Cerebral Circulation and Metabolism in Uremia

By Albert Heyman, M.D., John L. Patterson, Jr., M.D., and Rudolph W. Jones, Jr., M.D.

Data on 16 patients with uremia are presented. The cerebral blood flow was moderately decreased in patients with generalized vascular disease, but was normal in patients with minimal vascular involvement. In both groups the cerebral oxygen consumption (cerebral metabolic rate in terms of oxygen consumption, $\text{CMRO}_2$) was reduced significantly and to the same degree. In contrast, total body metabolism was not demonstrably reduced. These facts emphasize the vulnerability of the brain to uremia. There was poor correlation between the cerebral oxygen utilization and the patient’s mental state. No correlation was found between the cerebral oxygen consumption and the blood nonprotein nitrogen, the carbon dioxide capacity, or the sodium, potassium or chloride levels.

Little information is available as to the specific factors responsible for the neurologic and mental symptoms associated with uremia.\(^1\)\(^2\) The extensive histologic changes in the brain\(^3\)\(^4\) and the increase in intracranial pressure sometimes seen in patients with the uremic syndrome may account to some extent for these neurologic abnormalities. With such changes, alterations in cerebral circulation and metabolism are to be anticipated.

This paper presents observations on the cerebral blood flow and oxygen consumption in 16 patients with uremia. An attempt is made to correlate alterations in these functions with the mental status of the patient, the etiology of the uremia, and the derangement of the chemical structure of the blood.

Case Material and Methods

The 16 patients in this study have been classified into two groups, depending on the presence or absence of generalized vascular disease and hypertension. In 9 patients the uremic syndrome was associated with evidence of extensive vascular disease and long-standing severe hypertension. The mean arterial blood pressure in these 9 patients varied from 129 to 203 mm. Hg and averaged 166 mm. These patients had advanced retinal arteriosclerosis, usually with hemorrhages and exudates and, occasionally, papilledema. The diagnosis in 4 of these patients was chronic glomerulonephritis; in 5 others, malignant nephrosclerosis. The uremic syndrome in the other group of 7 patients was not associated with extensive vascular disease. Two of them had hydrenephrosis caused by lower urinary tract obstruction, one had lower nephron syndrome of unknown etiology, while 4 had chronic pyelonephritis. Two of the patients with pyelonephritis had moderate hypertension of recent duration and showed some abnormalities of the retinal vessels. The remaining 5 patients in this group had normal blood pressures with only slight or no evidence of vascular disease. These 7 patients are, for convenience, referred to subsequently as the “group without vascular disease.” The mean age of the patients in these two groups was approximately the same, averaging 43 years. The blood nonprotein nitrogen, hemoglobin, carbon dioxide capacity, serum sodium and plasma chloride levels were likewise similar. The serum potassium level was slightly higher in the group of patients without vascular disease.

The 16 individuals used as control subjects had an average age of 34 years and comprised patients who were convalescing from various acute illnesses, such as pneumonia and gonococcal arthritis. There was no evidence of intracranial complication in any of these patients. Both the control subjects and the patients with uremia had normal temperatures at the time of the cerebral studies. The determinations were made with the subjects in the supine position. If the patient was restless or uncooperative during the blood flow procedure, or if the control subject showed undue anxiety, the determination was rejected as invalid.

The cerebral blood flow (CBF) was measured by the nitrous oxide technique of Kety and Schmidt\(^4\) with the slight modifications previously described.\(^5\) The cerebral oxygen consumption (CMRO$_2$) was calculated from the cerebral blood flow and the cerebral arteriovenous oxygen difference determined manometrically.\(^6\) The cerebral vascular resistance (CVR) was calculated from the cerebral blood flow.
and the mean arterial pressure was measured directly with a damped mercury manometer. Total oxygen consumption of the body was measured by the open circuit technic. The basal metabolic rate was calculated from the oxygen consumption and carbon dioxide production according to the formula given by Weir.\textsuperscript{7} A group of 41 subjects studied under similar experimental circumstances were used as controls for this determination. The blood nonprotein nitrogen level was determined by the Koeh-McMeekin method; serum concentrations of sodium and potassium were measured with the flame photometer. The plasma chloride level was determined by the method described by Schales and Schales,\textsuperscript{8} and the carbon dioxide combining power by conventional manometric technic.

