Effect of Nutritional Alterations on Protein Synthesis in Transplantable Hepatomas and Host Livers of Rats

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ABSTRACT

The effects of selected, short-term, nutritional alterations on female Buffalo rats bearing transplantable hepatomas (5123 and 19) were investigated. In this study, nutritional alterations, which have been tried earlier dealing with the effects on hepatic protein metabolism of normal rats, were utilized. The host livers and hepatomas (intrahepatically transplanted) of tumor-bearing rats revealed little changes in polyribosomal aggregation or in vitro protein synthesis in fasted animals (2 to 3 days) that were tube-fed a single feeding of a complete diet, a complete amino acid mixture, a protein-free diet, or tryptophan. This is in contrast to the stimulatory effect elicited by these feedings to normal female Buffalo rats without tumors. Rats tube-fed hypertonic NaCl solution (6%) revealed a marked degree of polyribosomal disaggregation and inhibition of protein synthesis in host livers and similar but less marked changes in the intrahepatically transplanted hepatomas. Hepatoma-bearing (s.c. and intrahepatic) rats that were force-fed a threonine-devoid diet for 3 days revealed increased protein synthesis in the host livers and decreased protein synthesis in the hepatomas in comparison with similar rats force-fed a complete diet. Thus, the results of this study reveal that host livers of hepatoma-bearing rats are not responsive to certain nutritional stresses (complete amino acids or diet, protein-free diet, or tryptophan) as is the case with livers of normal rats. Hepatomas are resistant to some of the nutritional stresses studied; with two exceptions, the administration of hypertonic NaCl solution, where the response occurred but was less than that in the host liver, and the force feeding for 3 days of a threonine-devoid diet, where hepatoma protein synthesis was decreased while it became increased in the host liver.

INTRODUCTION

In recent years, much interest has developed regarding the role of nutrition in the pathogenesis of neoplasia (1, 2, 31, 32). Also, special attention has been directed toward nutritional intervention in the treatment of cancers (3, 4, 28). Having been concerned for many years with the role of selected nutritional disturbances on protein synthesis in the livers of normal animals, we have recently become interested in determining how tumor-bearing animals would respond to similar, experimentally induced, nutritional alterations.

In earlier studies from our laboratory, we have been concerned with the short-term effects of nutritional alterations or stresses on the liver, particularly concerning protein metabolism, of normal rats (16, 17, 19). Specifically, in our earlier studies, we investigated the effects of: (a) a single feeding of a complete mixture of amino acids or individual amino acids to fasted animals (21, 24, 27); (b) a single feeding of a purified diet devoid of protein or amino acids (23); (c) force feeding a purified diet devoid of single essential amino acids for 1 to 3 days (16). Under these experimental conditions, hepatic protein synthesis was found to be increased in comparison to control groups. On the other hand, a single administration (tube feeding or i.p.) of hypertonic (6%) NaCl solution caused a marked decrease in hepatic protein synthesis (7, 8).

Recently, we have become interested in studies dealing with protein metabolism in hepatomas and in host livers of rats bearing transplantable hepatomas (10, 20). In the present investigation, we have undertaken to determine whether nutritional alterations studied earlier in normal rats would have similar or different effects on hepatomas as well as on host livers of rats bearing transplantable hepatomas either s.c. or intrahepatically.

MATERIALS AND METHODS

Animals and Tumor Tissues. Female inbred Buffalo rats (obtained from Simonsen Laboratories, Gilroy, Calif.) were used to maintain Morris hepatoma 5123 induced by the ingestion of N-2-fluorenylphthalamic acid (9) and hepatoma 19 induced by the ingestion of ethionine (15) by serial s.c. transplantations. For these studies, the hepatomas were transplanted s.c. or intrahepatically into the left lobes of livers of 5- to 7-week-old Buffalo rats and were removed 20 to 28 days after transplantation. Rats were kept on a commercial diet (Wayne Lab-Blox; Allied Mills, Inc., Chicago, Ill.) throughout except that diet was removed overnight or for 2 to 3 days before treating with the different dietary regimens. Rats were killed by decapitation, and tumor tissues were dissected free of surrounding tissue and of necrotic tissue before being homogenized in a suitable buffer. Host livers were obtained from the same animals that had borne the hepatomas.

