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MASTER

**47CA TURNOVER OF A READILY EXCHANGEABLE CALCIUM POOL
IN PREGNANT AND LACTATING COWS***

by

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INTRODUCTION

Bovine parturient hypocalcemia and paresis, often commonly called milk fever, is a metabolic disease which occurs around the time of parturition and the onset of lactation in high-producing multiparous animals. The etiology of parturient hypocalcemia, with its concomitant hypophosphatemia, is unknown, though several theories as to cause have been espoused. Perhaps the most important theory has been that of Dryerre and Greig⁵ who postulated in 1925 that parathyroid insufficiency was responsible for the observed blood chemical findings. This theory was strongly challenged by electron micrographs of the parathyroids made by Capen and Young³ which suggested that the glands of cows with parturient paresis were indeed hyperactive. The work of Ramberg et al.¹⁰ and Mayer et al.⁹ exploded this theory because they conclusively showed by radioimmunoassay of parathyroid hormone (PTH) that the blood concentrations of the hormone have a statistically significant negative correlation with blood calcium concentration in cows during late gestation right up to parturition. Thus, as the blood calcium concentration falls prior to parturition the parathyroid concentration rises in an attempt to maintain calcium homeostasis.

A well-known major action of PTH is the resorption of the deep or so-called non-exchangeable fraction of bone. However, it has generally been considered that PTH has little influence on the readily exchangeable pools of calcium, which include the calcium of extracellular and intracellular fluid compartments and probably much of the bone surface calcium. These pools, which are determined from the plasma specific activity curve of an injected radioisotope of calcium, might possibly serve as a readily available source of

calcium to meet the stressful demand for calcium stimulated by the onset of both lactation and parturition.

A previous study using goats¹³ had shown that the ^{47}Ca kinetic parameters of such a pool, arbitrarily chosen between 20 and 60-70 hours post-injection because of the relative linearity of the plot during this time, were indeed changed during pregnancy and subsequent lactation. The measured parameters of what we defined as a readily exchangeable calcium pool (RECaP) are size (E) in grams and half-life ($T_{1/2}^1$) in hours. A third parameter, turnover rate (TR) in grams per hour, or transfer rate into and out of the pool, can be calculated by multiplying E times $0.693/T_{1/2}^1$, which is the reciprocal of the slope constant, k.

The work reported here was designed to determine what changes occurred in the kinetic parameters of the RECaP in the cow as a function of gestation, parturition and lactation. The information obtained from normally calving animals hopefully will contribute to a better understanding of data gained from severely parturient hypocalcemic and paretic cows. Ultimately, our goal is to be able to determine whether the RECaP serves as a significant source of calcium at the onset of lactation and parturition in comparison to calcium obtained through the action of PTH on deep bone in maintaining blood calcium of the cow within the normal range.

METHODS

^{47}Ca kinetics of six healthy, mature dairy cows, including five Jerseys and one Holstein which ranged in age from two to five years, were individually studied for variable lengths of time, ranging from several

months to almost a year. The animals were maintained on a ration of loose hay and grain, which was adequate with respect to all dietary requirements, and their outdoor housing provided shelter and sufficient room for exercise. Four of the six cows underwent uncomplicated parturitions during the course of study, whereas the other two animals were never lactating. However, each became pregnant, one (cow 4575) just prior to the last experiment reported. It should be noted that the kinetic parameters during the first half of gestation were not different from those obtained before breeding (see Table I).

Each cow was injected via the jugular vein with $25\text{--}35\mu\text{Ci}$ of ^{47}Ca of moderate specific activity which was obtained from Oak Ridge National Laboratory. Withdrawal of 30-40 ml of venous blood serially from within an hour to usually 80 hours post-injection, but as long as 144 hours post-injection, permitted the preparation of specific activity (SA) curves for each experiment. Fifteen ml of plasma from each blood sample were counted in an automatic well-type scintillation detector (Nuclear Chicago, Inc.) for the estimation of ^{47}Ca and then each sample was assayed for stable calcium⁷ and for inorganic phosphorus.⁴ The SA of each sample is given as the percent of the injected dose of ^{47}Ca per gm of total calcium, and its logarithm is plotted as a function of time after injection, as illustrated for one cow in Figure 1. A linear regression was made by a computer program of the points between 20 and 60-80 hours post injection, which time span arbitrarily defines the RECaP.¹² Reverse extrapolation to the y-axis yielded an intercept value, representing instantaneous distribution of the label at the time of injection, of 3.6% of the dose per gram of calcium which, when divided into 100% of the dose, gives a value for E of 27.8 grams of calcium in the RECaP. The $T_{1/2}$ of

the pool, 32.0 hours, was obtained by determining, with the use of the regression line, how much time elapsed when half of the dose was removed. TR, the product of E and $0.693/T_{1/2}^1$, was then calculated for the cow in this particular experiment to be 0.60 gram per hour.