**Results**

The individual and mean values obtained in the patients with uremia and in the control subjects are shown in table 1 and figure 1. The mean cerebral blood flow in the 16 patients with uremia was only slightly less than normal and measured 52 cc. per 100 Gm. brain per minute (\(1 > p > .05\)). In the 9 patients with uremia associated with generalized vascular disease, however, the mean cerebral blood flow was 45 cc., a value significantly less than that of the control subjects (\(p < .01\)). The uremic patients without generalized vascular involvement had a mean cerebral blood flow value approximately the same as normal individuals.

All but one of the 16 patients with uremia had cerebral oxygen consumption values below the normal mean and the values of only 4 were within the normal range (fig. 1). The mean cerebral oxygen utilization in these patients was only 2.2 cc. per 100 Gm. per minute, a value significantly less than that of 3.1 cc. found in the control subjects (\(p < .001\)). The patients with uremia associated with generalized vascular disease had a greater cerebral arteriovenous oxygen difference (5.1 volumes per cent) than those without vascular involvement (4.1 volumes per cent). The cerebral oxygen consumption in these two groups was consequently the same despite the differences in cerebral blood flow.

Little correlation was observed between the level of the blood nonprotein nitrogen and the cerebral oxygen utilization value (figure 2). Neither the anion-cation pattern as measured nor the individual values for carbon dioxide capacity, sodium, potassium and chloride levels showed a correlation with the cerebral oxygen consumption.

The total oxygen consumption in the 7 patients with uremia, on whom this determination was made, average 137 cc. per square meter per minute, or only 4 per cent below that of control subjects. The mean basal metabolic rate was 4 per cent above the mean value predicted from the standards of DuBois. The cerebral oxygen consumption in these 7 patients, however, was reduced to a rather marked degree, i.e., 30 per cent below that of the control subjects.

The 9 patients with uremia associated with vascular involvement had a cerebral vascular resistance of 3.9 mm. per cc. per 100 Gm. per minute, a value more than double those found in the control subjects (\(p < .001\)), and in the uremic patients without vascular disease (\(p < .001\)). This increase in vascular resistance did not correlate with the patients’ retinal findings. The 3 patients with papilledema and marked retinopathy did not have the highest cerebral vascular resistance values, but did show the highest blood pressure levels.

**Results of Repeated Studies in Individual Patients.** Repeated cerebral studies were carried out in 3 patients during the course of their
### Table 1.—Clinical, Chemical and Physiologic Data on 16 Patients with Uremia

