Effect of 6-Azauridine on Plasma Cell Tumors of Mice: Correlation of Antitumor Effect with Inhibition of Orotic Acid Metabolism

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SUMMARY

This investigation was undertaken to correlate the antineoplastic effects of 6-azauridine (AzUR) with the activity of orotic acid metabolism and its inhibition in vitro by AzUR in a series of plasma cell tumors of mice. Although AzUR suppressed tumor growth only moderately and to widely different degrees in different tumors, its antitumor effects in vivo appeared to follow its inhibition of orotic acid metabolism in vitro. It was noted that after initial suppression of orotic acid metabolism, enzyme activity returned to pretreatment levels despite continuation of AzUR. The simultaneous administration of AzUR with urethan, which was a much more potent agent than AzUR in murine plasma cell tumors, did not augment their individual effects.

These investigations suggest that the in vitro inhibition of orotic acid metabolism by AzUR may permit the selection of tumors susceptible to AzUR therapy. The development of enzymatic adaptation to continuous AzUR therapy suggests that intermittent, combined, or alternate therapy may enhance the antineoplastic effect of AzUR.

The use of a spectrum of transplantable plasma cell tumors of mice provides an experimental model for attempts to correlate specific biochemical characteristics with the antineoplastic effects of chemotherapeutic agents.

INTRODUCTION

6-Azauridine (AzUR) suppresses the de novo pathway of pyrimidine biosynthesis by inhibition of orotic acid metabolism (17, 19, 20, 34). This triazole analog of uracil riboside, which has little or no toxicity for normal human cells (21), exerts its effect by the competitive inhibition of orotidylate decarboxylase (Chart 1). Previous studies have suggested that AzUR inhibits the growth of those tissues which have high orotidylate decarboxylase activity, and that the development of resistance during therapy with AzUR appears to be associated with an adaptive increase in the de novo pathway of pyrimidine biosynthesis (17, 21).

The observation of a high level of orotic acid metabolism in the leukocytes of a patient with plasma cell leukemia (8) suggested that AzUR might be particularly effective against plasma cell tumors.

The recent development of a variety of transplantable plasma cell tumors of mice by Potter and his associates at the National Cancer Institute (11, 16, 27, 36, 38) has provided an experimental model for the study of plasma cell neoplasms. Some of these murine tumors synthesize abnormal homogeneous plasma proteins of individual electrophoretic mobility and physicochemical characteristics (16, 27, 36, 38). Others mimic human myelomatosis by producing osteolytic bone lesions typical of multiple myeloma (36) or an abnormal Bence-Jones-like urinary protein and renal lesion similar to the "myeloma kidney" of man (15). Like plasma cell tumors of man, no two of these murine tumors are precisely alike and each produces a unique paraprotein (13, 35, 37). This diversity simulates the spectrum of plasma cell neoplasms of man (31, 39) and provides an ideal series of plasma cell variants for testing antineoplastic agents. The demonstration that AzUR inhibited the growth of one type of murine plasma cell tumor (23) encouraged this project.

None of the presently available chemotherapeutic agents are consistently effective in the treatment of multiple myeloma (2, 29) with the possible exception of L-phenylalanine mustard (45). Although beneficial results have been reported in some patients after prolonged and intensive therapy with urethan (26, 30), controlled studies have failed to confirm these observations (24). In mice urethan has proved effective against some types of plasma cell tumors and ineffective against others (H. O. Conn, unpublished observations). While the precise mechanism of action of urethan is unknown, several experimental studies have suggested that this compound may affect the formation of the pyrimidine nucleus (10, 40, 44, 47), thereby interfering with the synthesis of orotic acid and subsequently of nucleic acids. The proximity of this metabolic block to the site of action of AzUR suggested the possibility that the administration of urethan might enhance the effect of AzUR, a compound to which clinical resistance rapidly develops (10, 21).

The study was undertaken to evaluate the antitumor effect of AzUR and urethan in a spectrum of plasma cell tumors of mice, and to correlate the antitumor effect of AzUR with the metabolism of orotic acid by various tumors.

