Physiological Disposition of Pentobarbital in Tumor-bearing Mice

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SUMMARY

Pentobarbital depressed macromolecular synthesis in Ehrlich ascites cells in vitro, and this depression was proportional to a decrease in oxygen consumption. However, survival time of animals bearing Ehrlich ascites cells was unaffected by pentobarbital. The acute toxicity of the drug was greatly enhanced by the presence of the tumor. Sleeping time was prolonged in mice carrying the following tumors: Ehrlich ascites, Sarcoma 180 ascites, and Yancey plasma cell solid. Seven-day Ehrlich ascites tumor-bearing animals treated with pentobarbital slept about three times longer than normal mice, but both groups awoke at the same plasma levels of the unbound drug. The plasma half-life of unchanged pentobarbital was about four times as long in tumor-bearing mice as it was in controls. No qualitative difference in catabolism other than rate was detected. Renal excretion of unchanged pentobarbital in tumor-bearing animals was 50% of control animals during the first 4 hr. In tumor-bearing mice the sleeping time of the nonmetabolizable barbiturate, barbital, was identical with that in normal animals. These data suggest that the tumor affected mainly pentobarbital metabolism. Tumor-bearing mice still responded to the pharmacological challenge of phenobarbital with the apparent induction of drug metabolizing enzymes. The prolonged pentobarbital sleeping time in tumor-bearing mice required the development of some type of tumor-host relationship.

INTRODUCTION

There have been numerous studies suggesting that barbiturates and other anesthetic, narcotic, and tranquilizing drugs are cytotoxic or antimitotic in many diverse organisms and cell types (cf. Ref. 2 for a review). Pentobarbital has been reported specifically to inhibit DNA synthesis in Ehrlich ascites cells (4), and hydrogen bonding between barbiturates and substituted purine bases has been demonstrated in vitro (24, 25). Our interest in the barbiturates as structural analogs of pyrimidines in microorganisms (26-28) led us to reexamine these inhibitory effects of barbiturates in order to determine their potential usefulness as antitumor agents.

During these studies it became apparent that the pharmacological actions of pentobarbital were greatly enhanced in tumor-bearing compared to normal mice, as had been reported for other drugs (14, 22, 29, 34-36, 44, 45). Since this altered response frequently was based on impaired drug metabolism, it also became of interest to characterize the role of tumor growth on the pharmacokinetics of pentobarbital (5).

This paper presents evidence that pentobarbital does inhibit DNA synthesis in Ehrlich ascites cells in vitro, but the effect is not specific and the drug acts as a general metabolic depressant. The drug is more toxic to Ehrlich ascites tumor-bearing mice than to normal mice and this toxicity is primarily related to impaired drug metabolism, a consequence of the development of a tumor-host relationship.

MATERIALS AND METHODS

Animals and Tumors. Male Swiss albino ICR mice weighing 25 to 35 g were used in all metabolism studies and to carry the Ehrlich and Sarcoma 180 ascites tumors. The mice were obtained either from Hazelton-Cardina, Inc., Burtonville, Md., or from Flow Laboratories, Rockville, Md. All animals were kept in plastic cages and fed a standard Purina laboratory chow diet (Ralston-Purina Co., St. Louis, Mo.) and water ad libitum. The Ehrlich ascites carcinoma has been maintained in this laboratory for 8 years and was originally obtained from the Department of Pharmacology, Yale University, New Haven, Conn. The tumor was transplanted to mice routinely every 6 days by i.p. injection of approximately 1 million washed cells. The mean survival time of the tumor-bearing animals was 12.9 days, considering the day of transplantation as Day 0. We carried these cells through 132 serial transplantations during the course of these experiments. The Sarcoma 180 ascites tumor has been maintained in this laboratory for the past 5 years and was also obtained from the Department of Pharmacology, Yale University. This tumor was maintained in the same way as the Ehrlich ascites tumor. BALB/c x A F, mice carrying the Yancey plasma cell solid tumor were the generous gift of Dr. Richard H.
The peritoneal cavity of mice, washed, freed of blood by synthesis; [2-14C]uridine incorporation was a measure of Gornall et al. (16). Activity on membrane filters according to the method of different concentrations and the appropriate isotopic nucleic manometric techniques described by Umbreit et al. (40). Protein was estimated by the biuret reaction as described by Ehrlich ascites cells was linear over the period of study in (55.5 mCi/mmole), L-[3-14C]leucine (254 mCi/mmole), [2-14C]uridine (43.7 mCi/mmole), [2-14C]thymidine (41.3:1.5, by volume), containing naphthalene (6%), PPO (0.4%), and POPP (0.02%). Radioactivity was measured in a Beckman DPM-100 liquid scintillation spectrometer. Counting efficiency was determined by the external standard method of Wang and Willis (41). The efficiency for 14C ranged between 60 and 88%.

