

Blood Pressure Does Not Rise Before the Onset of Microalbuminuria in Children Followed From Diagnosis of Type 1 Diabetes

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OBJECTIVE — To examine whether a rise in blood pressure could be detected before the onset of microalbuminuria (MA) in a cohort of children followed from diagnosis of type 1 diabetes.

RESEARCH DESIGN AND METHODS — The Oxford Regional Prospective Study is an incident cohort study of children with type 1 diabetes aged (mean \pm SD) 9.8 ± 3.7 years at diagnosis. Subjects were assessed annually from diagnosis, with measurement of HbA_{1c}, arterial blood pressure (random zero), and three urine samples for estimation of the albumin/creatinine ratio. During follow-up, 63 of 494 children developed MA at one or more annual assessments and were designated as cases for a nested case-control study. Each case was matched for sex and age at diagnosis with two normoalbuminuric control subjects. Blood pressure (BP) data were compared at corresponding years of diabetes duration.

RESULTS — Cases with MA were similar to normoalbuminuric control subjects with respect to age and BMI, but they had higher mean HbA_{1c} levels (mean difference 1.1%, $P < 0.001$). In the years before the onset of MA, the diastolic BP standard deviation score (SDS) was significantly higher than zero in cases (mean 0.49, $P < 0.001$) and in control subjects (0.50, $P < 0.001$). No difference could be detected between cases and control subjects before the onset of MA in either systolic or diastolic BP (mean difference systolic -1.2 mmHg [95% CI -4.7 to 2.7], mean difference diastolic 0.1 mmHg [-2.4 to 2.6]). However, within the cases, the onset of MA was associated with elevations in systolic and diastolic BP SDSs ($F = 16.1$, $P < 0.001$; and $F = 18.0$, $P < 0.001$). BMI, but not HbA_{1c}, was associated with systolic and diastolic BP SDSs in the subjects with MA ($F = 0.6$, $P = 0.4$; and $F = 12.3$, $P = 0.001$). However, the association of BP with MA remained significant for systolic BP ($P = 0.001$) and for diastolic BP ($P < 0.001$) after adjusting for BMI.

CONCLUSIONS — A rise in systemic BP cannot be detected before the first appearance of MA in children with type 1 diabetes. BP rises concurrently with the onset of MA and is also closely related to BMI.

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A complete listing of the Oxford Regional Prospective Study Group is listed in the APPENDIX.

Abbreviations: ACR, albumin/creatinine ratio; ANCOVA, analysis of covariance; BP, blood pressure; CV, coefficient of variation; MA, microalbuminuria; ORPS, Oxford Regional Prospective Study; SDS, standard deviation score.

A table elsewhere in this issue shows conventional and Système International (SI) units and conversion factors for many substances.

In type 1 diabetes, much of the excess morbidity and mortality caused by cardiovascular disease and end-stage renal failure occur in individuals with diabetic nephropathy (1). In addition to hyperglycemia, both environmental factors and a genetic susceptibility are thought to be important factors in the development of diabetic nephropathy (2–4). It is also generally accepted that elevated blood pressure (BP) accelerates the progression of diabetic nephropathy to end-stage renal failure (5), but its role in the pathogenesis of early (incipient) nephropathy is less certain. In recent cross-sectional studies, a familial predisposition to primary hypertension was associated with microalbuminuria (MA) (incipient nephropathy) (6), which suggests that BP may be important in initiating early renal disease. Longitudinal studies that have looked at the temporal relationship of BP and MA onset have not consistently shown either a rise in BP or a lack thereof before the onset of MA (7,8). However, these studies (7,8) were not incident cohorts, and the individuals examined had variable durations of diabetes. The studies may have excluded individuals with onset of MA occurring early in the course of diabetes who were, therefore, possibly more susceptible than those developing it after many years of diabetes (8). Studies have focused primarily on adult subjects, and there are relatively few prospective data in childhood that take into account the differential effects of growth on BP (9).

We have analyzed data from the Oxford Regional Prospective Study (ORPS) to assess whether arterial BP rises before or after the onset of MA. ORPS is a longitudinal natural history study of MA in children with type 1 diabetes who were followed from diagnosis. We report a case-control study, nested within this incident cohort, contrasting subjects who have developed MA with those who have not.

