Insulin Resistance, Insulin, Proinsulin, and Ambulatory Blood Pressure in Type II Diabetes

Jonathan H. Pinkney, Vidya Mohamed-Ali, A. Elizabeth Denver, Clare Foster, Michael J. Sampson, John S. Yudkin

Abstract

Both insulin resistance and insulin concentrations correlate with blood pressure in nondiabetic subjects, but there is no consensus on these relations in subjects with non-insulin-dependent diabetes, perhaps because of the use of nonspecific insulin assays and clinic blood pressure measurement. Therefore, we have investigated the relation between ambulatory blood pressure, insulin sensitivity (measured by an insulin sensitivity test), and levels of insulin and its principal precursors, measured by specific assays, in 24 subjects with non–insulin-dependent diabetes. Insulin sensitivity (glucose metabolic clearance rate) correlated strongly with mean 24-hour ambulatory systolic blood pressure ($r=-0.650, P<0.001$). In contrast, there was no relation between this blood pressure index and fasting levels of insulin ($r=0.096, P=NS$) or all insulin-like molecules ($r=0.077, P=NS$). Dichotomized on 24-hour ambulatory systolic blood pressure levels, the hypertensive group was more insulin resistant than the normotensive group (metabolic clearance rate, $3.6 [0.7]$ versus $6.5 [3.0] \text{mL} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}, P=0.006$), whereas there was no difference in insulin or proinsulin concentrations among the groups. In multiple regression analysis, insulin sensitivity was the major determinant of blood pressure. We conclude that in subjects with non–insulin-dependent diabetes mellitus, blood pressure is related to insulin sensitivity but not to fasting levels of insulin, suggesting that hyperinsulinemia is probably not the mediator of this relation. (Hypertension. 1994;24:362-367.)

Key Words • diabetes mellitus, non–insulin-dependent • insulin • blood pressure, ambulatory • proinsulin

As long ago as 1923, soon after insulin had become available, Klemperer and Strissower demonstrated that both diabetic and nondiabetic subjects exhibited transient falls in blood pressure after insulin injection. Seventy years after this simple experiment, the relation between insulin and blood pressure is unresolved and remains hotly debated.

In the modern era, with the advent of insulin assays, a correlation was first observed between blood pressure and levels of total immunoreactive insulin (IRI), both fasting and stimulated by glucose, in subjects with essential hypertension. Modan et al. showed that insulin concentrations correlated with casual blood pressure independently of glucose intolerance and body mass index (BMI) in the general population. Subsequently, both Ferrannini et al. and Shen et al. demonstrated that subjects with essential hypertension exhibited resistance to insulin-mediated glucose disposal. Reaven has proposed that insulin resistance leads to compensatory hyperinsulinemia, which, according to various lines of argument, might have a major role in the pathogenesis of essential hypertension.

In nondiabetic subjects, insulin resistance is paralleled by increased insulin concentrations, making it difficult to evaluate the relative contribution of either variable to the pathogenesis of hypertension. By contrast, in subjects with non–insulin-dependent diabetes mellitus (NIDDM), insulin resistance and insulin concentrations are dissociated. However, remarkably little information is available on the possible role of insulin in the etiology of hypertension in diabetes. Mbanya et al. found insulin concentrations to be associated with hypertension in a small group of NIDDM subjects, but surprisingly, perhaps, they found no relation between insulin and blood pressure in nondiabetic subjects with essential hypertension. Furthermore, the lack of hypertension in subjects with insulinomas and the experimental observation that acute hyperinsulinemia lowers rather than raises blood pressure both argue against a major role for insulin in blood pressure regulation. In addition, the proposal that subjects with impaired glucose tolerance and NIDDM may have an increased prevalence of hypertension consequent to hyperinsulinemia is challenged by observations that, at least in white subjects, these individuals may be insulin deficient when insulin is measured by a highly specific assay that does not cross-react with insulin precursor molecules, which comprise up to 30% of IRI in subjects with NIDDM.