Incorporation of Radioactivity by Ehrlich Ascites Cells Incubated in Vitro. Ehrlich ascites cells were obtained from the peritoneal cavity of mice, washed, freed of blood by differential hemolysis (11), and suspended in calcium-free buffer (33), pH 7.4, to an approximate concentration of 1 million cells/ml. This buffer also contained pentobarbital at different concentrations and the appropriate isotopic nucleic acid or protein precursor. The cell suspensions were then incubated at 37°C in separate flasks in a shaking water bath, and aliquots were removed at 30-min intervals throughout a 2-hr period. The cells in these aliquots were precipitated with cold 10% trichloroacetic acid and analyzed for radioactivity on membrane filters according to the method of Brown et al. (9). It was ascertained that [2-14C]thymidine incorporation into acid precipitates was an index of DNA synthesis; [2-14C]uridine incorporation was a measure of RNA synthesis; and L-[U-14C]leucine was an index of total protein synthesis. Incorporation of these precursors into Ehrlich ascites cells was linear over the period of study in the absence of drug.

Oxygen consumption of washed Ehrlich ascites cells was measured in a Warburg apparatus according to the standard manometric techniques described by Umbreit et al. (40). Protein was estimated by the biuret reaction as described by Gornall et al. (16).

Estimation of Sleeping Time in Mice. Sleeping time was defined as the time between the loss and return of the righting reflex after an i.p. injection of either pentobarbital (60 mg/kg) or barbital (300 mg/kg). In some experiments, the dose of pentobarbital to tumor-bearing mice was based on the body weights on the day after tumor transplantation. The animal was considered to have lost its righting reflex when it could no longer turn itself over after being placed on its back. Conversely, the mouse was deemed to have regained its righting reflex when it could right itself 4 times within 2 min.

The Fate of [2-14C]Pentobarbital in Mice Bearing the Ehrlich Ascites Tumor. Mice bearing the Ehrlich ascites tumor 7 days after transplantation of approximately 1 million cells and their normal controls were given i.p. injections of [2-14C]pentobarbital (60 mg/kg; 333 μCi/kg). At intervals, usually 30, 60, 90, 120, 150, or 240 min after dosing, blood was drawn from the periorbital space using heparinized capillary tubes according to the method of Riley (32), and plasma was obtained by centrifugation. Ten-μl samples of plasma were transferred to individual scintillation vials and counted for radioactivity as previously described. The metabolism of [2-14C]pentobarbital was determined by chromatographic separation of [2-14C]pentobarbital from its radioactively labeled metabolites in both plasma and urine. Normal and 7-day Ehrlich ascites tumor-bearing mice were given injections of [2-14C]pentobarbital and plasma was obtained at intervals as described previously. Urine was collected in the following manner. After a dosing with [2-14C]pentobarbital, the anesthetized mice were placed on separate grids over 600-ml beakers. After 240 min, the mice were sacrificed, the bladders were removed, and the urine was added to any urine already in the beakers. The total volume of urine plus water used to wash the beakers was recorded. Ten μl of plasma or urine were chromatographed with 150 μg of carrier pentobarbital on Whatman No. 3 paper at 20–25°C using the solvent system of Titus and Weiss (38) [n-butyl alcohol: 1% ammonium hydroxide (1:1, v/v)]. The chromatogram was developed by the descending technique for about 12 hr during which time the solvent front moved 30 to 40 cm. In this system unchanged pentobarbital migrated near the front (Rf 0.9), whereas the more polar metabolites of pentobarbital remained closer to the origin. After development, the chromatograms were cut accordingly by the RF’s for each sample and counted for total radioactivity. The radioactivity for each block was recorded, and the total radioactivity on the chromatogram was then estimated. After correction for background, the 14C activity associated with unchanged pentobarbital was calculated as a percentage of the total. The absolute amount of unchanged pentobarbital thus identified in plasma was calculated from its specific activity.