Dietary Components and Diets. After fasting for periods of 2 to 3 days, rats were tube-fed one feeding of a complete amino acid mixture (Stuart Amino Acids; Stuart Pharmaceuticals, Wilmington, Del.), 0.8 g/100 g of body weight, (0.5 g in 1 ml water) or a purified complete diet (16), 0.8 g/100 g of body weight (0.5 g in 1 ml water) 0.5 to 1.5 hr before killing. In some experiments, rats were fasted for 2 days and then received a protein-free diet, 2 g/100 g of body weight, (0.5 g in 1 ml water) 5 hr before killing. This diet was the same as used earlier (23) and consisted of dextrin, 84.5%; salt mixture (Hegsted IV), 4%; vitamin-sucrose mixture, 5%; corn oil, 5%; and cod liver oil, 1.5%. L-Tryptophan, 30 mg/100 g of body weight (10 mg in 1 ml water), was tube-fed to fasted (3 days) rats that were then killed 2 hr later. Hypertonic NaCl solution (6%), 5.3 ml/100 g of body weight, was tube-fed to overnight
fasted rats that were then killed 0.5 hr later. Control rats received distilled water.

In some experiments, rats were force-fed a complete diet for 1 day; then one half were force-fed the complete diet and the other half were force-fed a threonine-devoid diet for 3 days. The complete diet was the same as that used in earlier experiments (16). The percentage of dietary components was as follows: essential amino acids, 9.2; nonessential amino acids, 8.1; salt mixture (Hegsted IV), 4; vitamin-sucrose mixture, 5; corn oil, 5; cod liver oil, 1.5; and dextrin, 67.2. Dextrin was substituted for the threonine in the threonine-devoid diet. The diets were blended with distilled water so that each ml of diet contained 0.5 g of diet. Rats were force-fed at 8 a.m., noon, and 6 p.m., and each rat received on the average 0.75 g of diet per 10 g of initial body weight.

**Preparation of Polyribosomes.** Postmitochondrial supernatants were prepared from homogenates of livers of normal rats and of host livers and of hepatomas of tumor-bearing rats and were used for size distribution analysis of polyribosomes after addition of deoxycholate as described earlier (21). The degree of polyribosomal aggregation of livers and hepatomas under the different experimental conditions was evaluated from the patterns obtained by sucrose density gradients. This was conducted by calculating the relative distribution of monomer-dimers in relation to total ribosomes by measuring the area under the monomer and dimer peaks and the area under the entire pattern (monomer-dimers plus the other polyribosome fractions) of each gradient pattern.

**In Vitro and in Vivo Protein Synthesis.** Microsomes were prepared from postmitochondrial supernatants of livers of normal rats and of host livers and of hepatomas of tumor-bearing rats and were used for studies on incorporation in vitro as described earlier (20, 21). In these experiments, homologous cell saps of livers of normal rats and of host livers and of hepatomas of tumor-bearing rats and were used for size distribution analysis of polyribosomes after addition of deoxycholate as described earlier (21). The degree of polyribosomal aggregation of livers and hepatomas under the different experimental conditions was evaluated from the patterns obtained by sucrose density gradients. This was conducted by calculating the relative distribution of monomer-dimers in relation to total ribosomes by measuring the area under the monomer and dimer peaks and the area under the entire pattern (monomer-dimers plus the other polyribosome fractions) of each gradient pattern.

