Hemoglobin and the Risk of Cerebral Infarction: The Framingham Study

BY WILLIAM B. KANNEL, M.D.,* TAVIA GORDON,† PHILIP A. WOLF, M.D.,‡ AND PATRICIA McNAMARA*  

Abstract: Hemoglobin and the Risk of Cerebral Infarction: The Framingham Study

Risk of cerebral infarction over 16 years was ascertained in 5,185 men and women classified according to their hemoglobin, blood pressure and cigarette habit on entry to the Framingham Study. Within the normal range of hemoglobin values, risk was found to be proportional to the blood hemoglobin concentration in both sexes.

Men with hemoglobin values of 15 gm or greater and women with 14 gm or more had twice as many cerebral infarctions as did their cohorts with lower values. The risk of initial development of 82 cerebral infarctions was also strikingly related to antecedent blood pressure status in both sexes and to the cigarette habit in men. When allowance is made for associated blood pressure and cigarette habit—factors found to correlate with both blood hemoglobin values and incidence of cerebral infarction—hemoglobin level had only a modest residual effect, no longer statistically significant.

The pathogenetic, preventive and therapeutic implications of the interrelationship of blood hemoglobin, blood pressure and the cigarette habit and their association with cerebral infarction require further exploration.

Additional Key Words: cigarette habit, hypertension, cardiac function, risk factors, stroke profile

Vascular disease of the brain now constitutes the third leading cause of death and accounts for a considerable amount of disability in the elderly. Treatment and rehabilitation of the completed catastrophe is obviously less rewarding than its prevention. Prevention, however, requires a knowledge of the factors which predispose.

Strokes are not an inevitable accident of nature, as the term “vascular accident” implies, but rather the end result of a chain of circumstances evolving over decades. Epidemiological investigations of the manner in which strokes arise and evolve in a general population sample in Framingham and elsewhere have begun to identify highly vulnerable persons and the factors which predispose. Estimates of the risk associated with identified stroke precursors, singly and in combination, have been ascertained. The major risk factors for cerebral infarction thus far identified include hypertension, impaired cardiac function, ECG-LVH,
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elevated serum cholesterol, impaired glucose tolerance, and the cigarette habit. Using these variables it is possible to compute a stroke profile for each person, allowing estimates of the probability of developing a cerebral infarction over a wide range of risks—possibly 40-fold (fig. 1).¹

Using the five major risk factors identified for atherothrombotic brain infarction (ABI) in a multivariate analysis, it is possible to compute a risk profile for each person. If the population is placed in deciles according to their risk function score based on their findings at entry, instead of 10% of the incidence cases occurring in the upper decile, half of the cases occur there.

Previous investigation at Framingham suggested that hemoglobin level might be another of the contributors to the occurrence of cerebral infarction. This report is concerned with a more detailed analysis of the relation of antecedent hemoglobin concentration to the risk of cerebral infarction, taking into account other contributors.

**Methods**

To gain urgently needed information on the incidence and natural history of stroke and to uncover factors affecting its development, the Framingham Study has closely explored the stroke experience of a study population of 5,185 subjects found free of cerebrovascular disease at entry. During the 16-year period of surveillance being reported, 152 documented strokes (82 attributable to ABI, excluding transient ischemic attacks) occurred in this population sample (table 1). Exclusion of transient ischemic attacks represents

![Risk Function Diagram](image)

*Figure 1: Incidence of cerebral infarction (16 year follow-up) according to decile of risk. Men and women 35-74: Framingham Study.*
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a departure from previous practice when these were included in the category atherothrombotic brain infarction. Of the 82 cases of ABI four are omitted from the analysis; one man had his stroke prior to age 45, and three women had no hemoglobin determination prior to the occurrence of their ABI. Details of the sampling procedure, response rates and completeness of follow-up have been reported previously. Only 2% of the respondents invited to participate in the study are unaccounted for and completely lost to follow-up after 16 years of follow-up.

Subjects have been examined at two-year intervals in a clinic maintained in Framingham, Massachusetts, manned by National Heart and Lung Institute personnel and set up expressly for purposes of conducting an epidemiological investigation. The details of the laboratory methods and procedures employed for characterizing the population according to personal attributes and living habits have been reported elsewhere.

