Experimental Evaluation of Potential Anticancer Agents

I. Quantitative Therapeutic Evaluation of Certain Purine Analogs*

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SUMMARY

A study of the degree of reproducibility of the Carcinoma 755 system when employed to obtain therapeutic indices of purine antagonists has been carried out. Some 60 "active" purine analogs have been studied by this system, used in a quantitative manner, and the approximate LD10's, minimum effective doses, therapeutic indices (LD10/T/C 0.10), and maximum degrees of effectiveness (T/C at the LD10) of each of these compounds are recorded. Under the conditions employed, only 6-mercaptopurine ribonucleoside possessed a therapeutic index against Ca-755 which was clearly greater than that of 6-mercaptopurine, whereas several derivatives of 6-mercaptopurine possessed therapeutic indices of the same magnitude of 6-mercaptopurine.

When the limited number of purine analogs which have received clinical trial against human leukemias were compared as to "useful clinical activity" and therapeutic index in the Ca-755 system, it appeared that those with higher experimental therapeutic indices were more "useful" against certain human leukemias than were those with very low therapeutic indices in the Ca-755 system.

In the event that some of the future progress in cancer chemotherapy should be stepwise rather than by very large increments resulting from the discovery of completely new classes of drugs with profound broad spectrum "activity" against the host of diseases classified as "human cancer," it appears that a vital procedural requirement will be the possession of quantitative experimental drug evaluation systems which will predict in some reasonable degree the potential of congeners of known clinically useful agents (as well as new chemical classes) against specific types of human cancer.

It is hardly feasible to consider definitive clinical trial of the hundreds of known alkylating agents and purine analogs against the many classes of human cancer, much less routine broad spectrum clinical evaluation of the hundreds of thousands of other types of synthetic chemicals and natural products and the infinite number of crude antibiotic filtrates.

In view of the fact that the long list of different types of human cancer appear to respond so dissimilarly in vitro to the known classes of anticancer agents (11), it seems unlikely that any single animal or human neoplasm growing in vitro could be expected to predict the usefulness of all drugs against all "human cancer." It is perhaps more reasonable to expect an experimental tumor system which responds consistently and reproducibly to a chemical of proved effectiveness against a specific class of cancer in man to assess the potential usefulness of structural analogs of this agent against this one class of human cancer than to demand that a single experimental system predict the potential of all drugs against all "human cancer."

* This work was supported initially by a grant from the American Cancer Society and later by a contract with the Cancer Chemotherapy National Service Center (SA-43-ph-1907).

Received for publication December 19, 1960.
Without experimental systems which will allow one to compare and rate drugs of related structure in a quantitative sense, with some conviction that such ratings will carry over to one or more of the many cancer problems, it is impossible to guide efficiently new drug design and synthesis or selection of new congeners which might be worthy of extensive clinical trial.

With these thoughts in mind, we have placed a considerable amount of effort into a pilot study on the quantitative evaluation of purine analogs using an in vivo animal tumor system (Carcinoma 755 in BDF1 mice) which is very sensitive to certain purine antagonists even though this neoplasm bears no morphologic resemblance to the human neoplasms which are sensitive to purine antagonists. An effort such as this is of no practical value unless there is at hand reliable parallel clinical information on the response of a sensitive class of human cancer to some of the same agents employed in the experimental system so that the reliability of the screening system may be assessed.

In a past publication, the results obtained on assaying 125 purine analogs against Ca-755 were presented along with very approximate estimates of therapeutic indices of a considerable number of those which exhibited in vivo inhibitory activity (16). Most of these active compounds were derivatives of 6-mercaptopurine, thioguanine, or 6-chloropurine. It was pointed out that, even though more than 700 assays were carried out in this preliminary study, careful analysis of the detailed results revealed that extension of the dosage-response data would be required for relatively accurate establishment of therapeutic indices and reliable rating of active purines.

This present paper presents results of additional experiments carried out to determine the reproducibility and reliability of quantitative drug evaluation and rating in this in vivo system and attempts to provide the most reliable therapeutic index data possible from the assay data accumulated to date in this laboratory.

With the view to approaching some degree of uniformity in the definition of terms and criteria employed in quantitative drug evaluation, we have adopted definitions and criteria suggested by Dr. Leon H. Schmidt1 which we believe to be better than those we had used initially. It is hoped that more such data (on different classes of drugs and different experimental systems) can eventually be published in a somewhat similar manner so that there eventually can be developed a large body of comparable quantitative experimental data which might serve as a basis for comparison with broad spectrum clinical drug response data.

EXPERIMENTAL

PROTOCOLS, CRITERIA, DEFINITIONS, AND DATA ANALYSIS

There are two theoretically important types of information sought in experimental therapeutic studies in which in vivo systems are employed: (a) the maximum degree of effectiveness at a tolerated dose (usually the maximum tolerated dose) and (b) the therapeutic index or ratio between a maximum tolerated dose (MTD) and a minimum effective dose (MED). One would be unwise not to consider both types of information in experimental evaluation of potential anticancer agents. It is reasonable to assume that in most instances a drug which will provide a desirable therapeutic response at 1/100 of the toxic dose is preferable to one that must be administered at one-half the toxic dose to elicit a similar response. However, one must also consider that a drug with a profound effect over a narrow acceptable dosage range might be more useful than a drug with, at best, only moderate tumor-inhibiting activity over a wide nontoxic dosage range.

It should be apparent that there are a multitude of criteria and definitions one could choose for the "maximum degree of effectiveness," the "maximum tolerated dose," the "minimum effective dose," and the "therapeutic index." There are many factors including personal preference, peculiarities of specific systems, and type of biologic end-point (tumor weight or life span) that have influenced various investigators to adopt one or another specific definition of the above terms. It is unlikely that all investigators will find the criteria employed herein identical with those of their own choosing.

