Cerebral White Matter Lesions Are Associated With the Risk of Stroke But Not With Other Vascular Events

The 3-City Dijon Study

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Background and Purpose—White matter lesions (WMLs) have been shown to be associated with the risk of stroke in previous studies but little is known about the prediction of other vascular events. We evaluated the risk of stroke and other vascular events according to WML volume in a large population-based sample. We also studied WML volume by type (deep or periventricular) in relation to these events.

Methods—The 3-City Study is a population-based prospective cohort of people aged $\geq$65 years followed up for, on average, 4.9 years. Among them, 1643 participants free of prevalent vascular events had quantitative measurements of WML volume at baseline using a fully automatic method. The risks of incident major vascular events according to WML volume were evaluated using Cox proportional hazards models.

Results—The risk of incident stroke significantly increased with increasing baseline WML volume and was multiplied by 5 for those in the highest quartile of WML volume. Nonstroke vascular events’ incidence was not associated with WML volumes, whatever their type.

Conclusions—WMLs are an independent predictor of stroke in the elderly. This association is specific because WMLs are not associated with the risk of other vascular events. (Stroke. 2009;40:2327-2331.)

Key Words: MRI ★ myocardial infarction ★ stroke ★ vascular death ★ white matter

White matter lesions (WMLs) are commonly observed on cerebral MRI of asymptomatic elderly people$^{1,2}$ and in patients with stroke.$^{3,4}$ Several studies, including large population-based cohorts, have described a strong positive relationship between these brain lesions and advancing age or history of hypertension.$^{2,5}$ Other vascular factors such as tobacco consumption, diabetes mellitus, high cholesterol, and homocysteine levels have also been reported to be associated with WML severity.$^{6–8}$ Although their precise pathogenesis has not yet been fully clarified, WMLs are commonly considered an expression of chronic cerebral ischemia due to microvascular lesions, among which small vessel atherosclerosis appears to play an important role.$^{9–11}$

There is a growing literature reporting associations between elevated WML load and cognitive impairment, dementia, depression, and gait disturbances.$^{12–14}$ Recent studies also described WML grade as a predictor of incident stroke in the general population$^{15–17}$ and of stroke recurrence among patients with transient ischemic attack or stroke history.$^{18,19}$

WML and nonstroke major vascular events such as acute coronary syndromes and nonstroke vascular deaths share a similar pattern of vascular risk factors, leading to the hypothesis that WML might also be a useful predictor of that type of vascular event. However, little is known about this predictive value,$^{20–22}$ especially in the elderly general population.

Since a few years ago, new computerized quantitative methods allow to measure WML extent with high precision and reproducibility as compared with visual rating scales that have been used up until now. In a population-based sample of 1643 subjects aged 65 to 80 years old at entry, we therefore sought to examine the association between WML severity and stroke incidence over 5-year follow-up with the use of a fully automatic method that detects, quantifies, and localizes WML. A second purpose of the study was to assess the predictive value of WML on nonstroke vascular events.
Methods

Study Sample and Design
The 3-City (3C) Study is a multicenter prospective cohort study conducted in France designed to evaluate the relationship between vascular factors and dementia. The detailed study protocol has already been reported elsewhere. \(^{23}\) Briefly, between March 1990 and March 2001, noninstitutionalized men and women aged ≥65 years were randomly selected from electoral rolls of the cities of Bordeaux, Dijon, and Montpellier and were invited to enroll in the study; 9294 agreed (participation rate = 38%). The current analysis focuses on the Dijon center participants among whom 2763 subjects aged ≥80 years were invited to have a cerebral MRI examination at study entry. The acceptance rate was 82.7%; due to financial limitations, 1924 examinations were performed. Compared with subjects who did not have an MRI examination (n = 839), subjects who had an MRI were on average significantly younger (72.5 [SD = 4.1] versus 73.4 years [SD = 4.0]; P < 0.0001), were less often women (62.2% versus 71.0%; P < 0.0001), had more often an education level above baccalaureate degree (23.5% versus 17.8%; P < 0.0001); and were overall healthier (data not shown). Furthermore, 123 subjects whose MRI examination was of poor quality and 117 subjects who had a self-declared prevalent coronary heart disease (ie, a history of myocardial infarction or coronary bypass or angioplasty or vascular surgery for lower limb arteries) or a self-declared history of stroke were excluded from analyses, leaving a sample of 1684 participants free of major vascular events at baseline.

