B Vitamins in Cancerous Tissues

II. Nicotinic Acid

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The importance of this member of the B vitamin family in human and animal nutrition has been demonstrated many times, often dramatically, in the last few years (4, 5, 14, 12). There is little doubt that noncancerous tissues require a supply of this vitamin for continuation of their essential functions, but practically nothing is known about the requirements of cancerous tissues.

Willheim and Bacocho (17) noted some improvement in the general condition when large doses of nicotinic acid were fed to human patients bearing tumors, and Maisin (10) reported that nicotinic amide feeding was helpful in the inhibition of benzpyrene skin tumors in animals. In the case of liver tumors induced by feeding p-dimethylaminoazobenzene to rats on a rice-carrot basal diet, it was shown that nicotinic acid in combination with riboflavin has a protective action (9).

In attempting to judge the importance of nicotinic acid in cancer, it would be helpful to know the content of this vitamin in cancerous tissues and how the values change in the transformation from the noncancerous to the cancerous condition. Here, too, not much is known. von Euler and his coworkers (5) studied the ratio of reduced to oxidized cozymase in different tissues and reported that this ratio was higher for Jensen rat sarcoma than for normal rat muscle. Bernheim and Felsoianyi (1) analyzed rat tissues for coenzymes I and II and found that the Walker carcinosarcoma 256 contained much smaller amounts of the coenzymes than did the noncancerous tissues. They mentioned further that they found only traces in three human carcinomas.

Kensler, Sugiura, and Rhoads (8) determined the effect on the coenzyme I content of rat livers of feeding p-dimethylaminoazobenzene, and noted that the concentration was decreased in the damaged livers and fell to still lower levels in the cancers which were produced. Kensler, Dexter, and Rhoads (7) were interested further in determining whether the azo dye or its metabolites had any direct action on enzyme systems involving diphosphopyridine nucleotide, and were able to establish in vitro that p-phenylenediamine and N,N-dimethyl-p-phenylenediamine, both probable metabolites of the azo dye, had a strong inhibiting action on fermentation systems in which coenzyme I was the limiting factor. They called attention to the possibility of correlating this inhibitory action of the metabolites with the carcinogenic potency of the parent azo dye.

In connection with the functions of nicotinic acid in cellular metabolism, it is pertinent that the pyridinoproteins were shown to act directly in many of the fermentative transformations of carbohydrate. Thus they might play an important part in metabolic processes whether or not the metabolites eventually underwent oxidation with oxygen. On the other hand, enzymes such as the flavoproteins and cytochrome c appeared to function mainly in the transport of hydrogen from the pyridinoproteins to oxygen, and so might be considered less essential for metabolic systems, such as in cancer, where carbohydrate is transformed largely into lactic acid rather than into carbon dioxide and water. This concept would be in agreement with the low cytochrome c (2, 6, 15) and riboflavin (11) contents in cancerous tissues and might lead one to expect comparatively high nicotinic acid values in cancer, although there is unquestionably a great deal yet to learn about the functions of these compounds in living tissues.

MATERIALS AND METHODS

The tissue extracts described in the first paper of this series (11) were analyzed for nicotinic acid by the microbiological method of Snell and Wright (13). The results for noncancerous tissues are given in Table I and for cancers in Table II.

RESULTS AND DISCUSSION

The constancy of the nicotinic acid contents of the different tumors is striking. Most of them contained between 13 and 29 y of nicotinic acid per gm. of fresh tissue, the major exceptions being the two hepatomas produced by feeding rats p-dimethylaminoazobenzene on a basal Purina ration, where the values were 38 and 59. Considering the wide variation in nicotinic acid content of noncancerous tissues (Table I), the comparative constancy found for the tumors assumes a real significance.

