Case Report

A case of human linolenic acid deficiency involving neurological abnormalities[1, 2]

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ABSTRACT A 6-yr-old girl who lost 300 cm of intestine was maintained by total parenteral nutrition. After 5 months on a preparation rich in linoleic acid but low in linolenic acid she experienced episodes of numbness, paresthesia, weakness, inability to walk, pain in the legs, and blurring of vision. Diagnostic analysis of fatty acids of serum lipids revealed marginal linoleate deficiency and significant deficiency of linolenate. When the regimen was changed to emulsion containing linolenic acid neurological symptoms disappeared. Analysis indicated that linoleate deficiency had worsened but linolenate deficiency had been corrected. The requirement for linolenic acid is estimated to be about 0.54% of calories. *Am J Clin Nutr* 1982; 35:617–623.

KEY WORDS Linolenic acid deficiency, total parenteral nutrition, ω3 acids, linolenic acid metabolites, serum phospholipids, fatty acid patterns, essential fatty acids, polyunsaturated acids, neuropathy

Introduction

Since the identification of the fatty acids (FA) responsible for "essential fatty acid" activity by Burr and Burr (1), linolenic acid has been included in the list of active substances. As the technology improved for isolation of pure FA, doubt concerning the efficacy of linolenic acid increased, for in numerous studies linolenic (9,12,15-octadecatrienoic) acid and linoleic (9,12-octadecadienoic) acid have found to be of different biopotencies on a wide variety of biological phenomena (2). The most striking of the differences between linoleic and linolenic acids is the inability of the latter to permit reproduction in rats (3), a process that involves rapid proliferation of tissue. The nonequivalence of these two acids has been emphasized by observations that each administered at high levels inhibits the metabolism or utilization of the other (4).

Although a functional requirement for linolenic acid has not been demonstrated in mammals, from dose-response studies the quantitative nutritional requirement for biosynthesis of long-chain ω3 polyunsaturated acids derived from linolenic acid, has been measured and found to be approximately 0.5% of calories (5). Linolenic acid-deficient trout exhibit a shock syndrome and poor appetite, and 1% of linolenic acid is adequate for normal growth and reproduction (6). Although efforts to produce a linolenic acid deficiency in mammals have not induced impaired function or overt lesions observable macroscopically or by light microscope, intense study of changes in fatty acid composition and metabolism in linolenate deficiency is under way (7).

The long chain ω3 acids are found in high proportions in nervous tissues, and 22:6ω3 is the most abundant FA in the phospholipids

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of cerebral gray matter and the retina (8, 9). It is concentrated in synaptosomes (10) and photoreceptor outer segments (11). Differences in physical activity and ability to learn have been related to the low content of 22:6ω3 in brains of rats induced by a low linolenic acid diet (12). In recent years, interest in the essentiality or biological functions of linolenic acid has been increasing, because it is also the dietary precursor of 20:5ω3 which in turn is the precursor of thromboxanes and prostaglandins of the three series which influence platelet aggregation phenomena (13, 14). We now report a case of human linolenic acid deficiency induced by long-term intravenous hyperalimentation with a preparation high in linoleic acid but low in linolenic acid, and the correction of the attendant symptoms by a preparation containing linolenic acid.

