Salt Sensitivity in Humans Is Linked to Enhanced Sympathetic Responsiveness and to Enhanced Proximal Tubular Reabsorption


SUMMARY If high sodium intake is involved in the pathogenesis of essential hypertension, the effects of changing the sodium intake should be demonstrable in the susceptible part of the normotensive population. Therefore, we have investigated the effects of moderate salt restriction in 52 young normotensive subjects with and without a family history of hypertension; 22 (42%) responded to moderate salt restriction (200 to 50 mmol/day) over 2 weeks, with a significant fall in blood pressure shown by continuous automatic blood pressure recordings. Accordingly, these subjects were classified as salt-sensitive, and the remainder as salt-resistant. Compared to salt-resistant subjects, salt-sensitive subjects showed a 2.5-fold higher incidence of a positive family history of hypertension (p< 0.01), and a significantly higher blood pressure and lower salivary sodium concentration during the usual high sodium diet. Although there were no differences in Na,K-ATPase activity and in Na-K cotransport of erythrocytes, the pressor response to infused norepinephrine in salt-sensitive subjects was double that of salt-resistant subjects independent of the diet and this was linked to indirect evidence for enhanced proximal tubular sodium reabsorption. On the usual high sodium diet, 40% of the normal population may be salt-sensitive and prone to develop hypertension. Hypersensitivity to catecholamines (genetically determined?) may be the cause of salt sensitivity. A low sodium concentration in saliva deserves further study as a simple screening test to identify salt-sensitive subjects. (Hypertension 6: 152-158, 1984)

KEY WORDS hypertension • salt sensitivity • sympathetic hyperresponsiveness • genetics • proximal tubular sodium reabsorption

Although hypertensive subjects respond to salt restriction with a decrease in blood pressure,1-7 it is generally held that normotensive subjects do not respond to restriction of the usual daily sodium intake of between 10 and 20 g.7-10 This implies that normotensive subjects cannot become hypertensive because of a high sodium intake. By continuous automatic blood pressure recordings over several hours in a small group of young normotensive subjects, we had previously demonstrated a significant fall in blood pressure in about half the subjects after a moderate reduction of sodium intake from 200 to 50 mmol/day. We therefore proposed that these subjects were prone to develop hypertension in later life on their usual high sodium intake.11

In our present study, we have confirmed in a large group of healthy young subjects that salt-sensitive normotensive subjects exist and that salt sensitivity is linked to enhanced sympathetic responsiveness.12

Material and Methods

We studied 52 normotensive male medical students, aged 20 to 25 years both on their usual daily diet containing 200 mmol of sodium and 80 mmol of potassium, and after 2 weeks on a daily diet containing 50 mmol of sodium and an unchanged potassium and caloric intake. The sequence of the diets was randomized. The amount of sodium and potassium was that usually consumed in the usual diet in Western Europe. The low sodium diets were provided by the dietetic

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Presented in part at the 5th Meeting of the European Blood Pressure Group, Dublin, Ireland, June, 1982, and published in abstract form (see ref. 12).

Supported by the Fonds zur Förderung der wissenschaftlichen Forschung and by the Jubilaumsfonds der Nationalbank.

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Received April 21, 1983; revision accepted August 30, 1983.
department of the hospital; moderate salt restriction was achieved by eliminating food containing added salt and by not using salt for cooking and baking except for bread. The subjects received the diet in the hospitals but were not kept on a metabolic ward.

**Protocol**

After a 24-hour urine specimen had been collected, a needle was placed in a forearm vein of the fasting subject at 8:00 am. The subject then rested supine for 90 minutes, after which blood was taken for determination of plasma renin, aldosterone, norepinephrine, epinephrine, plasma creatinine, electrolytes, and Na,K-ATPase activity and Na-K cotransport in erythrocytes. During this time, pulse rate and systolic, diastolic, and mean blood pressures were recorded every minute using a Dinamap Model 845 with recorder 950 (Applied Medical Research Corporation, Tampa, Florida). Also during this time, about 3 to 5 ml of spontaneous saliva was collected. At 3 hours after blood collection, in vivo mineralocorticoid activity was measured by subtraction potential difference\(^{13}\) to relate it to concurrent plasma aldosterone levels. On the same day after 30 minutes of supine bed rest, the subjects also received a graded infusion of norepinephrine (0.1, 0.2, and 0.4 \(\mu g/kg/min\)), each over 5 minutes, while blood pressure and pulse rate were recorded every minute.

