Effect of White Matter Changes on Cognitive Impairment in Patients With Lacunar Infarcts

Hong Mei Wen, PhD; Vincent C.T. Mok, MD; Yu Hua Fan, MD; Wynnie W.M. Lam, MD; Wai Kwok Tang, MD; Adrian Wong, BSc; Ru Xun Huang, MD; Ka Sing Wong, MD

Background and Purpose—Cerebral white matter changes (WMC) and lacunar infarct are both believed to be consequence of small vessel disease. Whether the extent of WMC affect the type and degree of cognitive impairment in patients with lacunar infarct is not clear. The study was undertaken to determine if WMC influences cognition in patients with lacunar infarcts.

Methods—We recruited consecutive patients who were admitted to the acute stroke unit because of acute lacunar infarcts, mainly documented by diffusion-weighted magnetic resonance imaging. WMC were measured qualitatively and quantitatively. Patients were divided into quartiles according to the distribution of the volume of WMC. Cognition was assessed 12 weeks after stroke by psychometric tests (Chinese version of Mini-Mental State Examination [MMSE], Alzheimer’s Disease Assessment Scale-cognition [ADAS-cog], Mattis Dementia Rating Scale-Initiation/Perseveration subscale [MDRS I/P]) and was compared between patients with varying severity of WMC. Multivariate linear regression analysis was performed to find variables that influenced performance in the psychometric tests.

Results—Among the 94 included patients with acute lacunar infarcts, those patients (n=25) within the highest quartile of WMC were older, had more lacunar infarcts, more severe stroke, and lower prestroke cognitive function compared with those with less WMC. In addition, their performances in psychometric tests were significantly more impaired. Multivariate linear regression analysis revealed that WMC significantly influenced performance in MDRS I/P. WMC did not independently influence performance in MMSE and ADAS-cog.

Conclusions—Extent of WMC appears to be associated with executive dysfunction in stroke patients with lacunar infarcts. Further large prospective studies with extensive scales of executive function testing are required to confirm this issue. (Stroke. 2004;35:1826-1830.)

Key Words: lacunar infarction • white matter • cognition

Patients with lacunar infarcts are thought to have an increased risk of cognitive impairment and dementia. Cognitive impairment is a predictor of poor functional outcome in stroke survivors. Patients with lacunar infarcts have more severe white matter changes (WMC) than patients with nonlacunar infarcts among patients with ischemic stroke. Among elderly subjects, it is suggested that WMC are independently related to cognitive impairment and cognitive decline, and a threshold of WMC perhaps needs to be surpassed before such impairment is evident. In patients with lacunar infarcts, the pathway leading to dementia is less clear. WMC may or may not participate in the process of cognitive impairment. Some researchers observed an association between the severity of cognitive impairment and WMC. In other studies among patients with lacunar infarcts and deep WMC, cognitive impairment was not associated with lacunar infarcts and WMC. The purpose of this study was to elucidate whether WMC participated in cognitive impairment in patients with lacunar infarcts.

Materials and Methods

Subjects

Between January and June 2002, we evaluated all patients with or without previous stroke who were admitted to the acute stroke unit of Prince of Wales Hospital because of stroke or transient ischemic attack (TIA). A total of 294 patients with ischemic stroke were admitted during the study period. Brain computed tomography (CT) was performed on all patients within 24 hours of admission. Patients with past history or CT features of intracerebral hemorrhage were excluded (n=37). Among the 257 patients with ischemic stroke, 15 patients had obvious CT features of relevant cortical, large subcortical, or brain stem infarct. These patients were excluded from further analysis. Magnetic resonance imaging (MRI) including T1- and T2-weighted imaging were performed among the remaining patients (n=234). Eight patients were contraindicated for MRI because of pacemaker in situ, refusal, claustrophobia, or unstable medical
condition; hence, only CT was performed for them. Diffusion-weighted imaging (DWI) was also performed within 7 days of onset of symptoms in 226 patients.

