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Colostrum effects on the gastrointestinal tract, and on nutritional, endocrine and metabolic parameters in neonatal calves

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Abstract

Newborn calves are characterised by marked cardio-respiratory, metabolic and endocrine changes which continue during ensuing weeks and months. Thus, although the somatotrophic axis is basically functioning in neonatal calves, it is not yet mature. The speed of the adaptations of the various traits differs widely. The ability to digest colostrum and milk requires specific structures and functions of the gastrointestinal tract. Colostrum composition exhibits major changes after the onset of lactation. Colostrum intake is important for passive immunity, but also for the provision of carbohydrates, lipids, proteins, minerals and vitamins. In addition, colostrum contains hormones, growth factors, cytokines, enzymes, polyamines and nucleotides, which in the neonatal calf can exert biological effects. Thus, insulin-like growth factor I, which in colostrum is present in high amounts, may enhance gastrointestinal tract development and function of neonatal calves. Colostrum should be ingested as soon as possible after birth for efficient and sufficient absorption not only of immunoglobulins, but apparently also of (essential and non-essential) fatty acids and fat-soluble vitamins (β -carotene, retinol and α -tocopherol). The pattern of essential amino acids and the glutamine/glutamate ratio in blood plasma also greatly depend on whether and when colostrum is fed. In addition, there are considerable effects on hormones (especially on concentrations of insulin, glucagon, insulin-like growth factor-I, including its binding proteins, and cortisol) that are dependent on time and amount of colostrum fed. © 2000 Elsevier Science B.V. All rights reserved.

Keywords: Calf; Colostrum; Intestine; Metabolism; Hormone; Growth factor

1. Introduction

Even in new-born calves, which are born relatively mature, great morphological and functional changes are necessary. These are in part of a constitutional nature, such as changes in plasma

concentrations of nitrate, lactate and creatinine. In addition, calves must adapt to various environmental factors, including nutrition. The colostrum period lasts for about 1 week. Nutrition during this period can have effects later on in life. How much colostrum should be ingested has not been studied fully, except with respect to the immunoglobulin status. Studies with automatic feeders demonstrate that ingestion is much higher than is usually recommended (Nussbaum, Schiessler, Hammon and Blum, unpublished

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observations) and studies in suckling calves in cow-calf operations show considerable metabolic and endocrine differences compared with restricted bucket-fed calves (Egli and Blum, 1998). As shown in Table 1, colostrum contains proteins, essential and non-essential amino acids (EAA, NEAA), fatty acids (FA), lactose, vitamins and minerals, as well as non-nutrient substances, such as immunoglobulins, peptides, peptide hormones, growth factors, cytokines, biologically important proteins (such as lactoferrin), steroid hormones, triiodothyronine (T_3), thyroxine (T_4), nucleotides, polyamines and enzymes (Koldovsky, 1989; Campana and Baumrucker, 1995). Compared with mature milk, bovine colostrum is characterised by higher concentrations of insulin-like growth factor I (IGF-I), IGF-II, insulin and prolactin (PRL), and similar concentrations of glucagon, but it contains lower amounts of growth hormone (GH) (Ronge and Blum, 1988;

Grütter and Blum, 1991b; Vacher and Blum, 1993; Campana and Baumrucker, 1995; Hammon and Blum, 1997b). Concentrations of most of these hormones and growth factors are highest in colostrum before parturition but, with the exception mainly of casein and lactose, amounts available to the new-born calf of most of these substances, especially the bioactive ones, are highest in the first colostrum (Table 1). Colostrum is well known to be important for passive immunity. Furthermore, compared with mature milk, colostrum contains a much greater number of cells (including leukocytes), which are also thought to exert effects. This review summarises more recent findings in calves of the effect of colostrum intake on the gastrointestinal tract (GIT), and on the nutritional, metabolic and endocrine status during the first week of life, in extension of previous reviews (Baumrucker and Blum, 1993; Odle et al., 1996; Xu, 1996; Burrin, 1997; Guilloteau

Table 1

Composition (especially of nitrogen-containing, bioactive substances) of bovine colostrum and mature milk^a

