Treatment of Wilson Disease With Ammonium Tetrathiomolybdate

III. Initial Therapy in a Total of 55 Neurologically Affected Patients and Follow-up With Zinc Therapy

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Background: It is unclear what anticopper drug to use for patients with Wilson disease who present with neurologic manifestations because penicillamine often makes them neurologically worse and zinc is slow acting.

Objective: To evaluate the frequency of neurologic worsening and drug adverse effects with ammonium tetrathiomolybdate.

Design: Open-label study of 55 untreated patients (22 of them new) presenting with neurologic Wilson disease treated with tetrathiomolybdate varying from 120 to 410 mg/d for 8 weeks and then followed up for 3 years. Neurologic function was assessed with scored neurologic and speech tests.

Setting: A university hospital referral setting.

Patients: All untreated, newly diagnosed patients with neurologic Wilson disease.

Intervention: Treatment with tetrathiomolybdate.

Main Outcome Measures: Neurologic function was evaluated by neurologic and speech examinations. Drug adverse effects were evaluated by complete blood cell counts and biochemical measures.

Results: Only 2 (4%) of 55 patients treated with tetrathiomolybdate showed neurologic deterioration, compared with an estimated 50% of penicillamine-treated patients. Five of the 22 new patients exhibited bone marrow suppression and 3 had aminotransferase elevations. These numbers are higher than in the original 33 patients and appear to be due primarily to a more rapid dose escalation.

Conclusions: Tetrathiomolybdate shows excellent efficacy in patients with Wilson disease who present with neurologic manifestations. With rapid escalation of dose, adverse effects from bone marrow suppression or aminotransferase elevations can occur.

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The patients were diagnosed as having Wilson disease by means of standard criteria previously extensively published. In addition to the underlying diagnosis of Wilson disease, all patients were diagnosed as having symptoms of a movement disorder attributable to Wilson disease. The institutional review board of the University of Michigan reviewed and approved the project.

Each patient was admitted for up to 8 weeks in the General Clinical Research Center of the University of Michigan Hospital, Ann Arbor. After initial studies to confirm the diagnosis, obtain informed consent, and establish baseline neurologic and speech function, therapy with tetrathiomolybdate was initiated. In many patients the drug was started at 120 mg/d, with 20 mg between meals 3 times daily and 20 mg with meals 3 times daily. If the patient strongly desired a bedtime snack, a fourth 20-mg dose was given with the snack, for a total initial dose, Table 2 gives maximum and average dose data. Patients also started zinc therapy early in their 8-week stay, usually 50 mg 3 times per day. Patients did not receive additional tetrathiomolybdate after the initial 8 weeks of therapy.

Two types of toxic effects from tetrathiomolybdate have been encountered. One is an overtreatment anemia, often accompanied by leukopenia, and occasionally by thrombocytopenia. The other is a mild further elevation of aminotransferase enzymes, due to unknown mechanisms. When either was encountered, the patient’s tetrathiomolybdate dose was decreased and often the patient was given a drug holiday.

During the 8-week admission, a quantitative neurologic test and a quantitative speech examination were carried out at roughly weekly intervals, by previously published methods, standardized for, and extensively evaluated in, Wilson disease. The neurologist (P.H., M.C., and J.K.F.) and speech (K.J.K.) evaluators were not blinded during this open-label study. The main purpose of these weekly tests was to detect neurologic deterioration during initial treatment. An increase of 5 points (scale, 0-38) on the quantitative neurologic examination, or an increase of 3 points (scale, 0-7) on the speech examination, is taken as evidence of significant neurologic deterioration. The patients were discharged on a regimen of zinc maintenance therapy, then returned for an annual visit. The neurologic and speech tests were repeated on an annual basis. The main purpose of these annual examinations was to evaluate the extent of neurologic recovery, if any.