In a few experiments, mainly when ^{47}Ca was unavailable, ^{85}Sr , a photon-emitting radionuclide like ^{47}Ca , was injected into the cows. A SA (^{85}Sr activity/stable Ca) curve was plotted as a function of time and ^{85}Sr kinetic parameters were determined in a similar manner as for ^{47}Ca . Approximately 70 μCi of high specific activity ^{85}Sr (International Chemical Nuclear, Inc.) was the dose employed.

In response to criticism that our method of calculating the size of the RECaP yields over-estimated values of E, we recalculated the exchangeable pool size according to the method of Aubert, Bronner and Richelle², by determining E values (M is used in the above citation) for each of the two phases of the specific activity curve between the time of injection and 60-80 post-injection. The sum of E_1 and E_2 , representing exchangeable pools 1 and 2, was obtained by a curve fitting computer program. The two-exponential or compartment models yielded sums of the pool sizes that were almost always greater, albeit quite similar in general, than the values obtained by our monoexponential method of calculating E from the RECaP for all cows in all experiments (see Table II). Figure 2 illustrates E values obtained by the two methods for cow 361 through pregnancy, parturition and lactation. When a third exponential phase was derived by computer from the specific activity plots taken well beyond 80 hours post-injection, the sum of pool sizes, E_1 , E_2 and E_3 , obtained was considerably greater than our E. Thus, our method

of calculating E from ^{47}Ca specific activity curves yields a fairly good estimate of the size of the exchangeable calcium pools from the time of injection up to 80 hours after injection. However, values of turnover rate, V_T , calculated by the method employed by Ramberg et al.¹⁰, consistently produced values lower than the TR values obtained by our method of analysis of the RECaP. In the case of TR, then, our method results in overestimated values. The general pattern of changes obtained by either method were the same for E (Fig. 2) and TR (Figs. 3-8) for cows progressing through gestation, parturition and lactation.

For cow 2513 only, calcium ion determinations were made on a few samples of blood plasma prior to and after parturition with an Orion electrode. Values were obtained for heparinized samples taken both under oil and not under oil. Agreement was quite good between those samples taken under oil or not but the under-oil samples were always slightly lower.

RESULTS

In Table I are presented the ^{47}Ca kinetic parameters, E, $T_{1/2}$, and TR, derived from the plasma SA curves of four pregnant and subsequently lactating cows and two non-lactating cows, both of which were bred during the period shown. Considerable fluctuation occurred in values for E, especially, and these are reflected in the TR values. It is interesting to note that mean values of E, $T_{1/2}$, and TR were statistically the same for cow 363 in five experiments before and in seven experiments after the beginning of pregnancy. TR in this two year-old cow averaged about 1.3 gm/hr, whereas in a non-pregnant, non-lactating five year-old cow (4575) it was only about 0.8.

The changes in TR as a function of time are plotted in Figures 3 to 8. The values of TR of the two non-lactating cows remained relatively constant with time, whereas TR values increased, markedly in two cows (Figures 4 and 7), at the time of parturition and onset of lactation and either remained at the elevated level or continued to increase as lactation proceeded.

In the case of cow 361 (Figure 4) TR nearly doubled at parturition from about 1.5 a week or so prepartum to 2.6 gm/hr and then climbed to a peak value of about 4.7 during the height of lactation. TR nearly doubled also at parturition for cow 2513 (Figure 7). TR values of cows 364 (Figure 5) and 634 (Figure 8) increased only slightly at parturition. For cows 361, 634 and 2513 the ^{85}Sr -derived TR values were less than those obtained using ^{47}Ca . However, TR values determined from either ^{47}Ca or ^{85}Sr SA curves appeared to be similar for cows 363 (Figure 3) and 364 (Figure 5). The reason for the differential handling of ^{47}Ca and ^{85}Sr by some, though not all, cows remains obscure.