		Colostrum milkings					Mature milk ^b
		1	2	3	4	5/6	
Dry matter	(g/l)	245	190	160	155	153	122
Crude ash	(g/l)	18	10	10	8	8	7
Gross energy ^c	(MJ/l)	6.0	4.8	3.9	3.8	3.8	2.8
Crude fat	(g/l)	64	56	46	50	50	39
Nitrogenfree extracts	(g/l)	25	40	42	43	46	49
Crude protein	(g/l)	133	85	62	54	48	32
Essential amino acids ^d	(mmol/l)	390	230	190	140	115	ND
Nonessential amino acids ^d	(mmol/l)	490	290	240	170	140	ND
Immunoglobulin G ^e	(g/l)	81	58	17	12	ND ^f	<2
Lactoferrin	(g/l)	1.84	0.86	0.46	0.36	ND	ND
Transferrin	(g/l)	0.55	0.44	0.39	0.21	ND	ND
γ -Glutamyltransferase	(μ kat/l)	509	284	145	102	83	52
Alkaline phosphatase	(μ kat/l)	19	8	3	2	1	4
Aspartate Aminotransferase	(μ kat/l)	1.5	0.9	0.5	0.3	0.20.1	
Tumour necrosis factor- α	(μ g/l)	5	ND	ND	ND	3	<2
Insulin	(μ g/l)	65	35	16	8	7	1
Glucagon	(μ g/l)	0.16	0.08	0.08	0.05	0.03	0.01
Prolactin	(μ g/l)	280	180	150	120	ND	15
Growth hormone	(μ g/l)	1.4	0.5	<1	<1	<1	<1
Insulin-like growth factor-I	(μ g/l)	310	195	105	62	49	<2
Insulin-like growth factor-II	(μ g/l)	150	ND	ND	ND	ND	ND

^a Own studies.^b Measured > 14 days after parturition.^c Measured by bomb calorimetry.^d For content of individual amino acids, see Hammon and Blum (1999).^e For content of immunoglobulin A and M, see Vacher and Blum (1993).^f ND = not determined.

et al., 1997; Le Huërou-Luron et al., 1998; Blum and Hammon, 1999a,b).

2. Effects of colostrum intake and of ingested hormones and growth factors on the GIT

Ingestion of colostrum has marked effects on GIT development and function, and affects digestive enzymes and GI hormones (Guilloteau et al., 1997; Hadorn et al., 1997; Bühler et al., 1998; Le Huërou-Luron et al., 1998), and absorptive capacity (Hammon and Blum, 1997a). Colostrum intake modifies GIT development and digestive and absorptive capacities in neonates, not only through provision of nutrients, minerals, vitamins and energy, but probably also due to effects of growth-promoting factors in various species, including calves (Kelly, 1994; Burrin et al., 1995, 1996; Odle et al., 1996; Xu, 1996; Blättler, Hammon and Blum, unpublished observations).

There is recent evidence that amniotic IGF-I ingested by foetal sheep enhances GIT development (Kimble et al., 1999). IGF-I and insulin receptor mRNAs are present in the small intestine of 8-day-old calves (Cordano, Hammon and Blum, unpublished observations). Furthermore, IGF-I, IGF-II, Long-R³-IGF-I (an IGF-I analogue, which binds only slightly to plasma IGF binding proteins) and insulin bind to specific receptors in the duodenum, jejunum, ileum and colon of neonatal calves (Baumrucker et al., 1994b; Hammon and Blum, 1998c). Binding capacities of IGF-I, IGF-II and insulin in the mucosa of the small intestine and colon were greater in 8-day-old calves fed colostrum for 3 days than in those fed milk replacer (Hammon and Blum, 1998c), and IGF-I binding capacity in the small intestinal mucosa was upregulated by orally-administered IGF-I (Baumrucker et al., 1994b). Furthermore, orally administered recombinant human IGF-I (rhIGF-I), which has the same structure as bovine IGF-I, stimulated growth of the small intestine in neonatal calves based on [³H]-thymidine incorporation into enterocytes *ex vivo* (Baumrucker et al., 1994b). These data are in accordance with studies in other species, such as pigs (Burrin et al., 1996; Odle et al., 1996; Xu, 1996). However, in calves fed a formula for the first 8 days of life, to which supraphysiologi-

cal amounts of hIGF-I (3.8 mg/l, secreted with milk in amounts up to 0.2 g/l by transgenic rabbits) had been added, villus height, villus circumference and crypt depth were not significantly modified and the proliferation of small intestinal crypt cells was not enhanced (Fäh, Hammon, Brem and Blum, unpublished observations). Thus, effects of IGF-I on postnatal GIT development are controversial, in accordance with studies in pigs and laboratory animals (Burrin et al., 1996, 1999; Burrin, 1997).