During the 8-week period, assays of “safety variables” were carried out to detect adverse effects of tetrathiomolybdate therapy. These include complete blood cell counts, liver function tests, and amylase, lipase, creatinine, serum urea nitrogen, uric acid, urine protein, and iron variables, all carried out by standard technique in use at the University of Michigan Health System hematology and biochemistry laboratories.

Table 1. Initial Data on the New Sample of 22 Patients With Wilson Disease

<table>
<thead>
<tr>
<th>Patient No./ Sex/Age, y</th>
<th>Hepatic Copper, µg/g</th>
<th>Urine Copper, µg/d</th>
<th>Treatment</th>
<th>History (No. of Weeks)</th>
<th>Major Signs and Symptoms</th>
</tr>
</thead>
<tbody>
<tr>
<td>169/F/25</td>
<td>NA</td>
<td>127</td>
<td>Penicillamine (1 1/2)</td>
<td>Dysarthria, dystonia, severe chorea, nonambulatory</td>
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<tr>
<td>172/F/20</td>
<td>873</td>
<td>111</td>
<td>Zinc acetate (2)</td>
<td>Dysarthria, incoordination*</td>
<td></td>
</tr>
<tr>
<td>173/F/20</td>
<td>240</td>
<td>NA</td>
<td>Penicillamine (2)</td>
<td>Mild dysarthria and chorea</td>
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<tr>
<td>175/F/21</td>
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<td>Penicillamine (2)</td>
<td>Anarthria, severe dystonia and incoordination, nonambulatory</td>
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<tr>
<td>181/M/38</td>
<td>654</td>
<td>381</td>
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<td>Severe dysarthria, dystonia, tremor, incoordination, nonambulatory</td>
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<tr>
<td>183/M/30</td>
<td>414</td>
<td>607</td>
<td>None</td>
<td>Tremor, incoordination</td>
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<tr>
<td>194/M/11</td>
<td>403</td>
<td>122</td>
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<td>626</td>
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<td>203/M/30</td>
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<td>1077</td>
<td>115</td>
<td>Zinc acetate (2)</td>
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<td>208/M/21</td>
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<td>Penicillamine (3)</td>
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<td>209/F/27</td>
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<td>Zinc acetate (4)</td>
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<td>310</td>
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<td>Dysarthria, mild dystonia, incoordination</td>
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<td>211/F/28</td>
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<td>670</td>
<td>213</td>
<td>Penicillamine (3)</td>
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<td>Severe dysarthria, dystonia, tremor, incoordination</td>
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<td>NA</td>
<td>None</td>
<td>Dysarthria, dystonia, tremor, incoordination</td>
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</tr>
<tr>
<td>223/M/24</td>
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<td>340</td>
<td>Penicillamine (1)</td>
<td>Mild dysarthria, dystonia, severe tremor, incoordination</td>
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<td>128</td>
<td>None</td>
<td>Dysarthria, dystonia, tremor, incoordination</td>
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</tr>
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</table>

Abbreviation: NA, not available.

*Incoordination in all patients was related to bradykinesia.

Table 3 shows the results of the weekly quantitative neurologic testing. Patient 211 showed a 6-point deterioration in week 2, so we scored her as showing deterioration, although her scores varied quite widely during the next 3 weeks. None of the other patients showed a 5-point deterioration (increase) in score. The data demonstrated the minor fluctuations in symptoms from one time to another that are attributable to the level of stress, anxiety...
ety, fatigue, etc, that can impact on the expression of these signs and symptoms.

**Table 4** shows similar data for the speech quantitative testing. No patient showed a 3-point deterioration (increase) in score. Again, the data showed the minor fluctuations in dysarthria from one time to another that are attributable to the psychological and physical status of the patient on the day of testing, as discussed in the preceding paragraph.