MATERIALS AND METHODS

Plasma cell tumors, X-5563, X-5647, and SPC-1, which had been transferred continuously for many generations in C3Hf/Lw mice, were transmitted by s.c. implantation to C3H/101 mice.
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8-10 weeks old, which had been previously irradiated (200 R). Plasma cell tumors MPC-1 and MPC-2 were transplanted into 6- to 12-week-old BALB/c mice that had not previously been irradiated. In all instances fragments of tumor approximately 2 mm in diameter were transplanted into the right axillary region. The mice received standard Purina laboratory chow diet. All animals were weighed and examined for palpable tumors at weekly intervals during each experiment. Serum electrophoretic patterns were performed weekly on blood obtained by retrobulbar aspiration from representative mice in each treatment group. Studies of serum proteins were carried out by methods previously reported from this laboratory (9). Pooled urine samples were collected by manual expression from each treatment group of mice with MPC-2 tumors and Bence-Jones protein was measured. At the conclusion of each experiment the mice were examined, weighed, and sacrificed by exsanguination. Tumors were excised and promptly weighed. Appropriate chemical, hematologic, and histologic studies were performed. The antitumor activity of the chemotherapeutic agents was based on postmortem tumor weight. Statistical significance was determined by Student's unpaired "t" test.

Treatment was begun 24 hr after implantation of tumor. Each experiment included a control group, which received water, and treatment groups, which received AzUR, urethan, or a combination of the two drugs. All drugs were administered in the drinking water ad libitum. AzUR is not hydrolyzed to azauracil in the murine gastrointestinal tract (23). The mice ingested an average of 3 ml of water or of the solution of chemotherapeutic agent daily. This figure, which is in close agreement with previous estimates (23), was obtained by direct measurement of the volume consumed for each cage of mice and corrected for evaporation and other losses. All dosages were based on the daily ingestion of 3 ml per mouse and calculated as mg/kg/day.

Orotic acid metabolism was measured by incubating plasma cell tumor slices (50-80 mg) for one hour in 1.5 ml Krebs III buffer in the presence of 0.15 µmole of orotic acid-7-14C (1 µC/µmole). Under these conditions the decarboxylation continued linearly for at least one hour. The 14CO₂ was trapped in 0.2 ml of 2 N NaOH in the center wells of Warburg reaction vessels (8, 10). Radioactivity in 0.1-ml aliquots was measured with a Packard Tri-Carb liquid scintillometer. The mice were sacrificed by decapitation, the tumors excised and immediately sliced freehand, and slices added to the prepared vessels. Simultaneously, the effect of AzUR in vitro on orotic acid metabolism was determined after adding 0.05 µmole/ml AzUR to the reaction mixture and incubating for 15 minutes before addition of orotic acid-7-14C. All assays were performed in duplicate, and several mice with each plasma cell tumor were studied on at least two occasions.

To study the phenomenon of AzUR resistance, orotic acid metabolism in X-5563, MPC-1, and MPC-2 tumors was studied before AzUR administration, after 1 and 5 days of AzUR, and again after AzUR had been discontinued for 24 hours. The times of initiation of AzUR administration were staggered so that all
mice in these experiments, which were of the same age and sex and had been implanted with fragments of the same tumor at the same time, could be analyzed simultaneously. The drinking water containing AzUR was removed immediately prior to sacrifice. In addition, the effect of AzUR inhibition in vitro was determined as described above.

RESULTS

Inhibition of Tumor Growth

Plasma Cell Tumor X-5563 (Table 1). This tumor, when transmitted by s.c. implantation in irradiated C3H/101 mice, grew at a predictable rate, achieved enormous size at 5–6 weeks (Fig. 1) and caused death in 6–9 weeks. The mice, which appeared healthy and remained active until the tumors were extremely large, gained weight in excess of tumor weight. The tumor produced an abnormal γ-globulin, which could be detected in the serum 2–3 weeks after implantation as an electrophoretically homogeneous peak. The concentration of this myeloma protein was roughly proportional to the size of the tumor.

Both AzUR and urethan greatly inhibited growth of the tumor ($P < 0.001$). Urethan, however, decreased both transmissibility and growth more effectively than AzUR ($P < 0.001$). Urethan-treated mice (75 and 150 mg/kg/day) also appeared to thrive and gain weight during the experiments. Larger doses of urethan (300 mg/kg/day) were toxic, causing weight loss and, frequently, death. Although AzUR (30 mg/kg/day) inhibited tumor growth, it was toxic at this dosage level. The mice failed to thrive and frequently died. At higher dosages (60 mg/kg/day), the AzUR was prohibitively toxic. At dosages below the threshold of toxicity, there was no suppression of tumor growth.