Table 1—Mean of all measurements of age, BMI, and HbA_{1c}, and duration of follow-up of cases with MA and matched control subjects

Subject characteristics	Cases with MA	Control subjects with no MA	Mean difference between cases and control subjects	P
n	62	62 pairs		
Age at diagnosis	9.8 ± 3.7	9.8 ± 3.7	0.0 (0.1)	0.3
Mean age (years)	15.0 ± 3.3	14.8 ± 3.3	0.2 (0.2)	0.2
Mean BMI (kg/m ²)	22.1 ± 4.0	22.0 ± 2.6	0.5 (0.5)	0.3
Mean HbA _{1c} (%)	10.9 ± 1.6	9.8 ± 1.1	1.1 (0.3)	<0.001

Data are means ± SD or means (SEM).

RESEARCH DESIGN AND

METHODS—Eligible subjects were children diagnosed with type 1 diabetes before the age of 16 years who were within a geographically defined region. Ascertainment, recruitment, and preliminary data relating to MA have been reported previously (10). Ethical approval was obtained from the local ethics committees in the region. Written informed consent was obtained from parents, and children were asked to give assent before the study.

Of 494 children who had been followed for a median of 5 years (range 2–13), 63 had developed a urine albumin excretion within the range of MA (albumin/creatinine ratio [ACR] ≥3.5 and ≥4.0 mg/mmol in male and female subjects, respectively) in at least two of three first-void urine specimens (consecutive days) at one or more annual assessments. These children were designated cases for this study (10). Control subjects were selected from the remaining 431 children, who had not developed MA. Cases were matched for sex and age at diagnosis (within 1 year), using a 1:2 case-control allocation ratio. A total of 3 cases could be matched to only 1 control subject, and 9 cases were matched to 3 control subjects to compensate for missing data, resulting in a total of 133 control subjects. One case-control pair was excluded from the analysis because of insufficient BP data in the case. Data were excluded after the start of antihypertensive treatment for the one patient who was prescribed treatment.

Subjects were recruited at diagnosis and were thereafter assessed annually. Height was measured with wall-mounted stadiometers, and weight was measured with electronic scales. BMI was reported

in kilograms per meter squared. BP was measured using a random zero sphygmomanometer (Hawksley & Sons, West Sussex, U.K.) and an appropriately sized cuff on the nondominant arm, with the subject sitting down and the arm supported, after a period of rest. Systolic and diastolic BP were measured to the nearest 2 mmHg at Karotkoff sounds 1 and 5, respectively. Two measurements were taken, and the mean was calculated for both systolic and diastolic BP. Three early-morning (first-void) or timed overnight urine specimens were collected annually from each subject for measurement of ACR. Urine albumin was measured with a double-antibody enzyme-linked immunosorbent assay; the details of the method have been described previously (10). The interassay coefficient of variation (CV) was 12 and 10% at 1.5 and 16 mg/l, respectively. Creatinine was measured using a modified Jaffe method, and the CV was 2% at 2.2 mmol/l. MA was defined as an ACR ≥3.5 and ≥4.0 mg/mmol in male and female subjects, respectively, in two of three consecutive early-morning (first-void) specimens at an annual assessment. This corresponded to an albumin excretion rate of >20 µg/min (10). HbA_{1c} was measured by high-performance liquid chromatography with a between-batch CV of 3.5 and 2.2% at levels 5.6 and 10.1%, respectively, and a normal range of 4.4–6.4% (10,11).

Statistical methods

The BPs of each case were compared with the mean BPs of the control pair at corresponding years of diabetes duration. Years of duration of diabetes in both cases and control subjects were expressed relative to the onset of MA in the cases. Variables were compared between cases and

control subjects by first calculating the mean for a specific time period (before or after the onset of MA or the entire period of follow-up) for each case and for each control pair. The Student's *t* test for paired samples was then used for comparisons within case-control pairs. A general factorial linear model was used for cases and control subjects separately to examine the effect of HbA_{1c}, BMI, and the onset of MA on BP within individuals (12). All BP measurements were entered into the model, with a mean of 5.6 measurements per subject. Pooled normal data from European subjects were used for the calculation of age- and sex-specific standard deviation scores (SDSs) for BP (13). The single-sample Student's *t* test was used to compare BP SDSs to zero. Results are expressed as the mean ± SD unless otherwise specified. SPSS 6.0 was used, and statistical significance was defined as *P* < 0.05.