**Table 5** shows the results of repeat quantitative neurologic testing on annual return visits of the 19 patients who returned, compared with the baseline, which is the first recorded score during the initial 8-week admission. One patient died of variceal bleeding before return, and 2 dropped out. Only 1 patient (patient 210) showed significant (>5 points) deterioration, in this case between baseline and year 1, and this was clearly related to noncompliance with zinc therapy. Almost all of the patients showed some improvement in scores, generally with most of the improvement between baseline and year 1. This is perhaps best demonstrated by the improvement in mean scores at the bottom of Table 5, which shows statistically significant improvement between baseline and year 1. However, unlike the neurologic data, the means for each year in Table 6 suggest that, in some patients, improvement in speech may continue as long as year 3, and indeed, the means of years 2 and 3 are very close to being significantly different.

We saw 2 adverse effects from tetrathiomolybdate therapy in this study (Table 2). Five patients (patients 173, 175, 205, 209, and 216) exhibited bone marrow suppression (**Table 7**), which is attributable to overtreatment and bone marrow depletion of copper. Bone marrow suppression began between weeks 3 and 6 in the 5 patients. Three patients (patients 175, 206, and 208) exhibited elevations of serum aminotransferase enzymes (**Table 8**), due to unknown mechanisms. Enzyme elevations began at the beginning of week 4 in the 3 patients. Mild alkaline phosphatase elevations are expected, because of the initiation of zinc therapy. This is a harmless result of increased induction of the enzyme in the liver by zinc.15 Both the bone marrow suppression and the aminotransferase elevations were responsive to a drug holiday and/or a reduction in tetrathiomolybdate dose (Table 2).

No patient showed abnormalities of serum urea nitrogen, creatinine, uric acid, and urine protein levels during the 8 weeks of tetrathiomolybdate therapy (data not shown).

**Table 2. Data on Tetrathiomolybdate Dosage, Complications, and Dosage Interventions**

<table>
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<th>Patient No.</th>
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<th>Maximum</th>
<th>Average</th>
<th>Complications</th>
<th>Interventions</th>
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<tr>
<td>173</td>
<td>120</td>
<td>140</td>
<td>120</td>
<td>Mild anemia, leukopenia</td>
<td>None</td>
</tr>
<tr>
<td>175</td>
<td>120</td>
<td>200</td>
<td>180</td>
<td>Anemia, leukopenia, thrombocytopenia, and aminotransferase elevations</td>
<td>Drug holiday</td>
</tr>
<tr>
<td>181</td>
<td>120</td>
<td>260</td>
<td>180</td>
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<tr>
<td>205</td>
<td>200</td>
<td>200</td>
<td>180</td>
<td>Mild anemia, leukopenia</td>
<td>Drug holiday, then dosage reduction to 80 mg/d</td>
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<tr>
<td>206</td>
<td>140</td>
<td>200</td>
<td>140</td>
<td>Aminotransferase elevations</td>
<td>Drug holiday, then dosage reduction to 80 mg/d</td>
</tr>
<tr>
<td>208</td>
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<td>200</td>
<td>100</td>
<td>Aminotransferase elevations</td>
<td>Dosage reduction to 80 mg/d</td>
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<tr>
<td>209</td>
<td>120</td>
<td>200</td>
<td>120</td>
<td>Mild anemia, leukopenia, thrombocytopenia</td>
<td>Drug holiday, then dosage reduction to 80 mg/d</td>
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<td>216</td>
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<td>200</td>
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<td>Mild anemia, leukopenia</td>
<td>Drug holiday, then dosage reduction to 80 mg/d</td>
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<td>120</td>
<td>140</td>
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</table>

*Ellipses indicate none.*

In terms of efficacy, the major issue is to avoid the initial neurologic deterioration that occurs about 50% of the time with penicillamine therapy and results in about 25% of patients having permanent, additional, drug-induced...
Table 3. Weekly Quantitative Neurologic Scores During the 8 Weeks of Initial Tetrathiomolybdate Therapy*

<table>
<thead>
<tr>
<th>Patient No.</th>
<th>Weeks of Therapy</th>
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*Score range is 0 (normal) to 38. Ellipses indicate not measured.

