Elevation of Serum Protein-Bound Carbohydrates and Haptoglobin in Schizophrenia

Ulysses S. Seal and Harold Eist

The mean concentration of each of the serum protein-bound carbohydrates (hexose, hexosamine, fucose, and sialic acid) was significantly elevated in a group of 60 male schizophrenic patients. The total serum protein was elevated, ceruloplasmin was normal, and C-reactive protein was absent. Serum haptoglobin was significantly elevated. The distribution of haptoglobin types was normal. Haptoglobin concentration variation was significantly correlated with each of the carbohydrates and, to a lesser degree, with ceruloplasmin. In a group of 13 patients with normal erythrocyte sedimentation rate, the fibrinogen and haptoglobin concentrations were significantly elevated. There was no correlation between haptoglobin and fibrinogen concentrations in this group.

Evidence for abnormalities in the blood proteins of schizophrenic patients has been obtained with bioassay, immunologic, enzyme (1, 30), physicochemical (3), electrophoretic (3), and nonspecific chemical technics, which are surveyed by Fessel & Grunbaum (4). The deviations demonstrated have included, in addition to those considered specific to schizophrenia, an increase in total serum protein, increases in various electrophoretic globulin fractions, increases in the 4S and 19S classes of ultracentrifugal components, a decrease in albumin, and clotting abnormalities.

Purification studies of specific abnormal factors indicate that they are present in low concentration and cannot account for the gross deviations observed (6, 21, 26). Quantitative measurements of known serum proteins in schizophrenics’ sera have demonstrated decreased albumin (3, 9) and transferrin (5); increased γ-globulin (4, 11), orosomucoid (9), and haptoglobin (7); an increased incidence of rheumatoid

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The authors are grateful to Dr. William Swain for performing the fibrinogen assays and for supplying the control data for this assay, and gratefully acknowledge the technical assistance of Mary D. Lewis and Douglas Goodspeed.

Received for publication Apr. 26, 1966; accepted for publication June 20, 1966.
factor (4); the occasional presence of C-reactive protein (13); and normal concentrations of lipoproteins, ceruloplasmin (25), and bacterioidins (16). This pattern of changes, except for the absent C-reactive protein and normal ceruloplasmin, is common to many acute and chronic diseases (22).

Another feature of acute and chronic diseases is an increase in serum protein-bound carbohydrates (11, 28). Carbohydrates are covalently linked constituents of the serum globulins and hence can serve as an index of changes in concentration of these glycoproteins. However, no quantitative measurements of the serum protein-bound carbohydrates in schizophrenia have been reported. Two serum globulins particularly responsive to illness, inflammation, and trauma are the \( \alpha_2 \)-glycoproteins, ceruloplasmin and haptoglobin. They both increase in concentration in response to infection, trauma, and in many diseases (20, 25), but are differently affected by endocrine manipulations (15, 17). Haptoglobin, the hemoglobin-binding protein of serum, contains 20% carbohydrate and ordinarily accounts for the quantitative variations in the \( \alpha_2 \)-globulin fraction on paper electrophoresis. The concentration of this protein can range from 0 to 1 gm./100 ml. with a mean value for normal individuals of 100 mg./100 ml. of serum. It is decreased in diseases with a hemolytic component and by estrogen administration. Increases in haptoglobin are frequently accompanied by increases in erythrocyte sedimentation rate, fibrinogen, and orosomucoid (15). The concentration of haptoglobin may also be increased by administration of androgens or corticosteroids. Ceruloplasmin can increase two- to three-fold during illness from its normal mean value of 32 mg./100 ml. serum. This protein has been suggested to be a more sensitive indicator of inflammatory and tissue-destructive processes than the C-reactive protein (25). It also increases with antigenic stimulation and correlates with thyroid activity. The concentration of ceruloplasmin is increased during pregnancy and by estrogen administration (19).

Thus, measurement on the same serum or plasma sample of the protein-bound carbohydrates and of specific glycoproteins might provide a useful index or clue to the nature of the pattern of abnormalities which have been observed in the serum of schizophrenic patients.

Materials and Methods

The control population sample was taken from professional, laboratory, and maintenance personnel employed in the hospital. The male schizophrenic patients selected had been recently admitted and were carefully screened to eliminate other illnesses. All were veterans. The
duration of diagnosed mental illness in the group ranged from 1 to 20 years with a mean of 10.9 years. Ages ranged from 20 to 60 years with a mean of 38.6 years.

The blood samples were drawn in the morning between 8 A.M. and 10 A.M., allowed to stand 1 hr., and the serum separated by centrifugation. The separated serum was re-centrifuged and stored at -20° until assayed.