We have attempted to clarify the relation between blood pressure, insulin concentrations, and insulin resistance in subjects with NIDDM by studying measurements of insulin and its precursors by highly specific assays, directly assessing insulin resistance, and monitoring 24-hour ambulatory blood pressure.

Methods

Subjects

Approval for the study was granted by the local Ethics Committee, and all subjects provided written informed consent before entry. Twenty-four subjects (20 men, 4 women; 18 white, 3 Afro Caribbean, 3 Indian Asian) with NIDDM were...
recruited for the study from the Diabetic Clinic at the Whittington Hospital, London, UK. Subjects were weighed in light clothing, and height was measured without shoes. The mean (SD) age was 54.7 (7.6) years; BMI, 27.9 (4.3) kg • m−2; total glycated hemoglobin (Hb A1c), 10.2 (2.1)%; and median (range) duration of diabetes, 5.5 (0.5 to 23.0) years. Seven of the 24 subjects were obese (BMI >30 kg • m−2). Waist and hip circumferences were measured with a steel tape measure. Waist-hip ratio (WHR), taken as the ratio of the circumferences, was 0.94 (0.08). All subjects were currently being treated with diet and/or oral hypoglycemic agents. Subjects with clinical proteinuria (positive with Albustix, Ames Division, Miles Ltd) were not included in the study. The median (range) urinary albumin excretion rate calculated from single timed overnight urine collections was 7.2 (0.2 to 159.4) mg • 24 h−1; 4 of the 24 subjects being in the microalbuminuric range.13 Twelve of the 24 subjects had clinic diastolic blood pressure greater than 95 mm Hg on three successive occasions off treatment, 6 of these having been receiving antihypertensive drug therapy, which was withdrawn at least 4 weeks before the study.

Blood Pressure Recordings

Twenty-four-hour ambulatory blood pressure recordings were performed using the auscultatory technique (Takeda TM-2420 monitoring system, A&D Instruments). Patients were given diaries to record their activities. Recordings were taken every 15 minutes during the day and every 30 minutes at night (11 PM to 7 AM). Day, night, and 24-hour mean systolic and diastolic blood pressures were calculated based on sleeping and waking times recorded in the patients’ diaries. Clinic blood pressure recordings were taken after patients had been resting in a chair for 5 minutes. Recordings were taken by the same person (J.H.P.) on each occasion between 9 and 10 AM from the nondominant arm. The diastolic blood pressure was taken as phase V of the Korotkoff sounds. Three recordings were made, 1 minute apart, from which the mean was calculated.

Insulin Resistance

Insulin resistance was measured by an insulin sensitivity test performed after an overnight fast, with 150-minute continuous infusion of glucose (6 mg • kg−1 • min−1) and human soluble insulin (Actrapid, Novo Nordisk) (0.05 U • kg−1 • h−1) according to previously described modifications of the method described by Harano et al.17 This method gives results that correlate closely with those obtained by the euglycemic clamp technique.16 The right antecubital vein was cannulated for insulin and glucose infusions, and a left distal forearm vein was cannulated retrogradely for sampling of venous blood arterialized by warming the arm to 45° in an insulated blanket. Arterialized venous blood glucose was sampled at baseline and then was checked every 15 minutes (Reflolux, Boehringer BCL) throughout the procedure. From 120 to 150 minutes (steady state), venous blood was collected every 5 minutes for assay of plasma glucose by the glucose oxidase method (Glucose II Analyzer, Beckman Instruments). Insulin sensitivity was calculated as glucose disposal (metabolic clearance rate [MCR] in milliliters per kilogram per minute) during steady-state plasma glucose according to the formula Glucose Insulin Infusion Rate/Steady-state Plasma Glucose.