The combination of urethan (75 mg/kg/day) and AzUR (30 mg/kg/day) effectively suppressed tumor growth ($P < 0.001$). The combination, however, was little more effective than urethan alone. The addition of AzUR to urethan appeared to increase its antitumor effect slightly, while enhancing toxicity.

The abnormal plasma protein, which was first detectable electrophoretically as a homogeneous gamma peak when the tumors reached approximately 200 mg in weight, was produced in smaller amounts in the treated animals than in the control group (Chart 2). The concentration of the abnormal protein in all experiments was roughly proportional to the size of the tumor. There was no significant difference in hematocrit, total plasma proteins, total leukocyte counts, serum calcium, or serum uric acid among the different treatment groups.

Plasma Cell Tumor X-5647 (Table 2). This tumor, when transplanted s.c. in irradiated C3H/101 mice, grew at a fairly predictable rate and caused death in 6–12 weeks. It produced an abnormal, homogeneous beta globulin, which was detectable in the serum by electrophoresis 4–5 weeks after implantation.

<table>
<thead>
<tr>
<th>Treatment group</th>
<th>Dosage (mg/kg/day)</th>
<th>Transmissibility (%)</th>
<th>Mortality (%)</th>
<th>Tumor weight (mean ± S.D.) (gm)</th>
<th>Mouse weight, mean (gm)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Experiment S-2a</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Water</td>
<td>100</td>
<td>40</td>
<td>7.2 ± 1.8</td>
<td>21</td>
<td>32</td>
</tr>
<tr>
<td>6-Azauridine</td>
<td>30</td>
<td>100</td>
<td>2.7 ± 1.8</td>
<td>21</td>
<td>23</td>
</tr>
<tr>
<td>Urethan</td>
<td>75</td>
<td>76</td>
<td>0.9 ± 1.0</td>
<td>20</td>
<td>25</td>
</tr>
<tr>
<td>6-Azauridine</td>
<td>15</td>
<td>85</td>
<td>0.2 ± 0.4</td>
<td>20</td>
<td>20</td>
</tr>
<tr>
<td>plus Urethan</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Experiment S-8b</td>
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<tr>
<td>Water</td>
<td>95</td>
<td>5</td>
<td>7.4 ± 2.5</td>
<td>19</td>
<td>28</td>
</tr>
<tr>
<td>6-Azauridine</td>
<td>30</td>
<td>100</td>
<td>3.8 ± 2.7</td>
<td>18</td>
<td>23</td>
</tr>
<tr>
<td>Urethan</td>
<td>150</td>
<td>0</td>
<td>0.0</td>
<td>18</td>
<td>20</td>
</tr>
<tr>
<td>Urethan</td>
<td>300</td>
<td>0</td>
<td>0.0</td>
<td>18</td>
<td>15</td>
</tr>
<tr>
<td>6-Azauridine</td>
<td>15</td>
<td>0</td>
<td>0.0</td>
<td>18</td>
<td>19</td>
</tr>
<tr>
<td>plus Urethan</td>
<td></td>
<td></td>
<td></td>
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</tbody>
</table>

* Sacrificed on 39th day.
* Sacrificed on 41st day.
Both urethan and AzUR effectively decreased the growth rate of this tumor ($P < 0.01$). Urethan (75 mg/kg/day) was the more effective of the 2 drugs by virtue of its greater inhibition of tumor growth and the absence of toxicity. AzUR (30 mg/kg/day) caused moderate inhibition of tumor growth ($P < 0.01$) but at this dosage was toxic as shown by the relative weight loss. In smaller dosage (15 mg/kg/day), AzUR was nontoxic but caused only slight, statistically insignificant inhibition of tumor growth. The addition of AzUR (15 mg/kg/day) appeared to enhance slightly the antitumor effect of the smaller dose of urethan without causing obvious toxicity.

The abnormal β-globulin was first detectable when the tumor was approximately 500 mg in size. Neither urethan, AzUR, nor the combination of the two appeared to interfere specifically with the rate of synthesis of the abnormal protein, but merely slowed its appearance time and depressed its serum concentration by suppressing the growth of the tumor.

**Plasma Cell Tumor SPC-1 (Table 3).** This tumor when implanted s.c. into irradiated C3H/101 mice grew rapidly and caused death in 4–6 weeks. It produced electrophoretically detectable serum β- and γ-globulins.