RESULTS

Cases and control subjects were similar for age at diagnosis, mean age, and mean BMI (Table 1). Mean HbA_{1c} was significantly higher in the cases, with a mean difference of 1.1% (Table 1). No difference in either systolic or diastolic BP could be detected before the onset of MA (mean systolic BP difference −1.2 mmHg, 95% CI −4.6 to 2.7; mean diastolic BP difference 0.1 mmHg, −2.4 to 2.6; *n* = 49). There was a rise in both mean systolic BP and diastolic BP after the onset of MA in the cases compared with the control subjects, although the difference was of marginal significance (mean systolic BP difference 2.2 mmHg, 95% CI −0.3 to 4.4; mean diastolic BP difference 1.9 mmHg, −0.2 to 4.0; *P* = 0.080; *n* = 60) (Fig. 1). Table 2 shows the differences in systolic BP that were observed at −1, 0, 1, 3, and 5 years of diabetes duration relative to the onset of MA, and it shows the statistical differences that were within the power of the study to detect.

Systolic BP SDSs were significantly lower and diastolic BP SDSs were significantly higher than zero in both the cases (mean [SD] systolic SDS −0.92 [1.04], diastolic SDS 0.49 [0.82]) and the control subjects (systolic SDS −0.82 [0.57], diastolic SDS 0.50 [0.67]) before the onset of MA (*P* < 0.001). No significant difference was detected between cases and control subjects in either the median systolic or