Assays

Insulin, intact proinsulin, and des-31,32 proinsulin were assayed by in-house two-site immunometric assays using monoclonal antibodies 14B, 3B1, and A6 (Serono Diagnostics) previously characterized by Sobey et al18 and the anti-C-peptide antibody FEP 001 (Novo Nordisk). Insulin was captured with 14B and detected with 3B1 alkaline phosphatase conjugate. Intact proinsulin and des-31,32 proinsulin were

### Table 1. Blood Pressure Characteristics

<table>
<thead>
<tr>
<th>Blood Pressure</th>
<th>Group 1 (n=12)</th>
<th>Group 2 (n=12)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>24-Hour</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>SBP</td>
<td>120.5 (15.1)</td>
<td>152.4 (9.0)</td>
<td>Grouping variable</td>
</tr>
<tr>
<td>DBP</td>
<td>75.4 (9.1)</td>
<td>88.8 (10.1)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Daytime</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>SBP</td>
<td>121.7 (15.1)</td>
<td>153.8 (9.1)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>DBP</td>
<td>75.9 (9.0)</td>
<td>89.2 (10.9)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Nighttime</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>SBP</td>
<td>109.9 (16.3)</td>
<td>140.1 (21.5)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>DBP</td>
<td>68.3 (10.7)</td>
<td>84.9 (12.1)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Clinic</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>SBP</td>
<td>130.5 (24.0)</td>
<td>163.4 (17.9)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>DBP</td>
<td>81.8 (11.8)</td>
<td>94.7 (12.4)</td>
<td>NS</td>
</tr>
</tbody>
</table>

SBP indicates systolic blood pressure; DBP, diastolic blood pressure. Values are mean (SD) of clinic and ambulatory pressure indexes expressed in millimeters of mercury in group 1 (mean 24-hour ambulatory SBP below the median 138 mm Hg) and group 2 (mean 24-hour ambulatory SBP above the median).

Statistical Analysis

Data were analyzed with the Statistical Package for the Social Sciences (SPSS/PC). Skewed data distributions were logarithmically transformed before analysis. Data are expressed as mean and SD or median and range for skewed data. Data were analyzed in two ways: first by linear regression analyses in the entire group of 24 subjects, and second by comparing the population dichotomized on the basis of 24-hour mean ambulatory blood pressure below (group 1) and above (group 2) the median (138 mm Hg). Correlations are expressed as Pearson correlation coefficients (r). Intergroup comparisons were made with Student’s t test for normally distributed data and the Mann-Whitney U test for skewed data. The relative contributions of other variables to the relations observed between blood pressure indexes and insulin resistance were examined by multiple regression analyses. Values of P<.05 were regarded as significant.

### Results

Table 1 shows mean 24-hour ambulatory and clinic blood pressure indexes. Groups 1 and 2 were grouped on the basis of 24-hour ambulatory systolic blood pressure; with the exception of clinic diastolic blood pressure, all other blood pressure indexes were significantly higher in group 2 compared with group 1.

Table 2 shows the results for glucose MCR; concentrations of specific insulin, intact proinsulin, des-31,32 proinsulin; and the sum of these three molecular species (as an estimate of total IRI). Subjects with high ambulatory systolic blood pressure (group 2) were significantly more insulin resistant than those in group 1 (glucose MCR, 3.6
TABLE 2. Insulin Sensitivity and Fasting Concentrations of Specific Insulin, des-31,32 Proinsulin, Intact Insulin, and Their Sums According to Mean 24-Hour Ambulatory SBP Status

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Group 1 (n=12)</th>
<th>Group 2 (n=12)</th>
<th>( P )</th>
</tr>
</thead>
<tbody>
<tr>
<td>Glucose MCR, mL ( \cdot ) kg(^{-1} \cdot ) min(^{-1} )</td>
<td>6.5 (3.0)</td>
<td>3.6 (0.7)</td>
<td>&lt;.01</td>
</tr>
<tr>
<td>Insulin, pmol ( \cdot ) L(^{-1} )</td>
<td>61.7 (14.9-122.7)</td>
<td>58.7 (21.5-183.8)</td>
<td>NS</td>
</tr>
<tr>
<td>Intact proinsulin, pmol ( \cdot ) L(^{-1} )</td>
<td>12.9 (3.3-61.7)</td>
<td>15.5 (4.5-30.9)</td>
<td>NS</td>
</tr>
<tr>
<td>des-31,32 Proinsulin, pmol ( \cdot ) L(^{-1} )</td>
<td>5.6 (0.8-13.8)</td>
<td>6.4 (1.8-25.7)</td>
<td>NS</td>
</tr>
<tr>
<td>Total insulin-like molecules, pmol ( \cdot ) L(^{-1} )</td>
<td>88.8 (29.9-142.3)</td>
<td>86.2 (47.4-220.2)</td>
<td>NS</td>
</tr>
</tbody>
</table>