**RESULTS**

**Effect of a Single Feeding of Diet to Fasted Rats**

**Complete Diet or Complete Amino Acid Mixture.** Hepatoma-bearing rats that were fasted for 2 or 3 days and then subjected to a single feeding of complete diet or amino acids were studied for responses in the host liver and hepatoma (intrahepatically transplanted). The results of several such experiments are summarized in Tables 1 and 2. It is apparent that the host liver and hepatoma of hepatoma-bearing rats did not respond in a stimulatory manner to a single feeding of complete diet or complete amino acid mixture. Actually, the polyribosomes of host liver and hepatoma 5123 showed some disaggregation (Table 1) after the animals were tube-fed the complete diet or the complete amino acid mixture. In vitro protein synthesis of host liver and hepatoma 5123 showed little change after the complete diet but showed some decrease after the complete amino acid mixture (Table 2). In a few experiments, normal Buffalo rats without tumors were studied as controls. Rats receiving the complete diet revealed an improvement in hepatic polyribosomal aggregation (10%) and in in vitro hepatic protein synthesis (19%) in comparison to water-fed controls, others (5, 26, 30).

**Protein-Free Diet.** Hepatoma-bearing rats were fasted for 2 days; then one half were fasted for 2 days and then killed 0.5 hr later. Control rats received distilled water.

### Table 1

<table>
<thead>
<tr>
<th>Dietary treatment</th>
<th>Host liver</th>
<th>Hepatoma 5123</th>
<th>Host liver</th>
<th>Hepatoma 19</th>
</tr>
</thead>
<tbody>
<tr>
<td>Complete</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>-</td>
<td>42.6 ± 5.05</td>
<td>43.5 ± 1.86</td>
<td>(3)</td>
<td></td>
</tr>
<tr>
<td>+</td>
<td>49.4 ± 4.17</td>
<td>53.9 ± 2.86</td>
<td>(3)</td>
<td></td>
</tr>
<tr>
<td>Complete amino acids</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>-</td>
<td>41.1 ± 2.63</td>
<td>41.4 ± 2.59</td>
<td>(6)</td>
<td></td>
</tr>
<tr>
<td>+</td>
<td>49.7 ± 1.92</td>
<td>52.3 ± 6.92</td>
<td>(6)</td>
<td></td>
</tr>
<tr>
<td>Protein-free diet</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>-</td>
<td>36.9 ± 1.49</td>
<td>44.6 ± 1.35</td>
<td>(5)</td>
<td></td>
</tr>
<tr>
<td>+</td>
<td>43.6 ± 0.90</td>
<td>45.9 ± 1.34</td>
<td>(6)</td>
<td></td>
</tr>
<tr>
<td>Tryptophan</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>-</td>
<td>39.5 ± 1.64</td>
<td>47.2 ± 1.74</td>
<td>(6)</td>
<td></td>
</tr>
<tr>
<td>+</td>
<td>39.2 ± 3.45</td>
<td>46.9 ± 1.88</td>
<td>(6)</td>
<td></td>
</tr>
<tr>
<td>Hypertonic NaCl</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>-</td>
<td>45.1 ± 1.76</td>
<td>43.0 ± 1.30</td>
<td>(6)</td>
<td></td>
</tr>
<tr>
<td>+</td>
<td>69.5 ± 1.27</td>
<td>62.9 ± 1.09</td>
<td>(6)</td>
<td></td>
</tr>
</tbody>
</table>

- Mean ± S.E.
- Numbers in parentheses, number of experiments.
- 0.05 > p > 0.01.
- p < 0.01.
days, and then they were tube-fed a protein-free diet or water 5 hr before being killed. The results of these experiments are summarized in Tables 1 and 2. The polyribosomes of the host livers revealed some disaggregation (about 18 to 19% increase in the monomer-dimer fractions) while the polyribosomes of the hepatomas (5123 and 19) revealed little change in the experimental rats compared with the controls (Table 1). In vitro protein synthesis of the host livers and of the hepatomas showed essentially no changes between the control and experimental animals (Table 2). Also, we observed that many rats tube-fed the protein-free diet died shortly after the feeding (less than 5 hr after) and these were not used in our experimental results. In 2 experiments, normal Buffalo rats without tumors were used as controls. Such rats force-fed the protein-free diet revealed an improvement in in vitro hepatic protein synthesis (48%), but hepatic polyribosomal aggregation showed little or no change in comparison to water-fed control, results similar to those reported earlier (23).