Experimental procedures

Case report

In November of 1978, a 6-yr-old white female, previously in good health, sustained a 22-caliber rifle wound to the abdomen resulting in perforations of the duodenum, distal small bowel, transverse colon, and sigmoid colon with injuries to the inferior and superior mesenteric arteries and to the head of the pancreas. During the next 7 days she had three exploratory laparotomies with removal of 266 cm of small intestine, the ileocecal valve, and 34 cm of large bowel. She was admitted to a second hospital for 2.5 months where she experienced numerous complications including seizures, sepsis, and multiple draining abdominal enterocutaneous fistulae. An anastomosis of the distal duodenum to the descending colon, vagotomy, and pyloroplasty were performed. She was maintained with total parenteral nutrition (TPN) and was discharged to her local hospital. Two weeks later in February 1979, she was transferred to the Carle Foundation Hospital with peripheral edema, mild bilateral papilledema, muscle wasting and weakness, extensive abdominal and perineal dermatitis, mild obesity, conjugated hyperbilirubinemia, mild liver dysfunction, metabolic alkalosis, multiple enterocutaneous fistulae, delayed gastric emptying, and short bowel syndrome. Initial neurological examination revealed dermatitis, cheilosis, mild bilateral papilledema, normal mentation, normal cranial nerve function, normal muscle stretch reflexes, cerebellar function, and peripheral sensation to touch and vibration. During this hospitalization, she had closure of her fistulae, revision of her abdominal drainage procedure, and modification of the parenteral nutrition formula. She received basic TPN (40 g amino acids, 350 g dextrose, minerals and vitamins in 2000 ml daily). Preparation 2 (125 ml of 10% emulsion) was administered every other day. She was discharged on April 28, 1979, on home alimentation program receiving intermittent infusion during 14 to 16 h of each day. At that time her neurological examination was normal, papilledema resolved, and her height and weight normal for age. On June 14, 1979, the lipid source was changed to preparation 1, due to institutional availability. She initially received 150 ml of 10% emulsion of preparation 1 on alternate days and by September, 1979, was receiving 200 ml of preparation 1 per day. On December 26 the basic TPN was increased to 50 g amino acids and 400 g dextrose.

In November, 1979, she experienced the onset of episodes of distal numbness and paresthesias, and infrequent episodes of weakness leaving her unable to ambulate for 10- to 15-min periods. The numbness began distally on the bottom of her feet, involved the dorsum of her feet, spreading centrally, to the midlateral thigh areas. A vague pain was described in the lower extremities accompanying these episodes. Symptoms were worse at night and were associated with a pale appearance and a mottled discoloration of the distal lower extremities. Episodes of visual blurring of short duration began. Paresthesias and visual blurring increased from weekly to almost daily occurrence. In January 1980, she was admitted for evaluation. Neurological examination at that time was normal except for decreased peripheral vibratory sensation and a mild tremor of the left upper extremity. Findings, in addition, included a normal complete blood count, sedimentation rate, 20 channel chemistry analysis, T4, folate, zinc, vitamin B_{12}, electroencephalogram, electromyogram. Nerve conduction velocities measured in the left peroneal and the left posterior tibial nerves were 48.9 and 47.3 m/s, respectively. These latter values were considered within normal limits. the ophthalmological examination was normal. The serum selenium level was less than 10 pg/ml (normal greater than 12 pg/ml). Her height and weight were normal for age. FA patterns of serum lipids were measured in January 1980 in an effort to diagnose the cause of these abnormalities. In February 1980, the lipid source for the TPN was changed to preparation 2, 200 ml/day, because the analyses suggested a deficiency of serum ω3 acids. Over the next 12 wk, she experienced gradual and complete resolution of the paresthesias and episodes of weakness. On May 1, 1980, preparation 2 was increased to 250 ml/day. A second analysis was made of the FA patterns of her serum lipids on blood drawn August 20, 1980. Repeat nerve conduction velocities were performed in December of 1980 demonstrating rates of 56 and 51 m/s for the left peroneal and left posterior tibial motor nerves. The relationships of the neurological symptoms to the kinds and levels of TPN and to protein intake are shown in **Figure 1**.

Methods

Blood was drawn, allowed to clot, the serum collected, and shipped frozen to The Hormel Institute. The procedures for extraction of lipids and conversion to methyl esters were the same as reported previously (15). Gas chromatographic analysis of the methyl esters was performed on a Packard 428 gas chromatograph equipped with a flame ionization detector. An aluminum column ⅛" × 12' packed with 10% Silar 10 C on Gas Chrom Q, 100 to 120 mesh, was used and the gas chromatograph was programed from 160 to 230°C at 3°C/min. Data were calculated and arranged in tabular form by the PDP-12 computer.

