HEMOGLOBIN PRODUCTION FACTORS IN THE HUMAN LIVER

I. NORMAL, INFECTION AND INTOXICATION

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When it was found (6) that beef liver contained potent factors for hemoglobin regeneration in anemia due to bleeding in dogs, it was logical that a study of various liver material should follow. It was soon found (2) that fish liver was practically inert but that the liver tissue of many warm blooded animals contained these potent factors in abundance. Liver tissues from the pig, sheep, beef, reindeer, horse and chicken have been thoroughly tested and in general there is a remarkable constancy in the reaction of a given standardized anemic dog to animal liver feeding. In general we may say that the feeding of 300 gm. pig liver per day for 2 weeks, will effect the output of approximately 100 gm. new hemoglobin above the control level in these anemic dogs. Dogs have individual capacities of hemoglobin production which must be known before accurate standardization is established.

We have often speculated as to the concentration of these potent factors for hemoglobin regeneration in the human liver, normal and abnormal, as well as in the diseased animal liver. As opportunities presented during the past 7 years we have tested out these potent factors using our colony of carefully standardized anemic dogs.

It is obvious that the behavior of these potent factors for hemoglobin regeneration holds much of interest for the student of pigment metabolism as well as for the physician who would understand the therapy of anemia.

1 We are greatly indebted to Dr. Istvan Gaspar, Dr. Ralph R. Mellon, Dr. Herbert R. Brown and Dr. N. W. Popoff for valuable material.
The use of human tissue is common practice at the present time whether for diagnosis or to establish a virus strain in animals—for example the use of the spinal cord from man to convey the infection of poliomyelitis to monkeys. Much information of great value to the student of disease has come from this type of biological study of human tissue whether obtained by operation or at autopsy.

Method

The care of animals and general technique employed in the anemia colony have been described in detail elsewhere (4, 5). A good deal of work has been reported (3, 7) dealing with liver fractions containing these potent factors which promote hemoglobin formation in anemia due to bleeding in dogs. Taking advantage of this experience we have prepared the human liver tissue in such fashion as to insure the presence of these same factors in the material as finally used in the 7-day test period. The material was preserved in cold storage until used, usually for a period of between 2 and 10 weeks. We have found by many observations that the material does not deteriorate under these conditions as regards potency for new hemoglobin production. The control animal material is treated in exactly similar fashion and thus gives an accurate base line of comparison.

Iron analysis was done on samples taken from the laboratory specimens as described by Kennedy (1) and the figures expressed as milligrams per cent of Fe appear in the tables. It is obvious that the figures do not represent accurately the amount of tissue iron as the amount of contained blood is a variable factor which we cannot control in this material.

Experimental Observations

The tables below give the values for hemoglobin production as modified by the potent factors present in any given human liver. The control test on the same dog is also given in the same line and the last column gives a percentage comparison of human and animal liver. In estimating this percentage the amount of material used in each instance is introduced into the computation—for example the control intake may be 300 gm. and the human material 150 gm. If the new formed hemoglobin is the same in each instance, the percentage ratio
will be 200 per cent for the human material which obviously is twice as potent.

The control base line in these experiments is established by standard intakes of pig liver in amounts per day as indicated in the tables.

Table 1. Diagnosis and histological description of liver.