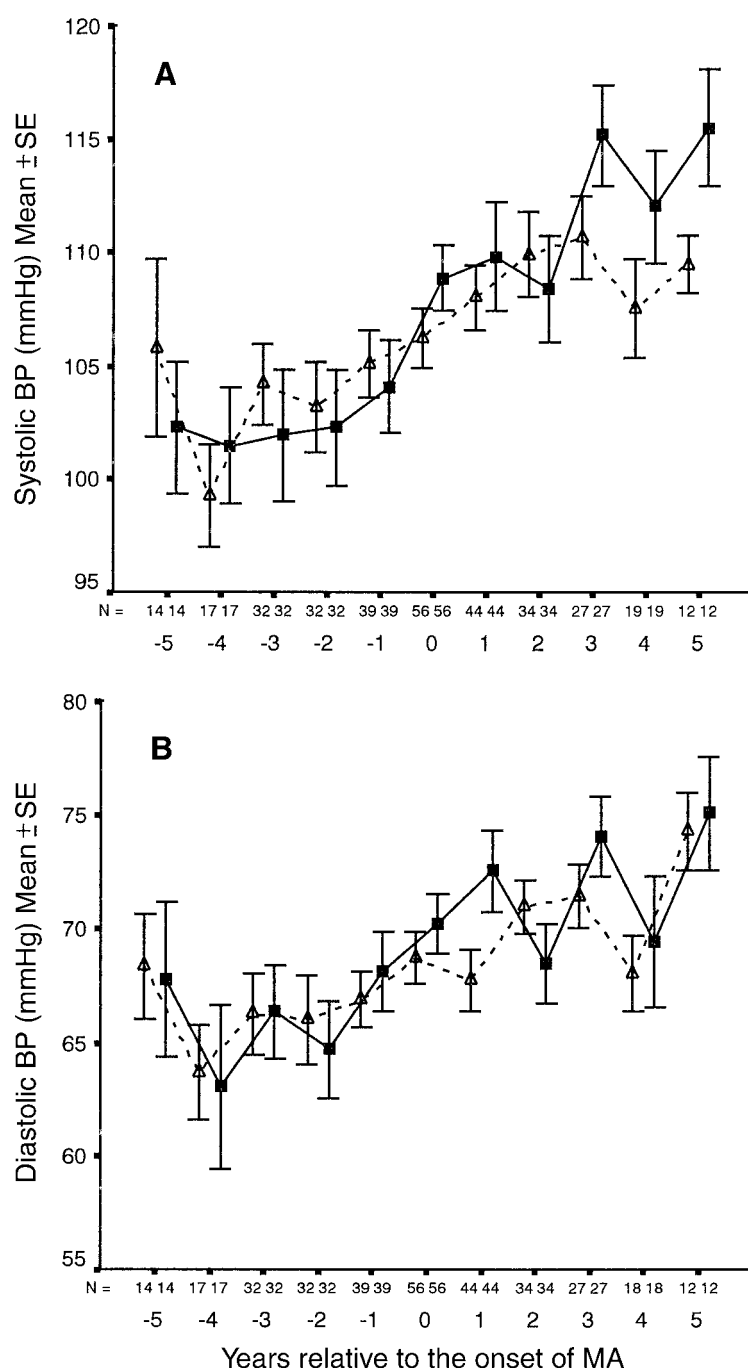


Figure 1—Systolic (A) and diastolic (B) BP in cases (■) and control subjects (△) across years of duration of diabetes relative to the onset of MA. Years before and after the onset of MA are negative and positive, respectively.

diastolic BP SDSs, either before or after the onset of MA (mean [SD] after MA onset: systolic SDS -0.54 [0.72] vs. -0.72 [0.43], $P = 0.091$; diastolic SDS 0.85 [0.69] vs. 0.68 [0.45], $P = 0.1$). Elevated BP values, defined as an SDS >2.0 in at least two annual assessments, were present in seven cases and four control

subjects for diastolic BP and in four cases and one control for systolic BP.

In the control subjects, the effect of BMI and HbA_{1c} on BP SDSs was examined using a general factorial univariate analysis of variance model. BMI, but not HbA_{1c} , was significantly associated with the systolic BP SDS within subjects (BMI

$F = 12.3$, $P = 0.001$; HbA_{1c} $F = 0.6$, $P = 0.4$). Similar results were found when diastolic BP SDS was used as the dependent variable (BMI $F = 25.6$, $P < 0.001$; HbA_{1c} $F = 1.9$, $P = 0.2$).

The analysis was repeated in the cases using analysis of covariance (ANCOVA) to determine the intraindividual effect of the onset of MA on the BP SDS. The onset of MA was significantly associated with change in systolic BP SDSs ($F = 16.1$, $P < 0.001$), and the association remained significant after adjusting for the effects of BMI (Table 3). A similar relationship was observed between the onset of MA and diastolic BP SDSs ($F = 18.0$, $P < 0.001$), and the association remained significant after adjustment for BMI (Table 3). In the control subjects, the time period matched to the onset of MA in the cases was not associated with either systolic or diastolic BP in the multivariate ANCOVA model.

CONCLUSIONS— This report is on a matched nested case-control study of 63 microalbuminuric subjects with a mean age of 9.8 years at diagnosis of type 1 diabetes and of 133 subjects who remained normoalbuminuric after a median follow-up of 5 years. Both tight matching of the two comparison groups for age, sex, and duration of diabetes and the similarity in BMI minimized the confounding potential of these variables on the analysis of BP changes over time. This also increased the power of the study to detect small differences in BP.

Our study was powered to detect both a difference in mean systolic BP of 4.9 mmHg across all the years before the onset of MA and a difference of 5.1 mmHg 1 year before the onset of MA at a 95% confidence level and with 80% power. However, no rise in BP was detected before the onset of MA. Similar findings were recently reported in two other childhood cohorts: one incident cohort and one retrospective study (14,15). However, in both the studies (14,15), the comparison between the cases and the control subjects was made at fixed years of duration of diabetes instead of at a fixed number of years before the onset of MA. As a result, the appearance of MA at a different duration of diabetes in each subject would have decreased the power of these studies to detect an early difference in BP. Furthermore, the effects of age on BP were not taken into account (14,15). In another nested case-control study with 32

Table 2—Differences in systolic BP (between cases and control subjects) that were observed in years relative to the onset of MA and the size of differences that the study was powered to detect

Years relative to onset of MA	Observed difference	95% CI*	Detectable difference	P
−1	−1.0	−4.6 to 2.6	±5.1	0.6
0	2.6	−0.5 to 5.8	±4.5	0.099
1	1.8	−2.5 to 6.1	±4.8	0.4
3	4.5	−0.8 to 9.9	±7.6	0.093
5	6.0	−0.9 to 13.0	±9.7	0.083

Data was at 95% confidence level and 80% power. *95% CI of the difference.

childhood cases and 32 control subjects matched for age, sex, diabetes duration, and pubertal status (9), no rise in BP was reported either 6 months before or 6 months after the onset of MA (9). Although some studies in adults reported a higher BP at baseline in subjects who subsequently progressed to MA (8), other studies did not detect a difference (7). The balance of evidence does not support the hypothesis that a rise in systemic BP is important in initiating diabetic renal disease.