Participants were invited to have 2 follow-up clinical examinations, scheduled 2 and 4 years after inclusion, following the baseline standardized protocol. In case of refusal, participants were requested to fill in a questionnaire by phone call or postal letter regarding occurrence of major health events, including vascular ones. Finally, a further study wave was scheduled at 6-year follow-up, which consisted of a self-reported questionnaire focusing on health events that had occurred since last contact. Eighty-nine participants (5.5%) died during follow-up; among subjects alive, participation rates were 99.2%, 96.5%, and 95.7% after the first, second, and third follow-up waves, respectively. Twenty-six additional subjects were excluded from the current analyses because they refused to participate in any follow-up examination or to complete any questionnaire after enrollment (sample size = 1658).

The study protocol was approved by the Ethical Committee of the University Hospital of Kremlin-Bicêtre and a signed agreement was obtained for each participant.

Baseline MRI Data

Baseline MRI acquisition has been described in detail previously.\(^{14}\) It was performed on average 4.2 months (SD = 3.0 months) after enrollment clinical examination. Briefly, MRI was performed on a 1.5-Tesla Magnetom (Siemens, Erlangen, Germany). A 3-dimensional high-resolution T1-weighted brain volume was acquired using a 3-dimensional inversion recovery fast spoiled-gradient echo sequence. T2- and proton density-weighted brain volumes were acquired using a 2-dimensional fast spin echo sequence with 2 echo times with slices 3.5 mm thick (0.5 mm between slice spacing). Each subject data set (T1, T2, and proton density) was readily reconstructed and visually checked for major artifacts before being sent to the database repository (Caen) where it was archived for further analyses. As described in a previous publication,\(^{24}\) we used the so-called optimized voxel-based morphometry protocol to compute gray matter, white matter (WM), and cerebrospinal fluid volumes of each subject. Total intracranial volume was computed as the sum of the gray matter, WM, and cerebrospinal fluid volumes (both ventricular and extracranial cerebrospinal fluid).

WML Volume Estimation

Fully automatic image processing software was developed to detect, measure, and localize WML. The detailed procedure has already been reported elsewhere.\(^{25}\) Among the various tissue segmentation techniques available, we selected a multispectral approach that uses different MRI sequences. Indeed, because of the heterogeneity of gray matter signals on the T2 images, the WM mask derived with a 3-class-only segmentation was suboptimal for accurate WML detection. Although such inhomogeneities have negligible impact when calculating the bias field correction, they could be at the origin of false-positive WML on the T2 images. Therefore, T1, T2, and proton density bias-corrected volumes were segmented into 7 classes using the same multispectral algorithm: (1) cerebrospinal fluid; (2) gray matter; (3) ependyma nucleus; (4) lenticular nucleus; (5) thalamus; (6) WM; and (7) WMH. The MR image analysis contained 3 major steps: (1) preprocessing, including registration, nonbrain tissue removal, and bias field correction; (2) detection of WM hyperintensities in T2 images, including removal of false-positives; and (3) postprocessing, including generation of WML probability maps at the individual and sample levels, morphometry, localization, and classification of WML.

Morphological parameters were computed for each detected WML, including center of mass coordinates, Euclidian distance to the ventricular system, and principal axes dimension. When its distance to the ventricular system was ≤10 mm, a WML was labeled as periventricular WML; otherwise, it was labeled as deep WML. WM lesion volume was studied continuously and as a categorical variable using quartiles. Total WML volume ranged from 0.50 to 2.75 mL; 2.76 to 4.00 mL; 4.01 to 6.20 mL; and 6.21 to 53.20 mL across increasing categories.

Because WML volume is highly correlated to the total brain volume, total intracranial volume was systematically controlled for in all analyses.