The variation of TR during lactation appears to be correlated to the level of milk production of a given cow. For example, TR ranged from 2.6 to 4.7 gm/hr in cow 361 (Table I), which was producing 32 pounds of milk per day on the average. This primiparous cow was considered to be a heavy lactator, although according to one rule-of-thumb for Jerseys a heavy lactator would produce over 45 pounds of milk a day. For the other cows, 364 (primiparous), 634 (multiparous) and 2575 (multiparous) average milk production was 17, 22 and 22 pounds daily, respectively. These animals were light lactators. However, cow 364 had a TR maximum which was about 3.4 gm/hr

whereas the other two cows exhibited lower maximal TR values of around 2.0.

Figures 8 to 13 present the plotted mean plasma concentrations of calcium and inorganic phosphorus during a particular experiment as a function of time. Cows 363 (Figure 9) and 4575 (Figure 14) which were not lactating showed only minor fluctuations in plasma calcium, which approximated 10 mg %. However, mean phosphorus concentrations varied considerably; for example, cow 363 ranged from 5.5 to almost 9 mg %. Some of this variation may have been caused by differences in dietary phosphorus intake, although we have no evidence for this. The cows which underwent normal parturitions demonstrated the anticipated declines in plasma calcium within 24 hours prior to and 2-3 days after partum (Figures 10-11 and 13-14). Following the onset of lactation in each cow the pre-partum calcium level was not attained until about two months post-partum. Plasma phosphorus concentration also fell concomitantly with calcium about the time of parturition in cows 364 (Figure 11) and 2573 (Figure 13), but no decrease was observed for cows 361 (Figure 10) and 634 (Figure 14).

The calcium ion and total calcium concentrations for cow 2513 obtained within 24 hours before and within a few hours after parturition are listed in Table III. Both the ionic and total calcium values remained about the same pre- and post-partum. Thus, the calcium ion percentage of the total calcium stayed at about 40%.

DISCUSSION

The results of the present study of ^{47}Ca kinetics in cows demonstrated that a combination of two physiological events, the initiation of lactation and parturition, exerted a far greater influence on the TR of the RECaP than did either pregnancy or even, probably, lactation per se. The data do not permit a distinction to be made as to which of the two concurrent events stresses calcium homeostasis more severely. However, the data do show that the TR value attained at the time of parturition was maintained or, in some cows, elevated during the post-partum lactation. Since TR values at some time during the period of milk production were at least double the maximal values obtained during gestation, it would appear, then, that the lactational demand for calcium from the RECaP is much greater than the calcium requirement for uterine contraction and all other functions at parturition.

A possible exception to the generalization that lactational onset and parturition produce an increased turnover of the RECaP is to be found in cow 2513. She was injected with ^{47}Ca and ^{85}Sr one day pre-partum and the experiment lasted through two days post-partum. However, the derived TR values were very similar to the values obtained during gestation. ^{47}Ca was then reinjected into the cow at three days post-partum, at which time the TR was elevated as it should have been. The reason for the delay in both E and TR increase is not known.

The kinetic data do not shed any light on a possible effect of PTH on the RECaP, although other data from this laboratory (unpublished results) indicate that the RECaP of goats is unaffected by thyroparathyroidectomy.

However, the level of dietary calcium intake, as well as phosphorus, may influence the kinetic parameters of the RECaP,¹ though certainly more data is needed on this relationship.

In all four parturient cows the blood plasma concentration of calcium fell one to two mg %, but this degree of hypocalcemia well exceeds the level of about 6-7 mg % below which paresis often occurs. What was surprising among the calving cows was the inconsistent pattern observed for plasma inorganic phosphorus concentrations. The well documented hypophosphatemia was expected, but only two of the four animals presented this finding. Whatever physiological or nutritional factors were influencing the phosphorus concentration can only be speculated upon.

Parturition in one cow (2513) did not affect the partition of blood calcium between the ionic and bound fractions as the calcium ions remained about 40% of the total. Although this cow did not exhibit an increase in TR at parturition as well, other data from this laboratory (unpublished observations) corroborate this finding. Nevertheless, insufficient information is available to rule out the possibility that the ionic percentage may increase relative to the percentage of protein-bound calcium around the time of parturition.