The family history of hypertension was evaluated by questionnaire administered to each subject and given to the family doctor. Those with established hypertension in parents or grandparents were considered positive; those with normotensive parents and grandparents, negative. The subjects were also tissue-typed for HLA-antigens.

**Measurements**

Methods of hormone measurements were: plasma renin by the method of Boyd et al.,\(^{14}\) aldosterone by the method of Ito et al.,\(^{15}\) and catecholamines by the method of Hörtnagl et al.\(^{16}\) Blood pressures and pulse rates used for comparison of the effects of the diets were the means of values recorded during the resting period. Due to the large number of measurements (n > 90), intraindividual changes could be calculated for each subject by the unpaired \(t\) test. Pressor response to infused norepinephrine was assessed as reported previously.\(^{11}\)

For the measurement of Na,K-ATPase and of cotransport, 250 \(\mu l\) erythrocytes were washed twice in physiological saline and were incubated in triplicate at 37°C for 1 hour with 150,000 cpm of \(^{86}\)Rb in 0.5 ml of a medium with or without 1.0 \(\times 10^{-4}\) mol of ouabain or 1.0 \(\times 10^{-4}\) mol of ouabain and 1.07 mmol of furosemide. The medium contained sodium, potassium, calcium, magnesium, chloride, phosphate, and glucose in concentrations of 145, 3.9, 1.50, 0.50, 140, 1.36, and 11.1 mmol/liter, respectively. Na,K-ATPase and cotransport were calculated from the difference of \(^{86}\)Rb uptake in the presence of ouabain and in the presence of ouabain and furosemide, respectively. Statistical methods were: the Wilcoxon matched pairs signed rank test, Student's paired and unpaired \(t\) test, the sign test of Dixon and Mood, and the \(u\)-test of Mann-Whitney.

**Results**

A low sodium diet reduced systolic, diastolic, and mean blood pressure levels significantly by more than 3 mm Hg in 22 of 52 individuals, as shown by the mean of at least 90 blood pressure measurements per subject per diet. The standard error of the mean for a single 90-minute period ranged between 0.42 and 0.84 mm Hg. Another study performed by us (Skrabal et al., unpublished data) has shown that, without intervention, mean blood pressure is reproducible within 2 mm Hg for the same subject even many weeks apart. The frequency distribution of change of blood pressure during the low sodium diet is shown in Figure 1. As calculated by the signed rank test of Dixon and Mood and the Wilcoxon test, the observed distribution of

![Figure 1](http://hyper.ahajournals.org/)

*Figure 1. Frequency distribution of change of blood pressure during the low sodium diet. The observed distribution of change of systolic, diastolic, and mean blood pressure did not correspond to a binomial distribution (Wilcoxon matched pairs signed rank test for diastolic blood pressure, \(p < 0.001\)). The shaded bars indicate subjects with a positive family history of hypertension.*
changes in systolic, diastolic, and mean blood pressure does not correspond to a binomial distribution: blood pressure rose in 17 subjects and fell in 35. Consequently, the group was dichotomized, and the 22 subjects who showed intraindividual significant decreases of blood pressure of more than 3 mm Hg were classified as salt-sensitive and the remainder as salt-resistant.

As shown in Table 1, salt-sensitive and salt-resistant subjects lost a similar amount of weight when changed from the usual to the low sodium diet, and there were no significant differences in plasma and urinary catecholamines. Uric acid also increased significantly in both groups, but the increase in the salt-sensitive group was twice as high as in the salt-resistant group. Concomitantly, uric acid clearance and fractional uric acid excretion decreased to half its initial value in salt-sensitive subjects ($p < 0.001$) during sodium restriction, but remained unchanged in salt-resistant subjects (Figure 2). Furthermore, although plasma renin and aldosterone levels were identical during the high sodium diet in both groups, salt-resistant subjects had a markedly more stimulated renin-aldosterone axis during the low sodium diet (Figure 3). The semilogarithmic regression of plasma aldosterone to in vivo mineralocorticoid activity gave the following regression equations: for salt-sensitive subjects, the subtraction PD (mV) = 51.9 log PA (ng/dl) − 39.8, $r = 0.71$, $n = 26$, $p < 0.001$; for salt-resistant subjects, the subtraction