In recent years each new suspected case of stroke has been examined on the hospital ward, or at the time of their return for their routine biennial clinic examination, by a consultant neurologist. The differential diagnosis was based mostly on clinical grounds. All protocols were reviewed by a panel of investigators, including a neurologist, to determine if they met uniformly applied minimal criteria. About 40% of deaths were autopsied. Angiograms were obtained on many, but not all of those suspected of transient ischemic attacks, extracranial vascular disease and subarachnoid hemorrhage. More angiograms were taken in recent years than early in the study.

Risk of 82 initial strokes attributed to atherothrombotic brain infarction was determined over 16 years of biennial examination in 5,185 men and women aged 30 to 62 years who were classified into subgroups according to hemoglobin content and a variety of other personal attributes and living habits. Criteria employed for the diagnosis of ABI have been reported previously. Briefly, minimal criteria consisted of the abrupt onset of a focal neurological deficit (e.g., hemiparesis and aphasia) in the absence of either a bloody spinal fluid or a source for embolus providing other conditions which could produce such a neurological deficit were absent. Hemoglobin was determined by the cyanmethemoglobin method.

Discriminant analysis was employed to assess the net effect of relevant interrelated factors under consideration. Because of small numbers of cases, at times all age groups combined were looked at with suitable adjustment for the variable age composition of the subgroups under consideration.

A full description of the statistical methods employed has been published elsewhere in Framingham Monograph Section No. 26, where reasonably complete technical notes are available. This monograph also contains more relevant data on the subject of hemoglobin and its net contribution to cardiovascular disease than can be accommodated by journal publication.

Results

During the first 16 years of the Framingham Study, 82 men and women had ABI exclusive of transient ischemic attacks. Almost all of these cases occurred in persons who were in the age range 45 to 74 years on the examination preceding their stroke. The analysis therefore focuses on ABI in this age range.

The incidence of ABI was distinctly higher in persons with hemoglobin values at the upper end of the distribution (table 2). Overall, the incidence at higher hemoglobin values (15 or more gm % in men, 14 or more gm % in women) was about twice that at lower values in each sex. While the numbers of cases in each ten-year age group were rather small, ABI incidence was greater at high

| TABLE 1 |
| Incidence of Various Types of Cerebrovascular Disease by Sex (Framingham Study: 16-Year Follow-Up) |

<table>
<thead>
<tr>
<th>Type of Disease</th>
<th>Total</th>
<th>Women</th>
<th>Men</th>
<th>Percent of Total</th>
<th>Percent of Women</th>
<th>Percent of Men</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total</td>
<td>152</td>
<td>78</td>
<td>74</td>
<td>100.0</td>
<td>100.0</td>
<td>100.0</td>
</tr>
<tr>
<td>Atherothrombotic brain infarction</td>
<td>82</td>
<td>40</td>
<td>42</td>
<td>53.9</td>
<td>51.3</td>
<td>56.8</td>
</tr>
<tr>
<td>Cerebral embolus</td>
<td>22</td>
<td>8</td>
<td>14</td>
<td>14.5</td>
<td>10.3</td>
<td>18.9</td>
</tr>
<tr>
<td>Subarachnoid hemorrhage</td>
<td>20</td>
<td>11</td>
<td>9</td>
<td>13.2</td>
<td>14.1</td>
<td>12.2</td>
</tr>
<tr>
<td>Intracerebral hemorrhage</td>
<td>10</td>
<td>6</td>
<td>4</td>
<td>6.6</td>
<td>7.7</td>
<td>5.4</td>
</tr>
<tr>
<td>Transient ischemic attacks</td>
<td>10</td>
<td>7</td>
<td>3</td>
<td>6.6</td>
<td>9.0</td>
<td>4.1</td>
</tr>
<tr>
<td>Other</td>
<td>8</td>
<td>6</td>
<td>2</td>
<td>5.3</td>
<td>7.7</td>
<td>2.7</td>
</tr>
</tbody>
</table>

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hemoglobin levels than at lower levels for all but one age-sex group.

To assess the relationship of ABI to hemoglobin over the entire range of values, a regression analysis by the method of Duncan-Walker was performed. The age-sex-specific regression coefficients (table 3), where hemoglobin is considered without regard to other associated risk factors ("univariate analysis"), are statistically significant at a 5% level only for one age-sex group (men 55 to 64), but if they are averaged over all age groups the average is statistically significant for men but not for women. The overall impression for both sexes is of a modest but consistent association between hemoglobin and ABI (table 3).

