SUMMARY

Accelerated albumin catabolism without a compensatory increase in anabolism leading to decreased serum albumin concentration in tumor-bearing animals was observed. Supplemental high-protein feedings augmented albumin synthesis, which resulted in a return of serum albumin to normal levels in tumor-bearing rats. Adrenalectomy abolished tumor-induced accelerated albumin catabolism.

INTRODUCTION

An uncontrolled cancer renders the host cachectic by markedly depleting the protein pools. This depletion results from a relative increase in catabolism of labile and stable protein pools, which presumably favors tumor growth by making amino acids and energy abundantly available.

Serum albumin appears to function as a labile protein source. Whipple (12) demonstrated the capacity of serum proteins to sustain totally host protein requirements even when acute increased protein needs arise, such as is seen in the nonsteady states of septicemia, anemia, and growth. Babson (2) and Hradec (6) demonstrated an increased turnover of serum albumin in tumor-bearing animals.

This study confirms the hypothesis that albumin catabolism is increased by the presence of a growing tumor. The effect is abolished by adrenalectomy, and high-protein feedings cause partial compensation with increased synthesis.

MATERIALS AND METHODS

A group of 103 Sprague-Dawley female rats (A. R. Schmidt Company, Madison, Wis.) weighing 175 to 200 g were divided into 10 groups. Rats in the normal diet groups were fed rat chow and water containing potassium iodide ad libitum. Animals in the high-protein-diet study were fed Sustagen (Mead Johnson and Company, Evansville, Ind.) and 5% Amigen (Baxter Laboratories, Inc., Morton Grove, Ill.) with potassium iodide in place of food and water for 1 week before the metabolic studies were conducted. Adrenalectomies were performed through standard flank incisions after tumor growth was established. A 0.9% NaCl solution with potassium iodide replaced water in this group, and prophylactic penicillin and streptomycin were given i.m.

Albumin was prepared from rat serum by precipitation of the globulins with 1% trichloroacetic acid in 95% ethanol and dialyzation of the supernatant liquid against distilled water overnight at 4°. After lyophilization, the albumin was analyzed by electrophoresis, and each preparation was found to be at least 95% pure. Iodination with ¹³¹I (carrier-free Na¹³¹I, Abbott Laboratories, Chicago, Ill.) was accomplished by the modified MacFarlane jet iodination technique of Franks et al. (5). All counting was done in a Tracerlab well scintillation spectrometer (25% efficiency). Analysis of each preparation showed the iodine:albumin ratio to be 0.8 to 1.2 atoms/molecule. Each animal studied received 4 to 6 million cpm of albumin¹³¹I i.v. delivered from a weighed tuberculin syringe. Blood samples were collected daily in weighed capillary tubes from the conjunctival plexus. Twenty-four-hr urine collections from individual metabolic cages were counted each day. Serum albumin determinations were made on each blood sample by the microtechnique of Debro et al. (4).

The Walker 256 tumor was examined histologically in randomly selected animals and was found to be a carcinoma with sarcomatous changes in larger tumors. The T. C. Rees sarcoma, obtained from E. D. Rees,¹ was originally a spontaneous tumor and is now maintained in tissue culture and by transplantation (9). Random bacterial cultures of both tumors yielded no growth.

The half-life, $t_{1/2}$, of circulating serum albumin was determined by plotting daily serum-relative specific activity (cpm/mg of albumin) versus time on semilogarithm paper. The hourly catabolism, $K$, of albumin was calculated by the formula

$$K = \frac{\text{Total cpm in 24-hr urine specimen}}{\text{Mean daily serum albumin specific activity (cpm/mg) \times 1/rat weight (g) \times 24 \text{ hr}}$$

Pool size, replacement rate, and turnover time were derived by the method of Tarver (11).

RESULTS

Table 1 shows that increased catabolism ($K$ mean 0.11 versus 0.081 mg/g/hr) as well as a shorter half-life of circulating albumin was present in tumor-bearing rats. On the other hand, the replacement rates, which are a reflection of synthesis, were the same in the 2 groups. This suggests that the disparity between synthesis and breakdown leads to the decreased serum albumin concentration in the tumor group. In

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Study Group

Animals bearing Walker 256 or T. C. Rees sarcoma were found to have accelerated albumin turnover. A high-protein diet partially compensated for increased catabolism by augmenting anabolism.