3. Metabolic changes

Intake of colostrum causes considerable metabolic changes. In new-born calves, as expected, blood plasma concentrations of total protein rise as a consequence of absorbed immunoglobulins (especially IgG). Changes depend on the timing and amounts of ingested colostrum and IgG, but are not altered after intake of milk or milk replacer (Hadorn and Blum, 1997; Hammon and Blum, 1999; Kühne et al., 2000; Rauprich et al., 2000a,b; Zanker et al., 2000). Plasma albumin concentrations partially reflect hepatic synthesis and mostly increase during the first week of life, dependent on the colostrum supply (Hadorn et al., 1997; Kühne et al., 2000; Rauprich et al., 2000a).

Total and individual plasma free EAA increased on day 1 of life after intake of colostrum, but not milk replacer, and remained higher if calves were fed colostrum for 3 days than if colostrum was provided only at the first meal (Hammon and Blum, 1999). Interestingly, plasma free glutamate concentrations increased, whereas those of free glutamine decreased, in colostrum-fed calves only, possibly reflecting enhanced tissue glutamine uptake (for example by rapidly dividing cells, such as those of the GIT) due to colostrum feeding (Hammon and Blum, 1999). Furthermore, we found that plasma EAA concentrations were transiently decreased if the intake of the first colostrum was delayed by 24 h (Zanker et al., 2000).

Plasma urea concentrations, if there are no hepatic and kidney dysfunctions, are dependent on intake, synthesis and degradation of protein, as we have shown in neonatal calves (Hadorn et al., 1997; Kühne et al., 2000; Zanker et al., 2000). In calves

fed a milk-based formula with similar amounts of nutrients as colostrum but only traces of growth factors (especially IGF-I), urea concentrations were elevated (Rauprich et al., 2000b). This suggests that non-nutritional factors (such as IGF-I and insulin) in colostrum exert an anabolic effect and thereby reduce plasma urea concentrations.

Nitrate (NO_3) is ingested through feed and water or is endogenously produced from nitric oxide (NO) and nitrite (NO_2). The substrate for the formation of NO is arginine (Arg), which under the influence of NO synthases (NOS) is transformed into citrulline. Interactions between NO and urea production, and thus with nitrogen metabolism, have been demonstrated in cattle (Kahl et al., 1997). Most interestingly and not reported before, we found very high NO_x ($=\text{NO}_2 + \text{NO}_3$, primarily NO_3) concentrations in blood plasma, saliva and urine in new-born calves before the first meal, while concentrations in their cerebrospinal fluid and in the blood plasma and milk of their dams were very low (Blum et al., 1998). Plasma concentrations decreased within the first days of life, but still remained relatively high for several months. The data indicate significant endogenous NO_3 production in neonatal calves. Different feeding (feeding colostrum or milk replacer in different amounts or delayed for 24 h after birth) and administration of GH and Long-R³-IGF-I had no effects on NO_3 and NO_2 concentrations in blood plasma, saliva and urine of neonatal calves, except when $>200 \mu\text{mol NO}_2$ or NO_3 were fed per kg body weight. Thus, we concluded that the high NO_3 concentrations in blood plasma and the high amounts excreted in saliva and urine in neonatal calves are primarily of a constitutional nature.

Activities of γ -glutamyltransferase (γ -GT), lactate dehydrogenase (LDH), glutamate dehydrogenase (GLDH) and aspartate aminotransferase (AST) were very high in first milked colostrum and then decreased to low values in mature milk (Zanker, 1997). Activities of these enzymes in neonatal calf plasma transiently increased after intake of first colostrum, but not of milk replacer, indicating that these enzymes were absorbed from colostrum (Baumrucker et al., 1994a; Hadorn and Blum, 1997; Zanker, 1997; Egli and Blum, 1998; Hammon and Blum, 1998b). The biological importance of increased plasma enzyme activities, if any, is not known. Because their

activities in plasma decrease rapidly, they are likely mostly degraded.