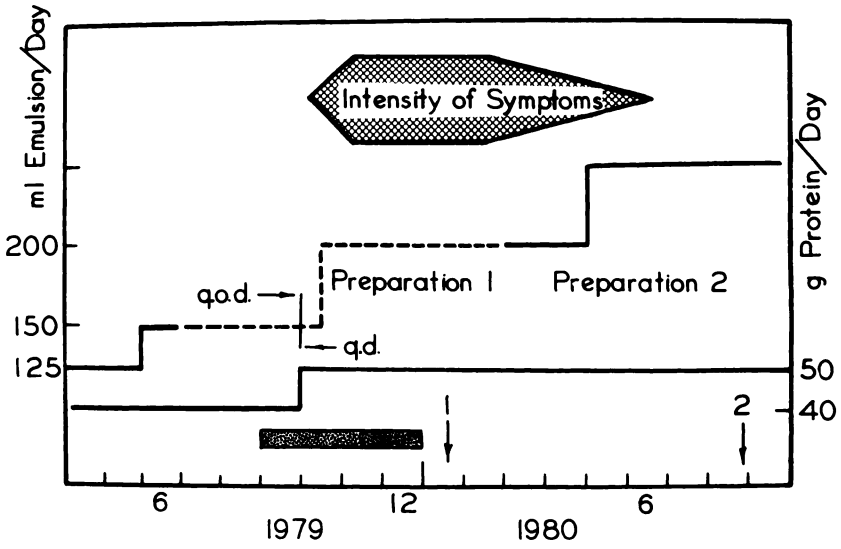

FIG. 1. The appearance of neurological symptoms in relationship to changes in the TPN regimen. The *stippled bar* indicated administration of Berocca c (vitamins B and C). Administration of 3 μg chromium per day was begun in December 1979. *Vertical arrows* indicate times when blood was drawn for FA analyses of serum PL (Tables 1 and 2). Both preparations were 10% emulsions. Doses before October 1979 were administered every other day (q.o.d.). Doses thereafter were administered daily (q.d.).

TABLE 1
Fatty acid pattern of serum PL in a child fed intravenously with a preparation containing no linolenic acid, compared with normal children*

FA	Individual (Female age 7.5)	controls (n = 72)		Significance	Normalcy ratio
		Mean	*SD*		
18:2ω6	15.50	21.56	6.65		0.72
18:3ω6	0.83	0.21	0.27	**	4.00
18:3ω3	0.00	0.21	0.19	*	
20:2ω9	0.00	0.21	0.21	*	
20:2ω6	0.38	0.54	1.14		0.71
20:3ω9	0.20	1.30	1.25		0.15
20:3ω6	2.94	3.67	1.39		0.80
20:4ω6	10.27	12.49	3.79		0.82
20:4ω3	0.06	0.34	0.38		0.18
20:5ω3	0.10	0.96	0.95		0.10
22:4ω6	0.65	1.87	1.01	*	0.35
22:4ω3	0.00	1.25	1.41		
22:5ω6	0.86	0.73	0.79		1.17
22:5ω3	0.27	0.62	0.56		0.43
22:6ω3	1.54	1.86	1.39		0.83
Double bond index	1.23	1.51	0.19	*	0.81
Total PUFA	33.60	47.98	6.31	**	0.70
Total ω6 acids	31.43	41.08	5.86	*	0.77
Total ω6–18:2	15.93	19.52	5.20		0.82
Total ω3 acids	1.97	5.23	2.16	*	0.38
Total ω3-18:3	1.97	5.02	2.16	*	0.39
6-Desaturation products	0.83	0.37	0.40	*	2.27
Elongation to C20	3.38	4.76	2.15		0.71
5-Desaturation products	10.57	14.76	4.74		0.72
Elongation to C22	0.92	3.74	2.05	*	0.25
4-Desaturation products	2.40	2.59	1.83		0.93
9-Desaturation products	22.95	13.04	4.00	**	1.76

Eack * indicates a difference from control values >1 SD.

Results and discussion

The polyunsaturated fatty acid (PUFA) composition of the serum phospholipids (PL) for the case under study during TPN with preparation 1 is shown in **Table 1**, and during TPN with preparation 2 in **Table 2**. These compositions are compared with the averages and SDs for each FA and calculated parameter measured on a population of control children collected in another study (15). The FA compositions of the extractable lipids from the two intravenous emulsions are given in **Table 3**.