Patients with DWI or CT showing acute lacunar infarcts affecting subcortical or brain stem areas were potentially eligible for the study. Lacunes were defined as well-defined areas of $\geq 2$ mm and $\leq 2$ cm with signal characteristics the same as cerebrospinal fluid on T1 and T2. If the lesions with these characteristics were $\leq 2$ mm, they were considered as perivascular space dilatation. Relevant infarct was defined as an infarct that could account for the patient’s presenting neurological deficits. Patients with clinical signs that could not be explained by the lacunar infarcts, normal imaging, coexisting presence of nonischemic lesions, eg, tumor, were excluded.

Among patients with relevant lacunar infarcts, the following patients were further excluded: those with known prestroke dementia-illnesses that were not caused by Alzheimer disease or vascular dementia, eg, Parkinson disease or chronic alcoholism, WMC associated with multiple sclerosis, major depression according to Diagnostic and Statistical Manual of Mental Disorders, 4th edition, as diagnosed by a psychiatrist (W.K.T.) at 12 weeks after index stroke, and communication problems hindering participation in cognitive assessment, such as language barrier, or severe visual or hearing loss. Patients with aphasia were not excluded in our study. Among all the included patients, sites of relevant lacunar infarcts were classified into 6 groups based on neuroimaging findings (T2-weighted MRI, DWI, and CT) with reference to the clinical presentation: subcortical white matter (corona radiata and centrum semiovale), striacapsule, thalamus, cerebellum, brain stem, and multiple sites. The volume of each lacunar infarct was estimated by means of the ABC/2. Total number and volumes of all lacunar infarcts were recorded for each patient.

White Matter Changes Assessment

White matter changes were defined as ill-defined hyperintensities $\leq 5$ mm on T2-weighted images (CT scans if MRI was not performed) but isointense with normal brain parenchyma on T1-weighted images. Volume of WMC was measured quantitatively for 87 patients who underwent MRI with Easy Vision 4.3. Segmentation methods were used to measure the volume of WMC. Briefly, seeds were dropped on structures of interest, afterwards, the seeds grew automatically to include all connected pixels unless the whole structure was outlined. The volumes of the pixels outlined were then calculated and showed automatically. The same neurologist (H.M.W.) graded the WMC for the patients. Seven included patients were contraindicated for MRI and severity of WMC was rated visually on CT according to the method reported by Wahlund et al.

Briefly, WMC is graded in 5 different brain regions: frontal, parieto-occipital, temporal, basal ganglia, and infratentorial regions. In general, grade 0 indicates no lesions (including symmetrical, well-defined caps or bands); grade 1 indicates focal lesions; grade 2 indicates beginning confluence of lesions; and grade 3 indicates diffuse involvement of the entire region, with or without involvement of U fibers. For the basal ganglia, grade 0 indicates no lesions, grade 1 indicates 1 focal lesion ($\leq 5$ mm); grade 2 indicates $\geq 1$ focal lesion; and grade 3 indicates confluent lesions. The total score was the sum of the grade given for each region. The same neurologist (Y.H.F.) graded the WMC for these patients. The correlation between the total scores of the visual rating scale and the volumes of WMC was excellent ($r=0.863$, $P<0.001$).

MRI

The MRI examinations were performed with a 1.5-T scanner, DWI spin echo planar technique (repetition time/time to echo (TR/TE)/excitation=180/122/4, matrix=128$\times$128, field of view [FOV]=230 mm, slice thickness/gap=applied gradients were used with a b value of 1000 and 500). Axial SE T1 (TR/TE/excitation=425/14/2, FOV=230 mm, slice thickness/gap=5 mm/0.5 mm, matrix of 256$\times$256, time of acquisition 4 minutes 28 seconds) and TSE T2 (TR/TE/excitation=2500/120/1, turbo factor of 15, FOV=230 mm, slice thickness/gap=5 mm/0.5 mm, matrix of 256$\times$256, time of acquisition 1 minute 39 seconds) images were also acquired. Because the slice thickness is 5 mm, any lesion smaller than 5 mm might be underdiagnosed because of the partial volume effect. The cutoff value of the lesion for diagnosis was therefore taken to be 5 mm.