Plasma Protein Binding of Pentobarbital. The determination of plasma protein binding of pentobarbital was carried out by a modification of the method of Toribara et al. (39). One-ml aliquots of plasma from normal and tumor-bearing mice were incubated for 1 hr at 37°C with 1 μCi of [2-14C]pentobarbital at the concentration of 2.0 × 10−4 m. After incubation the tubes were chilled on ice and 0.5-ml aliquots of the plasma were inserted into dry, opened

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dialysis bags. The bags were bent in a U-shape with the plasma at the bottom and placed in stoppered centrifuge tubes with the ends of the bags held in place by the stoppers. These tubes were then centrifuged for 3.5 hr at 1000 x g at 4°. Ten-μl aliquots of both the ultrafiltrate and the fluid retained in the bags were placed in separate scintillation vials and counted for radioactivity. The percentage of pentobarbital bound to the plasma protein was determined by the following formula:

\[
\% \text{ of pentobarbital bound} = [1 - (\text{cpm in ultrafiltrate})/(\text{cpm in fluid retained})] \times 100
\]

RESULTS

The Cytotoxicity of Pentobarbital in Ehrlich Ascites Cells in Vitro. Baserga and Weiss (4) reported that pentobarbital specifically inhibited DNA synthesis in Ehrlich ascites cells. Our results indicate a progressive inhibition of incorporation of precursor into macromolecules, and of oxygen consumption in Ehrlich ascites cells incubated in vitro with pentobarbital (Chart 1). In addition, a close quantitative relationship was found to exist between the drug-induced decrease in oxygen consumption and the incorporation of [2-14C]thymidine, [2-14C]uridine, or L-[U-14C]leucine into DNA, RNA, or protein, respectively, as the concentration of pentobarbital in the incubation medium was increased (Chart 2). The data suggest that the in vitro depression by pentobarbital of radioactivity incorporated into the DNA, RNA, and protein of the Ehrlich ascites cells was secondary to the well-known depressant effects of the drug on cellular metabolism, thus contrasting with the findings of Baserga and Weiss (4).

Effect of Pentobarbital on Tumor Growth. To determine whether these effects of pentobarbital on macromolecular synthesis of ascites cells could be exploited for chemotherapy, the drug was tested for carcinostatic activity. Pentobarbital at 3 different dose levels did not prolong the survival of these Ehrlich ascites tumor-bearing mice (Table 1). In fact, the survival decreased with increasing daily doses of the drug. Furthermore, the weight of the Ehrlich ascites cells recovered from 7-day tumor-bearing mice was not decreased by pentobarbital treatment, being 1.38 ± 0.21 and 1.26 ± 0.13 (in g ± S.E.) for the 0.9% NaCl solution- and drug-treated animals, respectively.

The Toxicity of Pentobarbital in Mice with the Ehrlich Ascites Tumor. In normal mice the acute i.p. lethal dose to 50% of the animals of pentobarbital was 125 mg/kg, a value that is similar to those reported in the literature (10, 18, 42). In mice with the 7-day Ehrlich ascites tumor the corresponding dose was 78 mg/kg, a reduction of approximately 40% (Chart 3).

When normal or mice bearing 3-, 5- or 7-day tumors were given injections i.p. of pentobarbital (60 mg/kg), both groups of animals lost the righting reflex within 3 to 4 min. However, following pentobarbital treatment, the sleeping time of mice with this tumor 7 days after transplantation was nearly 2.5 times that of normal mice similarly treated (Table 2). Furthermore, it is also seen in Table 2 that this increase in pentobarbital sleeping time was not unique for

* Mean ± S.E.
mice with the Ehrlich ascites tumor but also occurred in mice with the Sarcoma 180 ascites tumor or the solid Yancey plasma cell tumor. In all cases, the prolongation of sleeping time became more manifest in the advanced stages of tumor growth.

The Fate of Pentobarbital in Ehrlich Ascites Tumor-bearing Mice. After i.p. administration of [2-14C]pentobarbital to Ehrlich ascites tumor-bearing mice, the radioactivity in the peritoneal fluid was greater than that in the plasma at 30 min, but at 90, 150, and 240 min after dosing it reached equilibrium values of about 0.9 (Chart 4A). The distribution ratio of radioactivity between ascites fluid and ascites cells was about 1.3 during this time period (Chart 4B).

