IV. Effects on Nucleic Acid Metabolism in Vivo*

PETER B. DANNEBERG,† BETTY JO MONTAG, AND CHARLES HEIDELBERGER

(McArdle Memorial Laboratory, The Medical School, University of Wisconsin, Madison 6, Wis.)

In conjunction with the studies on the metabolism and incorporation of labeled 5-fluorouracil and 5-fluoro-orotic acid into RNA (2), investigations have been carried out to determine the effects of various fluorinated pyrimidines derivatives as inhibitors of nucleic acid biosynthesis. Because the fluorine atom in the pyrimidine molecule is attached to the same carbon that bears the methyl group of thymine, it was early surmised that these compounds would block the methylation reactions leading to the metabolic formation of DNA thymine. Preliminary evidence that this is so was presented in a report from this laboratory (12).

Although there has been abundant work on the effects of antifolics, alkylating agents, azaserine, N-methylformamide, etc., on the processes of nucleic acid biosynthesis, cf. Skipper (22), only scanty effort has been devoted to studios of the effects of purine or pyrimidine analogs on the incorporation of normal precursors into nucleic acids, such as those carried out here. In the biochemical screening of a large series of compounds, Davidson and Freeman have demonstrated the inhibition of $^{14}P$ incorporation into DNA of the 755 tumor by 6-mercaptopurine and 8-azaguanine (44); LePage and Greenlees have found that in vitro Ehrlich ascites cells the incorporation of formate-C$^{14}$ into nucleic acid purines was inhibited by 6-mercaptopurine, but not significantly by 8-azaguanine (17); Heidelberger and Keller reported that, in slices of Flexner-Jobling carcinoma, the incorporation of formate into nucleic acid purines was inhibited by 6-mercaptopurine, 8-azaguanine, and 2,6-diaminopurine (15). Eidinoff has found that 5-aminouridine inhibits the incorporation of labeled ureidosuccinic acid into nucleic acid pyrimidines and that 5-bromodeoxyuridine inhibits the incorporation of thymidine into nucleic acid thymine (7, 8).

Pruoff et al. (80) have shown that 6-azathymidine inhibits the in vitro incorporation of formate-C$^{14}$ into DNA thymine in bone marrow and Ehrlich ascites carcinoma cell suspensions.

Stone and Potter have measured the effect of a large number of pyrimidine analogs, including 5-fluorouracil and 5-fluoro-orotic acid, on the conversion of orotic acid-C$^{14}$ into acid-soluble uridine nucleotides in a soluble preparation from rat liver (23, 24).

In the present paper we report on the in vivo effects of 5-fluorouracil, 5-fluoro-orotic acid (5), 5-fluorouridine, and 5-fluoro-2'-deoxyuridine (8) on the incorporation of formate-C$^{14}$ into nucleic acid purines and pyrimidines, uracil-2-C$^{14}$, orotic acid-6-C$^{14}$, and thymidine-6-H$^{1}$ into nucleic acid pyrimidines; and of $^{14}P$ into DNA and RNA.

MATERIALS AND METHODS

In all experiments, Swiss albino mice obtained from Taconic Farms, Germantown, N.Y., bearing 6-day-old transplants of the Ehrlich ascites carcinoma were used. Unless otherwise indicated, the inhibitors were injected 30 minutes before the labeled precursors, and the mice were sacrificed 12 hours after administration of the precursor. All injections were intraperitoneal. Each experimental group consisted of three mice, whose livers, spleens, and ascites cells were pooled. Duplicate isolations were carried out on each pooled tissue. The doses of inhibitors ordinarily used were 150 mg/kg of 5-fluorouracil and 105 mg/kg of 5-fluoro-orotic acid. These doses produced significant tumor inhibition with a single injection (14). The proteins were precipitated and defatted in the usual way (25). The tissue precipitates thus obtained were made up to 8 ml with 10 per cent NaCl, phenolphthalein was added, and the pH was adjusted with 1 n NaOH until the indicator was red; then 0.5 ml of saturated NaHCO$_3$ solution was added to maintain a slight alkalinity. The samples were extracted for 30 minutes with frequent stirring at room temperature and, following centrifugation, were extracted with the same volume of 10 per cent NaCl for 1 hour at 85° C. The hot extraction was repeated for 30 minutes with 5 ml of NaCl. The combined hot extracts and the cold extract were separately filtered through glass wool into 5 volumes of 95 per cent ethanol to precipitate the sodium nucleotides. This amount of ethanol prevents the co-precipitation.

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† Lederle Post-Doctorate Fellow in Oncology.