Maximum tolerated dose (MTD) (LD10).—An LD10 read from plotted dosage-mortality data has been employed as the toxicity end-point herein rather than an estimated "maximum tolerated dose" based on some other consideration of mortality and host weight loss data, because it is a more reliable and reproducible end-point. It is just as important when obtaining data to be used in calculation of a therapeutic index to have accurate toxicity data as it is to be in possession of reliable tumor-inhibition data. The procedure of plotting and reading the LD10 from log-probability plots of dosage-mortality data is illustrated in Chart 1.

The question then arises whether one should use tumor-free or tumor-bearing animals in obtaining the toxicity data that provide the basis for

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1 Private communication and preliminary progress reports.
an MTD or LD\textsubscript{10}. Regarding this question, there are two pertinent and practical points which should be considered: (a) in general, does the fact that the host is bearing a tumor significantly influence the toxicity of a drug in short-term experiments? and (b) in the usual tumor-inhibition assay in which the animals are sacrificed (for tumor extirpation and weighing) one day following a course of chronic therapy, what is the chance that delayed drug-induced deaths might be missed by failing to prolong the observation period? There are probably instances where both factors could affect a toxicity end-point, but it seems probable that the latter could be a more frequent and serious cause of error. LD\textsubscript{10}'s read from plots of dosage-mortality data obtained with tumor-bearing animals and tumor-free animals (where the observation period was extended) are presented in Table 1. Because the differences in LD\textsubscript{10}'s obtained by the two above-mentioned procedures have not been great (for this class of compounds) and because much plottable toxicity data were already available as a consequence of the extensive tumor-inhibition studies, we have not re-determined LD\textsubscript{10}'s for all of the compounds in tumor-free animals with the extended observation period.

Definition of Maximum Tolerated Dose (LD\textsubscript{10}) employed: the LD\textsubscript{10} as read from an adequate log-probability plot of dosage-mortality data.

Minimum effective dose (MED) (T/C 0.10).—Here the choice of end-point among investigators has been even less uniform in the past. Reference to Chart 2 will indicate the procedure employed in reading the dose which will inhibit tumor growth to 10 per cent, 40 per cent, or 50 per cent of untreated control tumor weights from adequate dosage-tumor response plots.

With some animal tumor systems, if adequate numbers are employed, an inhibition to 40 per cent of untreated controls is almost always a statistically significant response and is meaningful if this degree of inhibition is not associated with

### Table 1

**Comparative LD\textsubscript{10}'s Obtained in Tumor-Free Mice and in Tumor-Bearing Mice (with Extended Observation Periods)**

All values taken from log-probability plots of dosage-mortality data.

<table>
<thead>
<tr>
<th>Compound</th>
<th>Tumor-free LD\textsubscript{10} (q.d. 1-11 days; observation, 1-21 days) (mg/kg/day)</th>
<th>Ca-755-bearing LD\textsubscript{10} (q.d. 1-11 days; observation, 1-12 days) (mg/kg/day)</th>
<th>LD\textsubscript{10} ratio: &quot;Ca-755-bearing&quot;/&quot;Tumor-free&quot;</th>
</tr>
</thead>
<tbody>
<tr>
<td>6-Mercaptopurine</td>
<td>40.0</td>
<td>43.0</td>
<td>1.1</td>
</tr>
<tr>
<td>6-Mercaptopurine ribonucleoside</td>
<td>250.0</td>
<td>260.0</td>
<td>0.9</td>
</tr>
<tr>
<td>6-Chloropurine</td>
<td>230.0</td>
<td>170.0</td>
<td>1.3</td>
</tr>
<tr>
<td>Thioguanine</td>
<td>1.6</td>
<td>2.2</td>
<td>1.4</td>
</tr>
<tr>
<td>Thioguanosine</td>
<td>1.7</td>
<td>2.7</td>
<td>1.0</td>
</tr>
<tr>
<td>8-Azaguanine</td>
<td>90.0</td>
<td>&gt;75.0</td>
<td>1.0</td>
</tr>
<tr>
<td>6-Ethyl-6-mercaptopurine</td>
<td>52.0</td>
<td>60.0</td>
<td>1.3</td>
</tr>
<tr>
<td>6-(Cyanomethylthio)purine</td>
<td>75.0</td>
<td>80.0</td>
<td>1.0</td>
</tr>
<tr>
<td>6-(Methylthio)purine</td>
<td>100.0</td>
<td>70.0</td>
<td>0.7</td>
</tr>
<tr>
<td>ca. 70.0</td>
<td>94.0</td>
<td>ca. 1.3</td>
<td></td>
</tr>
</tbody>
</table>
reduced caloric intake and large host weight change differences (control versus treated groups) which could in the absence of specific drug "activity" account for the observed effects. One reason for the present preference for a more demanding therapeutic response end-point (10 per cent of the untreated control tumor weight or T/C 0.10 or 90 per cent inhibition) is the obvious desire to minimize confusion which can be associated with host weight loss, and another is the desire to require a biologic response in quantitative experimental systems somewhat more in keeping with the clinical requirements even to observe a possible favorable response in advanced "human cancer." It seemed somewhat unrealistic to use the dosage which will provide 40–50 per cent inhibition of animal tumors as the "minimum effective dose" when such a response would go undetected in most clinical trials or would be of relatively little interest if detected. A further disadvantage to the use of a higher T/C in definition of a "minimum effective dose" in therapeutic index calculations is the possibility that misleading emphasis might be accorded agents with "flat" dosage-response curves that fail to provide complete or almost complete tumor inhibition even at the LD_{10} (much less tumor regression, which is the usual end point in clinical trials). The above is not intended to imply that agents with minimal therapeutic indices should not be considered for further study against other animal or human neoplasms or as a basis for congener synthesis, but it is suggested that these somewhat more demanding criteria are reasonable in quantitative rating studies for the reasons already mentioned.

