

Physical function and fitness in long-term survivors of childhood leukaemia

MARCO VAN BRUSSEL¹, TIM TAKKEN¹, JANJAAP VAN DER NET¹,
RAOUL H. H. ENGELBERT¹, MARC BIERINGS², MARJA A. G. C. SCHOENMAKERS¹,
& PAUL J. M. HELDERS¹

¹Department of Paediatric Physical Therapy & Exercise Physiology and ²Department of Paediatric Haematology, University Hospital for Children and Youth 'Wilhelmina Kinderziekenhuis', University Medical Center Utrecht, Utrecht, The Netherlands

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Abstract

Objective: To evaluate the physical function and fitness in survivors of childhood leukaemia 5–6 years after cessation of chemotherapy.

Materials and methods: Thirteen children (six boys and seven girls; mean age 15.5 years) who were treated for leukaemia were studied 5–6 years after cessation of therapy. Physical function and fitness were determined by anthropometry, motor performance, muscle strength, anaerobic and aerobic exercise capacity.

Results: On motor performance, seven of the 13 patients showed significant problems in the hand-eye co-ordination domain. Muscle strength only showed a significantly lower value in the mean strength of the knee extensors. The aerobic and the anaerobic capacity were both significantly reduced compared to reference values.

Conclusion: Even 5–6 years after cessation of childhood leukaemia treatment, there are still clear late effects on motor performance and physical fitness. Chemotherapy-induced neuropathy and muscle atrophies are probably the prominent cause for these reduced test results. Physical training might be indicated for patients surviving leukaemia to improve fitness levels and muscle strength.

Keywords: *Fitness, exercise, aerobic, anaerobic, quality of life, cancer*

Introduction

Childhood leukaemia has an increasing number of survivors; therefore more emphasis is focused on the long-term effects of disease and treatment. The success rate is attributed to the usage of more intensive systemic therapy. The chemotherapeutic treatment for children with leukaemia has short- and long-term effects on the neuromuscular and cardiovascular systems. *Vincristine*[®]-induced peripheral neuropathy is a well-defined complication of treatment for ALL [1]. Children with leukaemia show decreased muscle strength early in treatment [2, 3]. The magnitude of this decreased muscle strength and its impact on function and physical fitness are currently not well understood [2].

In children with leukaemia several scientific studies have been conducted investigating physical fitness [4–7]. In these studies, the main focus was

on cardiac—and pulmonary function. There is increasing evidence indicating that there are factors other than cardio-pulmonary factors, which limit the physical fitness of leukaemia patients [7, 8].

Obesity is an often occurring phenomenon after childhood leukaemia treatment [9–11]. Warner et al. [7] found in leukaemia patients a strong negative relationship between exercise capacity, including sub-maximal oxygen consumption and adiposity. According to Warner et al. this could be caused by a reduction in quantity and quality of mitochondria in the muscles of leukaemia patients [7]. This leads to a reduced oxygen uptake during sub-maximal exercise as well as the reduced capacity in leukaemia patients to oxidize fats as a fuel. This reduced oxidation of fats could lead to a form of adiposity [7].

In the literature there are several publications on exercise capacity in leukaemia patients after being

Correspondence: Tim Takken, Msc, PhD, Department of Paediatric Physical Therapy & Exercise Physiology, University Hospital for Children and Youth 'Wilhelmina Kinderziekenhuis', University Medical Centre Utrecht, Room KB.02.056. PO Box 85090, 3508 AB Utrecht, The Netherlands. Tel: +31302504030. Fax: +31302505333. E-mail: t.takken@umcutrecht.nl

58 treated medically [5, 12, 13]. However, no studies
59 investigated the anaerobic exercise capacity of
60 these patients, although it has been shown that the
61 anaerobic exercise capacity might be very important
62 in the performance of daily childhood activities with
63 chronic conditions [14]. Also a decreased anaerobic
64 performance in survivors of solid tumour cancers
65 was previously reported [15].

66 The objective of this study is to determine
67 whether physical function and fitness is reduced in
68 survivors of leukaemia 5–6 years after their final
69 treatment, compared to reference values of healthy
70 children and adolescents. (Physical function refers
71 to the capacity to perform activities of daily living.
72 Physical fitness refers to the exercise capacity as
73 measured under laboratory conditions (i.e. muscular
74 strength, cardiopulmonary fitness).)