<table>
<thead>
<tr>
<th>Case No.</th>
<th>Diagnosis</th>
<th>Age</th>
<th>Liver Weight</th>
<th>Laboratory Weight</th>
<th>Pathological Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>X-3011</td>
<td>Normal male—automobile accident—21 yrs.</td>
<td>1850 gm.</td>
<td>1680 gm.</td>
<td>Liver lobules and epithelium normal; a little lipochrome pigment is seen.</td>
<td></td>
</tr>
<tr>
<td>X-2410</td>
<td>Normal male—automobile accident—fractured skull—44 yrs.</td>
<td>1410 gm.</td>
<td>1210 gm.</td>
<td>Liver lobules normal; liver cells normal but for a very heavy deposit of lipochrome pigment. Careful study shows no material which gives iron stain. The iron content of this liver is unusually high but it is all within the cell protoplasm not in pigment granules. This is probably due to dietary factors.</td>
<td></td>
</tr>
<tr>
<td>X-2722</td>
<td>Normal male—fatal trauma—50 yrs.</td>
<td>1690 gm.</td>
<td>1550 gm.</td>
<td>Liver cells and lobules normal; lipochrome is present in moderate amounts.</td>
<td></td>
</tr>
<tr>
<td>X-2724</td>
<td>Normal male—automobile accident—57 yrs.</td>
<td>1550 gm.</td>
<td>1470 gm.</td>
<td>Liver cells and lobules are normal. Few liver cells show fat droplets and some lipochrome pigment.</td>
<td></td>
</tr>
<tr>
<td>X-2720</td>
<td>Normal male—trauma and death in 10 hrs.—60 yrs.</td>
<td>2200 gm.</td>
<td>2050 gm.</td>
<td>Liver cells and lobules normal. A few mononuclears appear in the portal stroma. Lipochrome is abundant in the central portion of the lobules.</td>
<td></td>
</tr>
<tr>
<td>X-2579</td>
<td>Normal elderly female—obesity—automobile accident—68 yrs.</td>
<td>2350 gm.</td>
<td>2320 gm.</td>
<td>The liver cells show many large fat droplets, a condition obviously related to the obesity. No pigment found. Kupffer cells normal.</td>
<td></td>
</tr>
<tr>
<td>X-2580</td>
<td>Normal elderly male—trauma and death in 12 hrs.—hemoglobin 105 per cent—64 yrs.</td>
<td>2050 gm.</td>
<td>2000 gm.</td>
<td>Liver cells and lobules normal. A few mononuclears appear in the portal stroma. Lipochrome is abundant in the central portion of the lobules.</td>
<td></td>
</tr>
</tbody>
</table>
Liver—laboratory specimen 1380 gm.
Histological specimen—liver lobules and cells are normal. Lipochrome pigment is abundant. Fat droplets are visible within the liver cells. Kupffer cells normal.

Liver—laboratory specimen 1800 gm.
Histological specimen—granular, frothy liver cells (glycogen). Slight lipochrome. slight congestion, few mononuclears in portal tissue. Practically normal.

Table 1 shows the results of biological analysis of 9 normal cases, death supervening in a few hours after lethal external trauma. There is considerable individual variation in the content of these human livers but it is obvious that the concentration of the factors influencing hemoglobin regeneration is definitely greater in the human liver as compared with the animal control—162 for the human and 100 for the control. This difference may be due to food factors.

The iron content of fresh liver tissue is 12.3 mg. per cent and only
one case deviates conspicuously from this average. The reason for this individual variation is not clear. It is at least possible that this high value may be due to diet factors especially rich in iron. The control animal liver contains on the average 19 mg. per cent Fe.

Table 2. Diagnosis and histological description of liver.

Liver—laboratory specimen 1560 gm.  
Histological specimen—normal liver tissue; a little lipochrome pigment seen in hepatic epithelium.

A-1257. Sudden cardiac death—liver normal—hemoglobin 90 per cent—23 yrs.  
Liver—autopsy weight 1550 gm.—laboratory specimen 1430 gm.  
Histological specimen—liver is practically normal. There are a few mononuclears in the periportal tissue. The liver cells show some lipochrome pigment. Kupffer cells are normal.

X-2642. Normal adult—cerebral hemorrhage—alcoholic?—40 yrs.  
Liver—autopsy weight 1900 gm.—laboratory specimen 1840 gm.  
Histological specimen—all liver cells show fat droplets, usually of large size. This suggests alcoholism. No excess pigment. No liver necrosis.

Liver—autopsy weight 1800 gm.—laboratory specimen 1640 gm.  
Histological specimen—liver cells normal. A moderate amount of lipochrome pigment found in liver cells of the central part of the lobules. Kupffer cells normal.

Liver—laboratory specimen 2670 gm.  
Histological specimen—there is some fatty degeneration but liver cells in general are normal. There is a moderate increase in portal connective tissue. Eosinophiles are numerous in liver capillaries. No pigment of any type seen. Kupffer cells normal.

X-2506. Trauma—fat embolism—hemoglobin 90 per cent—80 yrs.  
Liver—autopsy weight 960 gm.—laboratory specimen 940 gm.  
Histological specimen—liver sections typical of senile atrophy. Lipochrome pigment is abundant in liver cells particularly in the center of the lobules. Kupffer cells normal.