Although the interpretations of our quantitative findings are necessarily qualitative, it appears that the RECaP is turning over at a significantly increased rate at the time of parturition and the onset of lactation and subsequently through the peak period of milk production. This enhanced TR occurred at the same that the total plasma calcium concentration decreased and the plasma SA curve was downwardly displaced. To illustrate

this point Figure 15 shows two different SA curves of cow 361, one obtained during mid-gestation and the other at parturition. From the kinetic and blood mineral analyses, then, more calcium appeared to exist in the RECaP at partum but it was turning over faster than during gestation in order to meet the demand for calcium, while simultaneously total blood calcium was diminished.

The only sources of potential calcium transfer into blood and, thus, into a large fraction of the RECaP are via transfer from the intestine and bone. Since the parturient cow ingests little food, the major calcium inflow at this time would have to be from bone. However, it has been suggested that PTH is unable to exert its resorptive action at parturition because of a non-specific homeostatic failure.⁸ Thus, deep bone may also be rendered unavailable as a reserve of calcium following the spontaneous induction of hypocalcemia. The transfer of both skeletal and intestinal calcium into the exchangeable pool may either be partially or totally inhibited near full term by the action of another hormone, such as estrogen,¹² at various peripheral tissue sites. A low dietary calcium-to-phosphorus ratio may be somewhat beneficial in overcoming the homeostatic failure at parturition by stimulating the parathyroid glands, as suggested by Luick, et al.⁶ Certainly, it is well known that vitamin D will prevent severe hypocalcemia and paresis when administered for several days pre-partum and, thus, vitamin D may also be interfered with at this time.

Further experiments are necessary to determine the relative importance of the RECaP versus deep-bone mineral under the resorptive influence of PTH as sources of calcium at parturition. In addition, it remains to be shown whether blood estrogens have an inhibitory effect on PTH action within

a day or so pre partum when the concentrations of these steroids are known to surge to maximal levels. Perhaps the elusive etiology of parturient hypocalcemia and paresis will then be forthcoming.

SUMMARY

In studies designed to characterize parturient hypocalcemia, ^{47}Ca kinetics were measured in cows during gestation, parturition and lactation. From a plot of plasma specific activity (SA) as a function of time three kinetic parameters were generated for each cow during the experiments, which lasted for almost a year in some of the animals. The parameters of the readily exchangeable calcium pool, which is defined from the linear phase of the SA curve between 20 and 64 hours after injection of the radionuclide, are size in grams, half life in hours, and turnover rate (or transfer rate) in grams per hour. In two primiparous Jersey cows the turnover rate remained roughly constant throughout gestation, whereas it almost doubled in value at or shortly after parturition and the onset of lactation. Turnover rate was maximal during the peak period of milk production. Two multiparous cows exhibited smaller changes in turnover rate at parturition and during lactation. An additional two cows which were not lactating served as comparators. Their values of turnover rate remained quite constant with time and they were in good agreement with values of other similarly aged cows obtained during pregnancy. The lactational demand for calcium appeared to influence the turnover of the readily exchangeable calcium pool more than gestation and more than parturition by itself.

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Table I

Experimentally Derived ^{47}Ca Kinetic Parameters of the Readily Exchangeable Calcium Pool (RECaP) of Six Dairy Cows: Size (E) in Grams, Half-Life ($T_{1/2}$) in Hours, and Turnover Rate (TR) in Grams Per Hour