Baseline Data Collection and Definition of Covariates

Baseline data concerning demographic and socioeconomic characteristics, smoking habits, medical history, and medication use were collected by trained psychologists using standardized questionnaires during face-to-face interviews at home. High education level was defined as baccalaureate degree or higher and subjects were classified as never, former, or current smoker. Participants underwent clinical examination, including anthropometric and blood pressure measurements. Systolic blood pressure and diastolic blood pressure were determined as the average of 2 separate measures using a digital electronic tensiometer (OMRON M4). Hypertension was defined as either a current intake of blood pressure-lowering drugs or a systolic blood pressure ≥140 mm Hg or a diastolic blood pressure ≥90 mm Hg. Blood samples were collected and assayed for fasting cholesterol, triglycerides, and glucose levels. Hypercholesterolemia was defined as either a current lipid-lowering therapy or a fasting total cholesterol ≥240 mg/dL. Diabetes mellitus was defined as either a current intake of glucose-lowering drugs or a fasting glycemia ≥126 mg/dL. An ultrasound examination of the carotid arteries, which included detection and localization of atheroma plaques and centralized measurements of common carotid artery intima media thickness, was proposed to participants aged ≥85 years at baseline.

Vascular Outcome Assessment

During follow-up examinations, participants were systematically asked (during interview or by self-administered questionnaire) if they had a coronary event or a stroke since the last visit. All cases were further documented by medical data obtained from general practitioners, specialists, and hospital records where possible and were reviewed by 2 panels of experts, one for coronary events and one for stroke. Confirmed stroke cases were further classified as ischemic, hemorrhagic, or unspecified on the basis of available medical and radiological records. All deaths were reviewed by 3 medical doctors from the coordination center and coded according to the International Classification of Diseases, 10th Revision, vascular deaths being defined as deaths attributed to diseases of the circulatory system (International Classification of Diseases, 10th Revision codes I00 to I99). When a coronary event or stroke was suspected, the file was sent to the relevant expert committee.

In a first step of the study, we assessed a combined outcome of interest defined as the first occurrence of any of the following major vascular events during follow-up: stroke, coronary heart disease (stable and unstable angina pectoris, coronary balloon dilatation or artery bypass, myocardial infarction and coronary heart disease death [I210 to I219, I251 to 259, I461, and R960 International Classification of
Table 1. Characteristics of the Participants According to Quartile of Total WML Volume on Baseline MRI

