The Utilization of Tryptophan and Its Metabolites for Pyridine Nucleotide Synthesis in Tumors and Host Liver

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SUMMARY

Tryptophan injected in large quantities (500–1000 mg/kg) causes a statistically significant rise in the pyridine nucleotide content of livers from animals bearing Ehrlich ascites tumor but there is no corresponding rise in tumor nicotinamide adenine dinucleotide (NAD). Similarly, incorporation of isotope from ring-labeled tryptophan into the nicotinamide moiety of NAD occurs rapidly in host liver but very slowly in tumor. Radioactivity from tryptophan tended to accumulate in 3-hydroxyanthranilic acid in tumor but less so in liver. Quinolinic acid-2,3,7,8-14C is rapidly incorporated into liver NAD, but it failed to appear in tumor pyridine nucleotide in spite of evidence of its rapid penetration of the tumor. A study of the rate of decarboxylation of labeled quinolinic acid by a number of normal tissues and a group of experimental tumors revealed that liver and kidney were highly active, but all the tumor tissues examined failed to show a significant rate of decarboxylation. These data indicate there is a difference in the ability of host liver and kidney and tumor tissues to utilize tryptophan as a precursor of pyridine nucleotides.

INTRODUCTION

The observation of Weinhouse and others (8, 22) that tumor cell dispersions were more dependent than homogenates of most other tissues on added pyridine nucleotide for respiration, and the fact that most tumor tissues tend to have relatively low concentrations of pyridine nucleotide (6, 9) led to this study of pyridine nucleotide synthesis in tumors. Earlier studies (13, 18) indicated that the route of synthesis from nicotinic acid and nicotinamide is qualitatively similar in host liver and Ehrlich ascites tumor, and that synthesis may occur by the pathway described by Kornberg (12) involving nicotinamide mononucleotide as well as the acid nucleotide pathway described by Priess and Handler (16). In the present investigation, the utilization of tryptophan for pyridine nucleotide synthesis by Ehrlich ascites cells and by host liver has been compared.

The conversion of tryptophan to pyridine-containing intermediates probably proceeds through the series of interconversions shown in Chart 1. Nicotinic acid mononucleotide synthesis from tryptophan. PRPP, 5-phosphoribosyl-1-pyrophosphate; NacMN, nicotinic acid mononucleotide; ribose-5-P, ribose-5-phosphate.

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1 The research was supported by a grant from the National Cancer Institute of Canada.
2 Present address: Royal Victoria Hospital, Montreal, P.Q., Canada.
3 The following abbreviations are used: NAD, nicotinamide adenine dinucleotide; NacMN, nicotinic acid mononucleotide; 3HAA, 3-hydroxyanthranilic acid; ADH, alcohol dehydrogenase.
Swiss mice bearing the Ehrlich ascites carcinoma were used eight days after transfer of the tumor. The propagation and recovery of the tumor, the preparation of cell suspensions and extracts of acetone powders, the extraction of tissues in tri-chloroacetic acid or perchloric acid, the analytical methods for determination of NAD and other compounds, and the use of Dowex-2-formate and paper chromatography for the isolation of intermediates have been described previously (15, 18).

In Vivo Experiments

Dosage Experiments. Mice were injected intraperitoneally with various doses of l-tryptophan dissolved in 0.154 M NaCl. Control animals received a similar volume of 0.154 M saline (0.25 ml). Uninjected animals were used as zero-time controls. NAD contents were estimated by the alcohol dehydrogenase method (19) in extracts of liver and tumor.

Isotope Experiments. The isotopically labeled precursors were dissolved in 0.154 M NaCl and injected in volumes of 0.25 to 0.50 ml directly into the peritoneal cavity. In each experiment four tumor-bearing mice (8-day-old) were confined in a metabolism cage for 3 to 4 hours. This cage, of the type described by Roth et al. (20) allowed the separate collection of urine, feces, and expired 14CO2. Animals were killed by decapitation, and perchloric acid extracts were made of pooled livers and tumor cells.