77 Material and methods

79 Patients

80 Thirteen patients being treated for acute lym-
81 phoblastic leukaemia (six boys, seven girls) at
82 the Wilhelmina Children's hospital, Utrecht. The
83 Netherlands, participated in this study. Their
84 characteristics can be appreciated from Table I.
85

86
87
88 Table I. Anthropometric parameters and time of treatment
89 of the 13 ALL survivors.

90 Variables	M	SD	Range	
91 Age (years)	15.5	5.8	8.6–23.7	
92 Weight (kg)	54.24	19.5	25.1–80.7	NS
93 Height (m)	1.54	0.2	1.26–1.8	NS
94 BMI (kgm^{-2})	20.75	3.8	15.1–26.1	NS
95 Σ 7SF (mm)	96.3	46.6	49–182	NS
96 Time off treatment 97 (months)	61.9	6.8	46–73	

98 NS: not significantly different from reference values; BMI: body
99 mass index; Σ 7SF: sum of the seven skin-folds.

100
101 Table II. Patient characteristics and outline of treatment according to protocol ALL-8 and ALL-9.

	Treated with protocol ALL-8	Treated with protocol ALL-9
104 Number	6	7
105 Male-to-female ratio	3:3	3:4
106 Age (years)	17.9	13.5
107 Medication		
108 Induction	VCR/Pred/DNR/L-ASP+ MTX/Ara-c/Pred i.th	VCR/Pred/L-ASP+ MTX/Ara-C/Pred i.th.
109 Intensification	MD-MTX/6MP+ MTX/Ara-c/Pred i.th	MD-MTX/6MP+ MTX/Ara-c/Pred i.th.
110 Reinduction	VCR/Dexa/Adria/L-Asp/6MP, Ara-C, 6TG+ MTX/Ara-c/Pred i.th.	none
111 Maintenance	6 MP/MTX	6 MP/MTX+ Q 5 weeks: VCR/Dexa

112
113 VCR: vincristine, Pred: prednisone, DNR: daunorubicine, L-Asp: L-asparaginase, Ara-C: cytosine-arabioside, MTX: methotrexate,
114 Adria: doxorubicine, 6TG: 6-thioguanine, 6MP: 6-mercaptopurine, Dexa: dexamethasone, i.th: intrathecal.

Children who started chemotherapy in 1996 were treated according to the Dutch Childhood Leukaemia Study Group (DCLSG) protocol ALL-8 [16] and children who started chemotherapy in 1997 were treated according to the DCLSG protocol ALL-9 [17]. One patient with T-cell non-Hodgkin Lymphoma (T-NHL) was also treated according to protocol ALL-8 and was included in this study. Excluded were children with High-Risk ALL, receiving more intensive chemotherapy and children who were mentally disabled. Six of 13 were treated according to DCLSG protocol ALL-8 and seven of 13 according to Dutch Childhood Leukaemia Study Group protocol ALL-9. Children treated with protocol ALL-8 received $8 \times 1.5 \text{ mg m}^{-2}$ Vincristine over two periods of 4 weeks. Children treated with protocol ALL-9 received $34 \times 2.5 \text{ mg/dose}$ Vincristine during the whole treatment period of 2 years (Table II). In protocol 8, both dexamethasone and prednisone were used as corticosteroid-therapy, in protocol 9 dexamethasone alone was used the equivalent doses of steroids was 5–6 times higher in protocol 9 compared to protocol 8. On the other hand, the latter protocol contained more cytostatic agents (*daunorubicine, ara-C, 6-thioguanine*). Neither protocols included cranial irradiation. The eligible patients were participants in a previous study ($n=18$) from the group [3]. Thirteen patients of the original cohort participated in this study. Five did not participate: three for personal reasons, one for coming to the hospital too often and one left the country. The characteristics (age, gender and type of ALL) of these five patients did not differ from the other 13 patients. Informed consent was obtained from the parents and/or from the children if they were older than 12 years of age.