The serum protein-bound carbohydrates, hexose, fucose, and hexosamine, were measured as described by Wintzler (34). Sialic acid was measured by the method of Warren (31) as previously described (27). Serum protein was measured by a biuret method (32); ceruloplasmin by a modification (12, 27) of the method of Ravin (24). Haptoglobin was measured by a simplified Sephadex gel filtration method (19). Calibrated columns were operated manually in batteries of 12, thus permitting completion of 40–60 assays in 1 day. The precision of the measurements was ±3%. C-reactive protein was measured by a capillary tube immunoprecipitin method and presence of rheumatoid factor was determined by a latex-agglutination assay. Fibrinogen was measured quantitatively by the method of Jacobson (14) on plasma samples from blood collected with ethylene-diamine-tetraacetic acid (EDTA) as the anticoagulant.

**Results**

The concentration of serum protein and each of the protein-bound carbohydrates—hexose, hexosamine, fucose, and sialic acid—was significantly higher in the schizophrenic group as compared to the control group (Table 1). The mean haptoglobin concentration was also significantly elevated in the schizophrenic group with 66% of this group having values greater than 150 mg./100 ml. whereas only 10% of the

<table>
<thead>
<tr>
<th>Constituent*</th>
<th>Controls</th>
<th>Schizophrenics</th>
</tr>
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<tbody>
<tr>
<td></td>
<td>Mean</td>
<td>S.D.</td>
</tr>
<tr>
<td>Hexose</td>
<td>95.7</td>
<td>12.5</td>
</tr>
<tr>
<td>Fucose</td>
<td>12.4</td>
<td>1.8</td>
</tr>
<tr>
<td>Sialic acid</td>
<td>70.9</td>
<td>9.8</td>
</tr>
<tr>
<td>Hexosamine</td>
<td>83.0</td>
<td>10.1</td>
</tr>
<tr>
<td>Serum protein</td>
<td>7.26</td>
<td>0.41</td>
</tr>
<tr>
<td>Ceruloplasmin</td>
<td>31.8</td>
<td>6.05</td>
</tr>
<tr>
<td>Haptoglobin</td>
<td>105.0</td>
<td>44.0</td>
</tr>
</tbody>
</table>

*All values are given in mg./100 ml. except serum protein which is given in gm./100 ml.
control group had values above this level (Fig. 1). The mean ceruloplasmin levels in the two groups were virtually identical, as were the frequency distributions (Fig. 1). It is apparent that the mean elevation of haptoglobin (71 mg./100 ml.) could potentially account for only one-fourth of the mean serum protein (290 mg./100 ml.) elevation. The high carbohydrate composition of haptoglobin (5.2% hexosamine, 5% sialic acid, 8% hexose, and 1% fucose) suggested that a significant proportion of the elevation of these compounds might be attributed to the haptoglobin increase. This possibility was examined by calculation of the Pearson product-moment correlation coefficients for haptoglobin with each of these components (Table 2). The correlation with each of the carbohydrates was significant, and the strength of the correlation with fucose and hexosamine was 2–3 times stronger in the schizophrenic group than the controls. Indeed, it is of interest for analytical

Table 2. Correlation of Haptoglobin Levels with Other Measurements in Control and Schizophrenic Groups

<table>
<thead>
<tr>
<th></th>
<th>Controls (r)</th>
<th>Schizophrenic (r)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Protein</td>
<td>-0.06*</td>
<td>-0.03*</td>
</tr>
<tr>
<td>Sialic acid</td>
<td>0.52†</td>
<td>0.52†</td>
</tr>
<tr>
<td>Hexose</td>
<td>0.52†</td>
<td>0.53†</td>
</tr>
<tr>
<td>Fucose</td>
<td>0.32†</td>
<td>0.54†</td>
</tr>
<tr>
<td>Hexosamine</td>
<td>0.38†</td>
<td>0.65†</td>
</tr>
<tr>
<td>Ceruloplasmin</td>
<td>0.38†</td>
<td>0.36†</td>
</tr>
</tbody>
</table>

*Not significant.
†p < 0.001.
‡p < 0.01.

Fig. 1. Frequency distributions of haptoglobin and ceruloplasmin concentrations in control and schizophrenic groups. All mean values (X) are in mg./100 ml. serum.
purposes, that 25–40% of the serum protein-bound carbohydrate variation can be attributed to variation in a protein which comprises about 2% of the serum proteins. The variations in total protein and haptoglobin were not correlated. The correlation of haptoglobin variation with ceruloplasmin was statistically significant but weak for both groups.