Table 4. Weekly Quantitative Speech Scores During the 8 Weeks of Initial Tetrathiomolybdate Therapy*

<table>
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</tr>
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<td>No. of patients</td>
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</table>

*Score range is 0 (normal) to 7. Ellipses indicate not measured.
In the present study are compared with the original study4 in a longer period (Table 6).

The neurologic and speech recovery data over time in the present study are compared with the original study in Table 9. These data show the consistency between the 2 studies in terms of mean baseline values, occurrence of most of the improvement during year 1, and the degree of average improvement.

Alternatives to tetrathiomolybdate for initial therapy, besides penicillamine, include zinc, which appears to be favored by Hoogenraad et al.16 However, we view zinc as rather slow acting for acutely ill patients, taking perhaps 4 to 6 months to control copper toxicity, during which time the disease may progress. Another alternative is trientine. Although its mechanism is similar to that of penicillamine, it is a more gently acting drug and may not share penicillamine’s propensity to make the disease worse initially. We are currently in the midst of a double-blind clinical trial comparing tetrathiomolybdate and trientine for initial use in patients with a neurologic presentation.

A formal toxicity study of tetrathiomolybdate had not been done before these studies, although one is now under way. Approval by the US Food and Drug Administration for this clinical trial was based on extensive animal studies of tetrathiomolybdate during several decades, in which the only toxic effects found were due to copper deficiency.

Adverse effects from tetrathiomolybdate in these studies have been limited to mild bone marrow suppression producing anemia, leukopenia, and occasionally thrombocytopenia, and to mild elevations of aminotransferases.

<table>
<thead>
<tr>
<th>Table 5. Yearly Quantitative Neurologic Scores After Initial Tetrathiomolybdate and Maintenance Zinc Acetate Therapy</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Year</strong></td>
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<td><strong>No. of patients</strong></td>
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</table>

*Ellipses indicate not measured.
†A paired t test comparing year 2 vs year 3, on the 11 patients in whom both samples were obtained, gives P = .055.
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<table>
<thead>
<tr>
<th>Table 6. Yearly Quantitative Speech Scores After Initial Tetrathiomolybdate and Maintenance Zinc Acetate Therapy</th>
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<td><strong>Year</strong></td>
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<td><strong>Patient No.</strong></td>
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<tr>
<td>194</td>
</tr>
<tr>
<td>200</td>
</tr>
<tr>
<td>203</td>
</tr>
<tr>
<td>205</td>
</tr>
<tr>
<td>206</td>
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<td>208</td>
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<tr>
<td>209</td>
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<tr>
<td>210</td>
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<tr>
<td>211</td>
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<tr>
<td>212</td>
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<tr>
<td>214</td>
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<tr>
<td>216</td>
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<tr>
<td>218</td>
</tr>
<tr>
<td>222</td>
</tr>
<tr>
<td>223</td>
</tr>
<tr>
<td>227</td>
</tr>
<tr>
<td><strong>Mean</strong></td>
</tr>
<tr>
<td><strong>SD</strong></td>
</tr>
<tr>
<td><strong>No. of patients</strong></td>
</tr>
</tbody>
</table>
Ferse enzymes. The bone marrow effects appear to be due to depletion of copper and are responsive to a drug holiday or dose reduction. The frequency of anemia or leukopenia was much higher in the current study (5 of 22 patients) than in the original study (1 of 33 patients). One difference is that the number of patients receiving a daily dose of 200 mg or more was only 15 of 33 in the original study and was 14 of 22 in the present study. A second difference is that the dose escalation was considerably more rapid in the current study, usually taking less than a week, while it occurred during 2 to 3 weeks in the original study. Probably the most important difference is that in the original study, escalation was based on the presence of free copper in the blood. This was copper unaccounted for by ceruloplasmin or tetrathiomolybdate binding. In the current study, escalation was more arbitrary, aimed at quelling copper toxicity quickly, since we had seen so little problem with higher doses in the original study.