<table>
<thead>
<tr>
<th>Baseline Characteristics</th>
<th>All Sample (N=1643)</th>
<th>First Quartile (n=411)</th>
<th>Second Quartile (n=410)</th>
<th>Third Quartile (n=411)</th>
<th>Fourth Quartile (n=411)</th>
<th>P*</th>
<th>P†</th>
</tr>
</thead>
<tbody>
<tr>
<td>Range of WML volume, mL</td>
<td>0.50–53.20</td>
<td>0.50–2.75</td>
<td>2.76–4.00</td>
<td>4.01–6.20</td>
<td>6.21–53.20</td>
<td>...</td>
<td>...</td>
</tr>
<tr>
<td>Mean age, years (SD)</td>
<td>72.3 (4.1)</td>
<td>72.1 (4.3)</td>
<td>72.1 (4.0)</td>
<td>72.2 (3.9)</td>
<td>72.8 (4.0)</td>
<td>0.004</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Female sex, %‡</td>
<td>62.6</td>
<td>71.0</td>
<td>64.6</td>
<td>61.1</td>
<td>53.5</td>
<td>&lt;0.0001</td>
<td>0.87</td>
</tr>
<tr>
<td>High education level, %‡</td>
<td>36.3</td>
<td>36.0</td>
<td>34.6</td>
<td>37.5</td>
<td>37.0</td>
<td>0.84</td>
<td>0.92</td>
</tr>
<tr>
<td>Current smoker, %</td>
<td>5.5</td>
<td>3.2</td>
<td>6.6</td>
<td>5.8</td>
<td>6.6</td>
<td>0.02</td>
<td>0.04</td>
</tr>
<tr>
<td>Mean body mass index, kg/m (SD)</td>
<td>25.3 (3.7)</td>
<td>24.8 (3.8)</td>
<td>25.2 (3.8)</td>
<td>25.6 (3.5)</td>
<td>25.7 (3.9)</td>
<td>0.003</td>
<td>0.09</td>
</tr>
<tr>
<td>Hypertension, %‡</td>
<td>76.3</td>
<td>69.6</td>
<td>75.1</td>
<td>76.9</td>
<td>83.7</td>
<td>&lt;0.0001</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Diabetes, %‡</td>
<td>7.7</td>
<td>4.4</td>
<td>8.9</td>
<td>6.6</td>
<td>10.9</td>
<td>0.02</td>
<td>0.09</td>
</tr>
<tr>
<td>Hypercholesterolemia, %‡</td>
<td>56.4</td>
<td>58.4</td>
<td>57.1</td>
<td>56.5</td>
<td>53.7</td>
<td>0.57</td>
<td>0.82</td>
</tr>
<tr>
<td>Mean triglycerides, mg/dL (SD)§</td>
<td>105.2 (48.3)</td>
<td>101.3 (41.5)</td>
<td>106.6 (50.0)</td>
<td>105.1 (50.7)</td>
<td>107.9 (50.5)</td>
<td>0.44§</td>
<td>0.52§</td>
</tr>
<tr>
<td>≥1 carotid plaque, %</td>
<td>46.6</td>
<td>40.3</td>
<td>46.1</td>
<td>46.8</td>
<td>53.4</td>
<td>0.003</td>
<td>0.05</td>
</tr>
<tr>
<td>Mean CCA-IMT, mm (SD)</td>
<td>0.683 (0.106)</td>
<td>0.679 (0.106)</td>
<td>0.676 (0.103)</td>
<td>0.684 (0.102)</td>
<td>0.694 (0.114)</td>
<td>0.07</td>
<td>0.59</td>
</tr>
<tr>
<td>Incident stroke, no.</td>
<td>25</td>
<td>2</td>
<td>3</td>
<td>6</td>
<td>14</td>
<td>...</td>
<td>...</td>
</tr>
<tr>
<td>Incident other vascular event, no.</td>
<td>55</td>
<td>10</td>
<td>18</td>
<td>16</td>
<td>11</td>
<td>...</td>
<td>...</td>
</tr>
</tbody>
</table>

*Univariate analysis.  
†Multivariate analysis, adjusted for age, sex, total intracranial volume, smoking status, hypertension, and diabetes.  
‡High education level indicates baccalaureate degree or higher; hypertension, ≥140 mm Hg or diastolic blood pressure ≥90 mm Hg or intake of antihypertensive drugs; diabetes, fasting glycemia ≥126 mg/dL or intake of glucose-lowering drugs; hypercholesterolemia, serum total cholesterol ≥240 mg/dL or intake of hypolipidemic drugs.  
§Triglycerides were log-transformed for statistical analysis.  
CCA-IMT indicates common carotid artery intima media thickness.

Diseases, 10th Revision codes, and noncoronary vascular death. In a second step of the study, we dichotomized this combined outcome into 2 specific ones: (1) "stroke," including fatal and nonfatal strokes; and (2) "nonstroke vascular event," including acute coronary events and nonstroke vascular deaths.

Statistical Analyses

To evaluate the univariate cross-sectional association between WML load and participants’ baseline characteristics, we used analysis of variance for quantitative data and the χ² test for qualitative variables. Analysis of covariance and logistic regression were used for multivariate analyses, controlling for age, sex, total intracranial volume, and major vascular factors.

Cox proportional hazard regressions were used to estimate hazard ratios and 95% CIs for a first major vascular event according to WML volume at baseline.

Time to event (or censoring) was defined as the delay between the MRI examination and the event or the censoring. Due to delay between WML volume at baseline.

Results

Mean age of the participants was 72.3 years (SD=4.1 years) and 62.6% were women. Characteristics of the subjects according to quartile of total WML volume are described in Table 1. After multivariate adjustment, a strong relationship was observed between higher WML volumes and increasing age and hypertension and a weaker association was observed with tobacco smoking (current versus non- and former smokers) and carotid plaques.

