The concept of a tumor as a nitrogen trap has been developed and evidence presented that, with the host eating ad libitum, there is a movement of nitrogen from the carcass to the tumor (10). These experiments would indicate that the primary effect of the tumor on the host is the production of anorexia and that altered nitrogen metabolism is a secondary factor. In view of this it seemed of interest to force-feed tumor-bearing rats, and to study nitrogen and sodium chloride excretion and the presence or absence of characteristic systemic effects. 

METHODS

Young male Sprague-Dawley* rats of the same age and weight received subcutaneous grafts in both lumbar regions of a suspension of the Walker 256 carcinoma, under aseptic conditions. On the next day feeding of the high fat diet of Ingle (8) was begun by stomach tube, the rats being brought to full feeding on the fifth day, when they received two feeds of 13 ml. each. At this time they were placed in metabolic cages and force-fed twice a day, distilled water being available at all times. The urine was collected in bottles containing citric acid and a small crystal of thymol. The rats were weighed daily and the tumors measured at frequent intervals.

The 24-hour urine samples were analyzed for nonprotein nitrogen (12), sodium (11), and chloride (2). At intervals total nitrogen was determined on an aliquot of the food to ensure homogeneity. The animals were housed in an air-conditioned room with thermostatic temperature control. Twice-daily temperature records gave a mean of 25 ± 1°C. 

When the tumors had attained a large size, the rats were killed by cervical dislocation after hemoglobin had been determined on tail blood (6) and they had fasted 16 hours. A fragment of liver was disintegrated in the Waring Blender and catalase determined by a titrimetric procedure (7). The remainder of the liver was used for the determination of moisture by drying at 110°C, total nitrogen by the Kjeldahl method, and total lipid by extraction with ether in the Soxhlet apparatus. The adrenals were weighed on a torsion balance and fixed in formalin for staining with Sudan IV (4).

Total body weight of the rats was determined just before they were killed, and the tumors removed after death and weighed. Carcass weight was determined by subtracting the tumor weight from the total body weight. 

RESULTS

In the study of force-fed rats in metabolic cages, the experiments have been conducted on groups of four rats, two control and two tumor-bearing. The plotted values in the figures to be presented are the means of the two control and two tumor-bearing rats. Since the absolute level of excretion may vary from group to group, the data have not been pooled, but representative figures are given which have been reproduced in several experiments.

The size of the tumors from the zero time when the animals were placed in the metabolic cages are given in Table 1, along with the tumor weights calculated by Schrek’s formula (13). 

The mean body weights of the rats are plotted

<table>
<thead>
<tr>
<th>Time in days</th>
<th>Mean tumor diameter*</th>
<th>Tumor weight†</th>
</tr>
</thead>
<tbody>
<tr>
<td>4</td>
<td>13.7</td>
<td>2.9</td>
</tr>
<tr>
<td>7</td>
<td>21.8</td>
<td>11.3</td>
</tr>
<tr>
<td>10</td>
<td>30.9</td>
<td>31.2</td>
</tr>
<tr>
<td>12</td>
<td>56.7</td>
<td>54.3</td>
</tr>
</tbody>
</table>

* Single tumor.
† Total of both tumors.
against time in Chart 1, the carcass weight of the tumor-bearers being corrected according to Schrek's formula. It is evident that in the force-fed tumor-bearer there is not the loss of carcass weight found by Mider et al. under the conditions of their experiments. This is supported by a comparison of the final body weights of the controls with the carcass weights of the tumor-bearers in Table 2.

TABLE 2

<table>
<thead>
<tr>
<th>Type of rat</th>
<th>Initial weight (gm.)</th>
<th>Carcass weight (gm.)</th>
<th>Gain</th>
</tr>
</thead>
<tbody>
<tr>
<td>Run no. 3:</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Control 1</td>
<td>135</td>
<td>226</td>
<td>91</td>
</tr>
<tr>
<td>Control 2</td>
<td>137</td>
<td>244</td>
<td>107</td>
</tr>
<tr>
<td>Tumor B 1 (20 per cent)*</td>
<td>136</td>
<td>247</td>
<td>111</td>
</tr>
<tr>
<td>Tumor B 2 (24 per cent)*</td>
<td>137</td>
<td>255</td>
<td>98</td>
</tr>
<tr>
<td>Run no. 4:</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Control 1</td>
<td>220</td>
<td>248</td>
<td>28</td>
</tr>
<tr>
<td>Control 2</td>
<td>224</td>
<td>250</td>
<td>26</td>
</tr>
<tr>
<td>Tumor B 1 (23 per cent)*</td>
<td>219</td>
<td>245</td>
<td>26</td>
</tr>
<tr>
<td>Tumor B 2 (22 per cent)*</td>
<td>214</td>
<td>238</td>
<td>24</td>
</tr>
</tbody>
</table>

* Figures in parentheses express tumor weights as per cent of total body weight.

