Fetal Growth and Glucose and Insulin Metabolism in Four-year-old Indian Children

C.S. Yajnik[a], C.H.D. Fall[b], U. Vaidya[a], A.N. Pandit[a], A. Bavdekar [a], D.S. Bhat[a], C. Osmond[b], C.N. Hales[c], D.J.P. Barker[b]

[a]King Edward Memorial Hospital Research Centre, Pune, India, [b]MRC Environmental Epidemiology Unit, Southampton General Hospital, and [c]Department of Clinical Biochemistry, Addenbrookes Hospital, Cambridge, England

Studies in Britain have shown that adults who had a low birthweight have high plasma glucose concentrations 30 and 120 min after an oral glucose load, and an increased risk of Type 2 diabetes and impaired glucose tolerance. Both Type 2 diabetes and low birthweight are common in India. To determine whether low birthweight is associated with reduced glucose tolerance in Indian children, glucose tolerance tests were carried out on 379 4-year-old children, whose birthweights were recorded, in Pune, India. Among 201 children who had been looked after on the routine postnatal wards at birth, those with lower birthweights had higher plasma glucose and insulin concentrations 30 min after an oral glucose load, independently of their current size ($p = 0.01$ and 0.04, respectively). Mean glucose and insulin concentrations were 8.1 mmol l^{-1} and 321 pmol l^{-1} in children whose birthweight had been 2.4 kg or less, compared with 7.5 mmol l^{-1} and 289 pmol l^{-1} in those who weighed more than 3.0 kg. Among 178 children who had been looked after in the Special Care Baby Unit, those with lower birthweights also had higher plasma insulin concentrations at 30 min but there were no trends with plasma glucose. Our findings suggest that Indian children with reduced intra-uterine growth have reduced glucose homeostasis after a glucose challenge. This is consistent with the hypothesis that Type 2 diabetes mellitus in India may be programmed in fetal life.

KEY WORDS Low birthweight Impaired glucose tolerance Insulin resistance India

Introduction

Recent studies in Britain have shown that men and women who had a low birthweight have an increased prevalence of Type 2 (non-insulin-dependent) diabetes and impaired glucose tolerance (IGT).[1,2] Among 64-year-old men in Hertfordshire, England, the prevalence of impaired glucose tolerance or Type 2 diabetes fell progressively from 40 % in those who weighed 5.5 lb (2.5 kg) or less at birth to 14 % in those who weighed over 9.5 lb (4.3 kg).[1] Similar results were found among 50-year-old men and women in Preston, England.[2] The relation of Type 2 diabetes and IGT to low birthweight was independent of gestational age at birth, showing that it was linked to reduced growth rates *in utero* rather than to premature birth. In both studies concentrations of plasma glucose and insulin, and the prevalence of IGT and Type 2 diabetes, were higher in overweight people, and highest in men and women who were light at birth and obese as adults. The relation of IGT to low birthweight has recently been confirmed in young adults in the USA.[3,4]

These findings have led to the hypothesis that Type 2 diabetes originates through impaired development in fetal life.[5,6] Insulin has a central role in regulating fetal growth.[7] It responds to nutrient levels and ensures that growth rates are commensurate with the nutrient supply. It is suggested that fetal undernutrition in pregnancy results in growth retardation, permanently impaired development of the endocrine pancreas[8] and peripheral insulin resistance which continues into adult life.[6] Type 2 diabetes is thereby 'programmed' *in utero*.

Low birthweight and thinness at birth are common in India.[8] Type 2 diabetes is common in India,[9] and among Indians who migrate to the West,[10] and population studies in the UK and elsewhere suggest that Indian men and women are more insulin resistant than Europeans.[11,12] This is usually explained by the existence of a 'thrifty genotype',[13] but programming of glucose and insulin metabolism by fetal undernutrition is an alternative explanation. Animal experiments have shown that changes in the glucose concentration to which a fetus is exposed produce effects on glucose/insulin metabolism for at least two generations.[14] Insulin resistance in second and third generation migrants does not necessarily indicate the existence of a specific genotype.

A study of children in Salisbury, England,[15] has shown that thinness at birth is associated with elevated plasma

Correspondence to: Dr C.H.D. Fall, MRC Environmental Epidemiology Unit, Southampton General Hospital, SOUTHAMPTON SO16 6YD, England.