In our study, both mean systolic and diastolic BP were marginally higher after the onset of MA in the cases than in control subjects (mean systolic difference 2.3 mmHg, $P = 0.09$). The study was powered to detect a difference in mean systolic BP—as calculated across all the years after the onset of MA—of 3.2 mmHg at a 95% confidence level and 80% power. Despite this lack of significant mean differences, ANCOVA within individuals detected that the years after the onset of MA were associated with a rise in both systolic and diastolic BP, after adjusting for the effects of BMI in the cases. In contrast, the time period matched to the onset of MA in the cases was not associated with either systolic or diastolic BP changes in the control subjects. These findings were highly suggestive of small increases in BP concurrent with MA onset. Results from a number of other studies in both adults and children have also suggested concomitant changes in BP with the onset of MA (7,9,14). In these studies as well as in ours, the degree of change in BP may have been underestimated because of the effects of regression dilution, which can be described as the underestimation of a true effect due to the variability introduced by random fluctuations of BP (16). In some studies the relationship between BP changes and MA have been examined after adjusting

for the effects of regression dilution using 24-h ambulatory BP profiles (17). In one study, ambulatory measurements were taken at baseline in 44 normoalbuminuric subjects with type 1 diabetes and again 3 years later (17). In this study an increase in urine albumin excretion was always associated with a rise in BP (17). Concomitant increases in albumin excretion and BP could explain the higher BP levels before the onset of MA reported in two studies in adults (8,18); in these studies, subjects were selected because they had levels of urine albumin excretion that were higher than normal, but below the cutoff for MA (8,18).

Urine albumin excretion is a continuous variable. Although MA was transient in some of the cases in our study, we recently reported that subjects with persistent MA (2 consecutive years) and transient MA (1 year only) may be at a similar risk of diabetic renal damage, as estimated by the rate of increase of albumin excretion in the years before MA onset (19). Therefore, if a higher systemic BP were important in early renal damage, then the inclusion of subjects with both transient and persistent MA as cases should not have affected the power of our

study to detect a BP difference before MA onset. Our study did not have the power to detect—by either the means test or ANCOVAs—BP effects after MA onset separately for subjects with transient and persistent MA.

Although BP rises after the onset of MA within individuals, no significant difference in mean BP was detected between cases and control subjects in our study. Genetic or familial determinants of essential hypertension may only become evident during or after the pubertal growth spurt (20). Similarly, there are also few cases of MA before puberty (9,10). Therefore, there is only a small window between the onset of puberty and the development of MA when a genetic difference in BP could be detected. Consequently, a very large cohort would be required to detect a difference in BP between cases and control subjects. Many cross-sectional studies have shown significant differences in BP between subjects with MA and normoalbuminuric control subjects, but these observations may have been confounded by the differences in age and pubertal status (21). After puberty, but before the onset of MA, it should be easier to detect a potential genetic difference in BP, and this may explain the data reported in some studies in adults (8,18).

Interestingly, although the risk of MA was associated with a higher level of HbA_{1c} (10), we did not find a within-individual effect of HbA_{1c} on BP. A family history of hypertension has been associated with a greater prevalence of MA or overt diabetic nephropathy (6), and this association is greater in subjects with poor glycemic control (6). Similarly, a small study investigating putative genetic loci

Table 3—Effect of the onset of MA and of BMI on the variability of systolic and diastolic BP, within individuals, estimated using a general factorial linear model with type 3 sum of squares

	df	Systolic BP*		Diastolic BP†	
		F	P	F	P
Corrected model	62	4.3	<0.001	2.5	<0.001
Onset of MA	1	12.1	0.001	13.1	<0.001
BMI	1	1.2	0.3	2.7	0.1
Difference between subjects	60‡	4.0	<0.001	2.1	<0.001

Systolic or diastolic BP, entered as an SDS for age and sex, were the dependent variables. Time before or after the onset of MA was a binary variable, and BMI was a covariate (ANCOVA). *For the model $R^2 = 0.55$ (adjusted $R^2 = 0.42$); †for the model $R^2 = 0.40$ (adjusted $R^2 = 0.23$); ‡one case was dropped because of insufficient data on BMI.

for association with nephropathy showed an interaction between genes involved in the regulation of BP and elevated HbA_{1c} (22). A larger study than the one reported here would be required to reliably detect these interactive effects.