**Tryptophan Administration.** In many experiments, we tested whether the administration of tryptophan would produce an effect on host livers and on hepatomas of tumor-bearing rats. Tables 1 and 2 summarize the results. It is apparent that tryptophan administration did not influence the polyribosomal aggregation profiles of host livers or of hepatoma 5123. Likewise, in vitro protein synthesis showed little change due to tryptophan administration (Table 2). In some experiments, normal Buffalo rats without tumors were used as controls. These rats that were tube-fed tryptophan revealed an improvement in hepatic polyribosomal aggregation (41% decrease in monomer-dimer fraction) and an increase in in vitro hepatic protein synthesis (73%) in comparison to water-fed rats, results similar to those reported earlier by us (21, 24) and by others (11—13).

Since in earlier experiments with normal animals it was demonstrated that tryptophan administration affected mainly the microsomes but also the supernatant fraction of liver in leading to enhanced hepatic synthesis (21), it was decided to study both of these components of host livers and of hepatomas. Cell saps (supernatant fractions) of hepatomas were not used because they lack elongation factors. Table 3 summarizes these experiments. Although the supernatant fraction of host livers of rats treated with tryptophan showed some stimulatory effect, microsomes of host livers and of hepatomas 5123 and 19 of tryptophan-treated rats revealed essentially no changes over that found with fractions of host livers or of hepatomas of control, untreated rats. Earlier preliminary studies with in vitro protein synthesis of hepatoma 5123 of tryptophan-treated rats

### Table 2

<table>
<thead>
<tr>
<th>Dietary treatment</th>
<th>Host liver</th>
<th>Hepatoma 5123</th>
<th>Host liver</th>
<th>Hepatoma 19</th>
</tr>
</thead>
<tbody>
<tr>
<td>+</td>
<td>+16.3 ± 26.79&lt;sup&gt;a&lt;/sup&gt;</td>
<td>-10.5 ± 15.74</td>
<td>(4)&lt;sup&gt;a&lt;/sup&gt;</td>
<td></td>
</tr>
<tr>
<td>Complete amino acids</td>
<td>-58.0 ± 4.24</td>
<td>-33.0 ± 12.02</td>
<td>(2)</td>
<td></td>
</tr>
<tr>
<td>Protein-free diet</td>
<td>-1.6 ± 13.52</td>
<td>+1.7 ± 11.36</td>
<td>+2.5 ± 11.21</td>
<td>-13.6 ± 16.66</td>
</tr>
<tr>
<td>Tryptophan</td>
<td>+2.8 ± 10.94</td>
<td>+3.2 ± 3.50</td>
<td>-10.7 ± 8.74</td>
<td>-0.5 ± 6.35</td>
</tr>
<tr>
<td>Hypertonic NaCl</td>
<td>-61.5 ± 4.55</td>
<td>-31.0 ± 18.38</td>
<td>-62.2 ± 24.90</td>
<td>-30.1 ± 6.73</td>
</tr>
</tbody>
</table>

<sup>a</sup> Numbers in parentheses, number of experiments.  
<sup>b</sup> Mean ± S.E.  
<sup>c</sup> p < 0.01.