<table>
<thead>
<tr>
<th>Pt.</th>
<th>Diagnosis</th>
<th>Age</th>
<th>Mental Status</th>
<th>Retinal Arteriosclerosis</th>
<th>Mean Art. Pressure mm./Hg</th>
<th>CBF cc./100 Gm./Min.</th>
<th>CMRO₂ cc./100 Gm./Min.</th>
<th>CVR mm. Hg/cc./100 Gm./min.</th>
<th>Total O₂ Consumption cc./sq. m./min.</th>
<th>A-V O₂ Vol. %</th>
<th>NPN mg. %</th>
<th>CO₂ Capacity mEq./l</th>
<th>Chlorides mEq./l</th>
<th>Sodium mEq./l</th>
<th>Potassium mEq./l</th>
<th>Hemoglobin Gm. %</th>
<th>Hematocrit</th>
</tr>
</thead>
<tbody>
<tr>
<td>G. D.</td>
<td>Malig. nephrosclerosis*</td>
<td>43</td>
<td>Stuporous</td>
<td>Severe P.H.E.</td>
<td>203</td>
<td>60</td>
<td>2.2</td>
<td>3.4</td>
<td>95</td>
<td>3.7</td>
<td>225</td>
<td>14</td>
<td>84</td>
<td>128</td>
<td>5.0</td>
<td>12.5</td>
<td>36</td>
</tr>
<tr>
<td>R. B.</td>
<td>Malig. nephrosclerosis</td>
<td>48</td>
<td>Stuporous</td>
<td>Severe P.H.E.</td>
<td>395</td>
<td>37</td>
<td>2.3</td>
<td>5.2</td>
<td>—</td>
<td>6.2</td>
<td>87</td>
<td>10</td>
<td>—</td>
<td>—</td>
<td>12.7</td>
<td>40</td>
<td></td>
</tr>
<tr>
<td>H. S.</td>
<td>Malig. nephrosclerosis</td>
<td>34</td>
<td>Stuporous</td>
<td>Severe H.E.</td>
<td>161</td>
<td>47</td>
<td>2.0</td>
<td>3.5</td>
<td>—</td>
<td>4.3</td>
<td>270</td>
<td>10</td>
<td>82</td>
<td>129</td>
<td>3.4</td>
<td>8.5</td>
<td>25</td>
</tr>
<tr>
<td>M. T.</td>
<td>Malig. nephrosclerosis*</td>
<td>36</td>
<td>Alert</td>
<td>Severe P.H.E.</td>
<td>184</td>
<td>64</td>
<td>2.2</td>
<td>2.9</td>
<td>144</td>
<td>3.4</td>
<td>78</td>
<td>21</td>
<td>93</td>
<td>149</td>
<td>3.4</td>
<td>9.3</td>
<td>27</td>
</tr>
<tr>
<td>F. W.</td>
<td>Malig. nephrosclerosis*</td>
<td>36</td>
<td>Alert</td>
<td>Severe H.E.</td>
<td>175</td>
<td>45</td>
<td>1.4</td>
<td>3.0</td>
<td>—</td>
<td>3.0</td>
<td>126</td>
<td>16</td>
<td>—</td>
<td>—</td>
<td>8.1</td>
<td>24</td>
<td></td>
</tr>
<tr>
<td>B. G.</td>
<td>Glomerulonephritis</td>
<td>50</td>
<td>Stuporous</td>
<td>Moderate</td>
<td>130</td>
<td>49</td>
<td>2.6</td>
<td>2.7</td>
<td>—</td>
<td>5.2</td>
<td>200</td>
<td>10</td>
<td>107</td>
<td>130</td>
<td>4.7</td>
<td>10.0</td>
<td>31</td>
</tr>
<tr>
<td>M. S.</td>
<td>Glomerulonephritis*</td>
<td>48</td>
<td>Sl. confused</td>
<td>Severe</td>
<td>155</td>
<td>26</td>
<td>2.0</td>
<td>6.1</td>
<td>113</td>
<td>7.9</td>
<td>105</td>
<td>23</td>
<td>82</td>
<td>135</td>
<td>3.7</td>
<td>12.4</td>
<td>46</td>
</tr>
<tr>
<td>L. W.</td>
<td>Glomerulonephritis</td>
<td>47</td>
<td>Confused</td>
<td>Severe H.E.</td>
<td>129</td>
<td>49</td>
<td>2.2</td>
<td>2.6</td>
<td>—</td>
<td>4.4</td>
<td>105</td>
<td>18</td>
<td>100</td>
<td>134</td>
<td>4.8</td>
<td>9.2</td>
<td>—</td>
</tr>
<tr>
<td>A. P.</td>
<td>Glomerulonephritis*</td>
<td>39</td>
<td>Confused</td>
<td>Severe H.E.</td>
<td>165</td>
<td>30</td>
<td>2.3</td>
<td>5.5</td>
<td>—</td>
<td>7.5</td>
<td>218</td>
<td>16</td>
<td>—</td>
<td>112</td>
<td>4.2</td>
<td>9.1</td>
<td>33</td>
</tr>
<tr>
<td>Mean Values</td>
<td></td>
<td>44</td>
<td></td>
<td></td>
<td>166</td>
<td>45</td>
<td>2.1</td>
<td>3.9</td>
<td>2</td>
<td>117</td>
<td>5.1</td>
<td>158</td>
<td>15</td>
<td>92</td>
<td>132</td>
<td>4.2</td>
<td>10.2</td>
</tr>
</tbody>
</table>