During TPN with preparation 1, the content of linolenic acid in serum PL, normally 0.21%, was undetectable. The metabolites derived from 18:3ω3 were significantly decreased more than 1 SD, also indicating a deficiency of linolenic acid. The products of Δ4 and Δ5 desaturations were not significantly different from the values for the controls, but the products of Δ6 desaturation were significantly higher than control values due to the increased 18:3ω6 formed from linoleic acid. Δ9 Desaturation products (14:1ω5, 16:1ω7 + 18:1ω9) were also significantly increased. Polyunsaturated acids formed by chain elongation to C_{20} were decreased

TABLE 3
FA composition of the total extractable lipids of the two intravenous fat emulsions, both of which were administered as 10% emulsions

FA	Preparation 1 (one sample)*	Preparation 2 (two samples)*
12:0	0.26	
14:0	0.41	0.11
16:0	6.57	12.5
16:1	0.39	0.41
18:0	2.5	4.6
18:1ω9	12.3	31.4
18:2ω6	75.9	42.2
18:3ω6	0.38	
18:3ω3	0.66	6.9
20:2ω6	0.19	0.53
20:3ω9	0.42	
20:3ω6		1.2
20:4ω6	0.04	0.25
18:2ω6/18:3ω3	115.0	6.1

* Values are expressed as percentage of total FA.

TABLE 2
Fatty acid pattern of serum PL in the patient after TPN with a preparation containing linolenic acid, compared with normal children

FA	Individual (Female age 8.0)	controls (n = 72)		Significance	Normalcy ratio
		Mean	*SD*		
18:2ω6	11.56	21.56	6.65	*	0.54
18:3ω6	0.31	0.21	0.27		1.49
18:3ω3	0.17	0.21	0.19		0.83
20:2ω9	0.00	0.21	0.21	*	
20:2ω6	0.26	0.54	1.14		0.48
20:3ω9	0.99	1.30	1.25		0.76
20:3ω6	3.00	3.67	1.39		0.82
20:4ω6	9.46	12.49	3.79		0.76
20:4ω3	0.81	0.34	0.38	*	2.40
20:5ω3	0.68	0.96	0.95		0.71
22:4ω6	0.42	1.87	1.01	*	0.22
22:4ω3	0.00	1.25	1.41		
22:5ω6	0.52	0.73	0.79		0.71
22:5ω3	0.77	0.62	0.56		1.24
22:6ω3	4.35	1.86	1.39	*	2.34
Double bond index	1.38	1.51	0.19		0.91
Total PUFA	33.30	47.98	6.31	**	0.69
Total ω6 acids	25.53	41.08	5.86	**	0.62
Total ω6-18:2	13.97	19.52	5.20	*	0.72
Total ω3 acids	6.78	5.23	2.16		1.30
Total ω3-18:3	6.61	5.02	2.16		1.32
6-Desaturation products	0.31	0.37	0.40		0.85
Elongation to C20	4.07	4.76	2.15		0.85
5-Desaturation products	11.13	14.76	4.74		0.75
Elongation to C22	1.19	3.74	2.05	*	0.32
4-Desaturation products	4.87	2.59	1.83	*	1.88
9-Desaturation products	19.94	13.04	4.00	*	1.53

Each * indicates a difference from control values > 1 SD.

slightly, and products of elongation to C_{22} were decreased more than 1 SD. Total PUFA were significantly less than normal (2 SD), and the double bond index, or average number of double bonds per fatty acid, was also decreased (1 SD).

At this stage the patient was found to have a linoleic acid content of serum PL somewhat lower than, but within 1 SD of the normal average, perhaps because the volume of TPN was less than adequate. The first metabolite of linoleic acid, 18:3ω6, was elevated. The 20:2ω6, 20:3ω6, 20:4ω6, and 22:5ω6 were individually within normal range, but 22:4ω6 was significantly less than normal. As a group, the metabolites of linoleate were within normal range, but the total ω6 acids (including linoleate) were less than normal by 1 SD. These observations suggest an ω6 deficiency of a low or marginal degree compared with our previous experience with EFA deficiency induced by fat-free intravenous feeding (16–20). Even in the cases of much more severe ω6 acid deficiency, neurological symptoms have not been reported, so the ω6 deficiency present in this case probably does not account for the neuropathic effects observed.