Amount and timing of colostrum intake affect plasma glucose in neonatal calves. Thus, plasma glucose increased less after intake of the first colostrum than of milk replacer if milk replacer contained more lactose than colostrum (Grütter and Blum, 1991a; Hadorn et al., 1997; Hammon and Blum, 1998b; Kühne et al., 2000). However, postprandial plasma glucose concentrations on the following days increased more in calves initially fed colostrum than milk replacer, glucose or water, indicating prolonged effects of early colostrum intake on glucose metabolism. Colostrum intake also positively influenced absorptive capacity of carbohydrates, such as xylose (Hammon and Blum, 1997a; Rauprich et al., 2000b).

The plasma lipid and fat-soluble vitamin status in the neonatal period is influenced by the amount and timing of ingested colostrum. Thus, if colostrum was withheld for the first 24 h after birth, plasma non-esterified FA (NEFA) increased, whereas plasma concentrations of triglycerides (TG), phospholipids (PL), cholesterol, and essential and non-essential FA in TG, PL and cholesterol ester fractions, and of fat-soluble (pro-) vitamins (carotene, retinol, α -tocopherol) remained lower than in calves fed colostrum immediately after birth (Blum et al., 1997; Hadorn et al., 1997; Zanker, 1997). Besides decreased intake, the mechanisms of absorption of FA and fat-soluble vitamins in calves not fed colostrum on the first day of life may be responsible for the subsequent impaired FA and fat-soluble vitamin status. In addition, impaired post-absorptive transport and distribution of these substances (for example, due to failure of the induction and production of transport proteins) is also possible if colostrum is not provided shortly after birth. In contrast to fat-soluble vitamins, plasma water-soluble vitamins (B-6, B-12 and folic acid) were not dependent on timing of colostrum feeding (Blum et al., 1997). We have repeatedly shown that plasma TG, PL and cholesterol concentrations are higher in calves fed colostrum for 3 days than in those fed only milk replacer (Hammon and Blum, 1998b; Kühne et al., 2000). Interestingly, plasma concentrations of TG, PL, cholesterol, and essential and non-essential FA were still lower in calves fed milk replacer than in calves fed the same amount of these metabolites but via

colostrum (Rauprich et al., 2000b). The lipid status seems therefore not only to be dependent on the ingested amount of fat, but seems to be enhanced by colostrum intake. In addition, TG concentrations increased more in calves fed a milk replacer supplemented with hIGF-I (Fäh, Hammon, Brem and Blum, unpublished observations). Mechanisms for these colostrum effects are not known. We speculate that bioactive components (such as IGF-I and insulin) modify digestion and absorption of FA, by possibly altering lipase activity or FA binding proteins.

We have not found significant effects of the amounts of colostrum fed or the timing of the first colostrum feeding on calcium, magnesium, inorganic phosphorus and iron concentrations (Zanker, 1997).

4. Endocrine changes

Intake of colostrum has marked effects on GI and pancreatic hormones (Guilloteau et al., 1997; Blum and Hammon, 1999b). We found decreased plasma concentrations of gastrin and glucose-dependent insulinotropic polypeptide (GIP) in calves which did not receive colostrum during the first 24 h after birth (Hadorn et al., 1997). Both plasma concentrations of gastrin and GIP normalised quickly if calves were fed colostrum, demonstrating that these hormones could rapidly adapt to nutrient intake.

Colostrum insulin seems not to be intestinally absorbed, even if administered in pharmacological amounts (Grütter and Blum, 1991a). On day 1 of life, because of greater hyperglycaemia, plasma insulin concentrations were higher in calves fed milk replacer than colostrum, but this changed during ensuing days and plasma insulin concentrations postprandially increased more when colostrum was fed than when only milk replacer or water were fed, demonstrating prolonged effects of colostrum feeding (Grütter and Blum, 1991b; Mears, 1993; Hadorn et al., 1997, Hammon and Blum, 1998b). Postprandial plasma insulin responses were, however, much smaller than we found in veal calves (Hostettler-Allen et al., 1994; Hugi et al., 1997, 1998), indicating that the secretory capacity of insulin is not fully developed in neonatal calves. Plasma insulin concentrations immediately decreased and changed more

markedly than did all other studied hormones if food was withheld for 24 h in 8-day-old calves (Kin-sbergen et al., 1994; Hadorn et al., 1997).