Table 1

Metabolic data from 3 albumin turnover studies

<table>
<thead>
<tr>
<th>Study</th>
<th>Group</th>
<th>No. of rats</th>
<th>Pool size (mg/g rat)</th>
<th>Replacement rate (mg/g rat/hr)</th>
<th>$t_{1/2}$ (hr)</th>
<th>Mean catabolic rate (mg/g/hr)</th>
<th>Albumin concentration (g/100 ml)</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>Walker 256 tumor-bearing, normal diet</td>
<td>20</td>
<td>7.05 ± 1.84(^a),(^b)</td>
<td>0.10 ± 0.04</td>
<td>47 ± 3(^b)</td>
<td>0.110 ± 0.04(^b)</td>
<td>2.81 ± 0.52(^b)</td>
</tr>
<tr>
<td></td>
<td>Nontumor-bearing, normal diet</td>
<td>13</td>
<td>9.52 ± 3.01</td>
<td>0.10 ± 0.03</td>
<td>65 ± 8</td>
<td>0.082 ± 0.02</td>
<td>3.45 ± 1.04</td>
</tr>
<tr>
<td>II</td>
<td>T. C. Rees sarcoma-bearing, normal diet</td>
<td>7</td>
<td>43 ± 4(^b)</td>
<td>49 ± 5</td>
<td>0.079 ± 0.032(^b)</td>
<td>3.73 ± 0.84</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Nontumor-bearing, normal diet</td>
<td>8</td>
<td>7.52 ± 0.61</td>
<td>0.120 ± 0.01</td>
<td>44 ± 4(^b)</td>
<td>0.046 ± 0.021</td>
<td>4.26 ± 0.29</td>
</tr>
<tr>
<td>III</td>
<td>Walker 256 tumor-bearing, high-protein diet</td>
<td>9</td>
<td>8.62 ± 1.08</td>
<td>0.092 ± 0.01</td>
<td>66 ± 7</td>
<td>4.69 ± 0.45</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Nontumor-bearing, high-protein diet</td>
<td>10</td>
<td>6.20 ± 1.88</td>
<td>0.092 ± 0.01</td>
<td>66 ± 7</td>
<td>4.69 ± 0.45</td>
<td></td>
</tr>
</tbody>
</table>

\(^a\) Values are the arithmetic means ± 1 S.D.
\(^b\) Significantly different than control value, Student's t test, $p = 0.05$.

Table 2

Effect of adrenalectomy on albumin turnover in Walker 256 tumor-bearing rats

The $t_{1/2}$ of circulating albumin was essentially the same in all groups except for the nontumor-bearing tumor-bearing group value, which was significantly shorter than all other groups.

<table>
<thead>
<tr>
<th>Group</th>
<th>No. of rats</th>
<th>$t_{1/2}$ (mean ± 1 S.D.)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adrenalectomy, tumor-bearing</td>
<td>9</td>
<td>60 ± 9</td>
</tr>
<tr>
<td>Adrenalectomy, nontumor-bearing</td>
<td>8</td>
<td>54 ± 3</td>
</tr>
<tr>
<td>Nonadrenalectomy, tumor-bearing</td>
<td>10</td>
<td>48 ± 4</td>
</tr>
<tr>
<td>Nonadrenalectomy, nontumor-bearing</td>
<td>9</td>
<td>55 ± 6</td>
</tr>
</tbody>
</table>

the sarcoma study, it was again observed that the mean half-life, $t_{1/2}$, was significantly shorter and the albumin concentration was lower in the tumor group. All attempts to demonstrate differences in the $t_{1/2}$, catabolism, or albumin concentration values on the basis of tumor size failed. It was concluded that the tumor effect is not size dependent.

When tumor and control animals were placed on a high-protein diet, albumin metabolism was significantly changed. Unlike in animals on a normal diet, the replacement rate in tumor animals was greater than in control animals, but the usual acceleration of catabolism was still present. In response to greater synthesis, the serum albumin concentration and pool size increased to become indistinguishable from control animal levels.

Adrenalectomy (Table 2) performed on tumor-bearing rats removed the usual effect of tumor on the $t_{1/2}$ values. There was no significant difference between $t_{1/2}$ values in tumor-bearing and nontumor-bearing adrenalectomized animals. In addition, tumor-bearing adrenalectomized rats had essentially the same $t_{1/2}$ values as nontumor-bearing, nonadrenalectomized animals. As expected, the nonadrenalectomized, tumor-bearing rats had a significantly shorter mean $t_{1/2}$ value than all other groups.

**DISCUSSION**

Tumor growth appears to affect albumin metabolism by an acceleration of catabolism. Under usual dietary and physiological conditions, there is little if any anabolic response to increased breakdown, and the serum concentration falls. A high-protein diet induces accelerated synthesis of albumin, which partially compensates for the effect, although excessive catabolism continues. These data substantiate the work of Allison et al. (1), which demonstrated a return of serum albumin levels to normal in Walker 256 tumor-bearing rats when they were fed a high-protein diet. In addition, Jeffay and Winzler (8) showed that a high-protein diet increased albumin turnover, which was reflected by a shorter $t_{1/2}$ and increased replacement rate.

Adrenalectomy seems to abolish completely the tumor effect, which suggests that the adrenal cortex is necessary to produce the usual tumor-host albumin response. A relationship between the adrenal cortex and tumor growth has been previously described. Inhibition of tumor growth following adrenalectomy has been described by several workers (7, 10). The obvious similarity of steroid and tumor-induced mobilization of carcass protein is well known. The frequent finding of adrenal hypertrophy in tumor animals by Begg (3) further substantiates this relationship. However, the mechanism by which tumor produces altered adrenal function is not known. It is possible that increased utilization of amino acids causes increased adrenal activity with resulting accelerated mobilization of protein stores. However, as Hradec originally observed and as our data substantiate, very small tumors, even those of microscopic size, have as much effect on albumin metabolism as large tumors. In addition, a high-protein diet should reduce albumin catabolism by increasing the amino acid pool if this were the case, but as this study demonstrates this does not occur. It would appear that the adrenal response is not due to a depletion of the amino acid pool.
It appears that a growing tumor can alter host protein metabolism by as yet unexplained and complex mechanisms probably involving alterations of the adrenal cortical hormonal milieu, which can be partially compensated for by feeding of a high-protein diet.

REFERENCES

The Effect of Adrenalectomy and High-Protein Diet on Tumor-altered Albumin Metabolism

William R. Jewell and Larry Hunter