CCC 0742–3071/95/040330–07

Accepted 14 October 1994
DIABETIC MEDICINE, 1995; 12: 330–336

glucose concentrations 30 min after an oral glucose load, at the age of 7 years. This shows that the metabolic impairment associated with reduced fetal growth can be detected during childhood. We have measured plasma glucose and insulin responses to an oral glucose load in two samples of 4-year-old children in Pune, India. The first was a random sample of live births occurring in one hospital; and the second comprised babies admitted for special care.

Patients and Methods

Two groups of 4-year-old children were studied.

Routine admissions: 404 singleton babies, born in the King Edward Memorial Hospital (KEMH), Pune, India, during October 1987 to April 1989, weighing over 2000 g and admitted to the routine postnatal wards. They were selected from all 1998 live births recorded in the labour ward register for that period, using random number tables. Birth weight was recorded routinely for these babies but gestational age was not.

Special Care Baby Unit admissions: all 271 babies who survived the perinatal period, out of 446 singleton babies of birthweight less than 2000 g born during October 1987 to April 1989 and admitted to the Special Care Baby Unit (SCBU) of the KEMH. The KEMH was the only hospital in Pune with special care facilities and this group comprised babies transferred from other maternity units, as well as babies born in the KEMH. Gestation was determined by Dubowitz examination,[16] and the group included both premature and small-for-dates babies. They had been followed up by the paediatric department of the KEMH as part of a longitudinal study of neurodevelopment in low birthweight babies, and formed an accessible, though unrepresentative, sample of unusually small babies.

We wrote to the childrens' parents inviting them to the hospital, where the study was explained by a paediatrician and consent obtained. Children were admitted to hospital, with one parent, the evening before the test and fasted overnight. In the morning an indwelling forearm venous cannula (22G) was inserted after application of local anaesthetic cream. Fasting blood samples were taken for measurement of plasma glucose, insulin, proinsulin, and 32-33 split proinsulin. The child was then given a drink containing 1.75 g of anhydrous glucose per kilogram body weight in 150 ml of water. Further blood samples were taken at 30 and 120 min after the glucose load, for measurement of plasma glucose and insulin concentrations.

The child's weight was measured on a portable Seca scale to the nearest 500 g. Height was measured on a wall-mounted stadiometer (Microtoise, CMS Instruments, London, England) to the nearest 0.1 cm. Triceps and subscapular skinfold thicknesses were measured to the nearest 0.1 mm using Holtain skinfold callipers (CMS Instruments, London). Waist and hip circumferences were measured standing, at end expiration, to the nearest 0.1 cm, using steel tapes (CMS Instruments, London). The child's socio-economic status was assessed by a social worker using the Kuppuswamy score.[17] This is a standardized scoring system, based on a questionnaire administered to the parent(s), asking for details of their education, income, size and type of housing, and availability to the family of water and sanitation. Scores range from 1 down to 5, the least advantaged category. Ethical permission for the study was given by the KEM Hospital Ethics Committee.

Laboratory Investigations

Plasma glucose concentrations were measured in Pune using a standard glucose oxidase method (VP Super, Abbott, Irving USA). Plasma insulin, proinsulin and 32-33 split proinsulin concentrations were measured in Cambridge, England, using a two-site immunometric assay with either alkaline phosphatase or ^{125}I as label.[18,19] The insulin assay was standardized against the first international reference preparation coded 66/304 and its sensitivity (mean + three standard deviations of the zero signal) was 2.3 pmol l^{-1}. The intact and split proinsulin assays were standardised against standards obtained from the Lilly Research Laboratories (Indianapolis, USA).

Statistical Analysis

The measurements of plasma glucose concentrations at 30 and 120 min, and of plasma insulin, proinsulin, and 32-33 split proinsulin concentrations had skewed distributions. The values were transformed to normality for the analysis using either logarithms (plasma glucose and fasting insulin, proinsulin, and 32-33 split proinsulin), the square root (plasma insulin at 30 min) or the cube root (plasma insulin at 120 min). Quartiles, rather than standard deviations, have therefore been used to describe the data in Table 2. Comparisons between the sexes were made using *t*-tests. Adjustments of plasma glucose and insulin concentrations for current parameters: weight, age, and sex, were made in both groups of children combined, using multiple linear regression. Body mass index is not commonly used in children, and was related less closely to these variables than was weight alone. Analysis of the relation between glucose, insulin, proinsulin, 32-33 split proinsulin, and birthweight was by tabulation of means and trend tests from one-way analysis of variance; the two groups of children were analysed separately.