The urinary nonprotein nitrogen excretion is plotted in Chart 2. The nitrogen retention which is evident persisted until the animals were killed. The nitrogen intake of 420 mg. of nitrogen per day, determined by an analysis of a 26-ml. aliquot of the diet, indicates that the rats were in a constant positive nitrogen balance.

Daily excretion of sodium and chloride in normal and tumor-bearing rats are presented in Charts 3 and 4. It is apparent that a retention of sodium chloride does occur in the tumor-bearing animal.

Hemoglobin values, liver catalase activity, and adrenal weights are presented in Table 3, demonstrating that systemic effects are produced in the host, even when carcass weight is maintained. The characteristic loss of sudanophilia has been observed in the adrenals of the tumor-bearing rats.
higher values than are due to the amount of hemoglobin present. In conjunction with this lipemia there is an increase in the lipid content of the livers of the tumor-bearing rats, as well as an increase in moisture and nitrogen (Table 4).

<table>
<thead>
<tr>
<th>Type of rat</th>
<th>Hemoglobin (gm/100 ml)</th>
<th>Catalase (K×10⁴) (both in mg.)</th>
<th>Adrenal weight</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control 1</td>
<td>15.8</td>
<td>4,300</td>
<td>48.8</td>
</tr>
<tr>
<td>Control 2</td>
<td>15.5</td>
<td>3,900</td>
<td>37.9</td>
</tr>
<tr>
<td>Tumor B 1</td>
<td>10.1</td>
<td>2,060</td>
<td>98.5</td>
</tr>
<tr>
<td>Tumor B 2</td>
<td>11.3</td>
<td>2,300</td>
<td>80.4</td>
</tr>
</tbody>
</table>

It may be noted that in one experiment tumor-bearing rats received implants of pellets of testosterone propionate. The excretion of nitrogen, sodium, and chloride in these rats was at the same level as that observed in untreated tumor-bearers.

**DISCUSSION**

Under the experimental conditions of forced feeding, whereby anorexia is overcome, the tumor-bearing rats do not lose carcass weight but develop typical systemic effects, such as loss of liver catalase activity, anemia, adrenal hypertrophy, and loss of adrenal sudanophilia.

This might be considered as evidence against the concept of the nitrogen trap playing a major role in the lethal effect of tumors (10) and the suggestion that liver catalase effects might be the result of malnutrition of the host (5). Before these theories are discarded it will have to be established that there has not been a nitrogen loss from the carcass in these experiments and that the observed systemic effects are responsible for the lethal effect of a tumor.

It is possible that nitrogen may have been lost from the carcass and replaced by fat. The experimental animals exhibited the increase in liver nitrogen which is noted when carcass nitrogen is being surrendered to the metabolic pool (14).

The data in Table 4 suggest that the dry liver of the tumor-bearing rat is essentially lipid and protein, but these factors do not account for the total dry weight of the control liver, the balance presumably being mostly glycogen. Increased liver lipid has been reported in tumor-bearing mice, but only after a 48-hour fast (1).

It is not surprising that tumor-bearing rats on an adequate dietary intake retain more nitrogen than normal controls, since they are synthesizing additional protoplasm. The retention of sodium and chloride may be explained partly by the increased moisture content of the liver (9) and the high moisture content of the Walker 256 carcinoma (14), but this does not account for all the salt retained.

It will be of interest to determine the effects of high carbohydrate and high protein diets on the tumor-bearing rat and to delineate the minimum dietary intake required to prevent weight loss from the carcass of a tumor-bearing rat.

**SUMMARY**

Tumor-bearing rats force-fed a high fat diet retained more nitrogen, sodium, and chloride than did control rats.

The force-fed rats bearing tumors did not lose carcass weight, but developed anemia and exhibited the typical enlarged adrenals and loss of liver catalase activity.

It is suggested that the loss of carcass weight in tumor-bearing animals is not a necessary component of the reaction leading to the development of systemic effects.

**ACKNOWLEDGMENTS**

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