**TABLE 1. Blood Pressure Values and Biochemical Data in Salt-Sensitive and Salt-Resistant Subjects During High and Low Sodium Intakes (Mean ± SEM)**

<table>
<thead>
<tr>
<th></th>
<th>Salt-sensitive subjects (n = 22)</th>
<th>Salt-resistant subjects (n = 30)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>High salt diet</td>
<td>Low salt diet</td>
</tr>
<tr>
<td>Body weight (kg)</td>
<td>76.2 ± 2.45</td>
<td>−0.86 ± 0.247</td>
</tr>
<tr>
<td>Systolic blood pressure (mm Hg)</td>
<td>125.1 ± 1.59</td>
<td>117.4 ± 1.94</td>
</tr>
<tr>
<td>Diastolic blood pressure (mm Hg)</td>
<td>65.7 ± 1.56</td>
<td>61.1 ± 1.73</td>
</tr>
<tr>
<td>Mean blood pressure (mm Hg)</td>
<td>86.1 ± 1.36</td>
<td>81.0 ± 1.57</td>
</tr>
<tr>
<td>Pulse rate (bpm)</td>
<td>70.8 ± 1.42</td>
<td>69.3 ± 2.02</td>
</tr>
<tr>
<td>24-hr urinary sodium (mmol)</td>
<td>203.5 ± 12.97</td>
<td>37.4 ± 3.31</td>
</tr>
<tr>
<td>24-hr urinary sodium/creatinine ratio (mmol/g)</td>
<td>121.9 ± 7.71</td>
<td>20.7 ± 1.69</td>
</tr>
<tr>
<td>24-hr urinary potassium (mmol)</td>
<td>70.0 ± 4.29</td>
<td>84.2 ± 10.12</td>
</tr>
<tr>
<td>24-hr urinary potassium/creatinine ratio (mmol/g)</td>
<td>41.3 ± 1.97</td>
<td>52.0 ± 8.33</td>
</tr>
<tr>
<td>Serum sodium (mmol/liter)</td>
<td>138.3 ± 0.86</td>
<td>141.9 ± 1.10</td>
</tr>
<tr>
<td>Serum potassium (mmol/liter)</td>
<td>4.20 ± 0.116</td>
<td>4.29 ± 0.115</td>
</tr>
<tr>
<td>Serum creatinine (mg/dliter)</td>
<td>1.00 ± 0.033</td>
<td>1.07 ± 0.040</td>
</tr>
<tr>
<td>Uric acid (mg/dl)</td>
<td>5.67 ± 0.261</td>
<td>*6.97 ± 0.336</td>
</tr>
<tr>
<td>Plasma renin activity (pg/ml/hr)</td>
<td>337.7 ± 52.2</td>
<td>573.4 ± 79.1</td>
</tr>
<tr>
<td>Plasma aldosterone (ng/dl)</td>
<td>7.2 ± 1.01</td>
<td>21.6 ± 2.39</td>
</tr>
<tr>
<td>Plasma norepinephrine (ng/ml)</td>
<td>0.296 ± 0.038</td>
<td>0.250 ± 0.015</td>
</tr>
<tr>
<td>Plasma epinephrine (ng/ml)</td>
<td>0.066 ± 0.013</td>
<td>0.064 ± 0.017</td>
</tr>
<tr>
<td>Urinary aldosterone (μg/24 hr)</td>
<td>6.5 ± 0.97</td>
<td>15.0 ± 1.44</td>
</tr>
<tr>
<td>Urinary norepinephrine (μg/24 hr)</td>
<td>50.1 ± 8.50</td>
<td>42.6 ± 3.67</td>
</tr>
<tr>
<td>Urinary epinephrine (μg/24 hr)</td>
<td>11.9 ± 1.13</td>
<td>14.6 ± 1.30</td>
</tr>
</tbody>
</table>

Differences between the groups: *p < 0.05; †p < 0.01; ‡p < 0.001.