<table>
<thead>
<tr>
<th>Treatment group</th>
<th>Water</th>
<th>6-Azauridine</th>
<th>Urethan</th>
<th>6-Azauridine plus Urethan</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dosage (mg/kg/day)</td>
<td>30</td>
<td>75</td>
<td>15</td>
<td>75</td>
</tr>
<tr>
<td>Transmissibility (%)</td>
<td>20</td>
<td>22</td>
<td>5</td>
<td>15</td>
</tr>
<tr>
<td>Mortality (%)</td>
<td>100</td>
<td>100</td>
<td>100</td>
<td>100</td>
</tr>
<tr>
<td>Tumor weight (mean ± S.D., gm)</td>
<td>4.8 ± 1.9</td>
<td>5.1 ± 2.0</td>
<td>3.1 ± 1.6</td>
<td>4.0 ± 1.2</td>
</tr>
<tr>
<td>Mouse weight (mean, gm)</td>
<td>16</td>
<td>17</td>
<td>17</td>
<td>15</td>
</tr>
</tbody>
</table>

* Sacrificed on 36th day.

**Plasma Cell Tumor MPC-1 (Table 4).** Although urethan decreased tumor growth ($P < 0.01$) and mortality, AzUR had no effect on the growth of this tumor. In combination, these agents showed no additive or potentiating effect. There was no significant difference in hematocrit or in the time of appearance or concentration of the abnormal serum protein in any of the treatment groups.

**Plasma Cell Tumor MPC-2 (Table 5).** This tumor is unique in its production of both a homogeneous serum protein and a urinary protein with the temperature solubility characteristics of Bence-Jones protein. Neither urethan nor AzUR had any suppressive effect on transmission, tumor growth, mortality, or the concentration of abnormal plasma or urinary protein. The two agents were not administered in combination.

**Inhibition of Orotic Acid Metabolism by AzUR in Vitro.** The rate of orotic acid metabolism was measured in tumor tissue from untreated mice with four types of plasma cell tumors (Table 6). Orotic acid deearboxylation was greatest in X-5563 and least in X-5647. AzUR added in vitro exerted considerable inhibition of the metabolism of orotic acid by X-5563. Diminishing degrees of inhibition by AzUR were observed with MPC-2, X-5647, and MPC-1, in that order. In the last (MPC-1) the small degree of inhibition and the wide range rendered the inhibition of doubtful significance.
These data suggested that there was a positive correlation between the inhibition of orotic acid metabolism by AzUR in vitro and the suppression of tumor growth by AzUR in vivo, except for MPC-2, in which a smaller dose of AzUR had been administered in the in vivo studies. The degree of inhibition of orotic acid decarboxylation by AzUR did not appear to be related to the native level of orotic acid metabolism in these tumors.

The Effect of AzUR Treatment on Orotic Acid Metabolism and Its Inhibition by AzUR in Vitro. Orotic acid metabolism was measured in plasma cell tumors X-5563, MPC-1, and MPC-2 before, during, and after the administration of AzUR in vivo (30 mg/kg/day). In plasma cell tumor X-5563, orotic acid decarboxylation fell sharply after the administration of AzUR for one day. After 5 days of AzUR, it had returned to pretreatment levels, and after the cessation of AzUR, it rebounded to levels far in excess of pretreatment values (Chart 3). Inhibition of orotic acid decarboxylase activity by AzUR in vitro decreased from control levels after treatment with AzUR in vivo for 1 day. After 5 days of AzUR therapy, the in vitro inhibition of orotic acid metabolism by AzUR had disappeared. Inhibition by AzUR in vitro returned promptly after the cessation of treatment with AzUR. Similar patterns were observed in tumors MPC-1 and MPC-2 (Table 7).

### TABLE 6

<table>
<thead>
<tr>
<th>Plasma cell tumor</th>
<th>Control, mean ± S.D. (µmole/hour/100 mg tissue)</th>
<th>AzUR in vitro</th>
<th>Inhibition of tumor growth by AzUR in vivo (30 mg/kg/day)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Mean ± S.D. (µmole/hour/100 mg tissue) Mean (%) of control</td>
<td>Mean (%) of control</td>
<td></td>
</tr>
<tr>
<td>X-5563</td>
<td>5.28 ± 0.16</td>
<td>2.89 ± 0.23</td>
<td>45 55</td>
</tr>
<tr>
<td>X-5647</td>
<td>2.35 ± 0.07</td>
<td>1.59 ± 0.20</td>
<td>29 43</td>
</tr>
<tr>
<td>MPC-1</td>
<td>4.35 ± 0.50</td>
<td>3.37 ± 0.47</td>
<td>22 0</td>
</tr>
</tbody>
</table>

* MPC-2 tumor is excluded since only a smaller dose of AzUR in vivo had been used.