SBP indicates systolic blood pressure; MCR, metabolic clearance rate. Values are mean (SD) for MCR and median (range) for other variables. SBP status for group 1 was below the median of 138 mm Hg; group 2, above the median.

For all 24 subjects, insulin accounted for 72.8% (37.0% to 95.0%) of the total insulin-like molecules. Intact proinsulin and des-31,32 proinsulin accounted for 17.9% (4.0% to 61.0%) and 7.4% (1.0% to 18.0%) of total insulin-like molecules, respectively, these not differing between groups 1 and 2.

Table 3 shows the correlations between the measures of blood pressure and the metabolic indexes. In univariate analyses, both clinic and 24-hour mean ambulatory systolic blood pressures were inversely correlated with glucose MCR. The Figure shows the inverse relation between 24-hour mean ambulatory systolic blood pressure and glucose MCR. In contrast, the equivalent correlations for diastolic ambulatory blood pressure indexes were weaker than for their systolic counterparts, and clinic diastolic blood pressure did not correlate significantly with glucose MCR. In contrast to these relations, no significant correlations were found between any measure of blood pressure and fasting concentrations of insulin, its precursors, or the combined total of these molecules. However, in an analysis restricted to 13 white men, although similar results were obtained (24-hour systolic blood pressure correlating with glucose MCR \( r = -0.782 \), \( P < .01 \)) and insulin concentrations again unrelated to glucose MCR \( r = -0.139 \), \( P = NS \)), concentrations of intact proinsulin and des-31,32 proinsulin were also found to correlate significantly with blood pressure \( r = -0.706 \), \( P < .01 \) and \( r = -0.617 \), \( P < .05 \), respectively).

Because of these complex relations, multiple regression models were constructed (Table 4). In stepwise regression, MCR correlated most strongly with 24-hour mean ambulatory systolic blood pressure, displacing all other predictor variables from the model. When controlling for age, insulin concentration, and WHR, MCR was still significantly predictive of 24-hour mean ambu-
Some of the deficiencies of previous studies include:

1. In previous cross-sectional studies, weak and inconsistent relations between IRI concentrations and blood pressure were observed in non-diabetic subjects, and these relations were seen in subjects with NIDDM rather than relying on insulin concentrations as a marker of insulin resistance, an approach that is valid only in subjects with normal glucose tolerance. Moreover, the divergence of insulin concentrations and insulin resistance in NIDDM permits the contribution of these variables to be analyzed separately.

2. Our data, using sensitive and specific assays, confirm previous observations seen between obesity and hyperinsulinemia, raising questions as to which of these variables was actually associated with hypertension. An overlapping effect of obesity and insulin resistance on blood pressure was seen in the multiple regression analyses in this study, but after the inclusion of MCR, the further addition of either BMI or WHR failed to increase the predictive power of any of the models tested, suggesting that insulin resistance is more closely linked to blood pressure rather than either global or central obesity.

3. In subjects with NIDDM, there have been few studies on the relation between blood pressure and insulin concentrations. Mbanya et al found that hypertensive subjects with NIDDM had increased fasting concentrations of insulin, a result consistent with the hypothesis that elevated concentrations of insulin might play a role in the pathogenesis of hypertension. However, apart from these studies, there are many difficulties in measuring blood pressure with conventional mercury sphygmomanometers and that blood pressure measurements by physicians may overestimate normal blood pressure.

4. A better separation of MCR was observed in subjects dichotomized on insulin concentrations and insulin resistance in NIDDM, underlining the importance of using specific insulin assays in the study of the relation between insulin and blood pressure in NIDDM.

