication).

## Experimental proof

All our studies on the stress of lameness and mastitis have been observational; is there any supporting evidence from experimental studies in cows? There is none regarding long-term chronic activation of the hypothalamus–pituitary–adrenal axis. However, short-term administration of the synthetic corticoid, betamethasone, from day 10 to 19 of the oestrous cycle prevents the normal increase in oestradiol at the end of the cycle, thus inhibiting luteolysis that results in prolonged luteal phases and a 10-day delay in the occurrence of oestrus (Kanchev *et al.*, 1976). In addition, road transport or betamethasone reduces the amount of LH released by exogenous GnRH; and road transport delays and attenuates the LH surge induced by exogenous oestradiol (Dobson, 1987; Dobson *et al.*, 1987; Nanda *et al.*, 1990). Furthermore, acute stimulation with adrenocorticotrophin hormone (ACTH) in the late follicular phase suppresses LH pulsatility, decreases oestradiol concentrations in peripheral plasma, eliminates the LH surge and results in very delayed or absent ovulation (Dobson *et al.*, 2000; Figures 4 and 5). All these studies substantiate our hypothesis that events activating the hypothalamus–pituitary–adrenal axis (i.e. stressful

situations such as lameness or mastitis) interfere at both the hypothalamus and the pituitary level to disrupt LH and oestradiol secretion, and thus the expression of oestrus behaviour.

## Solutions

Hence, there lies the problem; what can we do about it now? One solution may be to treat lame cows with progesterone prior to a chosen insemination period, but this is throwing drugs at the effect, rather than addressing the cause.

### Prevention of production diseases

Extracting a variety of estimates concerning the incidence of lameness and mastitis in dairy herds throughout the world, there does appear to be an increasing trend (although not statistically significant) in spite of many attempts at prevention (Figure 6; Bigras-Poulin *et al.*, 1990; Grohn *et al.*, 1990; Kaneene and Hurd, 1990; Tranter and Morris, 1991; Bartlett *et al.*, 1992; Lam *et al.*, 1993; Oltenacu and Ekesbo, 1994; Chamberlain and Wassell, 1995; Hemsworth *et al.*, 1995; Clarkson *et al.*, 1996; Esslemont and Kossabati, 1996; Etherington *et al.*, 1996; Enting *et al.*, 1997; Frei *et al.*, 1997; Judge *et al.*, 1997; Beckett *et al.*, 1998; Shpigel *et al.*, 1998; Duffield *et al.*, 1999; Loeffler *et al.*, 1999; Galindo *et al.*, 2000; Stevenson, 2000; Heuer *et al.*, 2001; Leonard *et al.*, 2001; Hultgren, 2002; Regula *et al.*, 2004; Haskell *et al.*, 2006). Within these studies, the average incidence  $\pm$  s.e. (and range) of lameness was  $15.2 \pm 2.2\%$  (2–54), and for mastitis  $27.4 \pm 2.2\%$  (6–48). Indeed, the overall incidence of clinical diseases recently reported for UK farms is alarming but it is clear that the 'best' 25% farmers are capable of reducing the impact (Table 5). No doubt preventative efforts are being made because these diseases are damaging both on welfare grounds and in financial terms; estimates per annum for the UK national herd are £160 million for lameness and £100 million for mastitis.

Prevention is better than cure, and one approach is to develop on-farm schemes to prevent production diseases.

**Table 3** Point scoring scale for behavioural signs of oestrus<sup>a</sup>

Oestrus signs	Points
Flehmen	3
Restlessness <sup>b</sup>	5
Sniffing the vulva of another cow	10
Mounted but did not stand	10
Resting chin on the back of another cow	15
Mounting the rear of another cow	35
Mounting the head of another cow	45
Stood-to-be-mounted (STBM)	100

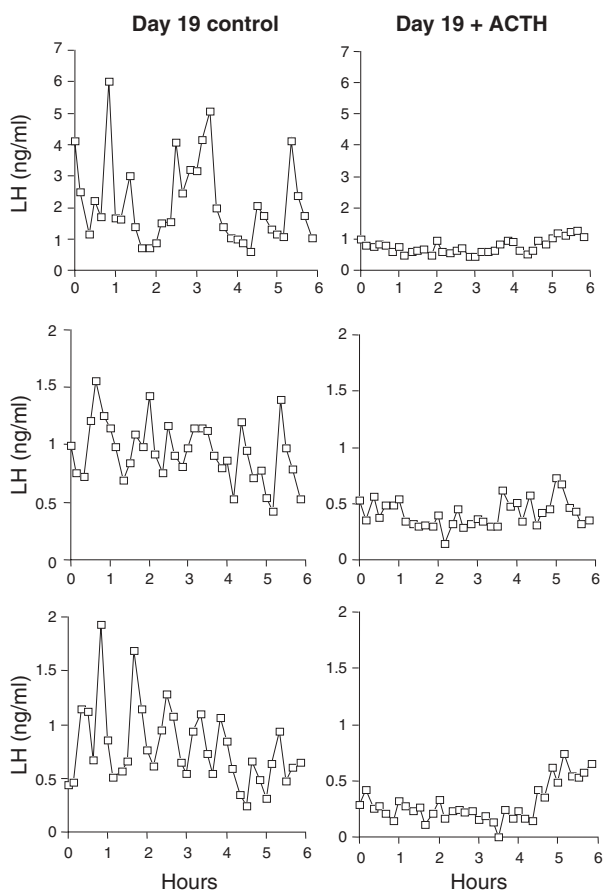
<sup>a</sup>Each time an oestrus sign was observed, the assigned number of points were recorded (Van Eerdenburg *et al.*, 2002).