The finding of a normal mean ceruloplasmin concentration and distribution in conjunction with the elevated haptoglobin levels suggested that the basis of the elevation was not an active inflammatory process, which was further substantiated by measurement of C-reactive protein. The sera of 59 of the 60 patients were negative for this indicator of inflammatory or traumatic processes. Since erythrocyte sedimentation rate (ESR) and fibrinogen and haptoglobin concentrations also have been reported to be correlated in some types of disease (15), plasma samples were drawn from 13 of the patients for their measurement. The results of these measurements are presented in Table 3. The individual haptoglobin levels varied over a fourfold range, and the mean level was significantly (p < 0.01) elevated over the control series. The ESR values were essentially normal, but the mean fibrinogen level was very significantly (p < 0.001) elevated over the normal mean. Calculation of correlation coefficients between the four pairings of the three series of measurements for this group yielded values for r < 0.2 which were not statistically significant.

Three common types of haptoglobin may be demonstrated by starch gel or polyacrylamide gel electrophoresis. The genetic basis of these types was established by Smithies who demonstrated their existence (29). The three phenotypes correspond to the heterozygote and respective homozygotes. The distribution of haptoglobin types in this group of 60 patients was determined, and, as shown in Table 4, the distribution corresponds closely to that of the normal population. Similar find-

<table>
<thead>
<tr>
<th>Statistic</th>
<th>ESR (mm./hr.)</th>
<th>Haptoglobin (mg./100 ml.)</th>
<th>Fibrinogen (mg./100 ml.)</th>
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</thead>
<tbody>
<tr>
<td>Mean</td>
<td>8</td>
<td>140</td>
<td>383</td>
</tr>
<tr>
<td>S.D.</td>
<td>4</td>
<td>53</td>
<td>45</td>
</tr>
<tr>
<td>Range</td>
<td>2–16</td>
<td>63–242</td>
<td>328–476</td>
</tr>
<tr>
<td>t*</td>
<td></td>
<td>2.46</td>
<td>4.29</td>
</tr>
<tr>
<td>p</td>
<td></td>
<td>&lt;0.01</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

*The comparison for haptoglobin was made with the control data presented in Table 1. The control fibrinogen statistics are: mean, 295 mg./100 ml.; S.D., 60 mg./100 ml. from a group of 19 subjects.
Table 4. Distribution of Haptoglobin Types in a Group of 59 Schizophrenic Patients

<table>
<thead>
<tr>
<th>Haptoglobin type*</th>
<th>1-1</th>
<th>2-1</th>
<th>2-2</th>
</tr>
</thead>
<tbody>
<tr>
<td>Schizophrenics</td>
<td>0.19</td>
<td>0.47</td>
<td>0.34</td>
</tr>
<tr>
<td>Normals</td>
<td>0.16</td>
<td>0.48</td>
<td>0.36</td>
</tr>
</tbody>
</table>

*Haptoglobin typing was done by polyacrylamide electrophoresis (2).*  

ings have been reported for a group of 65 schizophrenic patients in Europe (9).

**Comments**

The elevation of serum protein-bound carbohydrates would be a direct and predictable consequence of the serum globulin elevation which has been frequently reported in schizophrenic serums. The mean elevation of total protein in the present group is lower than that usually found which may reflect the fact that this group was not from an immobilized or chronic institutional population (33). Our finding of a normal ceruloplasmin concentration is in agreement with those investigators who have used methods measuring the concentration of the protein rather than methods sensitive to activators and inhibitors (25, 35). This finding is of importance for interpretation of the haptoglobin elevation. Clinically, elevations in haptoglobin concentration are ordinarily associated with infection, trauma, inflammation, or advanced cancer (15, 17, 20, 23). The haptoglobin increase is generally accompanied by an increase in erythrocyte sedimentation rate, fibrinogen, ceruloplasmin, C-reactive protein, and \( \alpha_1 \)-glycoprotein (orosomucoid), and a variable increase in \( \gamma \)-globulins. There is frequently a decrease in serum albumin as a result of increased metabolism and decreased synthesis (10). The mechanisms by which this constellation of changes are initiated and accomplished are unknown (22). In the instance of schizophrenia, a decrease in albumin and an increase in \( \gamma \)-globulins have been frequently reported. One report of a significant increase in orosomucoid has appeared (9). The concentration of ceruloplasmin was normal in the present group and C-reactive protein was absent. Thus, it is difficult to attribute the haptoglobin increase simply to an inflammatory or traumatic process. The finding of an elevation of fibrinogen in the presence of a normal ESR and uncorrelated with the haptoglobin level also is not consistent with such a process. An elevation in haptoglobin similar to that found in these patients with from 1- to 20-year histories of mental illness has also very recently been described in a group of 10 newly diagnosed, untreated acute schizophrenic patients (7). The mean elevation found was comparable to the value found in this group of pa-
tients. Thus, the increase in haptoglobin would appear to represent a long-term concomitant of schizophrenia, not due to infection, whose mechanism and significance remain open to investigation.

References