Results

Of the 404 children admitted routinely, 84 were no longer living at the address listed at birth. Of the remaining 320, the parents of 201 (63 %) agreed that their child could take part. Of the 271 children admitted for special care, 30 had died since discharge and 50

had moved. Of the remaining 191, the parents of 178 (93 %) agreed that their child could take part. All children had at least one blood sample taken, and the analysis includes all children. Eight children (all SCBU admissions) were found to be either HIV or HbSAg positive. Their samples were analysed for glucose in Pune but were not sent for insulin assay. Six children did not have results for 120 min glucose, 9 did not have results for fasting insulin, 6 for 30 min insulin, and 14 for 120 min insulin. This was due to difficulty in taking samples, or to clotting or haemolysis of specimens.

The children's ages ranged from 3.7 to 4.4 (median 4.0 years). Table 1 shows their mean birthweight, gestational age at birth, and anthropometry at the age of 4 years. Even among the routine admissions mean birthweight was low by western standards, but consistent with population studies in India.[8] Similarly, 4-year weight and height were below western mean values,[20] but similar to Indian community averages.[21] As expected, girls had smaller head circumferences and greater subscapular and triceps skinfold thicknesses than boys, but their waist-hip ratios were similar. The socio-economic status of children in the two groups was similar. Percentages of children in socio-economic groups one to five were 21, 46, 19, 14, and 2.

Glucose

Table 2 shows mean plasma glucose concentrations at 0, 30, and 120 min. There were no differences between boys and girls. In both groups of children, plasma glucose concentrations were positively related to their current weight, and fatness measured by subscapular and triceps skinfold thicknesses. The relation to weight was statistically significant for plasma glucose at 30 min ($p = 0.03$) and 120 min ($p = 0.0001$), but not for fasting glucose ($p = 0.2$). The p values for the relation of 0, 30, and 120 min plasma glucose to subscapular skinfold thickness were 0.2, 0.09, and < 0.0001, respectively, and for triceps skinfold thickness 0.07, 0.2, and < 0.0001.

Table 3 shows mean plasma glucose concentrations according to birthweight, divided into approximate quintiles. Among the routine admissions, 30 min plasma glucose concentrations fell with increasing birthweight ($p = 0.04$). This trend was stronger after allowing for current weight ($p = 0.01$). The highest 30 min plasma glucose concentrations were in children who were light at birth and heavy at 4 years. The mean concentration in children who weighed 2.5 kg or less at birth but more than 14 kg at 4 years was 8.2 mmol l^{-1} compared with 7.5 mmol l^{-1} in children who weighed more than 2.9 kg at birth and 12 kg or less at 4 years.

Plasma glucose concentrations at 30 min were higher in children who were more socio-economically advantaged. This was partly accounted for by their greater current size. Allowing for socio-economic status did not alter the relation of 30 min plasma glucose to birthweight. There was no relation of 30 min plasma glucose to birthweight among the special care admissions.

Fasting and 120 min plasma glucose concentrations showed no relationship to birthweight among either the routine or SCBU admissions. Seven children had impaired glucose tolerance as defined by a 120 min glucose concentration of 7.8 mmol l^{-1} or more. They had above average skinfold thicknesses, the mean values being 7.5 mm for subscapular and 10.0 mm for triceps, but their birth measurements were around the average with a mean birthweight of 2.938 ($n = 5$) in the routine admissions and 1.410 ($n = 2$) in the special care admissions.