<sup>b</sup>Can only be recorded once during a single 30-min observation period.

**Table 4** Mean  $\pm$  s.e. (range) of the total frequency and duration of behavioural signs of oestrus in non-lame and lame cows (Adapted from SL Walker, personal communication)

Oestrous signs		Total frequency	Duration (h)
Sniffing vulva	Non-lame	20.2 $\pm$ 3.1 (0 to 41)	13.2 $\pm$ 1.2 (0 to 18)
	Lame	21.9 $\pm$ 3.1 (1 to 49)	12.0 $\pm$ 1.2 (3 to 21)
Chin resting	Non-lame	<b>36.3 <math>\pm</math> 5.6</b> (16 to 78)	14.4 $\pm$ 1.3 (3 to 24)
	Lame	<b>*24.4 <math>\pm</math> 3.6</b> (0 to 59)	12.0 $\pm$ 1.3 (0 to 21)
Mounting rear of another cow	Non-lame	<b>14.1 <math>\pm</math> 3.4</b> (1 to 42)	11.4 $\pm$ 1.6 (3 to 24)
	Lame	<b>**6.1 <math>\pm</math> 1.1</b> (0 to 19)	9.3 $\pm$ 1.3 (0 to 18)
Mounted but did not stand	Non-lame	2.1 $\pm$ 0.7 (0 to 10)	<b>5.2 <math>\pm</math> 1.5</b> (0 to 15)
	Lame	0.9 $\pm$ 0.4 (0 to 7)	<b>**1.8 <math>\pm</math> 0.7</b> (0 to 12)
Stood-to-be-mounted (STBM)	Non-lame	9.3 $\pm$ 2.0 (2 to 26)	10.0 $\pm$ 1.2 (3 to 18)
	Lame	5.8 $\pm$ 1.4 (0 to 18)	6.8 $\pm$ 1.3 (0 to 15)
Total intensity points	Non-lame	<b>2200 <math>\pm</math> 300</b>	
	Lame	<b>**1400 <math>\pm</math> 200</b>	

Lower values in lame cows ( $n = 18$ ) compared to non-lame ( $n = 15$ ) are shown in bold (\* $P < 0.10$ , \*\* $P < 0.05$ ).



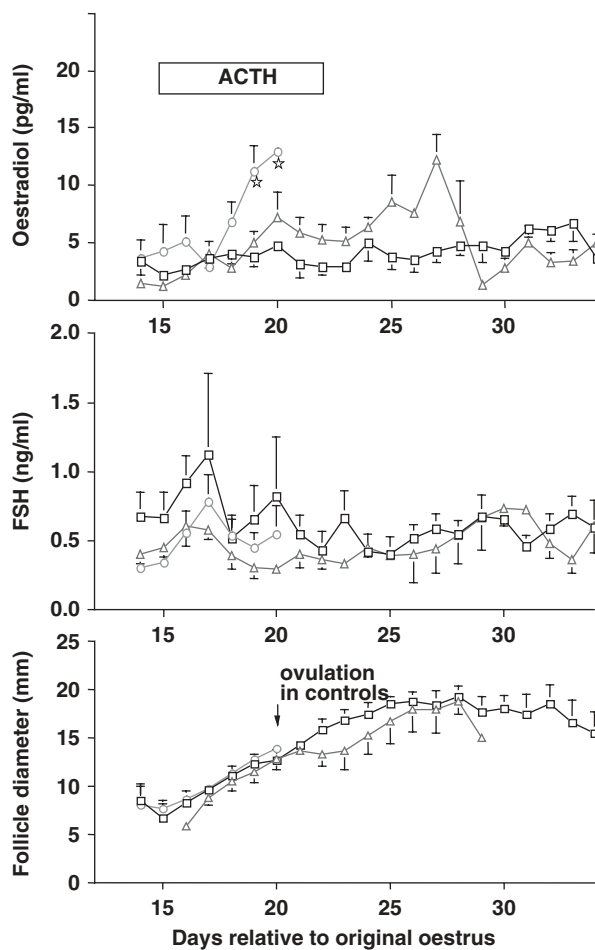
**Figure 4** Peripheral plasma concentrations of LH in three control heifers on day 19 of the oestrous cycle (a) and in three heifers on day 19 during treatment with 100 IU ACTH every 12 h for 7 days from day 15 of the oestrous cycle (b). Dobson *et al.*, 2000: reproduced with permission.