Over a mean follow-up period of 4.9 years (SD=1.1 years), 80 vascular events occurred, including 25 strokes (22 nonfatal and 3 fatal). Most of the strokes were ischemic (80% [n=20]), 4 were hemorrhagic, and one unspecified. Among ischemic strokes, 6 were lacunar, 6 were cardioembolic, one was atherosclerotic, and the remainder was not classifiable. The 55 non-stroke vascular events were divided into 45 nonfatal coronary events, 4 fatal coronary events, and 6 vascular deaths from other causes.

Baseline-adjusted (for age, sex, total intracranial volume) mean total WML volume (SE) was higher for participants having had a stroke during follow-up (9.1 mL [1.0]) than for those with a nonstroke vascular event (5.1 mL [0.7]) or those without any vascular event (5.4 mL [0.1]), Incidence rates of vascular events according to quartile of total WML volume are shown in the Figure. Stroke incidence increased with increasing volumes of WML, reaching a more than 7-fold higher rate in the fourth quartile as compared with the first quartile. No such pattern was observed for nonstroke vascular events (Figure).

Table 2 shows adjusted hazard ratios (95% CIs) for major vascular events according to baseline WML volume. Compared

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with the below-median group, subjects in the third and fourth quartiles of WML volume had a significant increased risk of stroke after adjusting for age, sex, and total WM volume (Model 1). Conversely, baseline WML volume was not associated with the occurrence of nonstroke vascular events. Separate analyses of the associations between WML and the different types of nonstroke vascular events (myocardial infarction, vascular death.) were not in favor of a differential association (data not shown). Additional adjustment for vascular risk factors, including smoking status, hypertension, diabetes, cholesterol, and triglycerides, did not alter the results (Model 2) nor additional control for carotid plaques (data not shown). The risk estimates for stroke were higher for periventricular WML than for deep WML volume, but the pattern was similar for both types of WML (Table 2).

The associations between WML volumes and outcomes detailed in Table 2 were unchanged when restricting outcomes to ischemic vascular events (ischemic strokes and acute ischemic coronary events), which accounted for most of the vascular events analyzed in this study (data not shown). Further analyses were performed to test possible 2×2 interactions, but none of them was significant.

**Discussion**

In this large population-based sample of elderly subjects, we found that baseline WML volume was a significant predictor of stroke that have occurred during a mean follow-up of approximately 5 years. This association was independent of potential confounders such as age, sex, hypertension, smoking status, diabetes, and dyslipidemia. It was also independent of the type of WML (periventricular WML or deep WML). We also found that WML volume was not associated with the occurrence of other major vascular events such as myocardial infarction and nonstroke vascular death.

Three prior population-based studies have also shown that severe WML grade was a predictor of stroke,15–17 although none have reported the association with other vascular events. Two small-scaled studies have suggested that patients with extensive

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**Table 2. Adjusted Hazard Ratios (95% CIs) for Vascular Events According to WML Volume on Baseline MRI and by Type of WML**