### Table 3

<table>
<thead>
<tr>
<th>Subcellular fractions used&lt;sup&gt;b&lt;/sup&gt;</th>
<th>Microsomes</th>
<th>Supernatant (host liver, TRP administered)</th>
<th>Specific activity (cpm/mg RNA, % change)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Host liver</td>
<td>-</td>
<td>+9.6 (7)&lt;sup&gt;c&lt;/sup&gt;</td>
<td></td>
</tr>
<tr>
<td>Host liver</td>
<td>+</td>
<td>-2.4 (16)</td>
<td></td>
</tr>
<tr>
<td>TRP host liver</td>
<td>+</td>
<td>+13.5 (14)</td>
<td></td>
</tr>
<tr>
<td>5123</td>
<td>-</td>
<td>+10.1 (2)</td>
<td></td>
</tr>
<tr>
<td>5123</td>
<td>+</td>
<td>+3.1 (16)</td>
<td></td>
</tr>
<tr>
<td>TRP 5123</td>
<td>-</td>
<td>+15.7 (4)</td>
<td></td>
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<tr>
<td>TRP 5123</td>
<td>+</td>
<td>+15.7 (4)</td>
<td></td>
</tr>
<tr>
<td>19</td>
<td>-</td>
<td>+7.5 (8)</td>
<td></td>
</tr>
<tr>
<td>TRP 19</td>
<td>+</td>
<td>-4.3 (14)</td>
<td></td>
</tr>
<tr>
<td>TRP 19</td>
<td>+</td>
<td>+2.4 (15)</td>
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<tr>
<td>19</td>
<td>-</td>
<td>+10.0 (6)</td>
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</tr>
<tr>
<td>TRP 19</td>
<td>+</td>
<td>-3.2 (14)</td>
<td></td>
</tr>
<tr>
<td>TRP 19</td>
<td>+</td>
<td>+18.2 (8)</td>
<td></td>
</tr>
</tbody>
</table>

<sup>a</sup> The abbreviation used is: TRP, tryptophan.  
<sup>b</sup> In each experiment, host livers and hepatomas of 3 to 4 rats of each group were pooled.  
<sup>c</sup> Numbers in parentheses, number of experiments. In each group, comparisons were made with microsomes of host liver or hepatoma using supernatants of host livers of rats not treated with tryptophan.
revealed similar findings (24).

Administration of Hypertonic NaCl Solution. In 6 experiments, we tested whether the administration of hypertonic NaCl solution to overnight-fasted rats would cause an effect on host livers and intrahepatically transplanted hepatomas. Tables 1 and 2 summarize the results of experiments in which hepatomas-bearing rats were tube-fed 6% NaCl solution 0.5 hr before being killed. Polyribosomes revealed disaggregation of host livers (53 to 54% increase in monomer-dimer fraction), of hepatoma 5123 (46% increase in monomer-dimer fraction), and of hepatoma 19 (18% increase in monomer-dimer fraction) in experimental animals compared with control animals (Table 1). In vitro protein synthesis revealed a 61 to 62% decrease in host livers and a 30 to 31% decrease in the hepatomas of hypertonic NaCl solution-treated rats (Table 2). Normal Buffalo rats without tumors that were tube-fed hypertonic NaCl solution revealed greater hepatic polymeosomal disaggregation (60% increase in monomer-dimer fraction) and decreased in vitro hepatic protein synthesis (50%) than in water-fed controls, results similar to those reported earlier (7, 8).

In addition to measuring in vitro protein synthesis using microsomal preparations as summarized in Table 2, in some experiments free polymeosomes of host livers and hepatomas of control and experimental rats were isolated and used for in vitro protein synthesis (12, 18). The differences in percentage in 5 experiments with hepatoma 5123 and in 4 experiments with hepatoma 19 in which the hypertonic NaCl solution-treated animals were compared with the controls are as follows: using hepatoma 5123, host liver —61.4 ± 3.2 (S.E.) (p < 0.01) and hepatoma —41.8 ± 5.1 (p < 0.01); using hepatoma 19, host hepatoma 5123, host liver —61.4 ± 3.2 (S.E.) (p < 0.01) and in 5 experiments with hepatoma 5123 and in 4 experiments with hepatoma 19 (18% increase in monomer-dimer fraction) and decreased in vitro protein synthesis revealed a significant decrease (24.5%) in the experimental groups compared to the control group. In one experiment, in vitro protein synthesis was assayed by using postmitochondrial supernatants of livers and of hepatomas and measuring [14C]leucine incorporation into proteins. The results revealed that the livers of the experimental group showed a 67.8% increase over that in the control group while the hepatomas of the experimental groups revealed a 47.2% decrease compared to that of the control group.