A-1203. Acute pneumothorax—normal viscera—40 ± yrs.  
Liver—autopsy weight 1390 gm.—laboratory specimen 1340 gm.  
Histological specimen—liver quite normal except for capillary congestion. No pigment to be seen.
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A-1466. Myasthenia gravis—normal liver—hemoglobin 100 per cent—56 yrs. Liver—autopsy weight 1680 gm.—laboratory specimen 1330 gm. Histological specimen—liver cells are normal. Lipochrome pigment in moderate amount is present in some liver cells. Kupffer cells normal.


TABLE 2

<table>
<thead>
<tr>
<th>Number</th>
<th>Cause of death</th>
<th>Iron content human liver</th>
<th>Liver intake per day</th>
<th>Hemoglobin output per 7 days feeding</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>fresh tissue mg. per cent</td>
<td>daily mg. gm. gm.</td>
<td>Human Control Human Control from Human from Control ratio Human to Control</td>
</tr>
<tr>
<td>A-1096</td>
<td>Aneurism</td>
<td>10.5</td>
<td>23</td>
<td>220 200</td>
</tr>
<tr>
<td>A-1257</td>
<td>Cardiac</td>
<td>7.3</td>
<td>15</td>
<td>200 300</td>
</tr>
<tr>
<td>X-2642</td>
<td>Brain hemorrhage</td>
<td>7.3</td>
<td>19</td>
<td>200 300</td>
</tr>
<tr>
<td>X-2578</td>
<td>Cyanide</td>
<td>13.9</td>
<td>32</td>
<td>230 300</td>
</tr>
<tr>
<td>X-2542</td>
<td>Heat stroke</td>
<td>—</td>
<td>—</td>
<td>380 300</td>
</tr>
<tr>
<td>X-2506</td>
<td>Trauma</td>
<td>16.1</td>
<td>22</td>
<td>130 300</td>
</tr>
<tr>
<td>A-1203</td>
<td>Pneumothorax</td>
<td>6.3</td>
<td>12</td>
<td>190 300</td>
</tr>
<tr>
<td>A-1466</td>
<td>Myasthenia</td>
<td>20.2</td>
<td>38</td>
<td>189 300</td>
</tr>
<tr>
<td>A-390</td>
<td>Senility</td>
<td>—</td>
<td>—</td>
<td>194 300</td>
</tr>
<tr>
<td>A-81</td>
<td>Arteriosclerosis</td>
<td>—</td>
<td>—</td>
<td>224 225</td>
</tr>
<tr>
<td>A-1185</td>
<td>Arteriosclerosis</td>
<td>—</td>
<td>—</td>
<td>185 300</td>
</tr>
<tr>
<td>Average</td>
<td></td>
<td>11.7</td>
<td>21</td>
<td>218</td>
</tr>
</tbody>
</table>

A-81. Arteriosclerosis—encephalomalacia—terminal bronchopneumonia—76 yrs. Liver—laboratory specimen 1570 gm. Histological specimen—atrophy of liver cells is conspicuous and a few fat droplets are seen. Slight cell infiltration of portal tissue. Central liver cells very small. Lipochrome abundant.

A-1185. Arteriosclerosis—coronary occlusion—hemoglobin 80 per cent—73 yrs. Liver—laboratory specimen 1300 gm. Histological specimen—liver shows a senile type of atrophy with increase of lipochrome pigment in the hepatic epithelium. A few fat droplets are present in liver.
cells. Kupffer cells normal. A few liver cells here and there contain a few pigment granules giving an iron stain.

Table 2 shows a group of human cases in which the viscera are relatively normal but show a variety of concomitant abnormalities. The liver itself is practically normal except for senile atrophy in many cases. Death took place suddenly in some cases or after a few hours in others. Arteriosclerosis is present in the majority of these cases.

The hemoglobin production factors in this liver tissue are obviously less abundant than in the normal liver material of Table 1. Even in these cases (Table 2) the potent factors are more abundant in the human liver than in animal liver—117 to 100. This figure of 117 may appear as the low normal or if we insist that Table 1 is the actual normal then these chronic senile changes may be in part responsible for the drop in the liver content of potent hemoglobin production factors.

Table 3. Diagnosis and histological description of liver.

Liver—autopsy weight 1850 gm.—laboratory specimen 1570 gm.
Histological specimen—swollen liver cells, much lipochrome in center of lobules, clusters of mononuclears in portal areas. No fat. Slight congestion.

Liver—laboratory specimen 2250 gm.
Histological specimen—swollen liver cells, few small necroses and nests of leucocytes, few fat droplets, slight inflammation of bile ducts and considerable portal inflammation and fibrosis. Little lipochrome pigment.