BP data transformed to SDS show that both cases and control subjects had lower systolic BP and higher diastolic BP than nondiabetic European children (13). This was not related to selection of control data, because in comparison with normal data from the U.S. (23), the median systolic BP SDS in our cohort was lower (cases before MA -0.49, control subjects -0.34) and the median diastolic BP SDS was higher (cases before MA 0.34, control subjects 0.36). In our study, BP was closely associated with BMI, and this may be higher, particularly at puberty, in individuals with type 1 diabetes compared with healthy subjects (24). Furthermore, puberty is associated with insulin resistance and peripheral hyperinsulinemia (25). The latter is hypothesized to stimulate reabsorption of sodium in the renal tubules, resulting in sodium retention in subjects with type 1 diabetes (26), which has been associated with a higher BP in subjects with type 1 diabetes (26). Sodium retention could also increase BP by increasing fluid retention and increasing vasoconstriction in response to angiotensin II (27); these are mechanisms that could be enhanced by insulin resistance (27). Sensitivity of BP to sodium is more prevalent in subjects with type 1 diabetes with or without MA (28). Interestingly, a higher diastolic BP SDS was also reported in another group of diabetic children from the U.K., who were compared with European nondiabetic children; however, no difference in systolic BP SDS was detected (29). In contrast to the differences in diastolic BP, the low systolic BP SDS in our study may be partly explained by the use of random zero sphygmomanometers. This instrument may underestimate systolic and diastolic BP by 3.1 and 2.4 mmHg, respectively (30), which in our data would correspond to median SDS differences of 0.28 and 0.24, respectively.

The combination of MA and raised BP is recognized as a clear indication for treatment in adults. Although there is a high incidence of MA during puberty (9,10), it is matched by a high regression rate of up to 50% (10,31,32). Using the same criteria, only five of our cases had a systolic BP above 2 SDs for age and sex,

and only one had an elevated diastolic BP. Therefore, the finding of MA in isolation in this age-group may not be specific enough as a marker of risk for nephropathy to warrant treatment with anti-hypertensive drugs, as is sometimes recommended in adults with type 1 diabetes. A rise of BP into the high normal range (as determined by ambulatory BP), concurrent with the development of MA, may be a more certain early indication of risk warranting preventive treatment.

In conclusion, our data suggest that BP does not rise before the onset of MA and, therefore, does not support the hypothesis that elevations in systemic BP may be an important initiating factor of diabetic nephropathy. The onset of MA is associated with a small concurrent rise in BP. Ambulatory 24-h measurement may improve the detection of small increases in BP concurrent with the development of early diabetic nephropathy.

APPENDIX — Members of the ORPS Steering Committee are Prof. D.B. Dunger, Dr. R.N. Dalton, Prof. J. Fuller, Prof. E.A.M. Gale, Prof. H. Keen, Dr. M. Murphy, Dr. H.A.W. Neil, Dr. C.J. Schultz, Dr. R.J. Young, and T. Konopelska-Bahu. Members of the ORPS group are Drs. R.A.F. Bell and A. Taylor, Horton General Hospital, Banbury; A. Mukthar, B.P. O'Malley, B.R. Silk, and E.H. Smith, Kettering District Hospital, Kettering; R.D.M. Scott, King Edward VII Hospital, Windsor; F.M. Ackland, C.J. Fox, and N.K. Griffin, Northampton General Hospital, Northampton; N. Mann, H. Simpson, P. Cove Smith, and M. Pollitzer, Royal Berkshire Hospital, Reading; R.S. Brown and A.H. Knight, Stoke Mandeville Hospital, Aylesbury; J.M. Cowen, J.C. Pearce, Wexham Park Hospital, Slough; and J. Edge, John Radcliffe Hospital, Oxford. The Box Study is coordinated by P.J. Bingley, Southmead Hospital, Bristol.

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