Isolation Procedures

3-Hydroxyanthranilic Acid. Tompsett (21) described the extraction of 3HAA into ether from urine adjusted to pH 3. In the present study a similar procedure was applied to the recovery of 3HAA from tissue extracts. The 8% perchloric acid extract was extracted three times with an equal volume of ether in a separatory funnel. The aqueous residue was accurately adjusted to pH 3 with KOH, the precipitated KClO4 was removed by centrifugation, and the supernatant fluid was extracted three times with an equal volume of ether. These three ether extracts, containing the 3HAA, were pooled and washed twice with an equal volume of glycine-HCl buffer (0.05 M, pH 3). 3HAA was isolated from the residual ether after concentration, by descending paper chromatography on Whatman #1 filter paper. The following solvent systems were used:
(a) methanol:n-butanol:benzene:water (2:1:1:1 by volume); (b) benzene:acetic acid:water (25:72:3 by volume); (c) n-butanol:acetic acid:water (2:3:5 by volume). 3HAA was detected as a bluish fluorescent spot under UV light. Carrier 3HAA was added at the stage of tissue homogenization to facilitate recovery. When the ether containing 3HAA was extracted with 10 volumes of 0.05 M phosphate buffer, pH 7, the 3HAA was recovered in the aqueous buffer phase. Recovery of carrier 3HAA was approximately 60%.

Nicotinamide, NAD, and Quinolinic Acid. The aqueous residue at pH 3 remaining after ether extraction was adjusted to pH 7 with KOH. After standing overnight at 0°C, the small amount of KClO4 was removed by centrifugation. The neutral extract was fractionated on a Dowex-2 formate column, and final purification of fractions by paper chromatography was carried out as previously described (13, 18).

Incubation of Ascites Cells with Tryptophan-14C

Packed tumor cells were washed three times in three volumes of Krebs-Ringer phosphate solution (pH 7.4) containing 0.089% glucose (w/v) and were finally suspended in three volumes of this solution. Reaction mixtures containing 1.5 ml of cell suspension and 0.50 ml of tryptophan in isotonic saline were placed in the main compartments of four modified Warburg flasks equipped with rotating sidearms. The calculated specific activity of added tryptophan was 5 x 105 dpm/μmole, and the concentration in the 2.0-ml system was 2 mM. The rotating sidearm of each Warburg flask contained 0.5 ml of 40% perchloric acid. NaOH (0.50 ml of 10% solution) and a small glass bead were placed in the large center well. In two flasks, designated zero time controls, the perchloric acid was tipped into the reaction mixture (by rotation of the sidearm) just before the tryptophan was added. These flasks were then stopped and incubated at 37°C for 30 minutes. The NaOH was removed from the center well of each flask and preserved for analysis for 14CO2. The contents of the main compartment were quantitatively transferred with washings of 8% perchloric acid to chilled centrifuge tubes. Two flasks, designated incubated samples, were stopped and incubated for one hour at 37°C. The perchloric acid was then added, and the vessels were incubated for an additional 30 min to allow efficient trapping of any 14CO2 in the NaOH. Perchloric acid extracts of the contents of all flasks were subjected to the procedure for extraction and isolation of 3HAA. Samples of the appropriate buffered washed ether extracts were added to 0.5 ml of hydroxide of Hyamine 10-X in counting vials, and the mixtures were taken to dryness in a desiccator over CaCl2. The residues were dissolved in 0.5 ml of methanol, and scintillator solution (18) was added. Samples of the ether extracts were also subjected to paper chromatography, and the distribution of radioactivity along the chromatograms in relation to marker compounds was determined by scintillation counting.

Quinolinic Acid Decarboxylase Activity

Extracts of acetone powders, which were usually freed of nucleotides by Sephadex treatment (13), were incubated with quinolinic acid-2, 3, 7, 8-14C in the presence of 5-phosphoribosyl-1-pyrophosphate to determine liberation of 14CO2. The CO2 formed, trapped in NaOH as described above, was liberated quantitatively and collected in Hyamine in Conway diffusion units; the Hyamine carbonate was counted by liquid scintillation. Assays of activity were performed on mouse liver, kidney, spleen, and muscle; rat brain and lung; and Ehrlich ascites carcinoma, Walker 256 tumor, methylcholanthrene-induced skin tumor in C3H mouse, C3HBA mammary carcinoma in C3H mouse, and LL6 tumor.