Cognitive Assessment

To avoid bias by a transient impairment of cognitive function in the acute stage of the stroke, all included patients were assessed at 12 weeks after stroke. The following psychometric tests were administered to all patients: Chinese version of Mini-Mental State Examination (MMSE), Alzheimer’s Disease Assessment Scale-cognition (ADAS-cog), and Mattis Dementia Rating Scale-Initiation/Perseveration subscale (MDRS I/P). MMSE served as a brief cognitive examination. The ADAS-cog is an extensive cognitive measure that evaluates the following domains: orientation, word recall, word recognition task, remembering test instruction on word recognition, naming objects and fingers, expressive language, comprehension of spoken language, word finding difficulty, commands, ideational praxis, and constructional praxis. The total score is 70. A higher score indicates more impaired performance. The MDRS I/P was used as a brief evaluation of executive dysfunction, which includes fluency for supermarkert items and articles of clothing, double alternating movements, and graphesthesic tasks. Its total score is 37. A lower score indicates more impaired performance. Because double alternating movements and graphesthesic task requires motor functions, we made special attention to rate-impaired performance caused by perseveration rather than by motor weakness or cerebellar dysfunction. The same psychologist (A.W.) administered the psychometric tests to all patients without knowledge of patients’ neuroimaging results.

Data on age, gender, years of education, and vascular risk factors, including hypertension, diabetes mellitus, and history of stroke or TIA, were collected during the acute admission for all the patients. Subjects were regarded as hypertensive if their systolic blood pressure was $\geq 160$ mm Hg or diastolic blood pressure $\geq 90$ mm Hg on at least 2 occasions, or if they were receiving blood pressure-lowering medication. Diabetes mellitus was diagnosed in keeping with the WHO criteria. TIA was defined as a focal brain deficit caused by vascular disease that cleared completely in $\leq 24$ hours. We performed National Institute of Health Stroke Scale (NIHSS) during the first few days after stroke as representation of patient’s stroke severity. We also recorded the patient’s changes in everyday cognitive functions during the previous 10 years by Chinese version Informant Questionnaire on the Cognitive Decline of the Elderly (IQCODE).

Statistics Analysis

To test for difference among the patients with different severity of WMC, the patients were divided into 4 groups defined by the quartile of WMC volume. We used analysis of variance (ANOVA) or analysis of covariance (ANCOVA) for comparisons of demographic continuous variables and $\chi^2$ for comparisons of categorical data. In the next set of analysis, multivariate stepwise linear regression was performed to identify variables (age, gender, years of education, hypertension, diabetes mellitus, number of lacunae, volume of WMC) that might independently influence performance of MMSE, ADAS-cog, and MDRS I/P. A similar multivariate analysis was also performed only among patients within the highest quartile of WMC to assess whether lesser WMC also had significant influence on cognition.

$P<0.05$ was considered statistically significant. The statistics were analyzed using SPSS 10.0 for Windows software package.

Results

Among the 257 patients with ischemic stroke or TIA who were admitted during the study period, 105 patients had relevant lacunar infarcts. Eleven of these patients were excluded from cognitive assessment because of severe depression ($n=3$), death ($n=1$), default follow-up ($n=4$),
chronic alcoholism (n=1), and language barrier (n=2). The mean age of the 94 included patients was 71.91 years (SD=10.82); 51.7% of them were women and their mean education attainment was 4.37 years (SD=4.17), 81.9% had hypertension, 34.0% had diabetes mellitus, and 23.4% had previous TIA or stroke. The mean NIHSS score at admission was 4.98 (SD=3.34). Mean IQCODE score was 3.31 (SD=0.37).

The distribution of WMC in different sections of the brain was shown in Figure 1. Most of the WMC were detected at the frontal and parieto-occipital regions (70%); 22% of the WMC were distributed in basal ganglia, whereas only 8% of WMC were found in infratentorial area and temporal lobe. The volumes of WMC ranged from 0 to 56.89 cm³, with a median value of 2.57 cm³. The total scores of the 7 patients who were rated visually based on CT were as follows: 13, 13, 8, 7, 4, 3, and 3, respectively.

Based on the correlation between the total score and volume of WMC: volume of WMC = 1.66 × WMC score + 3.51 (R²=0.745, P<0.001); the 7 patients were categorized accordingly. Among all included patients, 22 patients in the first (lowest) volume quartile with a mean volume of 0.07 cm³ (range 0 to 0.45 cm³), 24 in the second with a mean volume of 1.58 cm³ (range 0.52 to 2.57 cm³), 23 in the third with a mean of 4.43 cm³ (range 2.68 to 6.47 cm³), and 25 in the fourth (highest) with a mean volume of 18.04 cm³ (range 6.56 to 56.89 cm³).