Table 1. Mean birthweight and current anthropometry of 4-year-old children born in the King Edward Memorial Hospital, Pune, India, or admitted to the SCBU

	Routine admissions		Special care admissions	
	Boys	Girls	Boys	Girls
n	105	96	96	82
Birth				
Birthweight (kg)	2.789 ± 0.39	2.744 ± 0.33	1.567 ± 0.21	1.516 ± 0.27
Gestation at birth (weeks)	–	–	34.9 ± 2.4	34.7 ± 2.4
4 years				
Weight (kg)	13.2 ± 1.6	12.9 ± 1.9	12.3 ± 1.9	12.0 ± 1.7
Height (cm)	97.8 ± 4.4	97.6 ± 4.5	94.6 ± 4.7	95.1 ± 4.7
Head circumference (cm)	48.4 ± 1.4	47.6 ± 1.2	47.2 ± 1.6	46.5 ± 1.5
Subscapular skinfold (mm)	5.7 ± 1.6	6.4 ± 1.8	5.7 ± 1.7	5.8 ± 1.6
Triceps skinfold (mm)	8.3 ± 2.0	9.1 ± 1.9	7.9 ± 2.1	8.5 ± 1.9
Waist/hip ratio	0.95 ± 0.11	0.95 ± 0.06	0.94 ± 0.15	0.96 ± 0.07

Results expressed as mean ± SD.

Table 2. Mean plasma glucose, insulin, proinsulin, and 32-33 split proinsulin concentrations in 4-year-old children in Pune, India

	Routine admissions		Special care admissions	
	Boys	Girls	Boys	Girls
n	105	96	96	82
Plasma glucose (mmol l^{-1})				
0 min	4.4 (4.2,4.4,4.7)	4.4 (4.0,4.4,4.7)	4.4 (4.1,4.3,4.7)	4.4 (4.1,4.4,4.8)
30 min	7.9 (6.9,8.0,9.1)	7.8 (7.1,7.9,9.1)	7.8 (6.6,7.9,9.1)	8.0 (6.9,8.0,9.2)
120 min	5.4 (4.8,5.5,6.3)	5.4 (4.8,5.5,6.1)	5.1 (4.4,5.1,5.9)	5.3 (4.8,5.5,6.0)
Plasma insulin (pmol l^{-1})				
0 min	25 (19,27,35)	30 (22,32,44)	25 (16,26,39)	29 (20,31,51)
30 min	283 (198,264,400)	340 (230,299,443)	294 (166,276,426)	318 (229,306,409)
120 min	110 (61,117,193)	135 (69,131,205)	79 (31,67,146)	107 (50,111,183)
Proinsulin (pmol l^{-1})	2.0 (1.4,2.0,2.6)	2.1 (1.5,2.0,2.9)	2.1 (1.5,2.2,2.8)	2.1 (1.3,2.0,2.8)
32-33 split proinsulin (pmol l^{-1})	2.8 (1.8,2.7,4.1)	3.4 (2.2,3.4,4.6)	2.8 (1.9,2.8,4.1)	3.3 (1.9,3.2,4.6)

Numbers in parentheses = quartiles.

Table 3. Mean body weight and plasma glucose concentrations according to birthweight

Birthweight (kg)	Number of children	Weight at 4 years	Glucose (mmol l^{-1})		
			0 min	30 min	120 min
Routine admissions					
≤ 2.4	36	12.4	4.5	8.1	5.1
−2.6	36	13.0	4.5	8.3	5.6
−2.8	44	13.0	4.4	7.8	5.7
−3.0	42	13.1	4.3	7.9	5.2
> 3.0	43	13.9	4.4	7.5	5.4
All	201	13.1	4.4	7.9	5.4
p value for trend		0.0008	0.1	0.01[a]	0.7[a]
Special care admissions					
≤ 1.3	34	11.3	4.3	7.9	4.8
−1.5	47	12.2	4.5	7.9	5.3
−1.6	28	12.3	4.5	7.8	5.1
−1.7	28	12.6	4.2	7.9	5.2
> 1.7	41	12.3	4.5	7.9	5.3
All	178	12.1	4.4	7.9	5.2
p value for trend		0.02	0.8	0.8[a]	0.2[a]

[a]Allowing for childrens' current weight.

Insulin

Mean plasma insulin concentrations at 0, 30, and 120 min are shown in Table 2. Concentrations were higher in girls than in boys at all time points (0 min: $p = 0.004$, 30 min: $p = 0.04$, and 120 min: $p = 0.006$). Plasma insulin concentrations were positively related to the childrens' current weight, and fatness measured by subscapular and triceps skinfold thicknesses. The *p* values for the relation of 0, 30 and 120 min plasma insulin to current weight were all < 0.0001. The corresponding values for the relation to subscapular skinfold thickness were 0.02, 0.01, and < 0.0001, and for triceps skinfold thickness 0.04, 0.2, and < 0.0001. Insulin concentrations fell with increasing age (0 min: $p = 0.2$, 30 min: $p = 0.005$, 120 min: $p = 0.003$, allowing for current weight). Plasma insulin concentrations at 0 and 30 min were inversely related to head circumference at 4 years ($p = 0.0005$ and 0.03 allowing for current weight, age, and sex). The higher insulin concentrations in girls were partly accounted for by their greater skinfold thicknesses and smaller head circumferences.