## Table 4. Multiple Regression Models

<table>
<thead>
<tr>
<th>Model</th>
<th>MCR</th>
<th>Age</th>
<th>Insulin</th>
<th>WHR</th>
<th>Adjusted $r^2$</th>
<th>$T$ for MCR</th>
<th>$P$</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>-6.18</td>
<td></td>
<td></td>
<td></td>
<td>.51</td>
<td>-4.84</td>
<td>.0001</td>
</tr>
<tr>
<td></td>
<td>(-6.60 to -3.68)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>-5.87</td>
<td>0.14</td>
<td></td>
<td></td>
<td>.49</td>
<td>-3.40</td>
<td>.003</td>
</tr>
<tr>
<td></td>
<td>(-9.25 to -2.49)</td>
<td>(-0.91 to 1.18)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>-5.91</td>
<td>0.14</td>
<td></td>
<td></td>
<td>.46</td>
<td>-3.21</td>
<td>.005</td>
</tr>
<tr>
<td></td>
<td>(-9.52 to -2.30)</td>
<td>(-0.94 to 1.22)</td>
<td>(-14.96 to 6.36)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>-5.68</td>
<td>-0.08</td>
<td></td>
<td>-1.02</td>
<td>42.82</td>
<td>.45</td>
<td>-3.00</td>
</tr>
<tr>
<td></td>
<td>(-9.38 to -1.98)</td>
<td>(-1.03 to 1.12)</td>
<td>(-11.90 to 9.88)</td>
<td>(-68.57 to 154.21)</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

MCR indicates metabolic clearance rate; WHR, waist-to-hip ratio. Table 4 shows relation of glucose MCR and 24-hour systolic blood pressure and multiple regression analyses in 24 subjects with non-insulin-dependent diabetes mellitus, with mean 24-hour systolic blood pressure as the dependent variable. Changes are shown as adjusted $r^2$ and $T$ for MCR, with stepwise addition of age, insulin, and WHR. MCR remains a significant predictor of blood pressure after age, insulin, and WHR are included in the model. Partial regression coefficient ($\beta$) and 95% confidence intervals are shown. Predictor variables: model 1, MCR; model 2, MCR plus age; model 3, MCR plus age plus insulin; and model 4, MCR plus age plus insulin plus WHR.
from the small size of the patient sample, there were several additional possible sources of error in the study of Mbanya et al, including the use of nonspecific insulin assays and clinic blood pressure assessments. In the present study the clinic diastolic blood pressure, usually used to diagnose clinical hypertension, was not as closely related to glucose MCR as the ambulatory indexes (Table 3). Such sources of error could represent an obstacle to disentangling the relation between blood pressure and the true insulin level. Furthermore, the conclusions of Mbanya et al with regard to hypertensive NIDDM subjects appear inconsistent with their failure to find any relation between IRI concentrations and blood pressure in subjects with essential hypertension, unless there is a fundamental yet unrecognized difference in etiology between these two forms of hypertension. Thus, in contrast to the finding of Mbanya et al, our results suggest that there is no significant relation between any index of ambulatory blood pressure and fasting concentrations of insulin in NIDDM subjects. However, there is a consistent and strong correlation between insulin resistance and blood pressure.

Jarrett has recently criticized the hypothesis attributing an etiologic role to insulin in hypertension and atherosclerosis, pointing out that hyperinsulinemia results in part from underlying insulin resistance, which may be linked more closely to hypertension than are concentrations of insulin. Based on the strong correlation between insulin resistance and blood pressure, it may be hypothesized that these two variables share some single common mechanism or a closely linked antecedent. Laakso et al have suggested that insulin resistance is a key abnormality, closely linked with hypertension, and therefore perhaps responsible for the high prevalence of hypertension in NIDDM, demonstrating that hypertensive subjects with NIDDM were more insulin resistant than normotensive subjects with NIDDM. Baron et al have investigated the relation among blood pressure, insulin resistance, and skeletal muscle blood flow in nonobese, nondiabetic normotensive subjects and have shown that blood pressure was strongly inversely correlated with insulin sensitivity and with the insulin-mediated increase in skeletal muscle blood flow occurring during a hyperinsulinemic euglycemic clamp, leading them to suggest that both essential hypertension and insulin resistance in skeletal muscle may result from impaired insulin-mediated vasodilatation. A hypothesis that hypertension is associated with a defect of insulin action rather than overaction (for example, the suggested enhancement of renal sodium retention and sympathetic nervous system activity by hyperinsulinemia) is consistent with the finding of the present study that insulin resistance but not insulin concentration is closely related to blood pressure.