Utilization of 3HAA

The 3HAA-dependent formation of a substance absorbing at 360 nm (presumed to be aminoacrolein fumaric acid) was studied in extracts of acetone-dried host liver and Ehrlich ascites cells. The complete reaction mixture contained: 0.065 μmoles of 3HAA in 2.5 ml 0.02 M KH2PO4-K2HPO4 buffer, pH 7.3, acetone powder extract, 0.1 ml, in a final volume of 3.0 ml. Changes in optical density were observed at 360 nm (2).
Disappearance of 3HAA was observed as a change in absorbance at 298 m\(\text{m} \) in extracts of reaction mixtures deproteinized with trichloroacetic acid. Reaction mixtures contained: 0.35 \(\mu\)moles of 3HAA in 2.0 ml 0.02 m phosphate buffer, pH 7.3, and 0.1 ml of an extract of acetone-dried liver or ascites tumor. After 30 min of incubation at room temperature, the reaction was stopped with 2.1 ml of 10\% trichloroacetic acid, and the clear supernatant was used for analysis.

### Table 1

<table>
<thead>
<tr>
<th>Group</th>
<th>Liver ((\mu)g/(\mu)m wet weight)</th>
<th>Tumor ((\mu)g/ml packed cells)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tryptophan, 500 mg/kg</td>
<td>343 [4]</td>
<td>245 [3]</td>
</tr>
</tbody>
</table>

Pyridine nucleotide response to injected tryptophan. Mice bearing 8-day tumors were sacrificed 4 hr after the intraperitoneal injection of tryptophan 500 or 1000 mg/kg body weight in a volume of 0.25 ml. Control animals received 0.25 ml of 0.154 m NaCl. One group of animals, sacrificed at zero time, received no injections. The number of animals in each group is given in brackets. Analysis of variance showed that values for liver of the tryptophan-treated group were significantly different from controls (\(P < 0.001\)), while there was no significant difference between groups in the case of tumor.

### Table 2

<table>
<thead>
<tr>
<th>Experiment</th>
<th>Radioactivity recovered (% of injected dose)</th>
<th>Volume of tissue (ml)</th>
<th>Concentration of radioactivity (dpm (\times 10^3)/ml)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>A A B</td>
<td>A B A B</td>
<td></td>
</tr>
<tr>
<td>Ascitic plasma</td>
<td>19.0 2.1</td>
<td>27.0 30.0</td>
<td>1600 310</td>
</tr>
<tr>
<td>Packed tumor cells</td>
<td>7.0 4.0</td>
<td>12.0 14.5</td>
<td>1300 635</td>
</tr>
<tr>
<td>Liver</td>
<td>0.97 0.58</td>
<td>4.4 5.5</td>
<td>500 220</td>
</tr>
<tr>
<td>Expired CO(_2)</td>
<td>3.6 2.1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Urine</td>
<td>1.1</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Distribution of radioactivity four hours after injection of \(\sigma\)-trypotphan-benzene ring-U-\(^{14}\)C. In each experiment 4 mice were injected intraperitoneally with tryptophan-\(^{14}\)C, 40 mg/kg body weight (approx. 6 \(\mu\)moles per mouse), specific activity \(8.4 \times 10^6\) dpm/\(\mu\)mole.

### Table 3

<table>
<thead>
<tr>
<th>Experiment</th>
<th>Compound Packed tumor cells(^a)</th>
<th>Liver(^b)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>A A B</td>
<td>A B</td>
</tr>
<tr>
<td>Nam</td>
<td>Not studied</td>
<td>295</td>
</tr>
<tr>
<td>NAD(^b)</td>
<td>390 335</td>
<td>30,000 26,000</td>
</tr>
<tr>
<td>3HAA</td>
<td>800 820</td>
<td>140 80</td>
</tr>
<tr>
<td>QA</td>
<td>350</td>
<td>Not detected</td>
</tr>
</tbody>
</table>

Incorporation of \(\sigma\)-trypotphan-benzene ring-U-\(^{14}\)C by liver and ascites cells in vivo. Nam, nicotinamide; NAD, nicotinamide adenine dinucleotide; 3HAA, 3-hydroxyanthranilic acid; QA, quinolinic acid.

\(^a\) Radioactivity (dpm) per ml tissue.