Liver—laboratory specimen 2300 gm.
Histological specimen—liver cells swollen, few fatty cells, few tiny necroses, mononuclears and polymorphonuclears in portal tissue. Little lipochrome, moderate congestion, numerous polymorphonuclears in capillaries.

Liver—autopsy weight 1570 gm.—laboratory specimen 1320 gm.
Histological specimen—liver cells granular and swollen—a few fat droplets seen. Lipochrome present—no necrosis, slight congestion. A good many mononuclears found in portal areas.

A-1465. Scarlet fever—bronchopneumonia—hemoglobin 95 per cent—49 yrs. 
Liver—autopsy weight 2000 gm.—laboratory specimen 1900 gm.
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Histological specimen—liver shows cloudy swelling and very little fat. Lipochrome pigment moderate in amount in liver cells. Kupffer cells enlarged but show no pigment.


<table>
<thead>
<tr>
<th>TABLE 3</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hemoglobin Production Factors in Abnormal Human Liver</td>
</tr>
<tr>
<td>Acute Infections</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Number</th>
<th>Cause of death</th>
<th>Iron content in human liver</th>
<th>Liver intake per day</th>
<th>Hemoglobin output per 7 days feeding</th>
<th>ratio Human to Control</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>fresh tissue</td>
<td>daily intake</td>
<td>Human</td>
<td>Control</td>
</tr>
<tr>
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<td>---</td>
<td>---</td>
<td>---</td>
<td>---</td>
</tr>
<tr>
<td>A-187</td>
<td>Erysipelas</td>
<td>17.0</td>
<td>6</td>
<td>224</td>
<td>300</td>
</tr>
<tr>
<td>A-223</td>
<td>Erysipelas</td>
<td>8.3</td>
<td>21</td>
<td>320</td>
<td>400</td>
</tr>
<tr>
<td>A-195</td>
<td>Endometritis</td>
<td>11</td>
<td>278</td>
<td>300</td>
<td>31</td>
</tr>
<tr>
<td>A-174</td>
<td>Peritonitis</td>
<td>16</td>
<td>161</td>
<td>300</td>
<td>12</td>
</tr>
<tr>
<td>A-221</td>
<td>Pneumonia</td>
<td>21</td>
<td>421</td>
<td>225</td>
<td>37</td>
</tr>
<tr>
<td>X-352</td>
<td>Influenza</td>
<td>45</td>
<td>300</td>
<td>225</td>
<td>47</td>
</tr>
<tr>
<td>A-112</td>
<td>Typhoid</td>
<td>22</td>
<td>243</td>
<td>300</td>
<td>41</td>
</tr>
<tr>
<td>Average</td>
<td></td>
<td>217</td>
<td>---</td>
<td>117</td>
<td>---</td>
</tr>
</tbody>
</table>


A-174. Bladder perforation—general peritonitis 5-6 days duration—50± yrs. Liver—laboratory specimen 1130 gm. Histological specimen—liver cells are nearly normal but for slight cloudy swelling. There is moderate capsular fibrosis and portal increase in stroma. Lipochrome slightly increased.
A-221. Lobar pneumonia, Type I—39 yrs.
Liver—laboratory specimen 2950 gm.
Histological specimen—liver cells swollen and granular, few tiny fat droplets, few tiny focal necroses. Lipochrome moderate, slight portal fibrosis with mononuclears included.

X-352. Acute hemorrhagic bronchopneumonia (influenza)—30+ yrs.
Liver—laboratory specimen 2150 gm.
Histological specimen—diffuse fatty degeneration of liver cells, stroma normal. Lipochrome abundant.

A-112. Typhoid, 24 days duration—terminal bronchopneumonia—17 yrs.
Liver—laboratory specimen 1700 gm.
Histological specimen—typical numerous focal necroses, mononuclears abundant in portal tissue, liver cells swollen and granular.

Table 3 shows a group of acute infections in which the fever and intoxication lasted from 1 to 4 weeks. It is obvious that the potent factors for hemoglobin production are not present in high concentration in these livers. The average figure 117 per cent is identical with the average of Table 2—to be designated as subnormal or at least a low normal. In the more acute fulminating infections the values appear to be lower than in the infections which are prolonged over a few weeks. This is in harmony with Table 4.