Pancreatic glucagon has antagonistic effects to insulin. In our studies, plasma concentrations after first feeding increased more in calves which received colostrum than in those fed milk replacer (Hammon and Blum, 1998b). Additional colostrum feedings during the first 2 days of life increased glucagon concentrations but, after day 3 of life, glucagon concentrations were higher in milk replacer-fed than colostrum-fed calves (Kühne et al., 2000; Rauprich et al., 2000b).

Plasma cortisol concentrations decrease during the first week of life in neonatal calves and transiently decrease after intake of colostrum, milk or milk replacer (Ronge and Blum, 1988; Baumrucker and Blum, 1994; Lee et al., 1995; Hadorn et al., 1997). Plasma cortisol concentrations during the first week of life were higher in calves fed only milk replacer than in those fed colostrum (Hammon and Blum, 1998b; Kühne et al., 2000; Rauprich et al., 2000b). Gluconeogenesis is essential to cover the requirements of glucose in neonates. Both glucagon and cortisol stimulate gluconeogenesis and are probably important for glucose homeostasis in calves fed reduced amounts of colostrum.

Plasma T_3 and T_4 concentrations are high at birth and then rapidly decrease (Kahl et al., 1977; Grongnet et al., 1985; Ronge and Blum, 1988; Hadorn et al., 1997; Egli and Blum, 1998; Hammon and Blum, 1998b). Plasma concentrations in our studies were not influenced either by feeding different amounts of colostrum, by delaying colostrum feeding or by fasting, in contrast to Grongnet et al. (1985).

Plasma PRL concentrations usually increase after birth (Baumrucker et al., 1994b; Lee et al., 1995; Hadorn et al., 1997; Hammon and Blum, 1998b; Kühne et al., 2000). Because plasma PRL concentrations increased similarly on day 1 of life in calves fed either water, glucose or colostrum (which contains high amounts of PRL), colostrum PRL seems not to be absorbed (Hadorn et al., 1997). However, plasma PRL concentrations increased more during the first week of life in calves fed colostrum than in those fed milk replacer (Hammon and Blum, 1998b).

The somatotrophic axis functions in neonatal calves (Hammon and Blum, 1997b). Thus, GH

secretion is enhanced by the administration of GH-releasing factor analogue 1-29, but is not affected by the amount of ingested colostrum (Hammon and Blum, 1997b). However, GH administration only moderately enhanced plasma IGF-I concentrations in neonatal calves (Grütter and Blum, 1991b; Hammon and Blum, 1997b). This is likely due to the low hepatic GH receptor numbers at this time (Breier and Sauerwein, 1995). An injection of Long-R³-IGF-I (an IGF-I analogue) reduced plasma GH concentrations, demonstrating that feedback effects of IGF-I on GH in neonatal calves are established. Plasma GH concentrations in neonatal calves were not influenced by feeding different amounts of colostrum or milk replacer and did not consistently change during the first week of life (Grütter and Blum, 1991b; Mears, 1993; Baumrucker and Blum, 1994; Hadorn et al., 1997; Hammon and Blum, 1997b; Kühne et al., 2000; Rauprich et al., 2000a,b).

Both IGF-I and Long-R³-IGF-I are not absorbed in the small intestine, even immediately after birth, and do not appear in significant amounts in blood even if administered in pharmacological amounts in calves (Vacher et al., 1995; Hammon and Blum, 1997b; Fäh, Hammon, Brem and Blum, unpublished observations) and pigs (Donovan et al., 1997). However, plasma concentrations of PRL were elevated and insulin concentrations reduced in some studies in calves fed rhIGF-I (Baumrucker and Blum, 1994), suggesting that orally administered IGF-I may exert systemic effects indirectly. Although colostrum IGF-I is not absorbed, the timing and amount of colostrum ingestion greatly influence plasma IGF-I concentrations in neonatal calves (Ronge and Blum, 1988; Grütter and Blum, 1991b; Hadorn et al., 1997; Hammon and Blum, 1997b; Egli and Blum, 1998; Kühne et al., 2000; Rauprich et al., 2000a,b). In suckling calves (with free access to colostrum), plasma IGF-I concentrations increased from days 1–7 of life (Egli and Blum, 1998). In contrast, plasma IGF-I concentrations decreased most during the first week of life in calves fed only milk replacer, while concentrations decreased less if calves were fed colostrum at the first meal and least if fed colostrum for 3 days (Hammon and Blum, 1997b). Furthermore, plasma IGF-I during the first week of life decreased less in calves fed colostrum than in those fed an IGF-I-free, isoenergetic, isonitrogenous