The differences between salt-sensitive and salt-resistant subjects are underlined.
SALT SENSITIVITY IN HUMANS/Skrabal et at.

Figure 3. Plasma renin activity and plasma and urinary aldosterone levels in salt-sensitive and salt-resistant subjects at high and low levels of sodium intake (mean ± SEM).

Figure 4. Increase of mean blood pressure at 0.1, 0.2, and 0.4 µg/kg/min norepinephrine in salt-sensitive and salt-resistant subjects during high and low levels of sodium intake (mean ± SEM). Student's unpaired t test between salt-sensitive and salt-resistant subjects (p < 0.01) and Mann Whitney u-test (p < 0.005). Total height of bar-pressor response during high sodium diet. Shaded bar-pressor response during low sodium diet.

Figure 5. Relationship of salivary sodium concentration to change in blood pressure when subjects were changed from high to low sodium intake (mean ± SEM). (r = -0.41; p < 0.05, n = 37). Subjects with (•) and without (●) a family history of hypertension.

The increase in mean blood pressure during the norepinephrine infusion in both groups is shown in Figure 4. As can be seen, the increase in blood pressure during norepinephrine infusion in salt-sensitive subjects is nearly double that of salt-resistant subjects at all rates of infusion, and this difference also persists when the subjects were put on a low sodium diet. Figure 5 shows that subjects with the most marked decrease of blood pressure during the low sodium diet had also the lowest salivary sodium concentration and vice versa. The incidence of a positive family history of hypertension in salt-sensitive subjects was 15 of 22 (68.2%) and eight of 30 (26.7%) in salt-resistant subjects (χ² = 8.9, p < 0.01). Furthermore, the distribution of certain HLA-antigens shows remarkably different trends (Table 2).

Table 2. Frequency of the HLA-Loci in Salt-Sensitive and Salt-Resistant Subjects

<table>
<thead>
<tr>
<th>HLA Locus</th>
<th>Salt-sensitive subjects (n = 32)</th>
<th>Salt-resistant subjects (n = 32)</th>
<th>Total incidence (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>No.</td>
<td>Incidence (%)</td>
<td>No.</td>
<td>Incidence (%)</td>
</tr>
<tr>
<td>A 3</td>
<td>4 (4)</td>
<td>12.5 (18.2)</td>
<td>9 (7)</td>
</tr>
<tr>
<td>A 19</td>
<td>5 (4)</td>
<td>15.6 (18.2)</td>
<td>1 (0)</td>
</tr>
<tr>
<td>B 13</td>
<td>5 (4)</td>
<td>15.6 (18.2)</td>
<td>1 (1)</td>
</tr>
<tr>
<td>B 27</td>
<td>5 (5)</td>
<td>15.6 (22.7)</td>
<td>1 (1)</td>
</tr>
</tbody>
</table>

Data are from 22 salt-sensitive and 24 salt-resistant normotensive subjects, and also from 18 patients with borderline hypertension, age range 20 to 35 years, which were also classified into salt-sensitive (n = 10) and salt-resistant subjects (n = 8). The figures for normotensive subjects alone are given in parenthesis.
hypertension, a proportion of whom will certainly de-

Figure 6 demonstrates that there are no significant dif-

cferences in Na,K-ATPase activity and cotransport be-

tween salt-sensitive and salt-resistant subjects.

Discussion

If a high sodium intake is of relevance in the patho-
genesis of hypertension, great interindividual differ-

ces in salt sensitivity must exist, since only a small

part of the population develops hypertension during a

high sodium intake. Consequently, it should be possi-

ble to identify the salt-sensitive individuals in the pre-

hypertensive state. Therefore, we have studied normo-
tensive subjects with and without a family history of

hypertension, a proportion of whom will certainly de-

velop hypertension in later life. Although others did

do not show a fall of blood pressure after sodium restric-

tion from casual blood pressure readings, we have

shown an intrindividually significant fall of blood

pressure in 42% of normotensive subjects whom we

classified as salt-sensitive by continuous automatic

blood pressure recordings over several hours.