The other adverse effect, aminotransferase elevations in 3 of 22 patients, was not detected at all in our original study of 33 patients. We are not sure what causes aminotransferase elevations, but we speculate that tetrathiomolybdate is removing copper from various hepatic pools, including metallothionein, and that this causes some additional hepatitis. Since we have not seen this adverse effect from tetrathiomolybdate use in a variety of other clinical uses such as for cancer17 and macular degeneration, where it is used for antiangiogenic purposes, nor in a variety of animal studies, we suspect it occurs only in the face of high hepatic copper loading. Again, we suspect that the reason we saw aminotransferase elevations here but not in the original 33 patients relates to the more rapid and arbitrary tetrathiomolybdate dose escalation.

Both of these adverse effects are quickly responsive to a drug holiday and/or dose reduction. Both clearly are related to dose. For example, in the present study, 7 of the 8 adverse effects occurred in the 14 patients receiving 200 mg or more of tetrathiomolybdate per day (Table 2), whereas only 1 occurred in the 8 patients who received 140 or 120 mg. Since our data indicate no effi-

### Table 7. Blood Count Studies During the 8 Weeks of Initial Tetrathiomolybdate Therapy

<table>
<thead>
<tr>
<th>Weeks of Therapy</th>
<th>0</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>5</th>
<th>6</th>
<th>7</th>
<th>8</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Mean Blood Counts in the 17 Patients Who Were Stable</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>HGB, g/dL</td>
<td>13.2</td>
<td>13.1</td>
<td>13.0</td>
<td>13.2</td>
<td>13.3</td>
<td>13.2</td>
<td>12.9</td>
<td>12.4</td>
<td>13.0</td>
</tr>
<tr>
<td>WBCs/µL</td>
<td>4300</td>
<td>4800</td>
<td>4200</td>
<td>6200</td>
<td>4200</td>
<td>4200</td>
<td>4000</td>
<td>4400</td>
<td>4100</td>
</tr>
<tr>
<td>Platelets, × 10^3/µL</td>
<td>121</td>
<td>117</td>
<td>117</td>
<td>133</td>
<td>119</td>
<td>124</td>
<td>135</td>
<td>132</td>
<td>134</td>
</tr>
<tr>
<td>No. of patients</td>
<td>17</td>
<td>17</td>
<td>17</td>
<td>17</td>
<td>16</td>
<td>16</td>
<td>12</td>
<td>11</td>
<td>5</td>
</tr>
</tbody>
</table>

**Mean Blood Counts in the 5 Patients Who Showed Bone Marrow Suppression**

<table>
<thead>
<tr>
<th>Weeks of Therapy</th>
<th>0</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>5</th>
<th>6</th>
<th>7</th>
<th>8</th>
</tr>
</thead>
<tbody>
<tr>
<td>HGB, g/dL</td>
<td>13.8</td>
<td>12.2</td>
<td>12.0</td>
<td>11.5</td>
<td>11.0</td>
<td>10.5</td>
<td>9.8</td>
<td>10.8</td>
<td>10.3</td>
</tr>
<tr>
<td>WBCs/µL</td>
<td>5800</td>
<td>4200</td>
<td>4500</td>
<td>4000</td>
<td>3700</td>
<td>5800</td>
<td>3500</td>
<td>4400</td>
<td>4600</td>
</tr>
<tr>
<td>Platelets, × 10^3/µL</td>
<td>112</td>
<td>90</td>
<td>102</td>
<td>104</td>
<td>98</td>
<td>90</td>
<td>86</td>
<td>122</td>
<td>130</td>
</tr>
<tr>
<td>No. of patients</td>
<td>5</td>
<td>5</td>
<td>5</td>
<td>5</td>
<td>5</td>
<td>4</td>
<td>4</td>
<td>3</td>
<td>2</td>
</tr>
</tbody>
</table>