Table 4. Diagnosis and histological description of liver.

Liver—autopsy weight 1430 gm.—laboratory specimen 1250 gm.
Histological specimen—liver in general normal. There is a little lipochrome pigment in some of the liver cells. Kupffer cells show an occasional tiny yellow grain of pigment.

Liver—laboratory specimen 1570 gm.
Histological specimen—liver cells show cloudy swelling; no necroses but many mitoses seen. No leucocytes. Slight congestion. Lipochrome scanty.

A-204. Tuberculosis of kidney—pyelonephritis—emaciation—hemoglobin 65 per cent—56 yrs.
Liver—autopsy weight 900 gm.—laboratory specimen 740 gm.
Histological specimen—liver epithelium is relatively normal. Periportal large fat
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droplets in moderate amount in liver cells. Central lipochrome in moderate amount, no necroses.

X-509. Cystitis and pyelonephritis—uremia—49 years.
Liver—laboratory specimen 1620 gm.
Histological specimen—granular swollen liver cells. Leucocytes and polymorphonuclears in some portal areas. Little lipochrome.

A-1794. Diabetes—coma—hemoglobin 90 per cent—44 yrs.
Liver—autopsy weight 2270 gm.—laboratory specimen 1900 gm.
Histological specimen—liver sections practically normal; the liver cells show a frothy protoplasm suggesting abundant glycogen. Lipochrome pigment scanty.

Liver—autopsy weight 1900 gm.—laboratory specimen 1700 gm.
Histological specimen—liver sections essentially normal but for slight parenchymatous change.

Liver—autopsy weight 1450 gm.—laboratory specimen 1200 gm.
Histological specimen—liver cells are swollen and show some fat droplets. No pigment is seen. The portal stroma is increased and there is a little annular cirrhosis. A few small hyaline necroses are found. Kupffer cells normal.

A-1940. Thyrotoxicosis—basal metabolism +56 per cent—46 yrs.
Liver—autopsy weight 1150 gm.—laboratory specimen 1100 gm.
Histological specimen—liver lobules relatively normal. Some liver cells contain a few small fat droplets. Lipochrome is pretty abundant in the center of the lobule. Kupffer cells are normal.

A-1457. Thyroid adenoma with intoxication—hemoglobin 80 per cent—50 yrs.
Liver—autopsy weight 1080 gm.—laboratory specimen 900 gm.
Histological specimen—liver cells show some atrophy and increase in lipochrome pigment—otherwise normal. Kupffer cells normal.

A-1285. Hyperthyroidism and psychosis—embolism—hemoglobin 95 per cent—59 yrs.
Liver—autopsy weight 1350 gm.—laboratory specimen 1325 gm.
Histological specimen—liver lobules practically normal. A few fat droplets seen at margin of lobule and lipochrome pigment in the central portion. Kupffer cells normal.

A-1211. Thyrotoxicosis—hemoglobin 60 per cent—64 yrs.
Liver—laboratory specimen 1110 gm.
Histological specimen—liver cells in centers of lobules show moderate amounts of lipochrome pigment. Liver cells in peripheral half of lobules show much fatty degeneration. Kupffer cells normal.

A-64. Hyperthyroidism—organizing pericarditis—cardiac hypertrophy—56 yrs. Liver—laboratory specimen 1260 gm. Histological specimen—liver cells show atrophy, slight lipochrome pigmentation; there is slight portal fibrosis.