Skin-fold and muscle strength measurements were performed by the second author (TT) who is an experienced exercise physiologist and has significant familiarity with these measurements. All other measurements were performed by the first author (MvB). The medical-ethics committee of the

115 University Medical Centre Utrecht approved all
116 study procedures.

117 *Anthropometry*

118 The participants' body mass and height were
119 determined using respectively an electronic scale
120 and a stadiometer; subcutaneous adiposity was
121 determined from skin-fold measurements using
122 Harpenden skin-fold callipers (Holtain, Crymych,
123 UK). The measurements were taken at seven sites
124 (at the right side of the body); triceps, biceps,
125 subscapular, suprailiac, mid-abdominal, medial calf
126 and thigh in accordance with the American College
127 of Sports Medicine guidelines [18]. No percentage
128 of body fat was calculated because there are no
129 validated prediction formulae for leukaemia patients
130 [11]. Therefore, the sum of the seven skin-folds
131 was used as an index for body fat after Pollack et al.
132 [19]. Body Mass Index was calculated as body mass/
133 height². The BMI of the included patients were
134 compared and to international cut-off points for
135 body mass index for overweight and obesity [20].
136
137

138 *Motor performance*

139 The movement assessment battery for children
140 (Movement ABC test) tested the motor performance
141 of the patients [21, 22]. The Movement ABC screens
142 motor performance of children between 4–12 years.
143 The Movement ABC consist of test items for four age
144 groups: 4–6 years, 7–8 years, 9–10 years and 11–12⁺
145 years. As described in the manual, the instrument can
146 be used for children above this age as well [22]. In the
147 Dutch version of the Movement ABC the upper age
148 band is therefore listed as 11–12⁺. Children above
149 12 years of age were compared with the normative
150 percentile scores of the age band 11–12⁺ [22].
151

152 The test can be divided into two parts: a checklist
153 and a motor performance test. The motor test
154 measures three different aspects of motor perfor-
155 mance, i.e. manual dexterity, ball skills, dynamic
156 and static balance. Percentile scores of the child's
157 motor abilities were compared with a normative
158 age-matched sample of children [21]. A score below
159 the 5th percentile indicates that the child has
160 significant movement difficulties. In scores between
161 the 5th and 15th percentile, the child is at risk for
162 these difficulties. The motor performance is ade-
163 quate in scores above the 15th percentile [21].
164 Children were evaluated using the score forms for
165 their appropriate age group.
166

167 *Strength measurement*

168 Muscle strength was measured with a hand-held
169 dynamometer (Citec dynamometer CT 3001, C.I.T.
170 Technics, Groningen, the Netherlands) in six
171

different muscle groups (shoulder abductors, knee
extensors, foot dorsal flexors, wrist extensors, hip
flexors and grip strength). Maximum muscle
strength was tested using the 'break' method, in
which the examiner gradually overcomes the muscle
strength of the patient and stops at the moment the
extremity gives way. Grip strength was measured
using the 'make' method. With the subjects sitting
and the arms held 90° flexion at their sides, the
dynamometer was gripped as hard as possible for 3
seconds without pressing the instrument against the
body and without touching the elbow to the body.

During the test, the examiner manually stabilized
the body parts proximal to the tested limb segment.
Each person was tested once and in this session
every muscle group was measured three times and
the highest score was recorded. The highest value
was used for comparison. Reference values for
muscle strength (mean and SD for age and gender)
were obtained from Beenakker et al. [23] and van
der Ploeg et al. [24] and grip-strength from
Engelbert et al. [25] and used for analyses.

Exercise capacity

Wingate anaerobic exercise test. The Wingate
Anaerobic test (WAnT) as described by Bar-Or [26]
was performed on a calibrated electromagnetic
braked cycle ergometer (Lode Examiner, Lode BV,
Groningen, the Netherlands). The ergometer was
upgraded and calibrated by the manufacturer to
a maximal resistance of 800 W instead of the standard
400 W. External resistance was controlled and the
power output was measured using the Lode Wingate
software package. The seat height was adjusted to
the patients' leg length (comfortable cycling height).
The external load (torque; in Nm) was determined,
dependent of bodyweight (at 0.53 bodyweight and
0.55 bodyweight for girls and boys under 14 years
of age and 0.67 bodyweight and 0.7 bodyweight
for older girls and boys, respectively) according
to the user manual. The patients' feet were placed
in the Velcro toe-straps and the exercise protocol
was explained. The patients were instructed to exercise
for 1 minute at the cycle ergometer with an external
load of 15 W at 50–60 rpm. Thereafter, the sprint
protocol started. The patients were instructed to cycle
all-out for 30 seconds. Power output during the
WAnT was corrected for the inertia of the mass
of the flywheel (23.11 kg m⁻²). Measured variables
were mean power and peak power. Mean power
represents the average power output over the 30
seconds sprint. Peak power is the highest recorded
power output achieved during the 30 seconds sprint.