Normal mice cleared total radioactivity and unchanged pentobarbital from the plasma faster than did the tumor-bearing mice (Table 3). Thus, by 4 hr after dosing, only 12% of the 30-min 14C levels remained in the plasma of normal mice, whereas for tumor-bearing animals the corresponding level of radioactivity was still 67%. The plasma half-lives for total radioactivity were 61 and 370 min for the normal and tumor-bearing mice, respectively. For unchanged pentobarbital in the plasma after 4 hr, the concentration was only 2% of the 30-min plasma level in normal mice, but for tumor-bearing mice 26% of the 30-min value remained. The half-lives of the unchanged drug were 37 and 127 min in these animals, respectively.

Chart 3. Acute i.p. lethal dose to 50% of the animals of pentobarbital in mice with the Ehrlich ascites tumor. O, normal mice; x, tumor-bearing mice. The probit transformation and values for lethal dose to 50% of the animals were determined as described in the textbook of Goldstein et al. (15). Seven days after an i.p. injection of 10⁶ Ehrlich ascites cells or a corresponding volume of 0.9% NaCl solution to normal mice, animals (5/group) were given injections of pentobarbital at the doses indicated. Other tumor-bearing mice were not given injections and they served as controls. Twelve hr after the mice were dosed, the cages were inspected and the fraction of dead animals per group was recorded.

Table 2
Pentobarbital sleeping times in normal and tumor-bearing mice
On the days indicated, all mice (10/group) received an i.p. injection of pentobarbital (60 mg/kg) and the sleeping times were recorded.

<table>
<thead>
<tr>
<th>Experiment</th>
<th>Tumor</th>
<th>Day</th>
<th>Normal mice</th>
<th>Tumor-bearing mice</th>
<th>% control</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Ehrlich ascites</td>
<td>3</td>
<td>81 ± 9</td>
<td>84 ± 7</td>
<td>104</td>
</tr>
<tr>
<td></td>
<td></td>
<td>5</td>
<td>73 ± 7</td>
<td>93 ± 7</td>
<td>128</td>
</tr>
<tr>
<td></td>
<td></td>
<td>7</td>
<td>66 ± 9</td>
<td>159 ± 26</td>
<td>241</td>
</tr>
<tr>
<td>2</td>
<td>Sarcoma 180 ascites</td>
<td>3</td>
<td>53 ± 6</td>
<td>53 ± 6</td>
<td>100</td>
</tr>
<tr>
<td></td>
<td></td>
<td>5</td>
<td>42 ± 6</td>
<td>60 ± 8</td>
<td>143</td>
</tr>
<tr>
<td></td>
<td></td>
<td>7</td>
<td>46 ± 6</td>
<td>74 ± 4</td>
<td>161</td>
</tr>
<tr>
<td>3</td>
<td>Yancey plasma cell</td>
<td>3</td>
<td>64 ± 3</td>
<td>61 ± 4</td>
<td>95</td>
</tr>
<tr>
<td></td>
<td>solid</td>
<td>5</td>
<td>52 ± 5</td>
<td>60 ± 8</td>
<td>115</td>
</tr>
<tr>
<td></td>
<td></td>
<td>7</td>
<td>43 ± 6</td>
<td>150 ± 13</td>
<td>349</td>
</tr>
<tr>
<td></td>
<td></td>
<td>11</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

* Mean ± S.E.
Animals were given i.p. injections of pentobarbital (60 mg/kg body weight and containing 10 μCi[2-14C]pentobarbital). Blood was drawn from the periorbital space into heparinized capillary tubes at the times indicated. Plasma was obtained by centrifugation. Plasma aliquots were counted for total radioactivity and were spotted on Whatman No. 3 paper for chromatography as described in "Materials and Methods."

Table 3

<table>
<thead>
<tr>
<th>Time after dosing (min)</th>
<th>Control mice</th>
<th>Tumor-bearing mice</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Total plasma ¹⁴C radioactivity (dpm ± 10⁻⁶/ml)</td>
<td>% of plasma associated with metabolites</td>
</tr>
<tr>
<td>30</td>
<td>6.36 ± 0.35a</td>
<td>27.5 ± 9.0</td>
</tr>
<tr>
<td>90</td>
<td>4.24 ± 0.63</td>
<td>72.5 ± 3.3</td>
</tr>
<tr>
<td>150</td>
<td>2.27 ± 0.56</td>
<td>85.9 ± 0.7</td>
</tr>
<tr>
<td>240</td>
<td>0.78 ± 0.18</td>
<td>89.0 ± 0.5</td>
</tr>
<tr>
<td>Plasma tₜ₀ (min)</td>
<td>61</td>
<td>37</td>
</tr>
</tbody>
</table>

a Mean ± S.E.