**Definition of minimum effective dose employed:**

the dose inhibiting tumor growth to 10 per cent (T/C 0.10) of untreated control tumor weight as read from an adequate dosage-tumor response plot.

**Therapeutic index:**

The definition of therapeutic index employed is that of Schmidt: the ratio between the LD_{10} (as read from an adequate plot of dosage-mortality data) and the dose inhibiting tumor growth to 10 per cent (T/C 0.10) of untreated controls (as read from an adequate plot of dosage-tumor response data) or Therapeutic:

\[
\text{Index} = \frac{\text{Maximum Tolerated Dose (LD}_{10})}{\text{Minimum Effective Dose (T/C 0.10)}}
\]

**Chart 2.—Dosage-response plot, 6-mercaptopurine against Ca-755 (av. data from nine expts.)**

\[
\text{LD}_{10} = 40 \quad \text{mg/kg/day; IP; qd 1-11 days} \\
T/C 0.10 = 3
\]

\[
\text{T/C at LD}_{10} = 0\% \text{ (max. effectiveness)} \\
(20-90 animals per point).
\]
It has been the practice herein to record an agent as inactive if the plotted dosage-tumor response data did not indicate that the agent reproducibly inhibited tumor growth to <40 per cent of controls at dosage levels equal to or less than the LD₅₀. If a compound reproducibly inhibited tumor growth to <40 per cent of controls (without excessive host weight loss) at a dose less than the LD₁₀, but failed to inhibit tumor growth to 10 per cent or less at the LD₁₀, then the therapeutic index has been recorded as < 1 to indicate significant "activity" but minimal therapeutic index.

System and, in turn, the meaningfulness of differences observed between related compounds, repetitive dosage-response experiments have been carried out with 6-mercaptopurine (6-MP), 6-mercaptopurine ribonucleoside, 6-(methylthio)purine, and 6-(benzylthio)purine.

Large numbers of BDF₁ mice were given implants of Ca-755 and randomized into a control group of 40 and appropriate numbers of groups of ten each, making possible a simultaneous comparison of the tumor inhibition of each compound at a wide range of doses. Nine of these comparative experiments were carried out over a period of 2 months; 6-MP and its ribonucleoside were included in all experiments, 6-(benzylthio)purine was included in seven, and 6-(methylthio)purine in six of the experiments. The results obtained were plotted, and the doses inhibiting to a T/C of 0.10 were read from the plots and related to respective LD₁₀'s to provide the summarized comparative data presented in Table 2.

### Table 2

<table>
<thead>
<tr>
<th>Compound</th>
<th>Therapeutic indices LD₁₀/T/C 0.10 in experiments no.</th>
<th>Av.</th>
<th>Deviation from mean</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>Av. (%)</td>
</tr>
<tr>
<td>6-Mercaptopurine</td>
<td>14 11 18 (17) 25 ca. 18 20 20 15 17</td>
<td>17</td>
<td>24</td>
</tr>
<tr>
<td>6-MP ribonucleoside</td>
<td>81 58 62 62 61 98 71 71 125</td>
<td>76</td>
<td>20</td>
</tr>
<tr>
<td>6-(Benzylthio)purine</td>
<td>4 6 4 9 3 7 9</td>
<td>6</td>
<td>33</td>
</tr>
<tr>
<td>6-(Methylthio)purine</td>
<td>3 3 3 5 4 4 4 4</td>
<td>4</td>
<td>18</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Compound</th>
<th>Approximate relative therapeutic indices Av. Range</th>
</tr>
</thead>
<tbody>
<tr>
<td>6-Mercaptopurine</td>
<td>5.7 5.3 5.7 5.7 5.7 8.7 3.3 3.3 3.3 4.8 2.4-8.3</td>
</tr>
<tr>
<td>6-MP ribonucleoside</td>
<td>0.2 0.4 0.2 0.2 0.8 0.2 0.4 0.2 0.2 0.2</td>
</tr>
<tr>
<td>6-(Benzylthio)purine</td>
<td>0.2 0.2 0.2 0.2 0.4 0.2 0.4 0.2 0.2 0.2</td>
</tr>
</tbody>
</table>

NOTE: The LD₁₀ is the dose killing 10 per cent of the host animals as read from log-probability plots of dose-mortality data (see Charts 1 and 2). The T/C 0.10 is the dose inhibiting growth of the tumors to 0.10 or 10 per cent of controls as read from plots of dose-tumor-response data. Where indicated, the dose-tumor-response results on the different compounds were obtained in the same experiment (using randomized tumor-bearing animals from a large single population).

Maximal degree of effectiveness.—It has already been pointed out that the margin of safety which is suggested by a therapeutic index is but one parameter sought in drug evaluation. Another is the maximum degree of effectiveness at a maximum tolerated dose, regardless of the safety margin.

In an effort to provide an index of the "maximum inhibitory activity," the degree of tumor inhibition at the MTD (LD₁₀) has been read from plots of dosage-tumor response data and recorded in summary tables:

Maximum Degree of Effectiveness = T/C at the LD₁₀.

On the Reproducibility of Therapeutic Indices in the Ca-755 System

To gain further knowledge regarding the reproducibility of therapeutic indices in this in vivo system and, in turn, the meaningfulness of differences observed between related compounds, repetitive dosage-response experiments have been carried out with 6-mercaptopurine (6-MP), 6-mercaptopurine ribonucleoside, 6-(methylthio)purine, and 6-(benzylthio)purine.