#### Uremia Associated with Severe Hypertension and Vascular Disease

- **F. B.** Pyelonephritis
- **R. F.** Pyelonephritis
- **A. G.** Hydronephrosis* 49 Stuporous
- **H. H.** Pyelonephritis 63 Confused
- **A. M.** Pyelonephritis 31 Alert
- **C. M.** Prostatic obstruction 32 Sl. confused
- **P. T.** Lower Nephron disease 35 Unconscious

**Mean Values** 42

16 Control Pts. 34 Normal

P = papilledema.
H = hemorrhages.
E = exudates.

* Diagnosis confirmed by autopsy or surgical exploration.
† Statistically significant difference (p < .01) from mean value in control patients.
‡ Statistically significant difference from mean value in patients without prolonged hypertension and generalized vascular disease.
§ Standard Deviation.
illnesses (table 2). One of them (G.D.), with malignant nephrosclerosis, was studied early in the course of his illness, when there was no evidence of uremia other than an elevation of nonprotein nitrogen to 78 mg. per 100 cc. The cerebral oxygen utilization was normal at this time, but was decidedly reduced a month later when he returned in uremic stupor with a marked increase in nonprotein nitrogen. In another patient (A.G.), the clinical manifestations of uremia disappeared following bilateral nephrostomy of hydronephritic kidneys. This patient showed a gradual elevation in cerebral oxygen consumption along with a reduction in nonprotein nitrogen and improvement of mental function. The third patient (B.G.) had chronic glomerulonephritis. She eventually developed a remission of uremic symptoms with marked reduction in nonprotein nitrogen and improvement in mental state. The clinical improvement was associated at first with a slight rise in both cerebral blood flow and cerebral oxygen utilization, but these values later decreased without a corresponding change in the mental picture. There were no consistent changes in the cerebral blood flow in these individuals. With a single exception the cerebral vascular resistance remained remarkably constant.

There appeared to be considerably less correlation between mental state and cerebral oxygen consumption in the entire group of patients with uremia. The mean and the distribution of

**TABLE 2.—Clinical and Experimental Data Obtained in Repeated Studies in Three Patients with Uremia**

<table>
<thead>
<tr>
<th></th>
<th>G.D., Malignant Nephrosclerosis</th>
<th>A.G., Hydronephrosis</th>
<th>B. G., Chronic Glomerulonephritis</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>8/12/49</td>
<td>9/9/49</td>
<td>11/9/49</td>
</tr>
<tr>
<td>CBF, cc./100 Gm./min.</td>
<td>55</td>
<td>60</td>
<td>59</td>
</tr>
<tr>
<td>CMRO₂, cc./100 Gm./min.</td>
<td>3.5</td>
<td>2.2</td>
<td>1.2</td>
</tr>
<tr>
<td>CVR—mm. Hg/cc./100 Gm./min.</td>
<td>3.4</td>
<td>3.4</td>
<td>1.9</td>
</tr>
<tr>
<td>Mean arterial pressure mm. Hg.</td>
<td>189</td>
<td>203</td>
<td>110</td>
</tr>
<tr>
<td>NPN mg.%</td>
<td>78</td>
<td>225</td>
<td>289</td>
</tr>
<tr>
<td>CO₂ Cap. mEq./l.</td>
<td>22</td>
<td>14</td>
<td>10</td>
</tr>
<tr>
<td>Chlorides mEq./l.</td>
<td>84</td>
<td>100</td>
<td>95</td>
</tr>
<tr>
<td>Sodium mEq./l.</td>
<td>132</td>
<td>128</td>
<td>142</td>
</tr>
<tr>
<td>Potassium mEq./l.</td>
<td>3.7</td>
<td>5.0</td>
<td>5.8</td>
</tr>
<tr>
<td>Hemoglobin Gm.%</td>
<td>10.9</td>
<td>12.5</td>
<td>8.9</td>
</tr>
<tr>
<td>Mental Change</td>
<td>Alert</td>
<td>Stupor</td>
<td>Stupor</td>
</tr>
</tbody>
</table>

**FIG. 2.** The relationship between cerebral oxygen consumption and blood nonprotein nitrogen.
the cerebral oxygen utilization values were very similar in the patients classified as being alert, confused or stuporous (fig. 3).