Judging from the labeled composition of preparation 1, it was suspected to be relatively deficient in ω3 acids. Therefore, in the regimen of TPN, a switch was made to preparation 2 which is known to contain an appreciable amount of linolenic acid. Analyses of total extractable lipids from preparations 1 and 2 for fatty acid composition were performed and the data are shown in Table 3. The analyses confirmed that indeed, preparation 1 was very low in 18:3ω3 and that in preparation 2 linolenic acid was 6.9% of the total lipid fatty acids. Preparation 1 contained a very minor proportion of 18:3ω3 and a very high proportion of 18:2ω6. The wide disparity in content of these two acids, a ratio of 18:2ω6 to 18:3ω3 equal to 115, could have contributed to an accentuation of the linolenic acid deficiency through the competitive suppression of metabolism of linolenic acid to longer chain more highly unsaturated ω3 polyunsaturated acids. High levels of linoleic acid in the diet of rats have been shown to suppress the content of 20:5ω3, 22:5ω3, and 22:6ω3 in liver lipids (21). Indeed, linoleate fed at 5% of calories to rats suppressed the content of 22:6ω3 in liver lipids to about half of the level found when linoleate was 0.28% of calories. Therefore, preparation 1 having a ratio of 115:1 linolenic acid should strongly suppress the synthesis of long chain ω3 acids. The metabolites of 18:3ω3 which comprise a significant proportion of the total FA of brain and nerve have been found to be influenced by the levels of the precursor 18:3ω3, and 20:5ω3, and 22:5ω3 were not detected in brain FA when linoleate or arachidonate were the sole dietary fatty acids administered (22). Thus, the high proportion of dietary 18:2ω6 to 18:3ω3 present in preparation 1 probably suppressed the content of ω3 metabolites in nervous tissue in the case studied here.

After 6 months of TPN using preparation 2, the content of linoleate in serum PL was found to have decreased to 11.6%, to approximately half the average value found in the control children. This deviation from normal was greater than 1 SD of the normal group and indicated less than adequate intake of 18:2ω6. Total ω6 acids were decreased more than 2 SD from the average control value, and ω6 metabolites were decreased to 72% of normal confirming the ω6 deficiency. Although preparation 2 contained a moderately high proportion of 18:2ω6, either the volume of emulsion administered did not provide a sufficient amount of this nutrient to prevent advancing deficiency of ω6 acids, or the level of linolenic acid present may have inhibited the metabolism of linoleic acid (4). In rats receiving 0.6% of calories linoleic acid, the administration of 1% of calories of linolenic acid suppressed the archidonic acid content of liver lipids to about half the value present when linolenic acid was 0.05% of calories. Thus, if this phenomenon occurs in humans, the intake of linolenic acid at the level present in preparation 2 would be expected to suppress strongly the metabolism of linoleic acid to arachidonic acid (23).

TPN with preparation 2 did, however, reverse the ω3 deficiency measured in serum PL. The 18:3ω3 was found to be equal to the control value; 20:4ω3 exceeded the control value by 1 SD; 20:5ω3, 22:4ω3, and 22:5ω3 were within normal range; and 22:6ω3 exceeded the control value by more than 1 SD. Total ω3 acids and ω3 metabolites were 132 and 133% of control values, respectively. Thus, the ω3 deficiency was overcorrected. Although the total PUFA remained at 70% of control values and more than 2 SD from normal, yet the double bond index was con-

siderably improved. Although the proportion and amount of 18:2ω6 provided by the emulsion administered did not sustain normal levels of ω6 acids, the 18:3ω3 provided by the regimen was sufficient to overcorrect the ω3 deficiency.

The content of 20:3ω9 present in serum PL during TPN with preparation 1 was 15% of control value and the 20:3ω9/20:4ω6 ratio was 0.02 indicating normalcy, yet the child was marginally deficient in linoleic acid and very deficient in linolenic acid. During TPN with preparation 2 20:3ω9 was 76% of control value, and the 20:3ω9/20:4ω6 ratio was again normal at 0.11, although the linoleic acid deficiency worsened and the linolenic acid deficiency had been corrected. Thus, in these conditions in which 18:2ω6 and 18:3ω3 are both dietary variables, the triene/tetraene ratio is of no value to assess essential fatty acid status. This inadequacy of triene/tetraene ratio was noted also in nutritional experiments with rats (24).