In the second series of experiments, we decided to study the effect of force-feeding a threonine-devoid diet on hepatomas (5123 and 19) which were transplanted intrahepatically rather than s.c. As we have discussed earlier (10, 20), we feel that transplantable hepatomas growing intrahepatically are in a more natural environment than are those growing s.c. or i.m.

Table 4

Effect of Force-Feeding a Threonine-devoid Diet In our first series of experiments, female Buffalo rats bearing hepatomas 5123 transplanted s.c. 4 weeks before killing were used. Table 4 summarizes the data of 3 experiments where the tumor-bearing rats were force-fed for 3 days either a complete diet or a threonine-devoid diet. While there was no difference in body weights, the liver weights and percentages of lipid and glycogen were increased in the experimental group compared to the control group. In vivo hepatic protein synthesis as measured by [14C]leucine incorporation into hepatic and plasma proteins was increased in the rats force-fed the threonine-devoid diet in comparison with those force-fed the complete diet. These results are similar to those reported earlier, where the livers and plasma of normal rats that were force-fed the same diets were studied (16). Data derived from the s.c. transplanted hepatoma 5123 revealed little differences between tumor weight, glycogen, and protein in the control and experimental groups. However, in vivo tumor protein synthesis revealed a significant decrease (24.5%) in the experimental groups compared to the control group. In one experiment, in vitro protein synthesis was assayed by using postmitochondrial supernatants of livers and of hepatomas and measuring [14C]leucine incorporation into proteins. The results revealed that the livers of the experimental group showed a 67.8% increase over that in the control group while the hepatomas of the experimental groups revealed a 47.2% decrease compared to that of the control group.

In the second series of experiments, we decided to study the effect of force-feeding a threonine-devoid diet on hepatomas (5123 and 19) which were transplanted intrahepatically rather than s.c. As we have discussed earlier (10, 20), we feel that transplantable hepatomas growing intrahepatically are in a more natural environment than are those growing s.c. or i.m.
Therefore, we decided to use this approach in further experiments to determine whether the location within the body might alter the response to the deficient diet and also to determine whether a different hepatoma (hepatoma 19) might respond similarly or differently.

Table 4 summarizes the results of experiments in which rats bearing intrahepatically transplanted hepatomas (5123 or 19) were force-fed for 3 days a complete or threonine-devoid diet. The results reveal that host liver lipid and glycogen as well as hepatic and plasma protein synthesis were increased while tumor protein synthesis was decreased in the rats force-fed the threonine-devoid diet in comparison to those force-fed the complete diet. Liver and tumor weights were determined together, since they were not dissected out separately, and revealed insignificant changes between the control and experimental groups.

In one experiment in which rats were bearing hepatoma 5123 intrahepatically, changes in gastrocnemius muscles of rats force-fed the complete or threonine-devoid diet were investigated. The results revealed a 5.1% decrease in muscle weight and only a 0.5% decrease in the percentage of muscle protein in rats force-fed for 3 days the experimental diet compared to those force-fed the complete diet. In vivo protein synthesis, [14C]leucine incorporation into muscle protein (cpm per mg protein), revealed a 20.8% decrease in the gastrocnemius muscles of the experimental group compared to the control group. Thus, the skeletal muscle changes in tumor-bearing rats due to the threonine-devoid diet were similar to those reported earlier in normal rats (16, 22).