### TABLE 7

<table>
<thead>
<tr>
<th>Plasma cell tumor</th>
<th>Orotic acid metabolism (% of untreated control)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Control AzUR Control AzUR Control AzUR Control</td>
</tr>
<tr>
<td></td>
<td>Water for 5 days Water for 4 days followed by AzUR for 1 day AzUR for 5 days AzUR for 4 days followed by water for 1 day</td>
</tr>
<tr>
<td>X-5563</td>
<td>100 60 76 51 94 89 131 110</td>
</tr>
<tr>
<td>MPC-1</td>
<td>100 86 98 85 107 103 161 129</td>
</tr>
<tr>
<td>MPC-2</td>
<td>100 74 87 62 101 99 136 126</td>
</tr>
</tbody>
</table>

* Activity of tumor slices without addition of AzUR in vitro.
* Activity of tumor slices after incubation with AzUR (0.05 µmole per ml).

**Chart 3.** Adaptation of orotic acid metabolism in plasma cell tumor X-5563 to continuous administration of 6-azauridine (AzUR). One day after beginning AzUR, orotic acid metabolism decreased sharply but after 5 days of AzUR had returned to pretreatment levels, and one day after cessation, had surpassed control levels (open bars). The degree of inhibition of orotic acid metabolism by AzUR in vitro diminished as the duration of AzUR administration increased (shaded bars). One day after cessation of AzUR, inhibition of orotic acid metabolism by AzUR in vitro was again observed.
DISCUSSION

During the past decade, rapid progress has been made in the development of agents capable of blocking specific steps in metabolic pathways for various therapeutic purposes (7, 18, 25). AzUR, a compound which was synthesized as a pyrimidine antagonist (43), demonstrated potent antineoplastic effects against a variety of transplantable tumors of rodents (21, 23, 34). More recently, the virtual absence of toxicity of AzUR in man and some initial beneficial responses in leukemia and some hyperplastic diseases by AzUR have been demonstrated (6, 8, 10, 17, 21). The rapid appearance of clinical resistance to AzUR has, however, limited its usefulness (10, 17). The opportunity to correlate orotic acid metabolism, its inhibition by AzUR in vivo and in vitro, and the phenomenon of resistance to AzUR with the antitumor effects of AzUR prompted this investigation.

These studies demonstrated that AzUR inhibits the growth of some plasma cell tumors but not of others. Although it had been hoped that the native level of orotic acid metabolism of each tumor would determine its susceptibility to AzUR, there was no such correlation between the level of orotic acid metabolism and the antineoplastic effects of AzUR. The antitumor effects, however, did follow in general the degree of inhibition of orotic acid metabolism by AzUR in vitro. Although this correlation was not linear, the trend was evident (Table 6). Previous investigations by Breummer et al. (5) comparing inhibition of orotic acid metabolism by AzUR in vitro with the antineoplastic effects of AzUR in a series of murine ascites tumors yielded similar results. In their studies, inhibition of orotic acid metabolism by AzUR was proportional to tumor suppression in 3 tumors but not in 2 others. Differences in the tumors studied and in the technics employed make more precise comparison of these studies un rewarding.

Treatment with AzUR resulted in an early decrease in orotic acid metabolism of the tumors, followed by a rapid return to normal levels despite continued administration of drug. This adaptive increase in the ability to decarboxylate orotic acid was accompanied by decreasing inhibition of this function by AzUR in vitro. After AzUR had been stopped, orotic acid decarboxylation promptly surpassed pretreatment levels and inhibition by AzUR in vitro rapidly reappeared. This phenomenon of enzyme adaptation resembles the development of drug resistance encountered clinically (10, 17) and the adaptive enhancement of pyrimidine synthesis described by Bono et al. (3). It suggests that intermittent therapy with AzUR might prove more effective than continuous treatment. Furthermore, it implies that therapy with other antineoplastic agents combined or alternating with AzUR might be even more effective.