The mean univariate regression coefficient for hemoglobin may be compared with those for some other possible risk factors in table 4. As judged by the size of the mean univariate regression coefficients, after they are standardized for differences in the range of values, hemoglobin ranks close to the cigarette habit and ECG-LVH in men and (despite the fact that it is not statistically significant at a 5% level) is equivalent to glucose intolerance in women.

Clearly, blood pressure status must be taken into account in any evaluation of other factors contributing to stroke incidence. It is the most common, most potent risk factor to emerge from the prospective epidemiological study of stroke. Even modest hypertension revealed by casual blood pressure determination at all ages in either sex is associated with a substantially increased incidence of cerebral infarction (figs. 2 and 3). Risk rose in proportion to the systolic blood pressure even after accounting for other relevant associated variables. While the data are shown as smoothed curves, the actual observed data are also quite impressive. Contrary to popular belief, the effect of systolic pressure is as great as diastolic and, compared to diastolic pressure, does not wane with advancing age.

The cigarette habit was also associated with a distinct excess risk of ABI in men but not women (table 5). Blood pressure and, to a lesser degree, cigarette smoking were correlated with hemoglobin values (table 6). Taken as a set, the correlations were highly significant in a statistical sense, but of a low order,
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TABLE 3
Univariate and Multivariate Regressions of ABI Incidence on Hemoglobin by Age and Sex (Framingham Study: 16-Year Follow-Up)

<table>
<thead>
<tr>
<th>Age at exam preceding event, sex</th>
<th>Univariate</th>
<th></th>
<th></th>
<th></th>
<th>Multivariate</th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Regression coefficient (B)</td>
<td>Standard error (S.E. [B])</td>
<td>R/s.e. (B)</td>
<td>Regression coefficient (B)</td>
<td>Standard error (S.E. [B])</td>
<td>R/s.e. (B)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Men</td>
<td>45-54</td>
<td>0.037</td>
<td>0.025</td>
<td>1.48</td>
<td>0.017</td>
<td>0.025</td>
<td>0.65</td>
<td></td>
</tr>
<tr>
<td></td>
<td>55-64</td>
<td>0.048</td>
<td>0.019</td>
<td>2.53</td>
<td>0.028</td>
<td>0.018</td>
<td>1.57</td>
<td></td>
</tr>
<tr>
<td></td>
<td>65-74</td>
<td>0.005</td>
<td>0.032</td>
<td>0.16</td>
<td>-0.002</td>
<td>0.033</td>
<td>-0.07</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Weighted mean</td>
<td>0.035</td>
<td>0.014</td>
<td>2.50</td>
<td>0.020</td>
<td>0.014</td>
<td>1.48</td>
<td></td>
</tr>
<tr>
<td>Women</td>
<td>45-54</td>
<td>0.029</td>
<td>0.032</td>
<td>0.91</td>
<td>0.018</td>
<td>0.033</td>
<td>0.56</td>
<td></td>
</tr>
<tr>
<td></td>
<td>55-64</td>
<td>0.026</td>
<td>0.020</td>
<td>1.30</td>
<td>0.012</td>
<td>0.020</td>
<td>0.63</td>
<td></td>
</tr>
<tr>
<td></td>
<td>65-74</td>
<td>0.024</td>
<td>0.027</td>
<td>0.89</td>
<td>0.004</td>
<td>0.027</td>
<td>0.15</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Weighted mean</td>
<td>0.025</td>
<td>0.015</td>
<td>1.67</td>
<td>0.011</td>
<td>0.014</td>
<td>0.78</td>
<td></td>
</tr>
</tbody>
</table>

accounting for no more than 4% of the variance in either case. The diastolic pressure was more highly correlated with hemoglobin than the systolic, suggesting an influence on peripheral resistance. These modest correlations translate into sizeable gradients in prevalence of hypertension (fig. 4) and heavy cigarette smoking (fig. 5) in relation to hemoglobin values. Assessment of the relation of hemoglobin to ABI incidence, therefore, must take into account these correlated items.