Table 4 shows mean plasma insulin concentrations according to birthweight. Among the routine admissions 30 min plasma insulin concentrations fell with increasing birthweight. This trend was statistically significant ($p = 0.04$), allowing for 4-year weight, age, and sex. The 30 min plasma insulin concentrations also fell with increasing birthweight among the special care children. This was not statistically significant but became so ($p = 0.05$) after adjustment of birthweights for gestational age.

Plasma insulin concentrations at 30 min were higher

Table 4. Mean plasma insulin concentrations and ratio of insulin to glucose at 30 min according to birthweight

Birthweight (kg)	Insulin (pmol l^{-1})			Ratio of 30 min insulin/ glucose
	0 min	30 min	120 min	
Routine admissions				
≤ 2.4	27	321	94	4.4
−2.6	29	337	127	4.4
−2.8	28	309	143	4.3
−3.0	24	298	120	4.2
> 3.0	31	289	123	4.2
All	28	310	121	4.3
p value for trend	0.5[a]	0.04[a]	1.0[a]	0.08[a]
Special care admissions				
≤ 1.3	24	344	67	4.5
−1.5	32	313	105	4.3
−1.6	25	275	84	4.0
−1.7	21	299	93	4.2
> 1.7	28	292	102	4.1
All	27	305	91	4.2
p value for trend	0.4[a]	0.1[a]	0.5[a]	0.2[a]

[a]Allowing for childrens' current weight, age, and sex.

in socio-economically more advantaged children. This was accounted for by their greater current weight. Allowing for socio-economic status did not alter the relation of 30 min plasma insulin concentrations to birthweight.

Plasma insulin concentrations at 0 and 120 min were not related to birthweight in either group of babies. The seven children who had impaired glucose tolerance had higher mean 120 min insulin concentrations, 451 pmol l^{-1} compared with 103 pmol l^{-1} in the remainder ($p < 0.0001$), but similar insulin concentrations at 0 and 30 min.

Insulin/Glucose Ratio

In both groups of children the ratio of insulin to glucose at 30 min was higher in girls than boys ($p = 0.01$). The ratio rose with increasing 4-year weight ($p = < 0.0001$) and fell with increasing age ($p = 0.004$, allowing for weight). Allowing for sex, current weight, and age, the insulin to glucose ratio at 30 min was highest in the children of lowest birthweight, and fell with increasing birthweight (Table 4), although this was not statistically significant in either group of children. The ratios at 0 and 120 min were not related to birthweight.

Proinsulin and 32-33 Split Proinsulin

Mean fasting plasma proinsulin concentrations (Table 2) were similar in boys and girls. Concentrations were positively related to 4-year weight ($p < 0.0001$), but not to skinfold thicknesses. There was no relation of proinsulin to birthweight in either the routine or the special care admissions. Mean fasting plasma 32-33 split proinsulin concentrations (Table 2) were higher in girls than boys ($p = 0.006$). Similar to proinsulin, concentrations rose with increasing 4-year weight ($p < 0.0001$), but were not related to skinfold thicknesses. The 32-33 split proinsulin concentrations were not related to birthweight.

Discussion

We have studied plasma glucose and insulin concentrations after an oral glucose load in 4-year-old children in India. Among children who received routine postnatal care those who had lower birthweight had higher 30 min plasma glucose and insulin concentrations, independently of their current body size. Among children who were low birthweight babies, admitted to the special care baby unit, birthweight was unrelated to 30 min plasma glucose, but showed similar trends in plasma insulin. These findings are consistent with those of a recent study of 7-year-old children in Salisbury, England, among whom 30 min plasma glucose fell with increasing birthweight and ponderal index at birth.[15] Raised 30 min plasma glucose and insulin concentrations after an oral glucose load cannot be equated with impaired glucose tolerance, which is defined by values at 120 min. Our results, however, suggest that Indian children with reduced intra-uterine growth show impaired glucose homeostasis after a glucose challenge. This is the first evidence that glucose and insulin metabolism may be programmed *in utero* in Indian people.