Cardio-pulmonary exercise test (CPET). Patients
performed a cardio-pulmonary exercise test using

an electronically braked cycle ergometer (Lode Examiner, Lode BV, Groningen, the Netherlands). The test started with 1 minute of unloaded cycling, preceded to the application of resistance to the ergometer. After this minute, workload was increased with a constant increment of 10 or 20 W every minute. The protocol was selected to elicit a maximal exercise response within ~6–12 minutes [27]. This protocol continued until the patient stopped because of exhaustion, despite verbal encouragement of the test-leader. The highest achieved workload (W_{\max}) was recorded. During the cardio-pulmonary exercise test, subjects breathed through a facemask (Hans Rudolph Inc, USA) connected to a calibrated metabolic cart (Oxycon Champion, Jaeger, Viasys, Balthoven, the Netherlands). Expired gas was passed through a flow meter (Triple V volume transducer), an oxygen (O_2) analyser and a carbon dioxide (CO_2) analyser. The flow meter and gas analysers were connected to a computer, which calculated breath-by-breath minute ventilation (VE), oxygen uptake (VO_2), carbon dioxide output (VCO_2) and the respiratory exchange ratio ($RER = VCO_2/VO_2$) from conventional equations. Heart rate (HR) was measured continuously during the maximal exercise test through a bipolar electrocardiogram. Maximal effort occurred when one of the two criteria were met: $HR > 180$ beats per minute or $RER > 1.0$. Peak oxygen consumption ($VO_{2\text{peak}}$)

was taken as the average value over the last 30 seconds during the maximal exercise test. Relative $VO_{2\text{peak}}$ was calculated as absolute $VO_{2\text{peak}}$ divided by body mass. For both the anaerobic exercise test as well as the cardio-pulmonary exercise test, the patients were compared to recently obtained reference values from the laboratory using the same experimental procedures [28].

Statistics

All data were entered and analysed in SPSS 12.0 for Windows. Due to the small number of patients and the individual variability in response, there were no statistically significant differences between the patients in the two treatment protocols with respect to any of the variables. Therefore, the data of both groups were pooled and used together in the statistical analysis. Independent samples *T*-tests were used to test differences between patients and reference values. Alpha level was set at $p < 0.05$ for all analyses.

Results

The anthropometrical parameters of the patients indicated that none of 13 patients were obese and three patients were overweight, although mean scores did not differ from reference values. The results of the Movement ABC are shown in Table III and indicate that 7/13 of the patients had a score below the 15th percentile score in the 'ball skills' domain compared to healthy children. All patients scored above the 15th percentile in the manual dexterity domain. One patient scored between the 5th and 15th percentile on dynamic balance.

The strength measurement data (Table IV) indicated that only knee extension strength was significantly reduced from normal values. All other muscle tests were within normal ranges.

The measurements of the anaerobic capacity indicate that all values were significant lower in the survivors of ALL compared to the control

Table III. Frequencies of percentile scores of the Movement ABC test.

	Manual dexterity (number of patients)	Ball skills (number of patients)	Static and dynamic balance (number of patients)
$p > 15$	13	6	12
$p = 5-15^*$	0	3	1
$p \leq 5$	0	4	0
Total	13	13	13

*Scores between the 5th and the 15th percentile indicate that the child is at risk for motor delay.

Table IV. Muscle strength measurement values of six different muscle groups (mean, standard deviations (SD) and range, *z*-scores and *p*-values.