Comparison of mean hemoglobin values at specified systolic pressures in men aged 55 to 64 (the age-sex group with the largest number and strongest association) who went on to ABI with the cohort who remained free of it, in general but not invariably, revealed higher hemoglobin values in those afflicted (table 7). Further categorical analysis—cross-classifying subjects by blood pressure and hemoglobin status and adjusting for age and sex—reveals that, whether hypertensive or not, those with high hemoglobin values were at increased risk (fig. 6). This might suggest an independent effect of hemoglobin were it not for the fact that within each blood pressure category those with high hemoglobin values still had slightly higher mean blood pressures and the differences within each blood pressure category were not statistically significant with the numbers of cases available.

Resorting to noncategorical multivariate analysis, taking into account not only blood pressure but other contributors to ABI incidence including cigarettes, reveals a multivariate slope (B) somewhat diminished compared to the univariate slope (table 3). While the average univariate regression for both sexes combined was statistically significant at a 5% level, the multivariate regression was not. This suggests that a great deal of the apparent relationship between hemoglobin and ABI incidence is accounted for by other related items.

TABLE 4
Average Standardized Univariate Regression Coefficients of Brain Infarction Precursors (Men and Women 45 to 74: Framingham Study)

<table>
<thead>
<tr>
<th>Risk factor</th>
<th>Regression coefficient (B)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hemoglobin</td>
<td>4.37</td>
</tr>
<tr>
<td>Systolic blood pressure</td>
<td>7.49</td>
</tr>
<tr>
<td>Diastolic blood pressure</td>
<td>7.47</td>
</tr>
<tr>
<td>Glucose intolerance</td>
<td>2.81</td>
</tr>
<tr>
<td>Cigarette habit</td>
<td>4.31</td>
</tr>
<tr>
<td>Heart enlargement (x-ray)</td>
<td>3.05</td>
</tr>
<tr>
<td>ECG-LVH</td>
<td>4.60</td>
</tr>
</tbody>
</table>

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Relative odds of developing a cerebral infarction according to systolic blood pressure. Women 45-74: Framingham Study.

Factors. The multivariate analysis includes, besides hemoglobin, the following variables: systolic blood pressure, diastolic blood pressure, serum cholesterol, ECG-LVH, cigarette smoking and glucose intolerance.

**Discussion**

While the net effect of hemoglobin attenuates in multivariate analysis (which includes the variables blood pressure and cigarettes), this does not necessarily indicate that hemoglobin is unrelated to the incidence of ABI. Its impact may be mediated through an effect on blood pressure and in turn it may mediate the effect of cigarettes in predisposing to strokes.

**TABLE 5**

Average Annual Incidence of ABI by Age and Sex According to Cigarette Habit: Framingham Study, 16-Year Follow-Up

<table>
<thead>
<tr>
<th>Age/Sex</th>
<th>Person-years</th>
<th>Number of events</th>
<th>ABI Incidence/1000</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Total</td>
<td>Nonsmokers</td>
<td>Smokers</td>
</tr>
<tr>
<td>Men</td>
<td>45-54</td>
<td>12,616</td>
<td>4,684</td>
</tr>
<tr>
<td></td>
<td>55-64</td>
<td>9,044</td>
<td>4,330</td>
</tr>
<tr>
<td></td>
<td>65-74</td>
<td>2,804</td>
<td>1,620</td>
</tr>
<tr>
<td>Women</td>
<td>45-54</td>
<td>15,826</td>
<td>9,020</td>
</tr>
<tr>
<td></td>
<td>55-64</td>
<td>11,884</td>
<td>8,518</td>
</tr>
<tr>
<td></td>
<td>65-74</td>
<td>3,838</td>
<td>3,048</td>
</tr>
</tbody>
</table>
The findings herein reported, while more precisely documented than formerly, are not new. Gaisböck—not long after Vasques in 1892 and Osler in 1903 had recognized the coincidence of hypertension and polycythemia vera—pointed out that some patients with hypertension appeared "plethoric and apoplectic." He termed the condition "polycythemia hypertonica," which he believed was distinguished from true polycythemia vera by the associated hypertension. However, it has subsequently been found that increased red cell mass may be associated with hypertension even in myeloproliferative polycythemia rubra vera.

It is thus well recognized that polycythemia is associated with an increased risk of strokes, presumably as a consequence of an increased propensity to thrombosis and hypertension. It is not well appreciated that risk is also proportional to the blood hemoglobin content (and presumably red cell mass) within the normal range as well. None of the victims of cerebral infarction herein reported had polycythemia vera since these were specifically excluded from consideration.