Characteristics of participants by severity of WMC are shown in Table 1. Patients with greater WMC were older, had more lacunar infarcts, more severe stroke, and more impaired prestroke cognitive decline than those with lesser WMC. No significant differences were noted in terms of gender, education, hypertension, diabetes mellitus, sites of relevant lacunar infarcts, and total volumes of lacunar infarcts. Performances in psychometric tests were significantly more impaired among those with highest WMC than those with less WMC.

Multivariate analysis between cognitive function and variables that might influence cognition showed that age, gender, and education significantly influenced performance of MMSE. Only age influenced performance of ADAS-cog. Age and volume of WMC influenced performance of MDRS I/P (Table 2). A separate multivariate analysis after removing patients with highest WMC revealed that WMC had no

### Table 1. Demographic Variables and Clinical Features Across WMC Groups

<table>
<thead>
<tr>
<th>Grading of WMC</th>
<th>1st Quartile</th>
<th>2nd Quartile</th>
<th>3rd Quartile</th>
<th>4th Quartile</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y</td>
<td>63.55 (10.57)</td>
<td>71.50 (10.25)</td>
<td>72.87 (10.46)</td>
<td>78.80 (6.32)</td>
<td>&lt;0.001*</td>
</tr>
<tr>
<td>Female, %</td>
<td>45.50</td>
<td>66.70</td>
<td>52.20</td>
<td>40.00</td>
<td>0.28</td>
</tr>
<tr>
<td>Education, y</td>
<td>5.52 (3.87)</td>
<td>3.88 (3.97)</td>
<td>4.46 (4.67)</td>
<td>3.76 (4.18)</td>
<td>0.47</td>
</tr>
<tr>
<td>Hypertension, %</td>
<td>81.80</td>
<td>87.50</td>
<td>69.60</td>
<td>88.0</td>
<td>0.32</td>
</tr>
<tr>
<td>Diabetes mellitus, %</td>
<td>36.40</td>
<td>45.80</td>
<td>21.70</td>
<td>32.00</td>
<td>0.37</td>
</tr>
<tr>
<td>History of TIA/stroke, %</td>
<td>18.20</td>
<td>13.60</td>
<td>34.80</td>
<td>28.00</td>
<td>0.33</td>
</tr>
<tr>
<td>Total N of lacunae</td>
<td>1.68 (1.32)</td>
<td>2.52 (1.71)</td>
<td>2.32 (1.09)</td>
<td>3.26 (1.61)</td>
<td>0.006*</td>
</tr>
<tr>
<td>Total volume of lacunae</td>
<td>0.66 (0.52)</td>
<td>0.93 (0.86)</td>
<td>0.90 (0.60)</td>
<td>0.95 (0.60)</td>
<td>0.49</td>
</tr>
<tr>
<td>Site of relevant lacunar infarct</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>0.67</td>
</tr>
<tr>
<td>Striatocapsule</td>
<td>1</td>
<td>5</td>
<td>5</td>
<td>6</td>
<td></td>
</tr>
<tr>
<td>Subcortical white matter</td>
<td>6</td>
<td>7</td>
<td>4</td>
<td>6</td>
<td></td>
</tr>
<tr>
<td>Thalamus</td>
<td>5</td>
<td>3</td>
<td>5</td>
<td>3</td>
<td></td>
</tr>
<tr>
<td>Brain stem</td>
<td>9</td>
<td>5</td>
<td>5</td>
<td>8</td>
<td></td>
</tr>
<tr>
<td>Cerebellum</td>
<td>0</td>
<td>1</td>
<td>0</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Multiple sites</td>
<td>1</td>
<td>3</td>
<td>4</td>
<td>2</td>
<td></td>
</tr>
<tr>
<td>NIHSS</td>
<td>3.91 (2.91)</td>
<td>4.13 (2.35)</td>
<td>5.17 (2.98)</td>
<td>6.56 (4.23)</td>
<td>0.021*</td>
</tr>
<tr>
<td>IQCODE</td>
<td>3.12 (0.21)</td>
<td>3.27 (0.36)</td>
<td>3.27 (0.25)</td>
<td>3.53 (0.45)</td>
<td>0.001*</td>
</tr>
<tr>
<td>Cognitive performance†</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>MMSE</td>
<td>25.92 (1.09)</td>
<td>23.53 (0.97)</td>
<td>24.28 (0.98)</td>
<td>21.06 (1.02)</td>
<td>0.024*</td>
</tr>
<tr>
<td>MDRS I/P</td>
<td>29.96 (1.44)</td>
<td>26.57 (1.25)</td>
<td>28.01 (1.24)</td>
<td>24.10 (1.34)</td>
<td>0.038*</td>
</tr>
<tr>
<td>ADAS-cog</td>
<td>14.17 (2.07)</td>
<td>19.42 (1.84)</td>
<td>16.32 (1.86)</td>
<td>22.37 (1.98)</td>
<td>0.036*</td>
</tr>
</tbody>
</table>