Large numbers of BDF₁ mice were given implants of Ca-755 and randomized into a control group of 40 and appropriate numbers of groups of ten each, making possible a simultaneous comparison of the tumor inhibition of each compound at a wide range of doses. Nine of these comparative experiments were carried out over a period of 2 months; 6-MP and its ribonucleoside were included in all experiments, 6-(benzylthio)purine was included in seven, and 6-(methylthio)purine in six of the experiments. The results obtained were plotted, and the doses inhibiting to a T/C of 0.10 were read from the plots and related to respective LD₁₀'s to provide the summarized comparative data presented in Table 2.

A Summary of Quantitative Experimental Therapeutic Data Obtained to Date with Purine Analogs Against the Ca-755 System

Most of the positive data which have been obtained on Ca-755 response to purine analogs in this laboratory have been analyzed as described above, and the pertinent summary values (MTD, MED, Therapeutic Index, and Maximum Degree of Effectiveness) are presented in Table 3.
TABLE 3
QUANTITATIVE DRUG EVALUATION DATA, PURINE ANALOGS AGAINST CARCINOMA 755

<table>
<thead>
<tr>
<th>Agent</th>
<th>Maximum tolerated dose (LD₅₀) (mg/kg/day)</th>
<th>Minimum effective dose (T/C 0.10) (mg/kg/day)</th>
<th>Therapeutic index LD₅₀/ T/C 0.10</th>
<th>Maximum degree of effectiveness (T/C LD₅₀ in %)</th>
</tr>
</thead>
<tbody>
<tr>
<td>6-Mercaptopurine ribonucleoside</td>
<td>250.0*</td>
<td>3.7</td>
<td>68</td>
<td>0</td>
</tr>
<tr>
<td>6-Mercaptopurine</td>
<td>40.0*</td>
<td>3.0</td>
<td>13</td>
<td>0</td>
</tr>
<tr>
<td>6-(Cyanomethylthio)purine</td>
<td>75.0*</td>
<td>8.0</td>
<td>9</td>
<td>0</td>
</tr>
<tr>
<td>9-Ethyl-6-mercaptopurine</td>
<td>58.0*</td>
<td>6.6</td>
<td>8</td>
<td>0</td>
</tr>
<tr>
<td>6-Chloropurine</td>
<td>230.0</td>
<td>29.0</td>
<td>8</td>
<td>0</td>
</tr>
<tr>
<td>Thioguanine</td>
<td>1.6</td>
<td>0.58</td>
<td>3</td>
<td>0</td>
</tr>
<tr>
<td>Thioguanosine</td>
<td>1.7*</td>
<td>0.76</td>
<td>3</td>
<td>0</td>
</tr>
<tr>
<td>8-Azaqueaine</td>
<td>90.0</td>
<td>72.0</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>9-Butyl-6-mercaptopurine</td>
<td>&gt;250.0</td>
<td>14.0</td>
<td>ca. 18</td>
<td>0</td>
</tr>
<tr>
<td>6-(Cyclopentylthio)purine</td>
<td>ca. 250.0</td>
<td>14.0</td>
<td>ca. 18</td>
<td>0</td>
</tr>
<tr>
<td>6-(Propylthio)purine</td>
<td>125-250</td>
<td>19.0</td>
<td>7-14</td>
<td>0</td>
</tr>
<tr>
<td>1-(Purin-6-ylthio)-2-propanone oxide</td>
<td>ca. 250.0</td>
<td>ca. 25.0</td>
<td>ca. 10</td>
<td>&lt;5</td>
</tr>
<tr>
<td>6-(Cyclopentylthio)purine ribonucleoside</td>
<td>ca. 400.0</td>
<td>40.0</td>
<td>ca. 10</td>
<td>0</td>
</tr>
<tr>
<td>6-(Alythio)purine</td>
<td>60.0</td>
<td>6.4</td>
<td>9</td>
<td>0</td>
</tr>
<tr>
<td>6-(2-Thiazylthio)purine</td>
<td>ca. 125.0</td>
<td>15.0</td>
<td>ca. 8</td>
<td>0</td>
</tr>
<tr>
<td>6-(Alythio)purine ribonucleoside</td>
<td>190.0</td>
<td>32.0</td>
<td>6</td>
<td>0</td>
</tr>
<tr>
<td>6-(Cyanomethylthio)purine ribonucleoside</td>
<td>ca. 200.0</td>
<td>36.0</td>
<td>ca. 6</td>
<td>0</td>
</tr>
<tr>
<td>6-(Cinnamylthio)purine</td>
<td>250-500</td>
<td>90.0</td>
<td>3-6</td>
<td>0</td>
</tr>
<tr>
<td>6-(Pentylthio)purine</td>
<td>125-250</td>
<td>44.0</td>
<td>ca. 3-6</td>
<td>0</td>
</tr>
<tr>
<td>6-(Fluoroethylthio)purine</td>
<td>80.0</td>
<td>16.0</td>
<td>5</td>
<td>0</td>
</tr>
<tr>
<td>6-(Benzoylthio)purine</td>
<td>125.0</td>
<td>27.0</td>
<td>5</td>
<td>0</td>
</tr>
<tr>
<td>6-(Benzylthio)purine</td>
<td>75.0</td>
<td>14.0</td>
<td>5</td>
<td>0</td>
</tr>
<tr>
<td>6-(Acetylamino)thio)purine</td>
<td>72.0</td>
<td>18.0</td>
<td>4</td>
<td>&lt;10</td>
</tr>
<tr>
<td>6-(Pyridine-2-thio)purine</td>
<td>&gt;100.0</td>
<td>25.0</td>
<td>4</td>
<td>0</td>
</tr>
<tr>
<td>9-(Cyclopentyl-6-mercaptopurine</td>
<td>ca. 200.0</td>
<td>46.0</td>
<td>ca. 4</td>
<td>0</td>
</tr>
<tr>
<td>6-(m-Fluorobenzythio)purine</td>
<td>ca. 62.0</td>
<td>17.0</td>
<td>ca. 4</td>
<td>0</td>
</tr>
<tr>
<td>6-(Phenythio)purine</td>
<td>&gt;200.0</td>
<td>72.0</td>
<td>ca. 4</td>