During the 4 hr following treatment with [2-¹⁴C]pentobarbital, the urine of control mice contained 81.7 ± 4.5% of the administered radioactivity. However, mice bearing the 7-day Ehrlich ascites tumor appeared to eliminate less of the total dose of radioactivity via the urine, since only 37.3 ± 7.5% of the administered radioactivity was recovered in the urine. The chromatographic profiles of the urines were similar in both groups of animals, and unchanged pentobarbital represented about 22 and 24% of the total radioactivity in the urine in the control and tumor-bearing mice, respectively. Therefore, the urinary excretion of unchanged pentobarbital was 14.5% of the administered dose in the control mice, whereas for the tumor-bearing mice it was 6.8%.

Waking Plasma Levels of Pentobarbital in Control and Ehrlich Ascites Tumor-bearing Mice following Administration of [2-¹⁴C]Pentobarbital. Although the time required for the return of the righting reflex in tumor-bearing animals was approximately 3 times greater than that observed in control mice, the plasma levels of pentobarbital or its labeled metabolic products at the return of the righting reflex in control and tumor-bearing mice were similar (Table 4). Approximately 50% of the total radioactivity at this time was unchanged pentobarbital in both groups of mice. The plasma protein concentrations were 6.6 and 5.4 g/100 ml in normal and 7-day tumor-bearing animals, respectively, and the percentages (±S.E.) of [2-¹⁴C]pentobarbital bound to the plasma protein were 56.2 ± 1.2 and 35.8 ± 5.4 in normal and tumor-bearing mice, respectively. Thus, when the concentration of pentobarbital in plasma was corrected for the fraction of the drug bound, it was found that the waking level of unchanged pentobarbital in the plasma was identical in control and tumor-bearing mice (Table 4).

Barbital Sleeping Times in Mice with the Ehrlich Ascites Tumor. In order to distinguish between the roles of metabolism and urinary excretion of drugs in tumor-bearing mice, barbital was used as a comparison since it is excreted almost entirely unchanged by the kidneys (12). Therefore, the sleeping time with this drug depends primarily upon its rate of elimination via the kidney. Control and Ehrlich ascites tumor-bearing mice given injections i.p. of barbital (300 mg/kg) slept for the same length of time whereas, after pentobarbital, 7-day tumor-bearing mice slept approximately 2.5 times longer than did controls (Table 5).

Effect of Phenobarbital Pretreatment on Sleeping Time in Tumor-bearing Mice. Ehrlich ascites tumor-bearing ani-

Table 4

<table>
<thead>
<tr>
<th>Animals</th>
<th>Time for return of the righting reflex (min)</th>
<th>Radioactivity (dpm × 10⁻⁶/ml)</th>
<th>% identified as pentobarbital</th>
<th>Pentobarbital (µg/ml)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal mice</td>
<td>41 ± 7a</td>
<td>6.15 ± 0.38</td>
<td>58.4 ± 5.4</td>
<td>29.8 ± 2.6</td>
</tr>
<tr>
<td>Tumor-bearing mice</td>
<td>153 ± 35</td>
<td>5.36 ± 0.17</td>
<td>49.7 ± 1.9</td>
<td>21.0 ± 0.7</td>
</tr>
</tbody>
</table>

a Mean ± S.E.
demonstrated that the increased sleeping time could not be related to an immediate effect of the tumor but instead depended on the development of some type of tumor-host relationship.

**DISCUSSION**

We have shown that the *in vitro* incorporation of precursors into DNA, RNA, and protein was inhibited by pentobarbital to the same extent as oxygen consumption, indicating that the effect on incorporation was nonspecific and related to general inhibition of metabolism. These results contrast with the interpretation of Baserga and Weiss (4). Whyatt and Cramer (43) demonstrated equivalent inhibitory effects of pentobarbital on DNA, RNA, and protein synthesis, although these authors carried out their incubations anaerobically. Concentrations of pentobarbital that inhibited DNA, RNA, and protein synthesis in the Ehrlich ascites cells *in vitro* could not be achieved *in vivo* without significant toxicity to the host. The plasma levels of pentobarbital *in vivo* (&lt;0.2 mm) would not be expected to affect macromolecular synthesis.