Statistics were ANOVA or χ² test. Values are mean (SD).

*P<0.05.

†Analysis of covariance adjusted for age, gender, and years of education.

IQCODE indicates Informant Questionnaire on the Cognitive Decline of the Elderly.
independent influence in the performance of MDRS I/P on patients with less WMC.

Discussion

WMC are believed to be caused by incomplete white matter infarction associated with small vessel disease affecting the deep penetrating arteries. Because the most common vascular cause of lacunar infarct is also small vessel disease, WMC is found to coexist commonly with stroke patients having lacunar infarcts. In our present study, we noted that WMC occurred in >80% among our patients having lacunar infarcts. Although Van et al reported that among patients with lacunar infarcts those with severe WMC were younger than those with less severe lesions, we observed that patients with severe WMC were significantly older than those with lesser WMC. Our finding is similar to that of most other studies among stroke-free subjects showing that WMC is an age-related phenomenon. Furthermore, we observed that hypertension was present in almost 90% of patients having severe WMC. This is again consistent with other studies demonstrating strong association between hypertension and WMC. As in other series, most of the WMC were distributed in frontal and parieto-occipital lobes, whereas fewer WMC were found in basal ganglia, infratentorial area, and temporal lobe. Among patients with severe WMC, all of the 5 sections were equally affected.

The distinction between focal ischemic lesions of brain and concomitant WMC as cause of dementia is particularly relevant in patients with lacunar infarcts. However, the role of WMC on cognitive impairment is controversial. Some studies found a correlation between neuropsychological deficits and the extent of WMC, whereas others found no association between WMC and cognitive impairment. This inconsistency may be caused by the differences in study designs, inclusion/exclusion criteria, or the method in rating WMC or cognition. In our present study, we evaluated consecutive patients who were admitted to the hospital because of lacunar infarcts and we measured WMC quantitatively for majority of the patients. We found that WMC had an independent influence in the performance of the executive test (MDRS I/P) and that WMC had no influence in other cognitive measures as evaluated by MMSE and ADAS-cog. Impaired MDRS I/P might be secondary to impaired motor sensory deficits, rather than to the severity of WMC. However, even when NIHSS was entered into multivariate analyses for finding contribution of various factors in affecting MDRS I/P, NIHSS did not contribute to the variance of MDRS I/P.

Executive functions are those involved in complex cognitions, including solving new problems, conceptual reasoning, inhibiting of overlearned patterns of behavior, and modifying behavior in the light of new information. According to Funahashi, executive functions refer to “a product of the co-coordinated operation of various processes to accomplish a particular goal in a flexible manner.” Deficits in this domain are directly related to behavioral disorganization and functional decline. Some controversies exist regarding the relation between WMC and executive function. Wahlund et al found no significant association between increased signal hyperintensities and performance in any of the neuropsychological tests. Sabri et al found that lacunar infarcts and WMC did not in themselves indicate cognitive impairment in patients with cerebral microangiopathy. On the contrary, other studies have suggested a relation between WMC and executive skills in elderly subjects. In the present study, multiple linear regression analysis revealed that WMC was an independent predictor of executive dysfunction as assessed by MDRS I/P. Our finding was consistent with a recent report by Kramer et al showing that subcortical ischemic vascular disease is associated with subtle declines in executive function in nondemented patients, and executive measures correlate with the extent of WMC but not with the number of lacunar infarcts.