**Figure 3.** The mean values for cerebral oxygen consumption grouped according to the mental state of the patients with uremia. The arrows indicate the mean value in each group.

**Discussion**

These studies demonstrate that uremia is often associated with a profound depression in cerebral metabolism. The normal mean cerebral blood flow value in the group of uremic patients without vascular disease suggests that, in these patients at least, the decrease in cerebral oxygen consumption must have been caused by factors other than reduction in blood flow. However, in the presence of anemia of the degree found in some of these patients, it is quite possible that a "normal" blood flow could be inadequate for the needs of the brain. As previously stated, no definite correlation could be made between the reduction in cerebral oxygen consumption and the carbon dioxide capacity, nonprotein nitrogen and concentrations of sodium or potassium. It is possible that some of the other alterations associated with uremia, such as changes in pH, increase in phenolic substances in the blood, could have been responsible for the changes in cerebral functions. It seems as likely, however, that the reduction in cerebral oxygen utilization was not dependent on any single factor, but was the result of the combined effect of a number of chemical disturbances.

The fact that there was a marked reduction of cerebral oxygen consumption in uremia, whereas a depression in total body metabolism was not demonstrated, emphasizes the vulnerability of nervous tissue to this condition. However, some of the patients with chronic renal insufficiency showed relatively normal mental function, despite low cerebral oxygen utilization values. This was particularly noticeable in the 2 patients who had remissions of the uremic syndrome. Although these individuals regained considerable mental function, their cerebral oxygen consumption values remained well below normal. Kety and associates, from studies on patients with diabetic acidosis, suggested that there exists a critical cerebral oxygen utilization of 2.1 cc. per 100 Gm. per minute, at or below which consciousness disappears. It is of interest that several of our patients with uremia, while conscious, showed oxygen consumption values lower than this figure. Similar findings were obtained in our patients with dementia paralytica. It appears, therefore, that such a critical cerebral oxygen consumption, if it does exist, must vary with the nature of the disease.

The effects of specific chemical alterations on cerebral metabolism in uremia could possibly be determined by a more comprehensive study including selective correction of the various electrolyte derangements and removal of certain metabolites by means of artificial excretory mechanisms. These procedures might suggest methods of alleviating the cerebral dysfunction, which appears to be the cause of death in many of these patients. Further work in this direction seems desirable.

**Summary**

1. The cerebral blood flow (CBF), oxygen consumption (CMRO₂) and cerebral vascular resistance (CVR) were determined by the nitrous oxide technic in 16 patients with uremia caused by a variety of conditions.

2. A moderate decrease in cerebral blood flow was found in patients with uremia associated with severe hypertension and generalized vascular disease. The uremic patients with little
or no vascular involvement had a normal mean cerebral blood flow value.

3. The cerebral oxygen consumption in uremia was significantly reduced. This decrease was as marked in patients with normal cerebral blood flow as in those with reduced blood flow. A decrease in total body metabolism was not demonstrated. This suggests that nervous tissue is especially vulnerable to the effects of renal insufficiency.

4. In general, poor correlation was observed between the degree of reduction in cerebral oxygen utilization and the mental state of the patient with uremia. In some patients with uremia the cerebral metabolism was considerably reduced without marked impairment of mental function.

5. No correlation was found between the degree of reduction in cerebral oxygen consumption and the level of the blood nonprotein nitrogen, the carbon dioxide capacity or the sodium, potassium or chloride levels.

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