<td>0</td>
</tr>
<tr>
<td>6-(Methylthio)purine</td>
<td>&gt;94.0</td>
<td>36.0</td>
<td>ca. 3</td>
<td>0</td>
</tr>
<tr>
<td>6-(Benzylthio)purine</td>
<td>70.0</td>
<td>22.0</td>
<td>3</td>
<td>0</td>
</tr>
<tr>
<td>2-Amino-6-(methylthio)purine</td>
<td>15-30</td>
<td>5.6</td>
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<td>0</td>
</tr>
<tr>
<td>6-(Fluoroethylthio)purine</td>
<td>75.0</td>
<td>21.0</td>
<td>3</td>
<td>0</td>
</tr>
<tr>
<td>6-(Methylthio)purine</td>
<td>90.0</td>
<td>32.0</td>
<td>3</td>
<td>4</td>
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<td>trans-2,6-Mercaptopurin-9-yl)-cyclopentanol</td>
<td>ca. 125.0</td>
<td>50.0</td>
<td>ca. 3</td>
<td>0</td>
</tr>
<tr>
<td>6-(Benzylthio)purine ribonucleoside</td>
<td>ca. 150.0</td>
<td>40.0</td>
<td>ca. 3</td>
<td>&lt;10</td>
</tr>
<tr>
<td>6-(2-Thiazylthio)purine ribonucleoside</td>
<td>ca. 50.0</td>
<td>17.0</td>
<td>ca. 3</td>
<td>0</td>
</tr>
<tr>
<td>6-(Propylthio)purine ribonucleoside</td>
<td>ca. 200.0</td>
<td>70.0</td>
<td>ca. 3</td>
<td>0</td>
</tr>
<tr>
<td>6-(Acythio)purine ribonucleoside</td>
<td>&gt;450.0</td>
<td>200.0</td>
<td>ca. 3</td>
<td>0</td>
</tr>
<tr>
<td>3-(Purin-6-ylthio)pyrroline acid</td>
<td>ca. 250.0</td>
<td>ca. 75.0</td>
<td>ca. 3</td>
<td>0</td>
</tr>
<tr>
<td>6-Chloro-2-ethylpurine</td>
<td>&gt;125.0</td>
<td>47.0</td>
<td>ca. 3</td>
<td>0</td>
</tr>
<tr>
<td>9-ethyl-6-(methylthio)purine</td>
<td>64.0</td>
<td>32.0</td>
<td>2</td>
<td>0</td>
</tr>
<tr>
<td>2-Amino-6-(benzylthio)purine</td>
<td>12</td>
<td>5.2</td>
<td>2</td>
<td>0</td>
</tr>
<tr>
<td>6-(p-Nitrobenzylthio)purine</td>
<td>210</td>
<td>100.0</td>
<td>2</td>
<td>&lt;10</td>
</tr>
<tr>
<td>6-(Ethylthio)purine ribonucleoside</td>
<td>125.0</td>
<td>52.0</td>
<td>2</td>
<td>0</td>
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<tr>
<td>6-(Methylmidazol-2-ylthio)purine</td>
<td>7.0</td>
<td>4.2</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>2-Amino-6-(1-methyl-4-nitroimidazol-5-ylthio)purine</td>
<td>3.0</td>
<td>1.8</td>
<td>2</td>
<td>0</td>
</tr>
<tr>
<td>Purine-2,6-dithiol</td>
<td>250-500</td>
<td>150.0</td>
<td>ca. 2</td>
<td>0</td>
</tr>
<tr>
<td>6-Chlorobenzythio)purine</td>
<td>ca. 100.0</td>
<td>60.0</td>
<td>ca. 2</td>
<td>0</td>
</tr>
<tr>
<td>6-(Ocythio)purine</td>
<td>125-250</td>
<td>94.0</td>
<td>1-2</td>
<td>4</td>
</tr>
<tr>
<td>Aminomorpholinoside of Purinomycin</td>
<td>34.0</td>
<td>24.0</td>
<td>1</td>
<td>5</td>
</tr>
<tr>
<td>6-Mercaptopurin-2-ol</td>
<td>ca. 350.0</td>
<td>ca. 350.0</td>
<td>ca. 1</td>
<td>0</td>
</tr>
<tr>
<td>6-(Phenethio)purine</td>
<td>ca. 350.0</td>
<td>ca. 350.0</td>
<td>ca. 1</td>
<td>0</td>
</tr>
<tr>
<td>6-(2-Benzylthio)ethylthio)purine</td>
<td>ca. 125.0</td>
<td>110.0</td>
<td>ca. 1</td>
<td>ca. 8</td>
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<tr>
<td>6-(3,5,7-Trifluoroethylthio)purine</td>
<td>ca. 35.0</td>
<td>ca. 35.0</td>
<td>&lt;1</td>
<td>ca. 11</td>
</tr>
<tr>
<td>6-(2-Carboxyethylthiol)purine</td>
<td>ca. 100.0</td>
<td>&gt;100.0</td>
<td>&lt;1</td>
<td>ca. 14</td>
</tr>
<tr>
<td>N-(2-Purin-6-ylthio)ethylacetamide</td>
<td>ca. 125.0</td>
<td>&gt;100.0</td>
<td>&lt;1</td>
<td>ca. 14</td>
</tr>
<tr>
<td>6-(Pyridin-2-thio)purine</td>
<td>&gt;100.0</td>
<td>100.0</td>
<td>&lt;1</td>
<td>ca. 19</td>
</tr>
<tr>
<td>6-(Fluoroethylthio)purine</td>
<td>ca. 25.0</td>
<td>ca. 26.0</td>
<td>&lt;1</td>
<td>ca. 19</td>
</tr>
<tr>
<td>cis-2-(6-Chloropurin-9-yl)cyclopentanol</td>
<td>&gt;250.0</td>
<td>&gt;250.0</td>
<td>&lt;1</td>
<td>ca. 19</td>
</tr>
<tr>
<td>8-Azaqueaine</td>
<td>17.0</td>
<td>&gt;17.0</td>
<td>1</td>
<td>ca. 40</td>
</tr>
<tr>
<td>6-Chloropurine ribonucleoside</td>
<td>550.0</td>
<td>900.0</td>
<td>&lt;1</td>
<td>25</td>
</tr>
<tr>
<td>6-Hydrazinopurine</td>
<td>ca. 75.0</td>
<td>&gt;75.0</td>
<td>&lt;1</td>
<td>25</td>
</tr>
<tr>
<td>6-(Methylthio)purine ribonucleoside</td>
<td>20.0</td>
<td>&gt;20.0</td>
<td>&lt;1</td>
<td>15</td>
</tr>
<tr>
<td>4-Aminopyrazolo(3,4-d)pyrimidine</td>
<td>ca. 15.0</td>
<td>ca. 18.0</td>
<td>&lt;1</td>
<td>15</td>
</tr>
</tbody>
</table>