### TABLE 4

**Hemoglobin Production Factors in Abnormal Human Liver**

<table>
<thead>
<tr>
<th>Number</th>
<th>Cause of death</th>
<th>Iron content human liver</th>
<th>Liver intake per day</th>
<th>Hemoglobin output per 7 days feeding</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>from fresh tissue</td>
<td>mg.</td>
<td>daily intake</td>
</tr>
<tr>
<td>A-1682</td>
<td>Uremia</td>
<td>9.3 mg. per cent</td>
<td>17</td>
<td>178</td>
</tr>
<tr>
<td>X-354</td>
<td>Uremia</td>
<td>—</td>
<td>—</td>
<td>224</td>
</tr>
<tr>
<td>A-204</td>
<td>Pyelonephritis</td>
<td>—</td>
<td>—</td>
<td>105</td>
</tr>
<tr>
<td>X-509</td>
<td>Uremia</td>
<td>—</td>
<td>—</td>
<td>230</td>
</tr>
<tr>
<td>A-1794</td>
<td>Diabetes</td>
<td>11.6 mg. per cent</td>
<td>31</td>
<td>270</td>
</tr>
<tr>
<td>A-1768</td>
<td>Diabetes</td>
<td>8.6 mg. per cent</td>
<td>21</td>
<td>240</td>
</tr>
<tr>
<td>A-1327</td>
<td>Diabetes</td>
<td>4.3 mg. per cent</td>
<td>7</td>
<td>170</td>
</tr>
<tr>
<td>A-1940</td>
<td>Toxic thyroid</td>
<td>9.1 mg. per cent</td>
<td>14</td>
<td>160</td>
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<tr>
<td>A-1457</td>
<td>Toxic thyroid</td>
<td>13.7 mg. per cent</td>
<td>18</td>
<td>125</td>
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<tr>
<td>A-1285</td>
<td>Toxic thyroid</td>
<td>9.4 mg. per cent</td>
<td>18</td>
<td>185</td>
</tr>
<tr>
<td>A-1211</td>
<td>Toxic thyroid</td>
<td>14.5 mg. per cent</td>
<td>23</td>
<td>158</td>
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<tr>
<td>A-64</td>
<td>Toxic thyroid</td>
<td>—</td>
<td>—</td>
<td>180</td>
</tr>
<tr>
<td>A-373</td>
<td>Myxedema</td>
<td>—</td>
<td>—</td>
<td>158</td>
</tr>
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<td>A-68</td>
<td>Colitis</td>
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<td>—</td>
<td>214</td>
</tr>
<tr>
<td>A-162</td>
<td>Colitis</td>
<td>—</td>
<td>—</td>
<td>200</td>
</tr>
<tr>
<td>A-1751</td>
<td>Arthritis</td>
<td>23.8 mg. per cent</td>
<td>42</td>
<td>178</td>
</tr>
</tbody>
</table>

Average ........................................ 11.6 21 186 149

A-373. Myxedema—fibrous thyroid—basal metabolism = minus 43 per cent—62 yrs.

Liver—autopsy weight 1475 gm.—laboratory specimen 1100 gm. Histological specimen—liver cells show a good deal of atrophy with central lipochrome pigmentation. There are scattered fat droplets and a good deal of yellow pigment in Kupffer cells. Much arteriosclerosis of small arteries. Iron stain positive in pigment in Kupffer cells, not in liver cells.
A-68. Ulcerative colitis—ileostomy—cystitis—bronchopneumonia—hemoglobin
65 per cent—40 + yrs.
Liver—laboratory specimen 1500 gm.
Histological specimen—liver cells show periportal fatty degeneration, 3/4 of the
liver cells are normal. Lipochrome abundant.

A-162. Colitis—general peritonitis—empyema—pneumonia and abscess—long
continued suppuration for 2 months—63 yrs.
Liver—autopsy weight 1600 gm.—laboratory specimen 1400 gm.
Histological specimen—perihepatitis with organizing periportal fibrosis of mod-
erate degree. Occasional small necroses. A little fat in periportal liver cells.
Slight central atrophy with much lipochrome. Slight central congestion.

A-1751. Chronic arthritis—arteriosclerosis—bronchopneumonia—hemoglobin 60
per cent—67 yrs.
Liver—autopsy weight 1370 gm.—laboratory specimen 1250 gm.
Histological specimen—liver cells show atrophy and a few fat droplets. Lipo-
chrome pigment is well marked. There are central hyaline necroses in many lo-
bules. These areas of injury may involve 10 per cent of the liver parenchyma
examined.

Table 4 shows a considerable group of chronic intoxications in which
abnormalities of the kidney, pancreas and thyroid are represented.
The potent hemoglobin factors in these livers are present in high con-
centration which approximates the high values for the normal given
in Table 1. This is 149 per cent for Table 4 and 162 per cent for Table
1. In *anemia* the figures for these hemoglobin factors are uniform and
all seem close to the general average of 149. In connection with the
anemia usually present in chronic nephritis we may refer to Table 33
(Paper III) in which the values for extreme secondary anemia are
given.

*Diabetes* evidently is often associated with rather low liver values for
hemoglobin producing factors—in the 3 cases given an average of 99
per cent as compared with the general average of 149 per cent (Table
4). Some observers might wish to explain this on the basis of an inter-
relation of liver and pancreatic functions.