RESULTS

Dosage Experiments with Tryptophan

Preliminary experiments, in which animals were sacrificed at intervals from one to twenty-four hours after tryptophan injection, indicated that maximum NAD levels in liver occurred three to four hours after injection. The mean NAD contents of liver and tumor from tumor-bearing mice injected with tryptophan in doses of 500 and 1000 mg/kg are shown in Table 1. Increases of 135\% and 146\%, respectively, over the control values were observed in liver, while little change was observed in tumor. Analysis of variance showed that the differences in liver between groups were highly significant (\(P < 0.001\)). These observations on liver confirm the report of Kaplan et al. (10). Tumor, on the other hand, showed no statistically significant response to tryptophan dosage.

Studies with Tryptophan-\(^{14}\)C in Vivo

The utilization of tryptophan-\(^{14}\)C by tumor-bearing mice was studied in two independent experiments. Some variation between the two experiments in the distribution of radioactivity was observed (Table 2). In Experiment B there was a smaller proportion of injected radioactivity in the tissue extracts and a higher proportion in the urine. Apart from accidents in injection, no reason for this difference was evident. The smaller amount of expired \(^{14}\)CO\(_2\) in Experiment B may be the consequence of the lower uptake of the precursor by the tissues and lower availability of precursor for degradation. It should be noted that the concentration of acid-soluble radioactivity in tumor cells was more than double that in liver in both experiments. It would appear, therefore, that more labeled precursor was available for utilization in tumor cells than in liver four hours after injection.

In the tissue extracts, radioactivity was shown to be present in NAD, Nicotinamide, 3HAA (Table 3), and several unidentified compounds. Small amounts of radioactivity in liver and larger amounts in tumor, chromatographed as 3HAA, were noted. On the other hand, the incorporation of radioactivity into NAD and Nicotinamide was extensive in liver but negligible in tumor. Chart 2 shows the coincidence of elution from the Dowex-2-formate column of radioactivity and NAD (fluorometric method). The NAD was purified by paper chromatography prior to specific activity determination. After elution the identification of the material was confirmed by UV absorption spectra in water and 1 m KCN, and by the yeast ADH method. When a sample of the eluted material was subjected to hydrolysis in 0.1 n NaOH at 100\(^\circ\)C for 10 minutes and chromatographed, Nicotinamide was detected on the paper chromatogram, and the radioactivity was associated with this spot. On the other hand, the incorporation of radioactivity into NAD and Nicotinamide was extensive in liver but negligible in tumor. Chart 2 shows the coincidence of radioactivity and carrier quinolinic acid in the elution curve from the Dowex-2-formate column; a more definitive identification was not made.

Studies With Tryptophan-\(^{14}\)C in Vitro

When washed ascites were incubated with tryptophan-\(^{14}\)C, no \(^{14}\)CO\(_2\) evolution was detected. Radioactive 3-hydroxy-
Pyridine Nucleotide Synthesis

Table 5

<table>
<thead>
<tr>
<th>Compound</th>
<th>Packed tumor cells</th>
<th>Liver*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nam</td>
<td>0</td>
<td>1200</td>
</tr>
<tr>
<td>NAD</td>
<td>0</td>
<td>1900b</td>
</tr>
<tr>
<td>QA</td>
<td>2500</td>
<td>400</td>
</tr>
<tr>
<td>Unidentified</td>
<td>0</td>
<td>200</td>
</tr>
<tr>
<td>Experiment A</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Experiment B</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Incorporation of quinolinic acid-2,3,7,8-14C by liver and ascites cells in vivo. Mice were sacrificed 3 to 3.5 hr after intraperitoneal injections of QA-2,3,7,8-14C. Dosage: 130 mg/kg body weight (approximately 20 μmoles per mouse). Calculated specific activity: Experiment A, 6.5 × 10^-4 cpm/μmole; Experiment B, 13 × 10^4 cpm/μmole. Extraction of tissues and separation and identification of compounds are described in text. See Table 3 for abbreviations.

- Specific activity, 1.6 × 10^4 cpm/μmole.
- Specific activity, 2.8 × 10^4 cpm/μmole.