These studies did not show significant enhancement of therapy when AzUR and urethan were administered together. Since urethan was very effective and AzUR only minimally so, it is conceivable that the enhancement of AzUR treatment by urethan may easily have been obscured. Only one observation suggested that enhancement between AzUR and urethan may have occurred. In one experiment, mice that had received urethan or urethan plus AzUR for 40 days with complete suppression of tumor growth, were divided into 2 subgroups. In one subgroup the drugs were continued, and in the other they were stopped. Approximately one-fourth of the mice that had received urethan developed tumors within the next 2-3 weeks, whether urethan was continued or not. The tumors tended to grow more rapidly in the subgroup receiving water only. No tumors, however, appeared in those mice that had received urethan plus AzUR, whether the drugs were continued or not.

Although the major biochemical site of action of AzUR has been established, the modus operandi of urethan is uncertain. It has been postulated that this drug may exert its effect as an antimetabolite of early steps in pyrimidine synthesis (12, 40, 47) or as a mitotic poison (41). In contrast to the recent studies of Vogeler et al. (44), the absence of potentiation of AzUR and urethan in these studies suggests that urethan does not inhibit pyrimidine synthesis de novo. Further evidence of this is the failure of toxic doses of urethan (200 mg/kg/day) to reduce the total excretion of orotic acid and its riboside (combined mean daily excretion 57 µmoles per animal) in rats receiving simultaneously 400 mg/kg of AzUR, although the contribution of orotidine to this total, about 10%, was reduced (W. A. Creasey, unpublished observations). Care must be taken on reaching such a conclusion, however, in view of the recent analyses of Webb (46), which suggest that competitive inhibition of sequential steps in a metabolic pathway is no more effective in suppressing the overall pathway than the blockade of the maximally inhibited step in the sequence. This hypothesis has been confirmed for orotic acid metabolism by Rubin et al. (42).

The marked variation in response of the individual plasma cell tumors to urethan and AzUR is striking. Several tumors of C 3 H mice (X-5563, X-5647, and SPC-1) responded variably to urethan, but 2 tumors of BALB/c mice (MPC-1 and MPC-2) were generally resistant. The response to AzUR paralleled that of urethan but was always much smaller. Although these variations may reflect differences between the two strains of mice, it is probable that biologic and metabolic characteristics of the tumors themselves are responsible.

The therapeutic implications of such variability of response are disturbing. The broad spectrum of clinical disorders which occurs in human myelomatosis has been well-known for years; the remarkable variety of abnormal proteins synthesized by such tumors has been recognized more recently (14, 31, 39). The histologic appearance of these neoplasms may vary from patient to patient (4) and may be indistinguishable from a reactive plasmacytosis on one hand, or from a reticulum cell sarcoma on the other. Variants of the disease may show unique histologic features (28, 32, 33). It is possible that the biochemical characteristics of these tumors similarly may differ from each other, thus making it unlikely that any one antimetabolic agent will be uniformly effective against all cases of multiple myeloma. Certainly, the occasional dramatic remissions of individual patients with myelomatosis to any one of a variety of chemotherapeutic agents tends to support this hypothesis (1, 22, 26). A more rational approach to the therapy of myelomatosis is sorely needed.

Differences in the response of different species to different chemotherapeutic agents is equally impressive. In man, urethan is usually toxic in doses greater than 50 mg/kg/day. Mice, however, tolerated 3 times this dose without toxicity. Conversely, in mice AzUR was toxic at doses of 3 mg/kg/day while man or rats can tolerate doses 100 times as large without toxicity. Despite such species differences, the availability of a spectrum of plasma cell tumors of mice provides an experimental model for use in
correlating specific biochemical characteristics with the efficacy of chemotherapeutic agents. Each of these tumors maintains its unique characteristics on transplantation from generation to generation in the same purebred strain of mice, and each can be transplanted simultaneously in enough animals to evaluate in a controlled manner the effects of various chemotherapeutic agents. Such investigations may permit the development of a more rational approach to the chemotherapy of plasma cell tumors.

ACKNOWLEDGMENTS

The authors are indebted to Dr. Michael Potter of the National Cancer Institute who generously provided starter colonies of each of the plasma cell tumors of mice.

REFERENCES


Effect of 6-Azauridine on Plasma Cell Tumors

Fig. 1. Plasma cell tumor X-5563 in C3Hf/lw mice had achieved enormous size 40 days after implantation. Mice otherwise remained healthy and vigorous.
Effect of 6-Azauridine on Plasma Cell Tumors of Mice: Correlation of Antitumor Effect with Inhibition of Orotic Acid Metabolism

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