Cow 361				Cow 363			Cow 364			
Day	E	T _{1/2}	TR	E	T _{1/2}	TR	Day	E	T _{1/2}	TR
0	Bred 2/4/1969			Non-P, Non-L			0	Bred 1/31/1969		
82	53.8	23.5	1.59	54.1	24.4	1.54	86	51.3	22.0	1.62
106	69.0	32.0	1.49	69.0	34.5	1.39	110	87.0	37.0	1.63
139	41.7	21.5	1.34	41.7	20.5	1.41	143	54.1	25.5	1.47
190	38.5	24.0	1.11	34.5	22.0	1.09	194	40.8	22.0	1.29
220	43.5	20.5	1.47	-	-	-	224	41.7	18.0	1.61
232	33.3	22.0	1.05	-	-	-	236	40.0	21.0	1.32
246	70.4	31.0	1.57	-	-	-	250	83.3	30.0	1.92
258*	37.0	17.3	1.48	40.0	17.1	1.62	262*	43.5	16.8	1.79
266*	45.5	26.0	1.21	46.3	23.0	1.40	270*	51.8	24.0	1.50
272	Partum 11/4/1969			Bred 10/25/1969			273	Partum 10/31/1969		
273	69.0	18.5	2.59	53.2	24.2	1.52	277	48.1	20.0	1.67
287	51.3	14.0	2.54	41.7	26.0	1.11	291	45.5	17.0	1.86
287*	46.5	17.2	1.87	50.0	28.0	1.24	291*	43.5	16.0	1.88
329	66.7	14.0	3.30	33.3	26.0	0.89	333	83.3	18.0	3.21
343	74.1	15.0	3.42	43.5	20.4	1.48	347	82.0	16.5	3.44
357	79.4	14.6	3.77	-	-	-	361	76.9	15.7	3.39
385	90.9	15.0	4.20	-	-	-	389	78.7	18.5	2.95
399	80.0	17.0	3.26	48.8	22.0	1.54	403	100.0	28.0	2.48
418	128.2	19.0	4.68	-	-	-	422	106.4	25.0	2.95
Means				46.6	24.4	1.30				

* ^{85}Sr injection

P = pregnant; L = lactating

Table I (continued)

Day	Cow 2513			Cow 4575			Day	Cow 634		
	E	$T\frac{1}{2}$	TR	E	$T\frac{1}{2}$	TR		E	$T\frac{1}{2}$	TR
0	Bred 7/30/1969			Non-P, Non-L			0	Bred 1/29/1969		
168	34.5	25.0	0.96	27.8	23.3	0.83	265*	31.2	20.0	1.08
182	29.4	24.0	0.85	29.4	22.2	0.92	272*	32.3	20.0	1.12
210	25.6	24.0	0.74	23.8	26.0	0.63	277	57.1	32.2	1.23
224	26.3	20.0	0.91	25.6	27.0	0.66	290	Partum 11/18/1969		
281	25.7	18.0	0.99	-	-	-	291	62.5	26.5	1.63
281*	27.8	23.2	0.83	Bred 4/25/1970			291*	40.7	26.0	1.08
282	Partum 5/8/1970			-	-	-	333	39.2	19.0	1.43
285	47.6	18.2	1.81	-	-	-	347	54.1	17.0	2.21
285*	30.3	20.5	1.02	-	-	-				
294	64.5	23.0	1.94	<u>30.3</u>	<u>28.5</u>	<u>0.74</u>				
Means				27.4	25.4	0.76				

* ^{85}Sr injection

P = pregnant; L = lactating

Table II

Comparison of Exchangeable Pool Sizes (E versus $E_1 + E_2$ in Grams) obtained by Monoexponential versus Two Exponential Analysis of ^{47}Ca Kinetic Data

Cow 361			Cow 363		Cow 364		
Day	E	$E_1 + E_2$	E	$E_1 + E_2$	Day	E	$E_1 + E_2$
0	Bred 2/4/1969		Non-P,	Non-L	0	Bred 1/31/1969	
82	53.8	51.7	54.1	52.5	86	51.3	60.4
106	69.0	73.5	69.0	65.3	110	87.0	77.1
139	41.7	-	41.7	63.1	143	54.1	78.8
190	38.5	43.4	34.5	51.8	194	40.8	52.0
220	43.5	48.6	-	-	224	41.7	47.0
232	33.3	35.6	-	-	236	40.0	60.0
246	70.4	77.1	-	-	250	83.3	101.7
258*	37.0	-	40.0	61.2	262*	43.5	59.5
266*	45.5	70.3	46.3	61.1	270*	51.8	83.0
272	Partum 11/4/1969		Bred 10/25/1969		273	Partum 10/31/1969	
273	69.0	97.3	53.2	79.5	277	48.1	46.8
287	51.3	70.8	41.7	37.5			
287*	46.5	50.4	50.0	45.0	291	45.5	51.9
329	66.7	106.5	33.3	42.9	291*	43.5	49.3
343	74.1	104.4	43.5	61.2	333	83.3	74.9
357	79.4	197.5	-	-	347	82.0	174.2
385	90.9	105.0	-	-	361	76.9	117.6
399	80.0	119.8	48.8	67.7	389	78.7	106.5
418	128.2	124.1			403	100.0	109.3
Means			46.6	57.4	422	106.4	117.2