The neurological abnormalities observed in the patient during the period when she was maintained on preparation 1 could not have been induced by deficiency of ω6 acids alone. Although she was marginally deficient in ω6 acids at that time, her deficiency in ω6 acids markedly worsened during intravenous alimentation with preparation 2, during which time her neurological symptoms lessened. Conversely, a biochemically measurable deficiency of ω3 acids occurred during the time her symptoms appeared, and changing to TPN containing 18:3ω3 corrected the ω3 deficiency and the neurological symptoms. We therefore suggest that linolenic acid is a required dietary nutrient for humans and that ω3 PUFA are required for normal nerve function.

The PUFA are the substrate pool from which prostaglandins, prostacyclins, thromboxanes, and leucotrienes are synthesized. The profile of free FA during the period of ω3 deficiency is shown in **Figure 2** and is compared with the profile of the FA of serum PL. In FA, the 18:2ω6 was significantly less than normal, but the metabolites of 18:2ω6 were increased to 336% of normal. Linolenic acid and its metabolites were not detectable. The 20:3ω9, the increase of which has been used as indicator of essential fatty acid deficiency, was not detectable in FA, and in PL was 15% of the control value despite the marginal deficiency of ω6 acids and the marked deficiency of ω3 acids during this period. In FA the products of Δ4 desaturation were very significantly increased, the products of Δ5 and Δ6 desaturation were moderately elevated, products of Δ9 desaturation were significantly diminished, and products of elongation were significantly elevated to 354% of control values. Thus, the pattern of

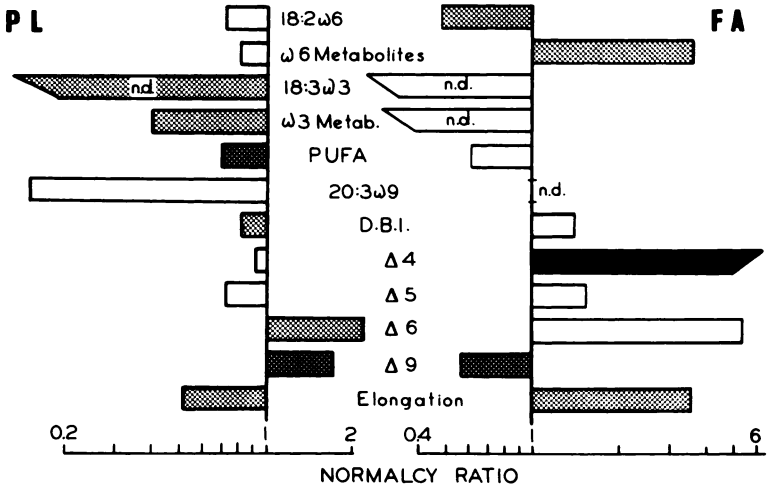

FIG. 2. PUFA profiles for PL and free FA of serum during regimen of TPN with preparation 1. The normalcy ratio is the observed value divided by control value, and is plotted on a logarithmic scale. *Open bars* represent changes less than 1 SD from control values; *light cross-hatch* more than 1 SD; *heavy cross-hatch* more than 2 SD; and *black* more than 3 SD. *Obliquely cut bars* indicate extreme values beyond the scale shown and n.d. indicates not detectable.

PUFA available in the FA pool for prostaglandin synthesis was radically altered during the period of ω3 deficiency. This probably influences the pattern of prostaglandins synthesized and may account for some of the symptoms observed.

The curative dose level of preparation 2, 250 ml 10% emulsion per day, provided approximately 1.625 g linolenic acid per day. This intake elevated the content of ω3 metabolites to 1.33 times control values. Assuming proportionality between dose and response, 1.22 g linolenic acid per day would have been sufficient to bring ω3 metabolites to control values. This intake is equivalent to 44 mg linolenic acid per kg body weight per day, or to 0.54% of total calories. This dose level compares closely to the 0.5% of calories of linolenic acid deduced to be the minimum nutrient requirement of the female rat (5). The ratio of linoleic acid to linolenic acid in preparation 1 was 115 and in preparation 2 was 6.1. The appropriate ratio to sustain control values of ω6 and ω3 acids in serum PL is not known, but it must lie between these two values. The higher than normal ω3 metabolites and the less than normal ω6 acids present in serum PL indicate that the linolenic acid content of preparation 2 is probably higher than optimal. Inasmuch as the dietary levels of 18:2ω6 and 18:3ω3 as well as their ratio affect the suppression of the metabolism of each by the other, an optimum intake of each cannot be stated at this time, but must be the subject of future research.

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