Note: In both toxicity and therapeutic evaluations the drugs were administered intraperitoneally q.d. 1-11 days with the exception of 6-hydrazinopurine, which was administered IP, q.o.d. (1-11 days). In all instances tumors were excised and weighed on the 19th day following implantation.

* The LD₅₀ was determined using tumor-free mice observed during and for 10 days subsequent to the course of drug administration. All other LD₅₀'s are based on data obtained in tumor-bearing mice which were observed for mortality during the course of treatment and for 1 day thereafter.

For definitions of MTD, MED, Therapeutic Index, and Maximum Degree of Effectiveness, see text.
instances, compounds have not yet been adminis-
tered at enough high doses to provide sufficient
mortality data to allow for a reliable dosage-mor-
tality plot, and the LD_{50}'s have been estimated
from minimal mortality data. Such estimates are
clearly indicated in Table 3, as are the therapeutic
indices calculated therefrom.

**STATUS OF KNOWLEDGE REGARDING CORRELATION
BETWEEN THE QUANTITATIVE RESPONSE OF THE CA-755 SYSTEM TO PURINE ANALOGS AND “USEFUL ACTIVITY” OF A FEW PURINES AGAINST ACUTE HUMAN LEUKEMIA**

In spite of the risky nature of the undertaking,
a preliminary effort has been made herein to com-
pare the quantitative response of the Ca-755 sys-
tem and the response of human acute leukemia to
certain purine analogs which have been studied clinically (and the results published). The results of this inadequate “experimental actives” comparative drug-response analysis are summa-
rized in Table 4.

**DISCUSSION**

To be able to state that there is a correlation
between the “response” of an animal tumor system
and a given class of human cancer to drugs of a
specific chemical family, it is necessary to be in
possession of data showing that, when the same
drugs are evaluated against both, the agreement in
“response” is significantly greater than could be expected by chance. It is not scientifically
allowable to jump to the conclusion of noncorre-
tlation unless divergent results have been obtained
under reasonably similar circumstances of drug
dosage, schedule, route, and stage of progress of
the respective diseases.

Unfortunately, one is hampered in almost any
test to assess the degree of correlation be-
tween specific animal tumor systems and given
types or classes of human cancer—even for single
families of drugs—because of two basic deficien-
cies in presently available information: (a) much
of the experimental data are at best semiquantita-
tive in nature and (b) in many instances the clini-
cal results on related drugs are sparse and incon-
clusive and hence have not been reported in the
literature; i.e., trial in a few patients with varied
types of neoplasms, some of whom were in a ter-
"minimum effective dose" in Ca-755-bearing
animals (without severe human toxicity) these
few “experimental actives” (Table 4) have proved
“useful” against certain human leukemias.

A listing of a considerable amount of quantita-
tive drug evaluation data is presented in Table 3.
Although these agents are arranged for conven-
ience in decreasing order of therapeutic index, the
reader is warned not to push comparisons beyond
the reliability (indicated in Table 2) of this type
of quantitative biologic data. The therapeutic
indices only of 6-mercaptopurine, 6-mercaptopu-
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"experimental actives” (Table 4) have proved
"useful" against certain human leukemias.
Likewise, when one compares the minimum effective doses in the Ca-755 system and the doses selected and employed in man, remissions in chronic granulocytic leukemia and a "hyporesponse" in adults with acute leukemia (7).

The degree of hepatotoxicity in man at doses far below the minimum effective dose in animals suggests that its usefulness might be limited as are the data) could have occurred entirely by chance (odds ca. 1 in 5,000). Likewise, when one compares the minimum effective doses in the Ca-755 system and the doses selected and employed in man, there is a suggestion of a relationship; i.e., same order in five of six "useful drugs"—inability to approach in man, the MED in animals, without severe toxicity with $\frac{1}{4}$ of the "nonuseful" drugs.