There are relatively few investigations in which the pharmacology of a drug has been compared in tumor-bearing and normal animals. Early studies indicated that urethan metabolism was impaired by the presence of a tumor in rodents (7, 30, 37), and sleeping time in rats was prolonged when a hepatic tumor had been induced (1). These effects were ascribed to an enzyme deficiency resulting from tumor growth. Indeed, Kato et al. (23) demonstrated that both *in vitro* microsomal drug-metabolizing enzyme activity and the components of the NADPH-linked electron transport system were depressed in hepatic microsomes from tumor-bearing rats when compared with controls.

In these experiments, the increased pentobarbital toxicity in mice bearing the Ehrlich ascites tumor was related to a decreased rate of plasma disappearance of drug in these animals. The persistently high percentage of unchanged pentobarbital in the tumor-bearing animals seen after treatment with [2-14C]pentobarbital was most likely related to a decreased metabolism of the drug. Decreased hepatic metabolism has been observed not only for pentobarbital but also for hexobarbital, strychnine, mebrobamate, progesterone, testosterone, octamethylpyrophosphoramide, carisoprodol, aniline, *p*-nitroanisole, amphetamine, aminopyrine, *N*-methylaniline, codeine, benzpyrene, *p*-nitrobenzoic acid, and neoprontosil *in vitro* and *in vivo* in tumor-bearing animals (14, 20-23, 34-36, 44, 45). We are not aware of other compounds studied in this manner. There was no difference, however, in sleeping times of tumor-bearing and normal mice following administration of the nonmetabolizable barbiturate, barbital. This observation supports our conclusion that the observed differences in sleeping time following pentobarbital were due to impaired metabolism in tumor-bearing animals, rather than other changes in the physiological disposition (such as excretion) of pentobarbital.

Other factors have been implicated in the alteration by the tumor of the action of drugs. In this study these factors

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**Table 5**

Pentobarbital and barbital sleeping times of normal and Ehrlich ascites tumor-bearing mice

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Day of tumor</th>
<th>Normal mice</th>
<th>Tumor-bearing mice</th>
<th>% control</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pentobarbital</td>
<td>5</td>
<td>73 ± 7*</td>
<td>93 ± 7</td>
<td>128</td>
</tr>
<tr>
<td></td>
<td>7</td>
<td>66 ± 9</td>
<td>159 ± 26*</td>
<td>241</td>
</tr>
<tr>
<td>Barbital</td>
<td>5</td>
<td>447 ± 62</td>
<td>456 ± 39</td>
<td>102</td>
</tr>
<tr>
<td></td>
<td>7</td>
<td>467 ± 73</td>
<td>467 ± 51</td>
<td>100</td>
</tr>
</tbody>
</table>

* Mean ± S.E.  
* p < 0.01

**Table 6**

Pentobarbital sleeping times of mice 2 hr after i.p. injection of Ehrlich ascites cells

See text for experimental details.

<table>
<thead>
<tr>
<th>Group</th>
<th>Treatment</th>
<th>Sleeping time (min)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>None</td>
<td>95 ± 11*</td>
</tr>
<tr>
<td>2</td>
<td>0.9% NaCl solution (2.5 ml)</td>
<td>84 ± 13</td>
</tr>
<tr>
<td>3</td>
<td>Tumor cell suspension (2.5 ml)</td>
<td>77 ± 9</td>
</tr>
<tr>
<td>4</td>
<td>7-day tumor-bearing mice</td>
<td>178 ± 32</td>
</tr>
</tbody>
</table>

* Mean ± S.E.
have been examined for their contribution to the exaggerated response of tumor-bearing animals to pentobarbital. A significant difference in brain sensitivity to the anesthetic effect of pentobarbital in the 2 groups of animals has been reported previously (13, 36). However, in our experiments, since the waking levels of pentobarbital in tumor-bearing and control animals were almost identical, we are forced to exclude this possibility. The mere presence of the tumor per se, as suggested by Mattes et al. (29), did not prolong sleeping time following pentobarbital administration, since a period of time after tumor implantation was required before the sleeping time was significantly increased. Therefore, some type of tumor-host relationship was involved in developing the inhibition of drug metabolism.

In these experiments, and those of others (22, 36), induction of microsomal enzymes by phenobarbital was still demonstrable in tumor-bearing animals, thus suggesting that the tumor effect on metabolism is not irreversible. Therefore, if a tumor-produced substance is responsible for the depressed metabolism (6, 17, 19, 21, 31, 46), its action can be counteracted. Rosso et al. (36) and Bartosek et al. (3) have recently presented evidence suggesting that there may be some factor in the serum of tumor-bearing rats that can apparently depress hepatic drug metabolism.

REFERENCES

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