In the present study concentrations of intact proinsulin and des-31,32 proinsulin were not related to any measure of blood pressure in all subjects, despite there being a significant correlation in the subgroup of 13 white men. Even in this subgroup, however, specific insulin levels showed no correlation with blood pressure. Levels of insulin precursor molecules correlated strongly with glucose MCR, and this observation might explain their association with increased blood pressure levels.

Our group previously noted a relation between clinic blood pressure and concentrations of insulin precursor molecules in NIDDM. In that study, concentrations of des-31,32 proinsulin and intact proinsulin, but not insulin, significantly correlated with clinic diastolic blood pressure independently of age and obesity. However, in that study ambulatory blood pressure was not monitored and insulin resistance was not measured. Two other studies have suggested relations between concentrations of insulin precursor molecules and blood pressure in subjects with lesser degrees of glucose intolerance. Recent work from the San Antonio Heart study, using an assay measuring all proinsulin-like molecules, has shown proinsulin concentrations to be more strongly related to casual blood pressure than insulin concentrations. However, the study population was ethnically mixed, obese, and comprised subjects with both normal and impaired glucose tolerance. By contrast, in a recent study of 919 white subjects from North London with normal glucose tolerance, we found significant correlations of casual systolic and diastolic blood pressure with fasting concentrations of insulin (r = -0.19 and 0.16; P < 0.01), des-31,32 proinsulin (r = 0.20, P < 0.01; r = 0.18, P < 0.01), and intact proinsulin (r = 0.25, P < 0.01; r = 0.16, P < 0.01), but after correction for age and BMI, the relations with intact proinsulin and des-31,32 proinsulin were no longer significant.

The finding of a relation between proinsulin concentrations and blood pressure in nondiabetic subjects, in whom the concentrations of proinsulin-like molecules are no more than 5% to 10% those of insulin, makes it implausible that increased concentrations of these molecules could have a direct role in the pathogenesis of hypertension, given their low metabolic activity at insulin receptors. The occurrence of NIDDM without hypertension also suggests that insulin precursors have no role in the pathogenesis of hypertension. More likely, any association between hypertension and proinsulin-like molecules is mediated by a common antecedent, with insulin resistance being a likely candidate.

Despite the findings of the present study, it remains possible that a relation exists between insulin concentrations and blood pressure in NIDDM. Whether or not any such relation could be observed might depend on the characteristics of the study population and the size of the sample. Fasting levels of insulin also might be an inadequate index of insulinemia. Alternatively, the pressor effect of insulin may be more chronic, and it could be that previous hyperinsulinemia in these subjects has brought about irreversible vascular changes related to present-day hypertension, as could be inferred from the prospective analysis from the San Antonio Heart Study. It is also clear that a study of this size and design will have the power to detect only major etiologic relations, whereas a more detailed picture of the relation between insulin concentrations and insulin resistance in the pathogenesis of hypertension would require a larger and longitudinal study. However, one can conclude that these results indicate that insulin concentrations per se are not likely to have an important influence on blood pressure in NIDDM. In contrast, the very strong relation between blood pressure and insulin resistance favors the hypothesis that insulin resistance and not "hyperinsulinemia" is central to the pathogenesis of hypertension.
Acknowledgment

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References

19. Pinkney et al. Insulin and Hypertension in Diabetes
Insulin resistance, insulin, proinsulin, and ambulatory blood pressure in type II diabetes.

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