### TABLE 4

**Present Status of Knowledge Regarding Possible Correlation Between the Quantitative in Vivo Response of Carcinoma 755 and Useful Response of Human Acute Leukemia to Purine Antagonists**

<table>
<thead>
<tr>
<th>AGENT</th>
<th>CARCINOMA 755*</th>
<th>HUMAN LEUKEMIA</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Minimum effective dose (T/C 0.10)</td>
<td>Maximum tolerated dose (LD10)</td>
</tr>
<tr>
<td>6-Mercaptopurine</td>
<td>3.0</td>
<td>40.0</td>
</tr>
<tr>
<td>6-Chloropurine</td>
<td>29.0</td>
<td>250.0</td>
</tr>
<tr>
<td>Thioguanine</td>
<td>0.58</td>
<td>1.6</td>
</tr>
<tr>
<td>6-(Methylthio)purine</td>
<td>56.0</td>
<td>94.0</td>
</tr>
<tr>
<td>Thioguanosine</td>
<td>1.8</td>
<td>3.0</td>
</tr>
<tr>
<td>8-Azaguaine</td>
<td>72.0</td>
<td>90.0</td>
</tr>
<tr>
<td>Aminonucleoside of purinomycin</td>
<td>24.0</td>
<td>34.0</td>
</tr>
<tr>
<td>4-Aminopyrazolo(3,4-d) pyrimidine</td>
<td>18.0</td>
<td>ca. 15.0</td>
</tr>
<tr>
<td>Purine</td>
<td>&gt;400.0</td>
<td>ca. 400.0</td>
</tr>
<tr>
<td>6-Methylpurine</td>
<td>&gt;2.0</td>
<td>1.7</td>
</tr>
<tr>
<td>2,6-Diaminopurine</td>
<td>Inactive</td>
<td>70.0</td>
</tr>
</tbody>
</table>

*All of the Ca-755 data obtained above were obtained using daily treatment (q.d. 1-11) by the I.P. route.
† E. Hall, unpublished data referred to by Burchenal (see Reference 4).
‡ This compound has been reported to have a higher therapeutic index than 6-MP when both drugs were administered orally to mice bearing Ca-755 (10). The above low value was obtained on I.P. drug administration. This compound has produced remissions in chronic granulocytic leukemia and a "leukopenic response" in adults with acute leukemia (7).
§ No published reports on clinical evaluation of this compound against human leukemia are available; however, the high degree of hepatotoxicity in man at doses far below the minimum effective dose in animals suggests that its usefulness might be doubtful.
¶ An occasional patient may derive some benefit from this compound, but most patients cannot tolerate amounts of the drug to achieve desired results. "It does not seem to be a practical agent for use alone in treating any form of leukemia at the present time because of the rarity of its action in clinical leukemia and its toxicity at therapeutic levels" (4).

It appears somewhat unlikely that the above seeming correlation between therapeutic index in the Ca-755 system and "useful activity" against human leukemia (limited as are the data) could have occurred entirely by chance (odds ca. 1 in 5,000). Likewise, when one compares the minimum effective doses in the Ca-755 system and the doses selected and employed in man, there is a suggestion of a relationship; i.e., same order in five of six "useful drugs"—inability to approach in man, the MED in animals, without severe toxicity with $\frac{1}{4}$ of the "nonuseful" drugs.
azaxanthine can be converted to its ribonucleotide by xanthine pyrophosphorylase (when the hypoxanthine-guanine pyrophosphorylase is missing or inactive) and that this base (8-azaxanthine) is in turn converted to 8-azaguanylc acid which inhibits the 8-azaguanine-resistant cell presumably because of metabolic entry by an alternate enzymic pathway which has capacity to discriminate between 8-azaguanine and 8-azaxanthine (3). Unfortunately, the xanthine pyrophosphorylase activity of mammalian cells is apparently quite low.

With regard to the route of administration employed in these structure-activity relationship studies, the parenteral route has been employed with the view to possibly gaining more comparable basic knowledge, in spite of the fact that the oral route is more practical and thus preferred in most clinical evaluation of antileukemic activity. Elion advantage of 6-mercaptopurine ribonucleoside over 6-mercaptopurine appears to be lost if both drugs are administered orally (Table 5).

There are about ten other 6-mercaptopurine derivatives listed in Table 3 which have therapeutic indices in the Ca-755 system which appear essentially the same as 6-MP (ca. 8–18), and about 96 which have therapeutic indices equal to or greater than that of thioguanine. Some of these compounds have been selected by clinical groups of the Cancer Chemotherapy National Service Center for preliminary study against human leukemias.

With regard to structure-activity relationships within the Ca-755 system, much has been learned. Although data on the inactive purines studied have not been included in this publication in order to conserve space, they will be considered in general terms below.