<table>
<thead>
<tr>
<th>Outcome</th>
<th>WML Volume</th>
<th>Events/Person-Years</th>
<th>Total WML Volume</th>
<th>Periventricular WML Volume</th>
<th>Deep WML Volume</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>Model 1*</td>
<td>Model 2†</td>
<td>Model 2†</td>
</tr>
<tr>
<td>Any vascular event (n=80)</td>
<td>Less than median</td>
<td>33/4139</td>
<td>1.0 (referent)</td>
<td>1.0 (referent)</td>
<td>1.0 (referent)</td>
</tr>
<tr>
<td></td>
<td>Third quartile</td>
<td>22/1978</td>
<td>1.4 (0.8–2.4)</td>
<td>1.4 (0.8–2.4)</td>
<td>1.5 (0.9–2.6)</td>
</tr>
<tr>
<td></td>
<td>Fourth quartile</td>
<td>25/1946</td>
<td>1.5 (0.9–2.5)</td>
<td>1.3 (1.0–2.3)</td>
<td>1.4 (0.8–2.5)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>P_{trend}‡</td>
<td>0.15</td>
<td>0.29</td>
</tr>
<tr>
<td>Stroke (n=25)</td>
<td>Less than median</td>
<td>5/1439</td>
<td>1.0 (referent)</td>
<td>1.0 (referent)</td>
<td>1.0 (referent)</td>
</tr>
<tr>
<td></td>
<td>Third quartile</td>
<td>6/1978</td>
<td>2.5 (0.8–8.4)</td>
<td>2.7 (0.8–9.0)</td>
<td>3.6 (1.0–12.5)</td>
</tr>
<tr>
<td></td>
<td>Fourth quartile</td>
<td>14/1946</td>
<td>5.0 (1.7–14.4)</td>
<td>5.7 (2.0–16.4)</td>
<td>6.2 (2.0–19.5)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>P_{trend}‡</td>
<td>0.002</td>
<td>0.0009</td>
</tr>
<tr>
<td>Nonstroke vascular event (n=55)</td>
<td>Less than median</td>
<td>28/4139</td>
<td>1.0 (referent)</td>
<td>1.0 (referent)</td>
<td>1.0 (referent)</td>
</tr>
<tr>
<td></td>
<td>Third quartile</td>
<td>16/1978</td>
<td>1.2 (0.7–2.3)</td>
<td>1.1 (0.6–2.1)</td>
<td>1.2 (0.7–2.3)</td>
</tr>
<tr>
<td></td>
<td>Fourth quartile</td>
<td>11/1946</td>
<td>0.8 (0.4–1.7)</td>
<td>0.7 (0.3–1.4)</td>
<td>0.8 (0.4–1.6)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>P_{trend}‡</td>
<td>0.71</td>
<td>0.35</td>
</tr>
</tbody>
</table>

*Adjusted for age, sex, total intracranial volume.
†Adjusted for age, sex, total WM volume, smoking status, hypertension, diabetes, cholesterol, triglycerides.
‡P for linear trend across categories of WML volume.
leukoaraiosis on CT scan had an increased risk of myocardial infarction, although nonsignificantly.20,22

The strengths of our study include its population-based design, its large number of participants, and its high participation rates at follow-up examinations. Among subjects alive, only 6 (0.4% of the sample) did not participate in any clinical examination and did not answer phone and postal questionnaires. In addition, we used a computerized fully automatic method of quantification of WMHs, which provides a highly reliable estimate of the volume of WML.25 Some limitations must be mentioned. The initial 3C Study sample was composed of volunteers who differ from the general population in terms of age, sex, and socioeconomic level. Furthermore, baseline MRI examinations were performed on participants aged ≤80 years who were healthier than those who did not undergo this examination. Finally, we excluded from analyses participants who had prevalent coronary heart disease or stroke to focus on first vascular events. Our final study sample does not therefore reflect the general elderly population of France, but rather a healthy subsample at baseline, hence explaining in part the low incidence rate of stroke in our study (3.2 per 1000 person-years) as compared with those of prior similar population-based studies.17,26 Finally, the method used to detect WML within the white matter mask was based on T2 only, which did not allow us to differentiate WML and silent infarcts or lacunes.

Our data suggest that although WMLs are strongly associated with age and vascular factors such as hypertension, WML load cannot be used as a marker of a generalized vascular alteration, but should rather remain considered specifically associated with the risk of incident stroke in the elderly. This result, if confirmed in other large studies, could help to set up strategies to identify elderly individuals at higher risk of stroke.

Sources of Funding

The 3C Study is conducted under a partnership agreement between the Institut National de la Santé et de la Recherche Médicale (INSERM), the Victor Segalen–Bordeaux II University, and Sanofi-Aventis. The Fondation pour la Recherche Médicale funded the preparation and initiation of the study. The 3C Study is also supported by the Caisse Nationale Maladie des Travaillleurs Salariés, Direction Générale de la Santé, MG2EN, Institut de la Longévité, Conseils Régionaux of Aquitaine and Bourgogne, Fondation de France, and Ministry of Research–INSERM Programme “Cohortes et collections de données biologiques.”

Disclosures

None.

References

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Stroke. 2009;40:2327-2331; originally published online May 14, 2009; doi: 10.1161/STROKEAHA.109.548222

Stroke is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
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Print ISSN: 0039-2499. Online ISSN: 1524-4628

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