The hemoglobin content of the blood influences its viscosity, oxygen-carrying capacity, dynamics of flow, and possibly its clotting characteristics. A high hemoglobin content may also reflect a contraction of the intravascular plasma compartment. It could also be the result of an increased erythropoietin elaboration by an ischemic kidney. Erythremia associated with renal artery disease has been found to be accompanied by hypertension. Kidney and renal arterial pathology producing inappropriate renin and erythropoietic elaboration have been demonstrated with increasing...
TABLE 6
Correlation of Hemoglobin with Blood Pressure and Cigarette Smoking (Men and Women 30 to 64: Framingham Study)\textsuperscript{a}

<table>
<thead>
<tr>
<th>Correlation of hemoglobin with cigarettes per day</th>
<th>30-34</th>
<th>35-39</th>
<th>40-44</th>
<th>45-49</th>
<th>50-54</th>
<th>55-59</th>
<th>60-64</th>
</tr>
</thead>
<tbody>
<tr>
<td>Men</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No.</td>
<td>121</td>
<td>333</td>
<td>279</td>
<td>262</td>
<td>204</td>
<td>174</td>
<td>82</td>
</tr>
<tr>
<td>Correl.</td>
<td>0.00</td>
<td>0.07</td>
<td>0.12*</td>
<td>0.00</td>
<td>0.09</td>
<td>0.19*</td>
<td>0.06</td>
</tr>
<tr>
<td>Women</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No.</td>
<td>119</td>
<td>307</td>
<td>266</td>
<td>167</td>
<td>141</td>
<td>99</td>
<td>31</td>
</tr>
<tr>
<td>Correl.</td>
<td>0.15</td>
<td>0.20*</td>
<td>0.10</td>
<td>0.17*</td>
<td>0.14</td>
<td>0.11</td>
<td>0.05</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Correlation of hemoglobin with systolic and diastolic pressure</th>
<th>30-34</th>
<th>35-39</th>
<th>40-44</th>
<th>45-49</th>
<th>50-54</th>
<th>55-59</th>
<th>60-64</th>
</tr>
</thead>
<tbody>
<tr>
<td>Men</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Systolic pressure</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No.</td>
<td>180</td>
<td>465</td>
<td>386</td>
<td>400</td>
<td>336</td>
<td>319</td>
<td>171</td>
</tr>
<tr>
<td>Correl.</td>
<td>0.13</td>
<td>0.18*</td>
<td>0.04</td>
<td>0.12*</td>
<td>0.09</td>
<td>0.08</td>
<td>0.07</td>
</tr>
<tr>
<td>Diastolic pressure</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Correl.</td>
<td>0.21*</td>
<td>0.21*</td>
<td>0.11*</td>
<td>0.19*</td>
<td>0.18*</td>
<td>0.19*</td>
<td>0.14</td>
</tr>
<tr>
<td>Women</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Systolic pressure</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No.</td>
<td>208</td>
<td>548</td>
<td>526</td>
<td>436</td>
<td>435</td>
<td>385</td>
<td>201</td>
</tr>
<tr>
<td>Correl.</td>
<td>0.08</td>
<td>0.05</td>
<td>0.17*</td>
<td>0.11*</td>
<td>0.17*</td>
<td>0.15*</td>
<td>0.14*</td>
</tr>
<tr>
<td>Diastolic pressure</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Correl.</td>
<td>0.14*</td>
<td>0.14*</td>
<td>0.18*</td>
<td>0.14*</td>
<td>0.18*</td>
<td>0.20*</td>
<td>0.20*</td>
</tr>
</tbody>
</table>

\*P = < 0.05.
\+P = < 0.01.

frequency. These could account for the erythrocytosis and associated hypertension. The kidney is generally conceded to act as an endocrine organ, sensing the degree of
blood oxygenation and controlling its level by the release of erythropoietin. More recent work has suggested that this oxygen-sensing function may reside rather in the carotid body which produces hormones which stimulate reticulocyte and erythropoietin release. However, the profound effect of renal blood flow on red cell production seems best explained by renal erythropoietin production and renal oxygen sensing.