These schemes certainly have a positive short-term impact to lower the incidence (Kingwill *et al.*, 1970; Green *et al.*, 2007), but effects on fertility have not been reported.

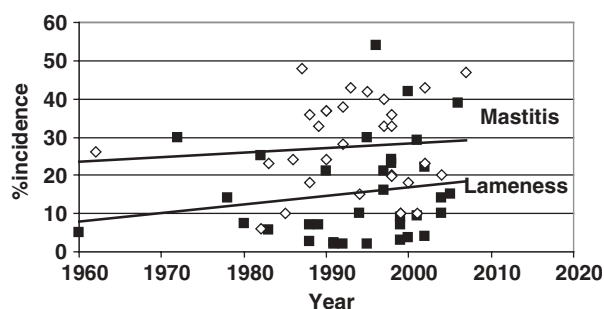
As far as preventing the losses associated with heat detection is concerned, again all farmers and vets have sufficient information available now to make improvements but despite demonstrable technical efficacy and cost effectiveness, uptake is low. To improve the situation, there is a need for mutual encouragement to address motivation and specific barriers on each farm, without which progress will be limited (Garforth *et al.*, 2006).

*More appropriate use of genetics*

Another solution to avoid the deleterious impact of production diseases on oestrus expression is to involve selective breeding. Regrettably, in 2003 across 15 countries, the average relative genetic emphasis for production, durability and health/reproduction was 59.5%, 28% and 12.5%, respectively (Miglior *et al.*, 2005). Greater attempts should be made to redress this balance with respect to lameness and mastitis, and several countries now include fertility indices in selection traits. However, more forward-looking approaches also need to be explored. In dairy cattle, most clinical treatments, for example re-lameness or mastitis,



**Figure 5** Mean  $\pm$  s.e. plasma oestradiol in the upper panel, FSH in the middle panel and follicle diameters in the lower panel for (○) six control heifers, (△) five heifers that formed a prolonged follicle and (□) six heifers that formed a persistent follicle after treatment with 100 IU ACTH every 12 h for 7 days from day 15 of the cycle. Stars indicate control oestradiol values different from prolonged and persistent follicle oestradiol values ( $P < 0.05$ ). Dobson *et al.*, 2000: reproduced with permission.



**Figure 6** Incidence of lameness (■) and mastitis (◇) in dairy cows reported over the last 50 years (references in text).

take place from 1 week before to 10 weeks after calving (Zwald *et al.*, 2004). Thus, calving is a period of great risk to a dairy cow and is to be avoided. Less frequent calving with more persistent lactations would be an advantage. Over a 3-year period (the UK average cow life-span after first

**Table 5** Annual incidence and mean % culling rates associated with the production diseases of dairy cows in >219 herds in UK 1998–2002 (derived from Whitaker *et al.*, 2004)

	'Worst' 25% farms	'Best' 25% farms	Overall mean for all farms
Annual incidence of clinical cases (%)			
Fertility problems			21.4
Lameness	41.5	2.4	20.7
Mastitis	76.4	8.2	38.2
Involuntary culling (%)			
Infertility	7.6	2.9	5.5
Lameness	2.7	1.0	1.8
Mastitis	6.7	1.8	4.2

calving), there really need only two high-risk periods (calvings), not the traditional three as at present. Persistent lactations achieve lower and later peak yields, but reasonable long-term milk production must be maintained to be financially acceptable. Progress through selective breeding should be possible as the heritability for persistent lactation has been estimated at 0.09 to 0.18 compared to 0.03 to 0.19 for fertility (Dekkers *et al.*, 1998; Haile-Mariam *et al.*, 2003; Muir *et al.*, 2004).

## Conclusion

The stresses and strains of high milk production have led animals onto a knife-edge; thus, anything (such as clinical disease, inadequate nutrition, poor housing) will tip cows off balance, thus disrupting hormonal equilibrium, reducing oestrus intensity, lowering LH that results in failure of ovulation and consequent sub-fertility. On-farm schemes to prevent lameness and mastitis, coupled with genetic approaches to improve persistency of lactation, are called for. Phenotypic trends during the last 20 years show that genetic improvement accounted for ~60% of the total increase in milk yield (JP Chenais and F Miglior, personal communication). Thus, production traits have contributed twice as much as durability/health traits, and in the Genotype–Environment interaction, the environment (how we keep animals, i.e. animal husbandry) has not kept pace with genetic 'advances'. Our inability to appropriately feed and house high-yielding cows is leading to increased stress and thus a failure to meet genetic potential for yield and fertility. We must provide realistic solutions soon, if we want to use AI successfully to maintain a sustainable dairy industry in the future.

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