The degree of changes in free amino acid levels in the blood and host livers of rats force-fed for 3 days a complete or threonine-devoid diet was evaluated in 2 experiments. The results revealed that free threonine levels were decreased 68% in plasma and decreased 75% in the host livers of rats force-fed the threonine-devoid diet compared to those of rats force-fed the complete diet. Otherwise, the other free amino acid levels showed only minor variations in the plasma and in the host livers of experimental animals compared with control animals. Similar changes in amino acid levels have been reported in normal rats force-fed the complete threonine-devoid diets (25).

DISCUSSION

This study was undertaken to determine whether selected nutritional alterations could influence protein synthesis in host livers and transplantable hepatomas of tumor-bearing rats. The nutritional alterations or stresses selected have previously been tested using livers of normal animals where interesting effects on hepatic polysomes and protein synthesis have been documented. Table 5 summarizes the effects reported on hepatic protein synthesis of normal animals in earlier studies as well as in this study and also the findings reported in this study dealing with animals bearing hepatoma 5123 or 19. The results indicate that the host livers did not respond as did the livers of normal animals under 3 conditions (complete diet or amino acids, protein-free diet, and thymophan). However, under 2 conditions (hypertonic NaCl solution and threonine-devoid diet), the host livers of tumor-bearing rats did respond like livers of normal rats. In general, the hepatomas did not respond to the nutritional alterations with 2 exceptions: with hypertonic NaCl solution, where the response occurred but was diminished compared with that of the host liver, and with threonine-devoid diet, where protein synthesis was decreased while it was increased in the host liver.

In searching for clues as to why the host livers of tumor-bearing rats did not respond in some cases as did the livers of normal rats, we first considered that the tumor-bearing animals may be eating less food and were, therefore, partially starving before the experiments were begun. However, in earlier reports as well as in this study, we found that fasted normal rats were still able to respond to the acute administration of diet or dietary components (14, 21, 24). Thus, fasting or partial starvation alone as induced in normal animals was probably not responsible for the differences in responses. Conceivably, the metabolic state of the host liver of tumor-bearing rats becomes altered or disturbed so that the host liver is not influenced by certain nutritional stresses. This view needs to be explored further.

In an earlier report, we demonstrated that the turnover of mRNA of hepatomas occurred at a slower rate than that of host livers (20). Conceivably, this difference suggests that hepatomas may respond more slowly to agents or conditions which act by influencing mRNA synthesis or turnover. This was considered in a few experiments where tumor-bearing animals were studied at several different time intervals following the nutritional stress to determine whether a delayed effect may develop in hepatomas. Our data failed to indicate that this was indeed the case in studies dealing with a complete amino acid mixture or with thymophan.

In a number of earlier reports (12, 18), it has been observed that the status of the hepatic polysomes as determined by sucrose density gradient analysis correlated well with their ability to synthesize proteins, as measured by in vitro [14C]leucine incorporation into proteins using cell-free preparations. From our present results, it appears that a similar correlation exists between the polysomal status in the hepatomas and the in vitro protein-synthesizing capacity of the ribosomes (Tables 1 to 3). Also, the status of the polysomes in the host livers coincides with the in vitro protein-synthesizing ability of their ribosomes (Tables 1 and 2). Thus, under a variety of states or conditions, the polysomal profiles offer insight into the protein-synthesizing capacity of the ribosomes.

In searching for an explanation as to the altered responses...
of the transplantable hepatomas in comparison with the host liver or with normal liver after some nutritional stresses, we considered that the difference may be related to the rapid cell division and growth in the tumors. However, preliminary experiments using regenerating livers reveal that rapid cell division and growth in itself may not be of importance. In these preliminary experiments, we investigated whether regenerating livers (1 or 2 days following partial hepatectomy) would respond to tryptophan. Our results revealed that the administration of tryptophan caused a shift toward heavier aggregation of polyribosomes and an increase in intracellular protein synthesis in the regenerating livers, similar to that observed after administering tryptophan to rats with normal livers or with livers already stimulated by cortisone acetate or phenobarbital (29).

REFERENCES
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