Table 6

<table>
<thead>
<tr>
<th>Tissue</th>
<th>CO₂ Production (cpm/mg protein/hr)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mouse</td>
<td></td>
</tr>
<tr>
<td>Liver</td>
<td>474</td>
</tr>
<tr>
<td>Kidney</td>
<td>89</td>
</tr>
<tr>
<td>Spleen</td>
<td>6</td>
</tr>
<tr>
<td>Muscle</td>
<td>1</td>
</tr>
<tr>
<td>Rat</td>
<td></td>
</tr>
<tr>
<td>Brain</td>
<td>1</td>
</tr>
<tr>
<td>Lung</td>
<td>3</td>
</tr>
<tr>
<td>Walker 256 tumor [1]</td>
<td>11</td>
</tr>
<tr>
<td>Walker 256 tumor [2]</td>
<td>2</td>
</tr>
<tr>
<td>MCA skin tumor in C3H mouse</td>
<td>0</td>
</tr>
<tr>
<td>C3HBA mammary carcinoma in C3H mouse</td>
<td>1</td>
</tr>
<tr>
<td>LL-6a. b</td>
<td>12</td>
</tr>
</tbody>
</table>

Quinolinic acid-2,3,7,8-14C decarboxylase activity. Each vessel contained: 2.5 μmoles 5-phosphoribosyl-1-pyrophosphate (PRPP); 2.5 μmoles quinolinic acid-2,3,7,8-14C (QA) (specific activity, approx. 130,000 cpm/μmole); 20 mg protein in 0.5 or 2.5 ml PRPP and QA were added in 0.25 ml of 0.5 M potassium phosphate buffer, pH 7.0. Extract in 0.05 M potassium phosphate, pH 7.0. Center well contained 0.3 ml 10% NaOH; rotatable sidearm contained 0.42 ml 60% (w/v) perchloric acid (PCA). Incubation was in air at 37°C. Zero time samples were treated with PCA before addition of QA. Incubation continued for 30 min after acid tip to assure complete collection of CO₂.

- Not treated with Sephadex.
- Transplantable spontaneous malignant pituitary tumor of rat.

3HAA Utilization in Vitro

Incubation of extracts of liver acetone powder with 3HAA resulted in the rapid formation of a compound absorbing at 360 mμ as described by Bokman and Schweigert (2). On the other hand, tumor cell extracts prepared in an identical fashion completely failed to catalyze formation of this compound or disappearance of 3HAA. The presence of tumor extract did not inhibit the activity of liver extract or catalyze the disappearance of the material formed in the presence of liver extract.

Utilization of Quinolinic Acid-14C in Vivo

The effectiveness of quinolinic acid as a precursor of NAD was assessed in two independent experiments (Table 4). The evolution of 14CO₂ in both experiments (0.32% in Experiment...
A and 0.80% in Experiment B of the injected radioactivity) indicated that the compound was metabolized. Since the specific activity of CO₂ evolved by the mechanism described by Ghoshal et al. (5) would theoretically be only 25% of that of the injected quinolinic acid, the amounts of ¹⁴CO₂ listed represent the decarboxylation of approximately 1.0 and 2.5 μmoles of quinolinic acid in Experiments A and B respectively. Urinary excretion accounted for 37% and 32% of the respective injected radioactive activity. The nature of the labeled compounds in urine was not investigated. In Experiment B, six to ten times as much radioactivity appeared in the tissues, although the amount of radioactivity injected had been calculated to be only twice as great. There is no obvious explanation for this unexpectedly large difference. In both experiments, however, the concentration of radioactivity in liver and tumor cells approached that in the ascitic plasma, indicating that quinolinic acid passed freely into tumor cells and the portal circulation. Therefore, the differences in distribution of radioactivity between tissues noted in Table 5 cannot be ascribed to lack of available precursor in tumor cells. In both experiments the largest radioactive component present in liver extracts was NAD (Table 5). Nicotinamide was also significantly labeled. On the other hand, the NAD which was recovered from tumor cells in expected amounts was not labeled. The radioactivity in tumor cell extracts was all accounted for as unused precursor. The specific activities of NAD isolated from liver were 25% and 22% of that of the injected quinolinic acid in Experiments A and B respectively; these values are 33% and 29% of the maximum specific activities possible, assuming the loss of one labeled carboxyl group and no isotope dilution.