**TABLE 5**

<table>
<thead>
<tr>
<th>Agent</th>
<th>Maximum tolerated dose (LD&lt;sub&gt;10&lt;/sub&gt;) (mg/kg/day)</th>
<th>Minimum effective dose (T/C 0.10) (mg/kg/day)</th>
<th>Therapeutic index LD&lt;sub&gt;10&lt;/sub&gt;/T/C 0.10</th>
<th>Maximum degree of effectiveness (T/C at LD&lt;sub&gt;10&lt;/sub&gt; in %)</th>
</tr>
</thead>
<tbody>
<tr>
<td>6-Mercaptopurine</td>
<td>80.0</td>
<td>4.8</td>
<td>17</td>
<td>0</td>
</tr>
<tr>
<td>6-Mercaptopurine ribonucleoside</td>
<td>135.0</td>
<td>3.5</td>
<td>39</td>
<td>0</td>
</tr>
<tr>
<td>Thioguanine</td>
<td>2.5</td>
<td>0.8</td>
<td>3</td>
<td>0</td>
</tr>
<tr>
<td>6-(Methylthio)purine</td>
<td>ca. 70.0</td>
<td>11.0</td>
<td>6</td>
<td>0</td>
</tr>
<tr>
<td>9-Ethyl 6-Mercaptopurine</td>
<td>130.0</td>
<td>9.0</td>
<td>13</td>
<td>0</td>
</tr>
<tr>
<td>6-Chloropurine</td>
<td>ca. 170.0</td>
<td>21.0</td>
<td>8</td>
<td>0</td>
</tr>
</tbody>
</table>

NOTE: In both toxicity and therapeutic evaluations the drugs were administered by the oral route, q.d. 1–11 days. The tumors were excised and weighed on the 12th day following implantation. The LD<sub>10</sub>'s were determined in tumor-bearing mice which were observed for mortality during the course of treatment and for 1 day thereafter.

and Hitchings have demonstrated that certain purine analogs possess higher therapeutic indices when evaluated against Ca-755 in the mouse via the oral route than when administered intraperitoneally (10). For this reason, a limited preliminary study was carried out to determine the quantitative response of the Ca-755 system to several purine analogs when such drugs were administered orally (q.d., days 1–11; tumor assessment, day 12). The results obtained are summarized in Table 5.

It is apparent from the quantitative data presented in Table 3 that, of the purines studied, only 6-mercaptopurine ribonucleoside possesses a therapeutic index against the Ca-755 system employed herein which is clearly significantly higher than 6-MP. 6-Mercaptopurine ribonucleoside has a minimum effective dose only slightly higher than 6-MP, but its maximum tolerated dose (LD<sub>10</sub>) is about 6 times that of 6-MP when both are administered I.P., q.d. 1–11 days. About half of this advantage of 6-mercaptopurine ribonucleoside over 6-mercaptopurine appears to be lost if both drugs are administered orally (Table 5).

Among the approximately 300 purines which have been screened in these laboratories, 68 have been found to be unequivocally "active" against Ca-755 under the conditions outlined. These compounds are almost all derivatives of either 6-mercaptopurine or 6-chloropurine. However, certain derivatives of these two purines have shown essentially no activity in this test system, pointing up the importance of both the nature and the location of changes made in the two basic structures. For example, although the ribonucleoside of 6-mercaptopurine possessed the highest therapeutic index of any purines studied, its 2', 3'-o-isopropylidene derivative was completely inactive. The significance of this observation is emphasized by the fact that a variety of 9-alkyl derivatives of 6-mercaptopurine were quite active. On the other hand, 9-acetic acid derivatives of 6-mercaptopurine were all inactive.

Even though the substitution of an amino, mercapto, or hydroxy group in the 2-position of 6-
mercaptopurine resulted in active compounds, substitution of a fluorine atom (in the 2-position of the ribonucleoside) or an ethyl group gave rise to inactive compounds. A fluorine atom in the 2-position of 6-(methylthio)purine inactivated this compound also, whereas this same substitution decreased the toxicity of 6-methylpurine about 200 times although the weak antinecancer activity of this compound was also lost.

Substitution on the sulfur atom of 6-mercaptopurine usually results in active compounds, possibly because these compounds are converted in vivo back to 6-mercaptopurine (15). However, methyl (purin-6-ylthio)acetate, 6-(m-tolylthio)-purine, and 6-(naphth-2-ylthio)purine were inactive. 6-(Dodecylthio)purine and 6-(2-hydroxyethylthio)purine were only slightly active. In the latter case, the lack of activity may be due to the ease of hydrolysis of this derivative to hypoxanthine.

Substitution of these various groups into 6-chloropurine has a similar effect on its activity against Ca-755 so that, although 6-chloro-9-ethylpurine was active, 9-butyl-6-chloropurine, 6-chloropurin-9-yl)acetic acid derivatives, 6-chloro-2-fluoropurine, 2-6-dichloropurine, 6-chloro-9-ethylpurine, and 6-chloro-8-ethylpurine were without discernible activity.

In addition to the above-mentioned derivatives of 6-mercaptopurine and 6-chloropurine, a number of o-alkyl and aryl derivatives of hypoxanthine and guanine, and N4-alkyl and aryl derivatives of adenine have been found to be inactive. The same is true for a variety of 2- and 9-substituted derivatives of these purines and also of 6-hydrazinopurine, a compound which was slightly active. Similarly, a series of purin-6-yl hydrazones had no inhibitory effect.

In summary, only purines containing sulfur or chlorine in the 6-position, and not all of these, have thus far shown a high degree of activity against Ca-755. It is also of interest that the only other purines found to possess notable biological activity (in this case, animal toxicity), with the exception of 6-methylpurine and purine ribonucleoside, are derivatives of adenine.

ACKNOWLEDGMENTS

We would like first to acknowledge the original synthetic, experimental therapeutic, and clinical work carried out in collaboration between the Burroughs-Wellcome Group and the Sloan-Kettering Group which led to the discovery of the antileukemic activity of certain purine antagonists in man. We also gratefully acknowledge the assistance of Dr. Leon H. Schmidt, who suggested the criteria and definition of therapeutic index employed herein.

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Experimental Evaluation of Potential Anticancer Agents I. Quantitative Therapeutic Evaluation of Certain Purine Analogs

Frank M. Schabel, Jr., John A. Montgomery, Howard E. Skipper, et al.


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