**Abbreviations:** HGB, hemoglobin; WBCs, white blood cells.

### Table 8. Liver Function Studies During the 8 Weeks of Initial Tetrathiomolybdate Therapy

<table>
<thead>
<tr>
<th>Weeks of Therapy</th>
<th>0</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>5</th>
<th>6</th>
<th>7</th>
<th>8</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Mean Liver Function Values in the 19 Patients Who Were Stable</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bilirubin, mg/dL</td>
<td>0.9</td>
<td>0.6</td>
<td>0.6</td>
<td>0.6</td>
<td>0.7</td>
<td>0.7</td>
<td>0.7</td>
<td>0.6</td>
<td>0.6</td>
</tr>
<tr>
<td>Albumin, g/dL</td>
<td>3.6</td>
<td>3.4</td>
<td>3.4</td>
<td>3.5</td>
<td>3.5</td>
<td>3.5</td>
<td>3.5</td>
<td>3.4</td>
<td>3.5</td>
</tr>
<tr>
<td>ALT, IU/L</td>
<td>36</td>
<td>36</td>
<td>37</td>
<td>37</td>
<td>34</td>
<td>36</td>
<td>36</td>
<td>54</td>
<td>74</td>
</tr>
<tr>
<td>AST, IU/L</td>
<td>38</td>
<td>34</td>
<td>32</td>
<td>31</td>
<td>32</td>
<td>32</td>
<td>41</td>
<td>36</td>
<td>44</td>
</tr>
<tr>
<td>LDH, IU/L</td>
<td>168</td>
<td>170</td>
<td>163</td>
<td>161</td>
<td>161</td>
<td>194</td>
<td>204</td>
<td>166</td>
<td>157</td>
</tr>
<tr>
<td>Alk phos, U/L</td>
<td>93</td>
<td>94</td>
<td>99</td>
<td>102</td>
<td>103</td>
<td>118</td>
<td>116</td>
<td>111</td>
<td>122</td>
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<tr>
<td>No. of patients</td>
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<td>18</td>
<td>19</td>
<td>17</td>
<td>17</td>
<td>13</td>
<td>11</td>
<td>6</td>
</tr>
</tbody>
</table>

**Mean Liver Function Values in the 3 Patients Who Showed Aminotransferase and Alk Phos Elevations**

<table>
<thead>
<tr>
<th>Weeks of Therapy</th>
<th>0</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>5</th>
<th>6</th>
<th>7</th>
<th>8</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bilirubin, mg/dL</td>
<td>0.9</td>
<td>0.9</td>
<td>0.6</td>
<td>0.6</td>
<td>0.8</td>
<td>0.8</td>
<td>0.9</td>
<td>0.4</td>
<td>0.4</td>
</tr>
<tr>
<td>Albumin, g/dL</td>
<td>3.7</td>
<td>3.5</td>
<td>3.4</td>
<td>3.3</td>
<td>3.2</td>
<td>3.1</td>
<td>3.4</td>
<td>3.3</td>
<td>3.2</td>
</tr>
<tr>
<td>ALT, IU/L</td>
<td>81</td>
<td>84</td>
<td>82</td>
<td>288</td>
<td>378</td>
<td>413</td>
<td>354</td>
<td>174</td>
<td>89</td>
</tr>
<tr>
<td>AST, IU/L</td>
<td>67</td>
<td>84</td>
<td>53</td>
<td>125</td>
<td>148</td>
<td>139</td>
<td>148</td>
<td>50</td>
<td>36</td>
</tr>
<tr>
<td>LDH, IU/L</td>
<td>251</td>
<td>301</td>
<td>221</td>
<td>210</td>
<td>198</td>
<td>188</td>
<td>251</td>
<td>190</td>
<td>164</td>
</tr>
<tr>
<td>Alk phos, U/L</td>
<td>137</td>
<td>133</td>
<td>137</td>
<td>170</td>
<td>212</td>
<td>225</td>
<td>271</td>
<td>469</td>
<td>489</td>
</tr>
<tr>
<td>No. of patients</td>
<td>3</td>
<td>3</td>
<td>3</td>
<td>3</td>
<td>3</td>
<td>3</td>
<td>2</td>
<td>1</td>
<td>1</td>
</tr>
</tbody>
</table>

**Abbreviations:** Alk phos, alkaline phosphatase; ALT, alanine aminotransferase; AST, aspartate aminotransferase; LDH, lactate dehydrogenase.