The absolute level of the vitamin in tumors is low compared with noncancerous tissues. For example, the lowest value for a normal animal tissue was 44 y per gm. (dca mouse brain), which is appreciably above the range for the cancers. This situation is different from that of riboflavin, which also was found to be low in cancerous tissues but not any lower than in a number of noncancerous tissues (11). The tentative conclusion may therefore be drawn that the transformation to the cancerous condition involves a decrease in the nicotinic acid content. This is most clearly seen in the case of the hepatoma induced by p-dimethylaminoazobenzene, where the adjacent noncancerous liver serves as a fairly satisfactory control tissue. It will be seen from Table III that the hepatomas contained about one-third to one-fourth of the nicotinic acid found in the adjacent normal liver.
## TABLE I: Nicotinic Acid Contents of Noncancerous Tissues

<table>
<thead>
<tr>
<th>Tissue</th>
<th>Sex</th>
<th>Number of samples</th>
<th>Solids content, (per cent)</th>
<th>Nicotinic acid content (g per gm. fresh tissue)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Liver—Wistar rat (rice-carrot diet)</td>
<td>♀♂</td>
<td>2</td>
<td>30.5</td>
<td>174</td>
</tr>
<tr>
<td>&quot; Wistar rat (Purina diet)</td>
<td>♀♂</td>
<td>3</td>
<td>29.6</td>
<td>103</td>
</tr>
<tr>
<td>&quot; C57 mouse</td>
<td>♀♂</td>
<td>3</td>
<td>107</td>
<td></td>
</tr>
<tr>
<td>dba &quot;</td>
<td>♀♂</td>
<td>3</td>
<td>28.4</td>
<td></td>
</tr>
<tr>
<td>&quot; C3H</td>
<td>♀♂</td>
<td>3</td>
<td>32.3</td>
<td></td>
</tr>
<tr>
<td>Human</td>
<td>♀</td>
<td>1</td>
<td>27.4</td>
<td>54</td>
</tr>
<tr>
<td>Whole heart—Wistar rat</td>
<td>♀♂</td>
<td>2</td>
<td>20.6</td>
<td>123</td>
</tr>
<tr>
<td>&quot; C57 mouse</td>
<td>♀♂</td>
<td>3</td>
<td>22.2</td>
<td></td>
</tr>
<tr>
<td>dba C3H</td>
<td>♀♂</td>
<td>3</td>
<td>23.7</td>
<td></td>
</tr>
<tr>
<td>Myocardium—Human</td>
<td>♀</td>
<td>1</td>
<td>23.8</td>
<td></td>
</tr>
<tr>
<td>Whole brain—Wistar rat</td>
<td>♀♂</td>
<td>2</td>
<td>21.2</td>
<td>64</td>
</tr>
<tr>
<td>&quot; C57 mouse</td>
<td>♀♂</td>
<td>3</td>
<td>22.8</td>
<td></td>
</tr>
<tr>
<td>dba C3H</td>
<td>♀♂</td>
<td>3</td>
<td>21.9</td>
<td></td>
</tr>
<tr>
<td>Cerebrum—Human</td>
<td>♀</td>
<td>1</td>
<td>22.5</td>
<td></td>
</tr>
<tr>
<td>Lung—Wistar rat</td>
<td>♀♂</td>
<td>2</td>
<td>19.1</td>
<td>51</td>
</tr>
<tr>
<td>Human</td>
<td>♀</td>
<td>1</td>
<td>21.4</td>
<td>18</td>
</tr>
<tr>
<td>Spleen—Wistar rat</td>
<td>♀♂</td>
<td>2</td>
<td>20.2</td>
<td>69</td>
</tr>
<tr>
<td>Human</td>
<td>♀</td>
<td>1</td>
<td>22.7</td>
<td></td>
</tr>
<tr>
<td>Kidney—Wistar rat</td>
<td>♀♂</td>
<td>2</td>
<td>22.7</td>
<td>117</td>
</tr>
<tr>
<td>Human</td>
<td>♀</td>
<td>1</td>
<td>20.3</td>
<td></td>
</tr>
<tr>
<td>Skeletal muscle—Wistar rat</td>
<td>♀♂</td>
<td>2</td>
<td>24.7</td>
<td></td>
</tr>
<tr>
<td>Human</td>
<td>♀</td>
<td>1</td>
<td>26.0</td>
<td></td>
</tr>
</tbody>
</table>