Our separate multivariate analysis had shown that after removing patients with severe WMC, the influence of WMC on executive function among patients with less WMC was not significant. We postulate that the effect of WMC on executive function may not be linear and a threshold should have been exceeded before executive function is affected. This observation is similar to a previous study showing that only severe WMC was associated with executive dysfunction among healthy elderly subjects. A larger study is needed to further explore this “threshold” hypothesis.

Our finding that WMC did not influence cognitive function as measured by MMSE or ADAS-cog are not surprising, because both of these tests are biased in evaluating cognitive functions that are predominantly associated with cortical lesions, such as memory or language, and are less sensitive in

### Table 2. Multiple Linear Regression Analysis of Factors Affecting Cognitive Performance

<table>
<thead>
<tr>
<th>Factor</th>
<th>MMSE</th>
<th>MDRS I/P</th>
<th>ADAS-cog</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>B (SE)</td>
<td>P</td>
<td>B (SE)</td>
</tr>
<tr>
<td>Age</td>
<td>0.117 (0.050)</td>
<td>0.222</td>
<td>0.211 (0.063)</td>
</tr>
<tr>
<td>Gender</td>
<td>-2.405 (1.056)</td>
<td>0.026</td>
<td>0.375</td>
</tr>
<tr>
<td>Education</td>
<td>0.342 (0.141)</td>
<td>0.018</td>
<td>0.222</td>
</tr>
<tr>
<td>N of infarct</td>
<td>-0.223</td>
<td>-0.579</td>
<td>-0.080</td>
</tr>
<tr>
<td>Volume of lacunar infarct</td>
<td>0.881</td>
<td>0.936</td>
<td>0.215</td>
</tr>
<tr>
<td>Volume of WMC</td>
<td>-0.062</td>
<td>-0.188</td>
<td>-0.013</td>
</tr>
<tr>
<td>Hypertension</td>
<td>0.863</td>
<td>0.215</td>
<td>0.243</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>-0.534</td>
<td>0.437</td>
<td>0.800</td>
</tr>
</tbody>
</table>
evaluating executive dysfunction that is mainly associated with subcortical lesions.

We observed that prestroke cognitive decline as measured by IQCODE increased with increasing severity of WMC. Although this may suggest that WMC had already been affecting patients’ cognition before stroke, other coexisting pathological processes, such as Alzheimer disease, might also affect patients’ cognition before stroke. Further study is needed to explore the determinants of prestroke cognitive decline among patients with lacunar infarcts.

There are some limitations of our present study. First, we did not evaluate the influence of cortical or hippocampal atrophy on cognition in our study. A recent study suggested that dementia in patients with subcortical ischemic vascular disease correlates best with cortical or hippocampal atrophy.\(^\text{31}\) Second, we also did not evaluate the influence of the site of relevant lacunar infarcts on cognition. Lacunar infarcts located in strategic sites are recognized to induce various severity and pattern of cognitive impairment.\(^\text{30,31}\) Although there was no significant difference in the sites of relevant lacunar infarcts between patients having varying severity of WMC, we were unable to statistically evaluate the influence of the sites of lacunar infarcts on cognition because the number of patients in each particular site was small. Moreover, the MDRS I/P measures only part of the performance in the complex executive domain, and more extensive battery should be used to confirm this observation. There are, however, some strengths of our study that are worth further mentioning. First, our study was a prospective study among patients with lacunar infarction. Second, our sample size exceeded that of many previously published studies on the relationship between WMC and cognition in patients with lacunar infarcts.\(^\text{11,16,32,33}\) Third, we used predominantly quantitative measure rather than visual rating scale in assessing the severity of WMC among our patients.

In conclusion, our present study shows that WMC in stroke patients with lacunar infarcts is associated with executive dysfunction.

References

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Stroke. 2004;35:1826-1830; originally published online June 17, 2004; doi: 10.1161/01.STR.0000133686.29320.58
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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