SI conversion factor: To convert bilirubin to micromoles per liter, multiply by 17.1.
cacy advantage of higher doses, we now recommend daily doses no higher than 120 mg/d for the initial treatment of Wilson disease, to minimize adverse effects.

In summary, tetrathiomolybdate shows excellent efficacy for the initial treatment of patients presenting with the movement disorder symptoms of Wilson disease. Only 2 (4%) of 55 patients worsened during the 8 weeks of tetrathiomolybdate therapy, compared with an estimated 50% who are treated initially with penicillamine. This stabilization of the clinical state during the initial period while copper toxicity is controlled then allows very good recovery of much neurologic function during the succeeding year or two.

Two adverse effects predominate. One is overtreatment of bone marrow suppression. Since the bone marrow requires copper for cellular proliferation, higher doses of tetrathiomolybdate causing bone marrow depletion of copper result in bone marrow cellular suppression. The other adverse effect is elevation of serum aminotransferase enzymes, possibly due to hepatic mobilization of copper in livers already loaded with copper. Both adverse effects are dose related and occur much less frequently if the daily dose of tetrathiomolybdate does not exceed 120 mg. Since there does not appear to be an efficacy advantage of higher tetrathiomolybdate doses, we recommend 120 mg/d for initial therapy in Wilson disease, to minimize adverse effects. Both adverse effects, if they do occur, are quickly responsive to drug holiday and/or dose reduction.

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Author contributions: Study concept and design (Dr Brewer); acquisition of data (Drs Brewer, Hedera, Carlson, Askari, and Fink, Ms Kluin and Sitterly, and Mr Dick); analysis and interpretation of data (Drs Brewer, Hedera, and Askari, Ms Kluin, and Mr Dick); drafting of the manuscript (Dr Brewer and Ms Sitterly); critical revision of the manuscript for important intellectual content (Drs Brewer, Hedera, Carlson, and Fink, Ms Kluin, and Mr Dick); statistical expertise (Mr Dick); obtaining funding (Dr Brewer); administrative, technical, or material support (Drs Brewer, Hedera, and Askari, Mr Dick, and Ms Sitterly); study supervision (Drs Brewer, Carlson, and Fink).

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Corresponding author and reprints: George J. Brewer, MD, Department of Human Genetics, University of Michigan Medical School, 4909 Buhl, Ann Arbor, MI 48109-0618 (e-mail: brewerg@umich.edu).

Table 9. Neurology and Speech Scores Over Time in the 2 Studies

<table>
<thead>
<tr>
<th></th>
<th>Original studya</th>
<th>Present study</th>
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<td><strong>Baseline</strong></td>
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<tr>
<td>Neurology Scores</td>
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<td></td>
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<tr>
<td>Mean</td>
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</tr>
<tr>
<td>SD</td>
<td>6.1</td>
<td>6.4</td>
</tr>
<tr>
<td>No. of patients</td>
<td>26</td>
<td>19</td>
</tr>
<tr>
<td><strong>Year</strong></td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td><strong>Speech Scores</strong></td>
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<td></td>
</tr>
<tr>
<td>Mean</td>
<td>3.3</td>
<td>3.5</td>
</tr>
<tr>
<td>SD</td>
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<td>1.2</td>
</tr>
<tr>
<td>No. of patients</td>
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<td>19</td>
</tr>
<tr>
<td><strong>Year</strong></td>
<td>3</td>
<td></td>
</tr>
<tr>
<td><strong>Speech Scores</strong></td>
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<td></td>
</tr>
<tr>
<td>Mean</td>
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<td>SD</td>
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</tr>
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<td>No. of patients</td>
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REFERENCES