*Thyroid abnormalities* show very wide fluctuations in the content
of hemoglobin producing factors in these livers. Some values are
unusually low and one extraordinarily high. This case A-1457, Table
4, shows nothing very unusual upon which to base an explanation of
the very high figure for liver potency—413 per cent. The case was one of very severe thyroid intoxication admitted in coma, death supervening in a few hours. There was found a slight terminal bronchopneumonia. The thyroid showed the usual histological picture. Liver normal. This may indicate some important influence of a thyroid hormone upon liver function but a satisfactory explanation is not apparent.

The last 3 cases in Table 4 show that in long continued infection and intoxication there may be no decrease in the liver content of these potent hemoglobin producing factors.

**DISCUSSION**

We may look at liver material as representing so many grams of potential hemoglobin which will be produced in these standard anemic dogs. When 300 gm. pig liver is fed daily for 14 days we expect on the average a return of 100 gm. hemoglobin or a ratio of 4200 to 100. That is 42 gm. of pig liver is equivalent to 1 gm. hemoglobin in this type of biological assay. When we use the ratio in Table 1 indicating that human liver is more potent than pig liver (162 to 100) we arrive at a figure of 26 gm. human liver as equivalent to 1 gm. hemoglobin as tested by biological assay.

In all these tables the potential hemoglobin values for the liver tissue are given as per gram fresh weight. Some may object that it would be better to calculate for each whole liver the total potential hemoglobin in grams which its weight represents. This figure can be readily computed from the tabulated data. It is obvious that the senile atrophic liver which may be 1/2-2/3 normal weight would show subnormal values even more apparent than the tabulated values (Table 2) if we allowed for this weight shrinkage. We may say that a normal adult human liver of 1700 gm. represents potential hemoglobin amounting to 65 gm. as tested by standard biological assay. In like manner a senile liver tested at 100 (Table 2) compared to 100 per cent control and weighing 1000 gm. represents but 24 gm. potential hemoglobin.

In like manner the figures for acute infections as given per gram of liver tissue may not mean a great loss for the whole liver but in some cases a "dilution" of the potential hemoglobin values due to the cloudy
swelling of the liver. For example a liver weighing 2100 gm. and testing 100 per cent (Table 3) represents 50 gm. potential hemoglobin as tested by the usual biological assay.

In the literature of liver feeding in experimental anemia there has been much written about the importance and potency of organic iron as it is found in the liver parenchyma. Some authors would have us believe that the potency of the liver is dependent upon this contained organic iron and that the blood regeneration following liver feeding is a true index of the content of organic iron. Plenty of evidence is submitted in these papers to show that liver potency may be high when the iron analysis is very low and vice versa. For example pig liver is rated as 100 per cent or the normal control level and it contains 19 mg. per cent Fe. Human liver in normal cases rates at 162 per cent potency yet the iron analysis shows but 12 mg. per cent. In secondary anemia due to bleeding (Table 33, Paper III) the liver shows a potency close to normal (135 per cent) and the iron analysis reads 5.3 mg. per cent. In other words we may observe complete dissociation of the iron content and the concentration of hemoglobin production factors within the liver.

SUMMARY

Human liver tissue has been assayed to determine the concentration of hemoglobin production factors in normal and abnormal states. Standardized dogs made anemic by bleeding have been used in this biological assay and the human liver tissue compared with control animal tissue.

Normal human liver tissue (external trauma) contains much more of these hemoglobin production factors than the normal control animal liver—the ratio being 162 to 100.

In this form of biological assay 42 gm. of animal liver or 26 gm. of human liver represent 1 gm. of potential hemoglobin.

A second group (Table 2) in which the viscera were practically normal except for atrophy, the cases presenting a good deal of arteriosclerosis and senile changes, shows a lower content of these hemoglobin production factors. The ratio of human to control here is 117 to 100. This is certainly the low limit of normal.

Acute fulminant infections reduce somewhat the store of these po-
tent hemoglobin production factors in the human liver (Table 3). The average value is 117 as compared with 100 control but the more acute cases show the lower values.

Chronic intoxications show values which are close to the human normal—151 per cent. The liver content of hemoglobin producing factors shows very wide fluctuations in cases of thyrotoxicosis. Diabetes may be associated with rather low values.

There may be complete dissociation of the organic iron content and the concentration of hemoglobin production factors in the liver.

BIBLIOGRAPHY