milk replacer (Rauprich et al., 2000b). In addition, plasma IGF-I concentrations were greatly reduced if first colostrum feeding was delayed for 24 h (Hadorn et al., 1997; Hammon et al., 2000) or after a withdrawal of feed for 24 h (Kinsbergen et al., 1994). In contrast to IGF-II (Hadorn et al., 1997; Hammon and Blum, 1997b), blood plasma IGF-I concentrations can therefore be modified by feeding in neonatal calves. Neonatal calves are able to produce IGF-I as IGF-I mRNA is expressed in the liver, GIT, spleen, thymus, lymph nodes and kidney (Cordano et al., 1998, 2000). These data are supported by the presence of immunoreactive IGF-I in the liver and pancreas of calves (Bestetti et al., 1992; Hammon and Blum, unpublished observations). Furthermore, administration of recombinant bovine GH (rbGH) increased plasma IGF-I concentrations in neonatal calves (Grütter and Blum, 1991b; Hammon and Blum, 1997b).

It is important to look at plasma IGF binding proteins (IGFBP) as they modify plasma IGF-I and -II concentrations and effects. Plasma IGFBP-3 concentration was not changed but plasma IGFBP-2 concentration increased more during the first week of life in calves fed milk replacer than in those fed colostrum or fed colostrum with a delay of 24 h (Skaar et al., 1994; Hammon and Blum, 1997b; Hammon et al., 2000). Plasma IGF-I concentrations were reduced in calves fed milk replacer or colostrum with a delay of 24 h, likely due to changes in IGFBP. Under-nutrition causes a reduction of IGF-I and IGFBP-3, and an increase in IGFBP-2 plasma concentrations (Thissen et al., 1994; Jones and Clemmons, 1995). Because the size of IGFBP-2 is smaller than IGFBP-3, it escapes capillaries more easily (Jones and Clemmons, 1995). Enhanced IGF-I binding to IGFBP-2, and less to IGFBP-3, in calves fed water or milk replacer instead of colostrum likely resulted in enhanced IGF-I clearance from the circulation. In addition, insulin may in part regulate plasma IGF-I concentrations through effects on IGFBP because IGFBP-1 and -2 concentrations are reduced by increased plasma insulin concentrations (Jones and Clemmons, 1995). Calves fed milk replacer instead of colostrum or those fed the first colostrum with a delay of 24 h had reduced plasma insulin concentrations, which possibly increased the IGFBP-2/IGFBP-3 ratio and thereby IGF-I clearance

from plasma (Hadorn et al., 1997; Hammon and Blum, 1998b; Hammon et al., 2000). When Long-R³-IGF-I was injected subcutaneously during the first week of life, plasma Long-R³-IGF-I concentrations transiently increased, whereas the plasma concentrations of endogenous IGF-I decreased during the first week much more than in controls (Hammon and Blum, 1997b). The subcutaneous administration of Long-R³-IGF-I raised plasma IGFBP-2 and reduced plasma GH concentrations (Hammon and Blum, 1997b). This latter evidence demonstrates that the neuroendocrine control of GH secretion in neonatal calves is functional, in agreement with Coxam et al. (1988). The decrease in plasma IGF-I concentrations may, in addition, have been due to enhanced IGF-I clearance as a consequence of elevated IGFBP-2 plasma concentrations (Hammon and Blum, 1997b). Long-R³-IGF-I injection also reduced plasma insulin concentrations in neonatal calves (Hammon and Blum, 1998a), which may have additionally increased plasma IGFBP-2 concentrations.

5. Conclusions

Ingestion of colostrum is important for morphological and functional development of calves. The GIT is the most markedly affected organ. Intake of the first colostrum causes typical metabolic and endocrine changes.

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