Although the mean value recorded during this rest-
ing period gives apparently a very good index of the

24-hour blood pressure profile,

some of the blood pressure changes observed may still be random and

may be due to factors hardly controllable such as dif-

ferent levels of personal emotional stress (e.g., due to

events concerned with the medical curriculum), so that

we may have misclassified some of the subjects. The

biochemical and other differences observed in the two

groups are therefore even more remarkable. Since a

positive family history of hypertension was nearly

three times more frequent in the salt-sensitive group

than in the salt-resistant group, we conclude that the

phenomenon of salt sensitivity may be inherited. The

varying incidence of certain HLA-antigens (Table 2) is

also suggestive for a genetic basis of this observation.

Due to the low overall incidence of the different loci,

an even larger study is needed to confirm the presently

observed trends. The significantly higher systolic, dia-

tolic, and mean blood pressure levels in the salt-sensi-
tive group on the usual high sodium intake suggest that

some of these subjects may already be slowly develop-
hypertension, if they continue their usual high so-
dium intake.

What could be the biochemical basis of this ob-

erved difference of salt sensitivity? Since both groups

excreted the amount of sodium given in the diet after 2

weeks on the low sodium diet, we can safely assume

that both groups are in a steady state of sodium bal-

cance. Since the subjects received and consumed the

sodium-restricted diet from the dietician department of

the hospital, we consider a single determination of

urinary sodium excretion as adequate control, espe-
cially since completeness of the collection was ensured

by the measurement of urinary creatinine excretions

(Table 1). Both groups also lost a similar amount of

weight (and presumably body water) during reduction

of sodium intake; apparently, salt-sensitive subjects do

not retain appreciably more sodium during the high

sodium intake. However, it is remarkable that, in salt-

resistant subjects, the renin-aldosterone axis had to be

stimulated nearly twice as much to achieve sodium

balance during the low sodium diet (Figure 3). This


corresponds to observations made by Kawasaki et al.

and Fujita et al. in salt-resistant hypertensive subjects.

Our interpretation of this finding is that salt-sensitive

subjects have more effective mechanisms with which to

maintain sodium balance at low levels of sodium intake and therefore need a less stimulated renin-aldo-

sterone axis. A genetically determined enhanced sensi-
tivity of aldosterone receptors would have been an

attractive hypothesis, but the relationship between al-

dosterone levels in plasma and in vivo mineralocorti-

coid activity at the cellular level was not statistically
different in both groups.

The other important difference observed between

salt-sensitive and salt-resistant subjects was the mar-
kedly enhanced blood pressure responsiveness to in-

fused norepinephrine (Figure 4). This difference be-
tween the salt-sensitive and the salt-resistant subjects

persisted at high and low levels of sodium intake and

was not due to different levels of plasma and urinary

catecholamines (Table 1). We have also confirmed our

and other previous observations that salt restriction

lowers the pressure response to infused norepineph-

rine. It is remarkable that in our study moderate sodi-

um restriction from 200 to 50 mmol/day did not raise

plasma and urinary catecholamines, as is seen with

more extreme variations of sodium intake and that

plasma catecholamine levels in salt-sensitive and salt-

resistant normotensive subjects were not different,

which is in contrast to the results of Fujita et al. and

Campese et al. in hypertensive subjects. Unfortunat-

ely, we were unable to determine plasma concentration
of norepinephrine during the graded infusion, so that it is uncertain whether salt-sensitive and salt-resistant subjects achieved comparable blood levels of norepinephrine. It would have been important to measure norepinephrine levels during the infusion since Dietz and Coworkers have demonstrated that stroke-prone SHR rats may have a defect in norepinephrine uptake during salt loading. It is also important to consider the work of Polgar et al., who performed norepinephrine infusions in normal subjects and observed that hypertensives responded to acute hypertonic saline infusions with a natriuresis in a fashion similar to patients with stable essential hypertension.