	Patients		Controls			
	<i>M</i>	SD (range)	<i>M</i>	SD (range)	<i>Z</i> -score	<i>p</i> -value
Grip strength	117.4	75.20 (36.0–290.0)	120.5	57.0 (57.4–192.0)	–0.32	0.35
Shoulder abductor	161.8	64.17 (75.0–298.0)	144.7	46.2 (93.7–226.3)	0.58	0.1
Knee extensor	252.1	81.13 (129.0–350.0)	299.7	98.9 (166.0–396.0)	–0.67	0.001
Foot dorsal flexor	206.6	81.77 (78.0–346.0)	185.7	50.9 (127.5–248.9)	0.41	0.25
Wrist extensor	142.3	68.46 (64.0–280.0)	153.2	66.0 (75.0–237.0)	–0.14	0.8
Hip flexor	212.0	78.31 (112.0–336.0)	206.6	65.6 (129.4–291.4)	0.14	0.6

Control values obtained from references [23–25].

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Table V. Anaerobic and aerobic exercise performance of the 13 ALL survivors.

Variables	$M \pm SD$	Range	M predicted $\pm SD$	p -value
<i>Wingate Anaerobic test</i>				
Mean power (W)	376.1 (171.9)	163–587	492.9 (276.9)	0.000
Peak power (W)	538.6 (289.6)	218–1094	867.32 (508.2)	0.000
<i>Cardio-pulmonary exercise test</i>				
VO_{2peak} ($L \min^{-1}$)	1.99 (0.99)	0.93–3.398	2.69 (1.15)	0.001
$VO_{2peak/kg}$ ($ml \text{ kg}^{-1} \min^{-1}$)	36.64 (18.3)	17.15–62.65	49.58 (21.22)	0.001
W_{max} (W)	155 (82.41)	60–280	222.98 (97)	0.000
VE_{max} ($L \min^{-1}$)	64.69 (36.1)	27.60–146.5	94.9 (37.9)	0.001

VO_{2peak} : peak oxygen uptake; $VO_{2peak/kg}$: peak oxygen uptake related to body mass, W_{max} : maximal work load; VE_{max} : maximal ventilation.

group (Table V). Table V also shows the data of the cardiopulmonary exercise test. VO_{2peak} , $VO_{2peak/kg}$, W_{max} and VE_{max} were significant lower in the survivors of leukaemia compared to reference values.

Discussion

This study found that long-term survivors of childhood leukaemia had a lower level of physical function and fitness compared to healthy children. Although the disease in the present patient group is in remission, they may experience late effects from the anti-leukaemia therapy (chemotherapy) affecting multiple organ systems. Chemotherapeutic agents have known toxicities on different organ systems and can affect the function of lung, heart and muscle [29–31]. Corticosteroid therapy, in particular protocols with *dexamethasone*, are associated with obesity or overweight as an early and late side effect [32].

Movement ABC

The Movement ABC showed that there were a number of patients with problems in hand-eye co-ordination. The outcome values of the movement ABC are quite remarkably compared to earlier described values. Reinders-Messelink et al. [33] studied motor performance in 17 children during and after chemotherapy. They found balance problems to be most severe during treatment. The manual dexterity skills showed an opposite pattern. The percentage of patients with manual dexterity problems was higher after treatment compared at the start. In the study of Schoenmakers et al. [3] the percentage of patients with manual dexterity problems (11%) was somewhat lower compared to the percentage of patients reported by Reinders-Messelink et al. [33] (33.3%). The percentage of patients with manual dexterity problems in the study (7.7%) was also lower than the number of patients reported by Reinders-Messelink et al. [33]. The patients in the study of Schoenmakers et al. [3] were the same patients (13 of the 18) tested in the current study. The outcome might be due to the small sample

size in all these studies. Just like the study of Schoenmakers et al., gross motor disturbance was found more frequently occurring than fine motor problems [3]. Unlike the study of Reinders-Messeling et al. there were no balance problems with the patients of the present study. The greatest problems were seen with the ball skills (hand-eye co-ordination). A relationship between the motor problems and vincristine-induced neurotoxicity seemed plausible, but the effect of other neurotoxic drugs, like methotrexate and steroids, could not be ruled out [33–35].

Strength measurement

The findings of the present study indicates that 5–6 years after treatment muscle strength of the knee extensors was still reduced compared to reference values, other muscle groups were within the normal range, however. This might be explained by the effect of chemotherapy on muscle fibres (especially type II fibres) and the neural drive. Harila-Saari et al. [1] showed in their study both demyelination and a loss of descending motor fibres or loss of muscle fibres in a population after treatment from childhood ALL, indicating impairment within both the central and peripheral motor nervous system. Atrophy of type II fibres of the proximal muscle, especially those in the lower limbs, are manifestations of corticosteroid-related myopathies [36]. Decreased muscle strength has been identified in young adults surviving ALL in their childhood [37]. Lehtinen et al. [38] found a decreased motor nerve conduction in the peripheral nerves even 5 years after treatment, while 33% of their population still had clinical neurological findings [38].