* ^{85}Sr injection

P = pregnant; L = lactating

Table II (continued)

Day	Cow 2513		Cow 4575		Day	Cow 634	
	E	E ₁ +E ₂	E	E ₁ +E ₂		E	E ₁ +E ₂
0	Bred 7/30/1969		Non-P,	Non-L	0	Bred 1/29/1969	
168	34.5	-	27.8	30.9	265*	31.2	-
182	29.4	46.7	29.4	40.4	272*	32.3	-
210	25.6	39.4	23.8	38.5	277	57.1	75.2
224	26.3	36.8	25.6	29.6	290	Partum 11/18/1969	
281	25.7	26.8	-	-	291	62.5	66.5
281*	27.8	29.9	Bred 4/25/1970		291*	40.7	37.4
282	Partum 5/8/1970		-	-	333	39.2	44.9
285	47.6	52.7	-	-	347	54.1	83.2
285*	30.3	37.2	-	-			
294	64.5	76.2	<u>30.3</u>	<u>-</u>			
Means			27.4	34.8			

* ⁸⁵Sr injection

P = pregnant; L = lactating

Table III

Plasma Calcium Ion, Total Calcium, and Inorganic Phosphorus
Concentrations of Cow 2513 Before and After Parturition

<u>Time</u>	<u>Sample Method</u>	<u>Ca Ion Conc'n</u>	<u>Total Ca Conc'n</u>	<u>% Ca Ion</u>	<u>PI Conc'n*</u>
1:55PM 5/7	No Oil	3.64	8.8	41.4	4.3
1:55PM 5/7	Under Oil	4.08	8.8	46.4	4.3
7:52AM 5/8	No oil	3.72	9.3	40.0	3.8
12:30PM 5/8	Parturition				
1:00PM 5/8	No Oil	3.68	9.3	39.6	2.5

* Concentration in mg/100 ml plasma

FIGURE CAPTIONS

Fig. 1. Semilogarithmic plot of plasma specific activity illustrating the method used for determining the ^{47}Ca (or ^{85}Sr) kinetic parameters of the readily exchangeable calcium pool. By the method of least squares a regression line was fit for the points between about 20 and 64 hours after intravenous injection of the radionuclide. This method was first used in studies of goat kinetics.¹⁰ See text for description of calculation of E , $T_{1/2}$, and TR .

Fig. 2. Plot of exchangeable pool size in grams comparing values obtained from a monoexponential model (using linear phase only of specific activity plot between 20 and 60-80 hours post-injection) versus a two exponential model (using both phases of specific activity plot between 0 and 60-80 hours post-injection) as a function of time. Note that in general values of E calculated from the monoexponential RECaP by our method is less than the sum of the two pool sizes, E_1 and E_2 , calculated from the two exponentials. If longer periods of time had been chosen, a third exponential would be needed to fit the specific activity curve and adding a third pool size, E_3 , to the earlier pools would increase the size of the exchangeable pool accordingly.

Fig. 3. Plot of TR of Jersey cow 363 as a function of time.

Fig. 4. Plot of TR of Jersey cow 361 as a function of time.

Fig. 5. Plot of TR of Jersey cow 364 as a function of time.

Fig. 6. Plot of TR of Jersey cow 4575 as a function of time.

Fig. 7. Plot of TR of Jersey cow 2513 as a function of time.

Fig. 8. Plot of TR of Holstein cow 634 as a function of time.

Fig. 9. Plot of plasma calcium and inorganic phosphorus concentrations of cow 363 as a function of time.

Figure Captions (continued)

Fig. 10. Plot of plasma calcium and inorganic phosphorus concentrations of cow 361 as a function of time.

Fig. 11. Plot of plasma calcium and inorganic phosphorus concentrations of cow 364 as a function of time.

Fig. 12. Plot of plasma calcium and inorganic phosphorus concentrations of cow 4575 as a function of time.

Fig. 13. Plot of plasma calcium and inorganic phosphorus concentrations of cow 2513 as a function of time.

Fig. 14. Plot of plasma calcium and inorganic phosphorus concentrations of cow 634 as a function of time.

Fig. 15. Semilogarithmic plots of plasma specific activity of cow 361 obtained during midgestation and at parturition. Note the downward displacement of the linear portion of the SA curve at the time of parturition.