We believe that enhanced sympathetic responsiveness may be the cause of salt sensitivity. Low level stimulation of renal nerves is known to cause proximal sodium reabsorption without changing renal blood flow or renal resistance and this effect is blocked by phentolamine. With the same level of sympathetic stimulation in salt-sensitive and salt-resistant subjects (as indicated by similar plasma and urinary catecholamines), an increased sensitivity to norepinephrine in salt-sensitive subjects would lead to enhanced sodium reabsorption at the proximal tubules, so that a less stimulated renin-aldosterone axis at the low level of sodium intake (Figure 3) would still guarantee adequate overall sodium reabsorption. Evidence for an enhanced proximal tubular salt and volume reabsorption in the salt-sensitive group is also the enhanced uric acid reabsorption, as indicated by the twofold higher rise of plasma uric acid and fall of uric acid clearance in this group (Figure 2). At the high level of sodium intake, however, salt-sensitive subjects should also suppress their renin-aldosterone axis more than salt-resistant subjects in order to counter-balance the effects of enhanced sympathetic responsiveness. But, as shown in Figure 3, salt-sensitive subjects are unable to suppress their renin-aldosterone axis more than salt-resistant subjects; obviously, both systems are already completely suppressed and outside their regulatory range. Consequently, in salt-sensitive subjects, blood pressure rises and sodium balance is achieved by pressure natriuresis. A generalized enhanced sympathetic responsiveness in salt-sensitive subjects would also decrease the volume of the vascular bed (e.g., as seen in pheochromocytoma). Therefore, if we assume that salt-sensitive subjects are those prone to develop hypertension in later life, enhanced sympathetic responsiveness would explain why, at the beginning of hypertension, contraction of the intravascular volume and not expansion is found (although this contraction may still be associated with a relative fluid overload for the given capacity of the vascular bed).

If our concept is correct, why is blood pressure not higher in salt-sensitive than in salt-resistant subjects during the low sodium intake, considering that they have similar levels of plasma norepinephrine but increased vascular response? One possible explanation is that plasma renin activity (and probably also circulating angiotensin II) in salt-sensitive subjects on average is only half that of salt-resistant subjects (Table 1).

How does the currently favored hypothesis of an excess of a ouabain-like natriuretic hormone or of a generalized sodium transport defect fit into our concept? Since both cardiac glycosides and a raised intracellular sodium concentration are known to enhance the response of blood vessels to sympathetic stimulation, either mechanism may have mediated the enhanced pressor response to infused norepinephrine in the salt-sensitive group. However, in two different bioassays and in a sensitive digoxin-radiimmunoassay, we were unable to detect a sodium transport inhibitor in any of the groups at any level of sodium intake (unpublished data). Furthermore, Na,K-ATPase activity and Na-K cotransport of erythrocytes were not different in salt-sensitive and salt-resistant subjects (Figure 6). Alternatively, differences in the number or affinity of alpha-adrenoreceptors, or in the relation between alpha- and beta-receptors, or in norepinephrine release, uptake, or metabolism may exist between salt-sensitive and salt-resistant subjects. These differences may be inherited or imprinted later by different psychological and physiological responses to stress.

We do not suggest that salt sensitivity is a qualitative phenomenon. Rather, it appears to be a quantitative phenomenon, with those who are most sensitive responding with the most marked change of blood pressure. Therefore, the chosen cutoff point for dichotomizing the individuals has been of minor importance, and other cutoff points have provided similar results (see, for example, Figure 5). Reducing sodium intake to a level where at the distal tubules a less stimulated renin-aldosterone axis can counterbalance the effects of enhanced sympathetic responsiveness on proximal tubular sodium reabsorption could be a measure to prevent the development of hypertension in the salt-sensitive portion of the population. A low sodium concentration in spontaneous saliva, which is also compatible with the effects of enhanced sympathetic stimulation of the salivary gland, deserves further study as a possible simple marker for salt sensitivity.

Acknowledgments
Part of this work will be submitted as the doctoral thesis of Helge Herholz and Mathias Neumayer. We thank Prof. Dr. Herbert Braunsteiner for his continuous support, Eva Cerny for expert technical assistance, Prof. Florian Lang and Prof. Peter Deeyen for helpful discussion, and Janet Gschntzer for secretarial assistance.

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Salt sensitivity in humans is linked to enhanced sympathetic responsiveness and to enhanced proximal tubular reabsorption.

F Skrabal, H Herholz, M Neumayr, L Hamberger, M Ledochowski, H Sporer, H Hörtnagl, S Schwarz and D Schönitzer

_Hypertension_. 1984;6:152-158
doi: 10.1161/01.HYP.6.2.152

_Hypertension_ is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
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Print ISSN: 0194-911X. Online ISSN: 1524-4563

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