The reason why only a reduced strength in the knee extensors was used might be explained by the fact that lower extremity strength appears more affected than upper extremity strength in deconditioning studies [39]. Especially weight-bearing muscles in the lower extremities are the most affected muscles during periods of under loading [39].

286 *Anaerobic exercise capacity*

287 The anaerobic exercise capacity of the patients in the
288 present study was significantly reduced compared to
289 the control group. This finding is in accordance with
290 the findings of McKenzie et al. [15] in childhood
291 and adolescent survivors of solid tumour cancers.
292 During short-term high intensity exercise such as the
293 WAnT Type IIa and Type IIx muscle fibres are
294 heavily recruited [26]. It is well known that during
295 catabolic periods such as cachexia and corticosteroid
296 treatment the major amount of muscle atrophy
297 occurs in type II muscle fibres [36]. Presumably
298 type I fibres are more resistant to atrophy in these
299 conditions. Moreover, recent studies suggest that
300 WAnT performance is also related to intra- and
301 inter-muscular co-ordination [40]. Thus, the
302 reduced anaerobic capacity might be a result of
303 both an impaired motor co-ordination and a reduced
304 active muscle mass during exercise. In these patients,
305 deviant scores were also found on the Movement
306 ABC which could confirm the hypothesis of
307 impaired motor co-ordination.
308

310 *CPET*

311 The various parameters of the cardiopulmonary
312 exercise test indicate a significant decrease of the
313 aerobic exercise capacity. The VO_{2peak} , W_{max} and
314 VE_{max} were significantly reduced compared to refer-
315 ence values, in concordance with other studies [5].
316 The significantly lower VO_{2peak} indicates that the
317 physical fitness of ALL survivors is reduced com-
318 pared to healthy children. VO_{2peak} is the product of
319 cardiac output and the arterio-mixed venous oxygen
320 difference (the Fick equation). Abnormalities in
321 cardiac output may indicate reduced cardiac func-
322 tion. The patients had a maximal heart rate between
323 169–201 beats per min. at maximal exercise with,
324 respectively, a respiratory exchange ratio between
325 0.95–1.41. This indicates that ALL survivors can
326 achieve high heart rates in combination with a
327 metabolic acidosis, as is usually found in healthy
328 children. The fact that there was no decrease of the
329 blood saturation indicates that there was no major
330 impairment in pulmonary function. The significant
331 lower aerobic exercise capacity could be due to a
332 combination of metabolic and neuromuscular
333 impairments.
334

335 There is some evidence that exercise training can
336 improve physical fitness and health-related quality
337 of life of leukaemia patients [41, 42]. This improve-
338 ment makes it a relevant issue in the care for
339 survivors of ALL. Exercise physiologists and other
340 professionals could assist in designing appropriate
341 exercise training programmes for attenuating cancer-
342 related fatigue and improving physical fitness [36]

in order to help increase physical fitness in children
surviving cancer [43, 44].

Because of the small patient group with a hetero-
geneous age range from a single centre it is difficult
to determine the generalizability of the current
findings. Moreover, the cross-sectional design of
the study does not show the rate of recovery
after the treatment phase. Longitudinal multi-
centre studies should be initiated to study the effects
of the disease, treatment and rehabilitation in this
patient group.

Conclusion

In conclusion, it was found that even 5–6 years after
cessation of therapy there still are clear late effects
of chemotherapy in patients treated for childhood
leukaemia. Aerobic and anaerobic physical fitness
and motor performance were consider-
ably lower compared to healthy children.
Chemotherapy-induced muscle atrophy, myopathy
and neuropathy might be the cause of the signifi-
cantly reduced test scores. The results indicate that
prescription of exercise in general by health-care
professionals would be advisable so that these
children are encouraged to be just as active as they
were before treatment. If children are already active,
but still have a reduced exercise capacity, a tailored
exercise programme should be initiated.

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