The response rate and completeness of measurements in this study were relatively high for a study involving multiple blood samples from young children. The children studied were selected samples of the population. The 'routine admissions' were all born in the KEM hospital, one of several hospitals with maternity facilities in Pune. However, they included children from a wide range of social circumstances since some were paying patients and others were poor enough to receive free treatment. Our analysis was based on internal comparisons. The selection of hospital patients and failure to trace some subjects would therefore introduce bias only if the relation between birthweight and glucose/insulin concentrations differed in those born in hospital and outside, and those traced and not traced. This seems unlikely. The 'SCBU admissions' were a heterogeneous group, comprising children born small-for-dates and/or prematurely, and children born in other hospitals, referred because this was the only SCBU in the city.

There is a high neonatal mortality rate among low birthweight babies. Only 271 (61 %) of the babies in our special care sample survived to be discharged from hospital. A further 30 were known to have died since discharge from hospital. The children studied were, therefore, only 40 % of the low birthweight babies originally admitted to the SCBU. This heterogeneity, and factors influencing survival, may bias the relationship between birthweight and glucose/insulin metabolism. Hence the two groups of children were analysed

separately and not compared. Although there was no relation of 30 min plasma glucose concentrations to birthweight among the SCBU admissions, findings for plasma insulin were similar in the two groups. A recent study suggested that the association between insulin resistance and low birthweight reflected better survival of low birthweight babies who are insulin resistant.[4] However, the similarity between our findings in India and those of a recent study of children in Salisbury,[15] where perinatal and child mortality is low, suggest that selective mortality is not a major determinant of the association between low birthweight and impaired glucose/insulin metabolism.

A link between low birthweight, and raised concentrations of glucose after an oral load has been shown in three studies of adults in Britain,[1,2,22] and confirmed in two studies in the USA.[3,4] The associations are strong, graded and found within each social class and at every level of adult body mass index. In adult studies birthweight is linked to both 30 and 120 min plasma glucose and to 120 but not 30 min plasma insulin.[1,2] In our children we found no relationships between birthweight and 120 min glucose or insulin concentrations. Thus the reduced glucose homeostasis associated with low birthweight is evident only at 30 min after an oral glucose challenge in childhood but persists for a longer time in adult life.

Impaired fetal growth could be linked to reduced glucose tolerance through either insulin deficiency or resistance. The two cannot be distinguished by oral glucose tolerance test data. Fasting insulin concentrations, often used as a proxy for insulin resistance in adults, were not raised in children of lower birthweight. The ratio of insulin to glucose concentrations at 30 min, however, were higher in children who had been lighter at birth (Table 4). This suggests that their higher glucose concentrations at 30 min were due to insulin resistance rather than deficiency. A link between insulin resistance and impaired fetal growth is also suggested by the strong association between lower head circumference and raised fasting plasma insulin concentrations. Head circumference at 4 years is largely determined *in utero* and during the first 6 postnatal months.[23].

As in other studies,[24] we found that girls had higher fasting insulin concentrations than boys, which was only partly explained by their greater skinfold thicknesses. This could reflect greater insulin resistance in girls than in boys. In clinical practice in India disorders associated with insulin resistance, including gestational diabetes and polycystic ovaries disease, are common in young women. In the West plasma insulin concentrations are related to current weight across its whole range in both children and adults. We found that this continuous relationship was present even in relatively underweight children in India as it is among non-obese adults in India.[25]

Low birthweight and thinnness at birth are common in India.[8] We suggest that the high prevalence of Type 2 diabetes and IGT in Indian people may be linked to reduced fetal growth.

Acknowledgements

We thank social workers: A. Vairagar, K.N. Raut and V. Gaikwad who traced the subjects, research nurses Gokhale and Jadhav who looked after the children on the ward and helped carry out the glucose tolerance tests, and computer staff: V.M. Joshi (Pune) and V. Cox (Southampton). We also thank the laboratory staff at the KEM Hospital, Pune and the Department of Clinical Biochemistry, Addenbrookes Hospital, Cambridge. The study was funded by the Wellcome Trust and the Medical Research Council of the UK.

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