## TABLE II: Nicotinic Acid Contents of Cancerous Tissues

<table>
<thead>
<tr>
<th>Sample No.</th>
<th>Tissue</th>
<th>Sex</th>
<th>Solids content, per cent</th>
<th>Nicotinic acid content (g per gm. fresh tissue)</th>
</tr>
</thead>
<tbody>
<tr>
<td>158, 159, 160</td>
<td>Rat carcinosarcoma (Walker 256)</td>
<td>♀♂</td>
<td>13.9</td>
<td>10 (17-20)</td>
</tr>
<tr>
<td>176, 180, 184</td>
<td>C57 mouse sarcoma (methylicholanthrene)</td>
<td>♀♂</td>
<td>17.3</td>
<td>29 (26-25)</td>
</tr>
<tr>
<td>207, 208, 209</td>
<td>dba mouse adenocarcinoma</td>
<td>♀♂</td>
<td>18.3</td>
<td>20 (17-26)</td>
</tr>
<tr>
<td>250, 251, 252, 274, 275</td>
<td>C3H &quot;</td>
<td>♀♂</td>
<td>16.3</td>
<td>28 (18-42)</td>
</tr>
<tr>
<td>105</td>
<td>Human mammary carcinoma</td>
<td>♀</td>
<td>35.7</td>
<td>25</td>
</tr>
<tr>
<td>106</td>
<td>&quot;</td>
<td>♀</td>
<td>27.2</td>
<td>27</td>
</tr>
<tr>
<td>212</td>
<td>&quot;</td>
<td>♀</td>
<td>19.1</td>
<td>13</td>
</tr>
<tr>
<td>213</td>
<td>&quot;</td>
<td>♀</td>
<td>16.1</td>
<td>29</td>
</tr>
<tr>
<td>214</td>
<td>&quot;</td>
<td>♀</td>
<td>34.4</td>
<td>21</td>
</tr>
<tr>
<td>215</td>
<td>&quot;</td>
<td>♀</td>
<td>46.8</td>
<td>28</td>
</tr>
<tr>
<td>216</td>
<td>&quot;</td>
<td>♀</td>
<td>35.3</td>
<td>15</td>
</tr>
<tr>
<td>217</td>
<td>&quot;</td>
<td>♀</td>
<td>18.0</td>
<td>22</td>
</tr>
<tr>
<td>218</td>
<td>&quot;</td>
<td>♀</td>
<td>16.4</td>
<td>29</td>
</tr>
<tr>
<td>219</td>
<td>&quot;</td>
<td>♀</td>
<td>17.8</td>
<td>28</td>
</tr>
<tr>
<td>220</td>
<td>&quot;</td>
<td>♀</td>
<td>19.7</td>
<td>15</td>
</tr>
<tr>
<td>225</td>
<td>&quot;</td>
<td>♀</td>
<td>14.8</td>
<td>27</td>
</tr>
<tr>
<td>221</td>
<td>&quot;</td>
<td>♀</td>
<td>19.6</td>
<td>18</td>
</tr>
<tr>
<td>222</td>
<td>&quot;</td>
<td>♀</td>
<td>16.7</td>
<td>21</td>
</tr>
<tr>
<td>223</td>
<td>&quot;</td>
<td>♀</td>
<td>14.3</td>
<td>23</td>
</tr>
<tr>
<td>224</td>
<td>&quot;</td>
<td>♀</td>
<td>16.7</td>
<td>26</td>
</tr>
<tr>
<td>281</td>
<td>&quot;</td>
<td>♀</td>
<td>18.7</td>
<td>11</td>
</tr>
<tr>
<td>286</td>
<td>&quot;</td>
<td>♀</td>
<td>20.4</td>
<td>28</td>
</tr>
<tr>
<td>288</td>
<td>&quot;</td>
<td>♀</td>
<td>20.0</td>
<td>12</td>
</tr>
<tr>
<td>289</td>
<td>&quot;</td>
<td>♀</td>
<td>17.5</td>
<td>24</td>
</tr>
<tr>
<td>290</td>
<td>&quot;</td>
<td>♀</td>
<td>20.0</td>
<td>30</td>
</tr>
</tbody>
</table>
This result is in agreement with the decrease in coenzyme I reported for the induction of this type of cancer (8).

