Many theories of biochemical processes in cancer assign a conspicuous rôle to quantitative changes in glutathione. Variations in the reduced form are said to be responsible for the alleged abnormal proteolysis in malignant tissue; variations in the equilibrium between the reduced and the oxidized form are said to be partly responsible for, or at least to reflect, the disturbed oxidation-reduction balance.

Such difficulty surrounds the collection and preparation of human normal and neoplastic material that most of the studies of glutathione in human cancer are confined to the concentrations found in blood. It is not unreasonable to suppose that the quantitative alterations in tissue glutathione content, sufficient to initiate or to stimulate a malignant process there, might be accompanied by quantitative alterations of this constituent in the blood. This investigation was undertaken to show what differences, if any, can be found between the reduced and the oxidized glutathione contents of the blood of cancerous and of non-cancerous individuals.

It has been stated that reduced glutathione exists almost entirely in the formed elements of the blood. Its content per million red blood cells was proposed as a unit by Gabbe (1) in order to eliminate the effects of anemia upon the blood figure. The white blood cell content is disregarded because the proportion of leukocyte to erythrocyte is so small as to be negligible. The use of the reduced glutathione-erythrocyte ratio in cancer blood, as well as in normal blood, as an approximation of the red cell content, will be justified in a subsequent paper (page 315).

A low reduced glutathione content of cancer blood has been reported by Fornieles Ulibarri (2), Bach and Bach (3), Truhaut and Minopoulos (4), Willheim and Stern (5), and Woodward and Fry (6). Willheim and Stern also obtained lower erythrocyte glutathione values in bloods from patients with cancer than from those with non-cancerous conditions. Whole blood figures within the normal range were observed by Varela, Apolo and Vilar (7) in three cases of epithelial neoplasms, and an elevation in both the whole blood and the red cell value was reported in one case of carcinoma of the pylorus, by Moschella and Trimarchi (8). Woodward and Fry (6) reported normal whole blood oxidized glutathione concentrations in five cancer cases.

A survey of methods has purposely been avoided. All methods probably determine glutathione plus other reducing substances which
function as such under the conditions of the determination. The concentrations of the latter are presumably much smaller than those of glutathione, and, inasmuch as a specific method for glutathione is not available, results obtained by the same method furnish the only possible approximation for comparative purposes. That all of the reducible material in acid blood filtrates is really oxidized glutathione has been questioned by Schelling (9). Its nature will become of major importance in the study of pathological conditions when quantitative variations from the normal figure will have been discovered.

**Experimental Studies**

The glutathione determinations were made exactly as described by Woodward and Fry (6). Reduced glutathione (GSH) was estimated by potassium iodate titration in a sulphosalicylic acid blood filtrate to which potassium iodide had been added. Total glutathione (GSH + GSSG) was estimated by the same procedure after zinc reduction of the sulphosalicylic acid filtrate. Oxidized glutathione (GSSG) was calculated by subtracting the reduced from the total figure.

Red blood counts were made on the oxalated blood in order to obtain an accurate measure of the number of erythrocytes in the sample studied.

Results are reported only for cases with definite diagnoses. In confirmation, only biopsies, autopsies, and x-ray evidence of bone metastasis were accepted. Inasmuch as no correlation could be seen between the type, location, or treatment of the lesion and any of the glutathione figures, no purpose would be served by the presentation of the individual values. A possible exception with regard to location is exhibited by lesions of the liver, which organ is considered to be a repository of glutathione. The treated cases are segregated because it is conventional to do so. The subjects, therefore, are divided into five groups: (1) untreated cases, which were presumably free from liver metastasis or disease; (2) cancer cases treated by irradiation, also presumably free from liver damage; (3) cancer cases in which lesions of the liver were known to be present at the time that the blood sample