Abnormal erythropoiesis resulting in an increased red cell mass apparently occurs in some hypertensive persons. Lawrence et al. in an analysis of 150 patients with polycythemia found some degree of hypertension in approximately 50%. He noted a fall in blood pressure with radiophosphorus therapy in hypertensives but a rise in blood pressure in normotensives. This suggests a statistical artifact of regression toward the mean as an explanation. In myeloproliferative polycythemia vera the increased red cell production is apparently

<table>
<thead>
<tr>
<th>TABLE 7</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Mean Hemoglobin Value by Systolic Blood Pressure Comparing Those Free of ABI With Those Developing ABI (Men 55 to 64: Framingham Study)</strong></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Systolic Blood Pressure (mm Hg)</th>
<th>Mean Hemoglobin Value (gm %) ABI*</th>
<th>ABI</th>
<th>No. of Events No. ABI</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt; 120</td>
<td>17.5</td>
<td>14.6</td>
<td>1</td>
</tr>
<tr>
<td>120–139</td>
<td>16.0</td>
<td>14.6</td>
<td>2</td>
</tr>
<tr>
<td>140–159</td>
<td>14.7</td>
<td>14.7</td>
<td>4</td>
</tr>
<tr>
<td>160–179</td>
<td>15.0</td>
<td>14.8</td>
<td>5</td>
</tr>
<tr>
<td>180–199</td>
<td>14.6</td>
<td>14.8</td>
<td>4</td>
</tr>
<tr>
<td>200–219</td>
<td>15.8</td>
<td>14.8</td>
<td>3</td>
</tr>
<tr>
<td>220+</td>
<td>16.8</td>
<td>15.0</td>
<td>2</td>
</tr>
</tbody>
</table>

*Mean hemoglobin on biennial exam prior to occurrence of ABI.
autonomous. In primary, secondary and "relative" polycythemia, hypertension also appears to occur in excess, thus far for largely unexplained reasons. Hall, and Russell and Conley found that persons with Gaisböck's syndrome tend to be moderately overweight, stocky, tense and plethoric; all were smokers with hypertension extraordinarily common. These findings are consistent with those herein reported.

The closer correlation of hemoglobin content to diastolic than to systolic blood pressure in every age group in both sexes (table 6), despite the fact that systolic pressure is more accurately ascertained and varies over a wider range, may be physiologically significant. It suggests an effect on peripheral resistance. This is best explained by the known effect high hematocrits have on blood viscosity.

The possibility exists that at least part of the association between the cigarette habit and ABI incidence in men is mediated through an effect on blood hemoglobin content. Eisen, in 1956, also found a relationship between the cigarette habit and the packed cell volume; when smoking ceases, a reversal of this effect occurs. However, the association of heavy smoking with higher hemoglobin values is equally as strong in women as in men; yet no relationship of the cigarette habit to ABI incidence could be demonstrated in women (table 5). This requires explanation.

Slowing of blood in the microcirculation due to intravascular aggregation of blood cells has been reported in vascular disease. The significance of this has been a matter of controversy with more importance attached to arterial than venous sludging. Adhesive platelets may play a role in this. Blood viscosity has been reported increased in patients with cerebral and other vascular disease. It has been found that an excess of cerebrovascular accidents occurs during sleep. Yet it has not been convincingly demonstrated that blood viscosity and factors which affect it—red cell concentration, total proteins, hexosamines,
Hemoglobin and Risk of Cerebral Infarction

Protein-bound carbohydrate and sialic acid—
are critically altered so as to promote strokes
at this time. Shifts in water between the blood
and tissues in all likelihood do occur during
sleep, but it is not clear that this significantly
affects the dynamics of cerebral blood flow.
Microemboli of sludged red blood cells and
aggregated platelets could, in a compromised
cerebral circulation, precipitate vascular acci-
dents by critically further reducing flow in
arterioles and capillaries, but this is entirely
speculative.

Strokes have been considered a natural
consequence of reaching a venerable stage in
life. The incidence does indeed increase
precipitously with age and no combination of
age-related predisposing factors can entirely
account for this age trend. However, whether
this implies a biological effect of aging, altered
tissue response to factors which promote
atherosclerosis, or simply a time-dose product
of exposure to acquired contributors to stroke
is unclear. It is abundantly clear, however, that
at any age and in either sex susceptibility varies
over a wide range depending on the number of
ingredients of the stroke profile the potential
victim has.

While the evidence is not conclusive
blood, hemoglobin concentration may belong
to this list of ingredients. Although the
evidence does not justify a return to the ancient
practice of leeching, the finding does have
possible pathogenetic, preventive and therapeu-
tic implications.

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