The comparative constancy of the vitamin level in tumors may be an indication of the essential nature of the vitamin for cancer metabolism.

### Table III: Nicotinic Acid Contents of Cancerous and Noncancerous Rat Liver Tissues

<table>
<thead>
<tr>
<th>Diet</th>
<th>Days on diet</th>
<th>Sample No.</th>
<th>Tissue</th>
<th>Sex</th>
<th>Solids content, per cent</th>
<th>Nicotinic acid content (γ per gm. fresh tissue)</th>
</tr>
</thead>
<tbody>
<tr>
<td>p-Dimethylaminoazobenzene,</td>
<td>199</td>
<td>169</td>
<td>Hepatoma</td>
<td>♂</td>
<td>17.6</td>
<td>24</td>
</tr>
<tr>
<td>rice, carrots</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>p-Dimethylaminoazobenzene,</td>
<td>134</td>
<td>107, 111</td>
<td>Mixed cancerous and noncancerous tissue</td>
<td>♂</td>
<td>28.4</td>
<td>144, 121</td>
</tr>
<tr>
<td>Purina</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>p-Dimethylaminoazobenzene,</td>
<td>199</td>
<td>170</td>
<td>Noncancerous liver adjacent to</td>
<td>♂</td>
<td>(30.5)</td>
<td>100</td>
</tr>
<tr>
<td>Purina</td>
<td></td>
<td></td>
<td>hepatoma</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>p-Dimethylaminoazobenzene,</td>
<td>210</td>
<td>197, 280</td>
<td>Hepatomas</td>
<td>♂</td>
<td>17.6</td>
<td>38, 59</td>
</tr>
<tr>
<td>Purina</td>
<td>290</td>
<td>279</td>
<td>Mixed cancerous and noncancerous tissue</td>
<td>♂</td>
<td>(28.4)</td>
<td>83</td>
</tr>
<tr>
<td>p-Dimethylaminoazobenzene,</td>
<td>210</td>
<td>196, 278</td>
<td>Noncancerous liver adjacent to</td>
<td>♂</td>
<td>(30.5)</td>
<td>127, 147</td>
</tr>
<tr>
<td>Purina</td>
<td>290</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

In view of the considerations presented in the introduction whereby one might be led to expect high nicotinic acid contents in tumors, it is interesting to speculate on the significance of the finding that this vitamin is actually decreased in cancer. Since the transformation to the cancerous state is accompanied by an increased ability of the cells to metabolize carbohydrate glycolytically (16), the most obvious conclusion is that nicotinic acid is not associated with the increased glycolysis. On the other hand, the constancy of the nicotinic acid content in various tumors is an indication that this vitamin is essential for at least some aspects of cancer cell metabolism. It may be that the cancer cell is able to utilize its nicotinic acid much more efficiently in glycolytic processes than are noncancerous tissues. If this should be the case, it would account for the apparent anomaly of low nicotinic acid content and high glycolysis. The low vitamin level might simply be a reflection of low storage capacity of the cancer cell. These questions await further investigation.

### SUMMARY

The results of nicotinic acid assays on a variety of cancerous and noncancerous tissues are reported. Whereas values ranging from 18 to 178 γ per gm. of fresh tissue were found for noncancerous tissues, the range for the cancers was from 13 to 59 γ per gm., with most of the values falling between 18 and 29 γ per gm.

It is concluded that the transformation to the cancerous state involves a decrease in nicotinic acid content, although whether this signifies low utilization of this vitamin or low storage capacity and efficient utilization is not clear. The comparative constancy of the vitamin level in tumors may be an indication of the essential nature of the vitamin for cancer metabolism.

### REFERENCES


B Vitamins in Cancerous Tissues. II. Nicotinic Acid

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