Utilization of Quinolinic Acid-¹⁴C in Vitro

Because the conversion of quinolinic acid-2,3,7,8-¹⁴C to nicotinic acid mononucleotide involves the liberation of one mole of ¹⁴CO₂, the rate of this decarboxylation can be examined in extracts of acetone powders of various normal and tumor tissues (Table 6). Mouse liver and kidney possess considerable activity, and small amounts of activity are observed in Walker and LL-6 tumors. It is clear, however, that the distribution of the enzyme is limited, and that the tumors examined are not highly active in utilizing quinolinic acid.

DISCUSSION

Tryptophan was shown to be an effective precursor of the nicotinamide moiety of NAD in host liver. The NAD content of liver was significantly increased by administration of large doses of tryptophan, and labeled tryptophan was extensively incorporated into the nicotinamide moiety of NAD. The specific activity of the isolated NAD was approximately 2% of that of the injected precursor, a value which is of the same order of magnitude as values obtained using tracer doses of nicotinamide (13). In contrast to liver, ascites cells appear to utilize tryptophan poorly for NAD synthesis. Tryptophan was ineffective in stimulating NAD synthesis in dosage experiments, and labeled tryptophan was only minimally incorporated into NAD, the specific activities of tumor NAD being only 1.7% and 3.9% of the values for liver NAD in two experiments. This situation should be contrasted with observations previously described (13, 18) which indicated that tumor cells use nicotinamide and nicotinic acid for NAD synthesis at rates which compare favorably with those prevailing in liver.

The difference between liver and tumor in utilization of tryptophan could result from a number of factors. One possibility was that tryptophan was more rapidly taken up by the portal circulation and liver cells than it was by the ascites cells. The isotope experiments in which similar concentrations of acid-soluble radioactivity were found in tumor cells, ascites plasma, and liver provided evidence that this was not an important factor. The high concentration of acid-soluble radioactivity in tumor also implies that tryptophan was not used so rapidly for protein synthesis in tumor cells as to be unavailable for other processes. Although radioactivity appeared in unidentified compounds eluted from the column, none appeared to be disproportionately large in tumor compared with liver; the largest amount of radioactivity was present in the fraction containing unused precursor.

Another possible explanation of the observed difference between ascites cells and host liver is that one or more of the reactions involved in the conversion of tryptophan to NaeMN proceeds at a slower rate in ascites cells. Auerbach and Waisman (1), Cho et al. (4), and others have shown that tumors arising from liver tissue appear to be deficient in the enzyme tryptophan pyrrolase, which initiates the conversion of tryptophan to nicotinamide. The present study has shown that subsequent steps in the reaction sequence are reduced or absent in Ehrlich ascites cells. Traces of 3HAA were found following the administration of labeled tryptophan, but the utilization of 3HAA was not demonstrable. Quinolinic acid, which is an effective precursor of NAD in liver, is completely inert in ascites cells, although it penetrates the cells. This failure of quinolinic acid to act as a precursor of NAD excludes the possibility that proximal metabolic products of tryptophan metabolism in liver could serve as precursors of pyridine nucleotides in ascites cells.

The impaired utilization of 3HAA and quinolinic acid in the tumor is of interest, since Boyland (3) and others have suggested that 3HAA may play an etiologic role in bladder tumors, and Kerr et al. (11) showed that a kidney bearing a hypernephroma produced more 3HAA than did the contralateral normal kidney. The Ehrlich ascites carcinoma may be an example of a tumor that produces 3HAA but fails to use it efficiently.

The presence of traces of radioactivity in NAD in in vivo experiments with tryptophan-¹⁴C suggests that the overall tryptophan → NaeMN pathway may proceed at a very slow rate in ascites cells in vivo. It is possible, however, that tumor NAD was labeled by another mechanism, perhaps by the utilization of labeled nicotinamide formed in liver. The finding in tumor of radioactivity associated with nicotinamide which was small with respect to liver nicotinamide but large with respect to tumor NAD is consistent with the operation of this latter mechanism.

Liver utilizes both preformed nicotinic acid and nicotinamide and tryptophan for synthesis of pyridine nucleotides, while tumors appear to be restricted to the use of preformed niacin. This condition suggests the possibility that the toxicity of niacin analogs in vital host tissues in the model tumor-host
system under investigation might be alleviated by dosage with tryptophan, while the tumor would remain vulnerable to attack. Preliminary experiments with 6-aminonicotinamide appear to support this hypothesis.

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REFERENCES

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