---

**Table I: Reduced Glutathione and Gabe's Quotient in Cancer and in Non-Cancer Blood**

<table>
<thead>
<tr>
<th>Type of Subject</th>
<th>Number of Cases</th>
<th>Red Blood Cells (in Millions)</th>
<th>GSH in Mg. %</th>
<th>GSH/Rbc.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Untreated cancer cases</td>
<td>47</td>
<td>1.9-5.9 4.3</td>
<td>18.1-47.9 34.4</td>
<td>3.7-12.9 8.1</td>
</tr>
<tr>
<td>Treated (irradiated) cancer cases.........</td>
<td>7</td>
<td>3.5-5.7 4.3</td>
<td>25.5-48.5 35.4</td>
<td>6.9-10.9 8.3</td>
</tr>
<tr>
<td>Untreated cancer cases with liver invol...</td>
<td>5</td>
<td>3.4-5.1 4.2</td>
<td>21.8-36.2 28.0</td>
<td>4.9- 8.0 6.8</td>
</tr>
<tr>
<td>Non-malignant cases</td>
<td>12</td>
<td>2.6-5.4 4.2</td>
<td>15.3-46.0 33.7</td>
<td>5.9-10.7 8.0</td>
</tr>
<tr>
<td>Normal subjects</td>
<td>13</td>
<td>3.5-6.2 5.0</td>
<td>23.0-44.2 35.5</td>
<td>4.3- 9.3 7.2</td>
</tr>
</tbody>
</table>
THE BLOOD GLUTATHIONE IN HUMAN CANCER 313

was removed; (4) non-malignant cases; (5) apparently normal individuals.

In Table I are summarized the findings with regard to the whole blood and erythrocyte reduced glutathione contents of these five classes. The reduced, total, and oxidized glutathione averages are presented in Table II.

### Table II: Reduced, Total, and Oxidized Glutathione in Cancer and in Non-Cancer Blood

<table>
<thead>
<tr>
<th>Type of Subject</th>
<th>Number of Cases</th>
<th>GSH in Mg. %</th>
<th>GSH + GSSG in Mg. %</th>
<th>GSSG in Mg. %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Untreated cancer cases</td>
<td>42</td>
<td>18.1-47.9 34.2</td>
<td>21.5-54.5 40.2</td>
<td>0.9-10.7 6.0</td>
</tr>
<tr>
<td>Treated (irradiated) cancer cases</td>
<td>6</td>
<td>25.5-48.5 34.6</td>
<td>30.9-52.5 39.9</td>
<td>3.0- 8.6 5.3</td>
</tr>
<tr>
<td>Untreated cancer cases with liver involvement</td>
<td>3</td>
<td>21.8-36.2 27.6</td>
<td>25.5-41.7 34.9</td>
<td>3.7-12.8 7.3</td>
</tr>
<tr>
<td>Non-malignant cases</td>
<td>10</td>
<td>15.3-46.0 35.0</td>
<td>18.4-50.0 38.8</td>
<td>1.8– 5.5 3.8</td>
</tr>
<tr>
<td>Normal subjects</td>
<td>12</td>
<td>23.0-44.2 35.5</td>
<td>31.4-52.5 41.1</td>
<td>2.4– 9.2 5.8</td>
</tr>
</tbody>
</table>

**DISCUSSION**

The average glutathione contents of the blood in untreated and treated cancer cases and in non-malignant conditions appear to be practically identical with those of the normal subjects. In the cases with liver damage the contents were somewhat lower, as was to be expected. Moreover, the ranges of the results from which these averages were drawn show fairly close agreement. The slightly increased red cell GSH content of cancer blood is not significant, in view of the decreased erythrocyte count, and especially in view of a similar increase in the blood of the non-malignant patients, where the erythrocyte count is likewise low.

Since, as Gabbe (1) has pointed out, the blood cells contain nearly all of the reduced glutathione, low figures are to be expected in anemic conditions. While the patients in this series present a lowered average erythrocyte count, an advanced stage of anemia, with a count lower than three millions, was seen in but three cases. It is, therefore, possible that the low whole blood figures reported by Fornieles Ulibarri (2) and by Truhaut and Minopoulos (4) were the result of a greater degree of anemia in their patients than in this series. Moreover, in view of the fact that the erythrocyte glutathione appears to be slightly elevated in non-malignant conditions, it seems justifiable to indicate that comparisons of malignant and non-malignant cases should not be used as evidence that cancer lowers the blood glutathione concentration below the normal level.

**Conclusions**

1. The average reduced glutathione content of the blood from untreated (non-irradiated) and treated (irradiated) cancer cases, as well
as blood from several patients with non-malignant conditions, was found to be practically the same as that of normal blood.

2. The average reduced glutathione content of cancer erythrocytes was found to be slightly higher than that of normal blood, but the same as that from several non-malignant cases.

3. The average oxidized glutathione content of cancer blood was found to be the same as that of normal blood.

BIBLIOGRAPHY