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tion of sodium chloride, which sometimes accompanies the sodium nucleates when small volumes of ethanol are used for the precipitation. The sodium nucleates were hydrolyzed with 2 ml. of 70 per cent perchloric acid at 95° C. for 11 hours (19), the solution was diluted 1:10 with water and passed through 3 X 0.5 cm. columns of Darco, G-60, charcoal. The inorganic salts were removed by washing with 50 ml. of water, and the purine and pyrimidine bases were eluted with ethanol:concentrated NH₄OH:water, 73:3:24 (v/v). The mixture was dried and separated by one-dimensional paper chromatography with isopropanol:conc. HCl:water, 170:41:59 (v/v) according to Wyatt (26). This method gave good separation of all the bases if the hot and cold extracted nucleates were run separately. The positions of the spots were located with an ultraviolet lamp, if the hot and cold extracted nucleates were run separately. The separated bases were assayed for radioactivity in flow counters, and corrected for self-absorption. The paper discs were eluted with 0.1 N HCl and they were cut out with a paper punch (14-in. diameter), assayed for radioactivity in flow counters, and corrected for self-absorption. The paper discs were eluted with 0.1 N HCl at 37° C. for 12 hours, and the absorption at 260, 280 μm, and the absorption maximum of the individual bases was determined. The identity and purity of the bases were established by specific activities of two to three separate experiments, with duplicate analyses on two pools of tissues. The reproducibility of the experiments was fairly good. However, there were a few widely aberrant values. These were included in the averages quoted when the radioactivity in the samples counted was statistically significant and the spectrophotometric purity of the bases was adequate.

It has previously been reported from this laboratory (12) that the incorporation of labeled formate into the methyl group of DNA thymine is strongly inhibited by 5-fluorouracil and 5-fluoroorotic acid. This is further confirmed by the experiments given in Table 1, where it may be seen that both drugs produced essentially complete inhibition of this process in spleen and ascites cells and

### TABLE 1

**EFFECTS OF 5-FLUOROURACIL AND 5-FLUOROOROTIC ACID ON NUCLEIC ACID BIOSYNTHESIS IN MICE BEARING THE EHRlich ASCITES CARCINOMA**

<table>
<thead>
<tr>
<th>LABELLED PRECURSOR</th>
<th>μMOLERS/NO. MOUSE</th>
<th>NUCLEIC ACID</th>
<th>SPECIFIC ACTIVITY OF CONTROLS</th>
<th>PER CENT SPECIFIC ACTIVITY OF CONTROLS</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>L X S A</td>
<td></td>
<td>L X S A</td>
<td>5-Fluorouracil (150 mg/kg)</td>
</tr>
<tr>
<td>Formate-C₁⁴</td>
<td>10</td>
<td>DNA thymine</td>
<td>413</td>
<td>4370</td>
</tr>
<tr>
<td>=</td>
<td>3</td>
<td>Mixed cytosine</td>
<td>405</td>
<td>1750</td>
</tr>
<tr>
<td>=</td>
<td>1</td>
<td>Adenine</td>
<td>514</td>
<td>7640</td>
</tr>
<tr>
<td>=</td>
<td>1</td>
<td>Guanine</td>
<td>1410</td>
<td>8650</td>
</tr>
<tr>
<td>Uracil-2-C₁⁴</td>
<td>10</td>
<td>DNA thymine</td>
<td>115</td>
<td>514</td>
</tr>
<tr>
<td>=</td>
<td>2</td>
<td>RNA uracil</td>
<td>1040</td>
<td>9410</td>
</tr>
<tr>
<td>=</td>
<td>2</td>
<td>Mixed cytosine</td>
<td>455</td>
<td>1410</td>
</tr>
<tr>
<td>Orotic-6-C₁⁴ acid</td>
<td>10</td>
<td>DNA thymine</td>
<td>760</td>
<td>4860</td>
</tr>
<tr>
<td>=</td>
<td>2</td>
<td>RNA uracil</td>
<td>86000</td>
<td>26,000</td>
</tr>
<tr>
<td>=</td>
<td>1</td>
<td>RNA cytosine</td>
<td>56,000</td>
<td>16,700</td>
</tr>
<tr>
<td>=</td>
<td>1</td>
<td>DNA cytosine</td>
<td>8540</td>
<td>3490</td>
</tr>
<tr>
<td>Thymidine-6-H³</td>
<td>5</td>
<td>DNA thymine</td>
<td>120</td>
<td>1080</td>
</tr>
<tr>
<td>Phosphate-P³</td>
<td>&lt;0.1</td>
<td>DNA</td>
<td>625</td>
<td>6250</td>
</tr>
<tr>
<td></td>
<td>1</td>
<td>DNA</td>
<td>551</td>
<td>1770</td>
</tr>
</tbody>
</table>

*L* = liver; *S* = spleen; *A* = ascites cells.

The design of the experiments has been described under "Materials and Methods." The data reported in Table 1 usually represent the mean a lesser effect in liver. Formate was also found to be incorporated into mixed nucleic acid cytosine, possibly by carbon dioxide fixation, but this process was not significantly inhibited by the fluorinated pyrimidines. It is known from the excellent work of Friedkin (9) and Cohen (3) that the methylation reaction leading to thymidyllic acid is catalyzed by a tetrahydrofolic acid coenzyme. The same type of coenzyme has been shown by Goldthwait et al. (10) to be involved in the conversion of formate into the 2- and 8-carbons of the purines. That 5-fluorouracil and 5-fluoroorotic acid act specifically to inhibit the reaction leading to the formation of the methyl group of thymine, and not as folic acid antagonists, is shown by the lack of effect of the compounds on the intracellular conversion of formate into the mixed nucleic acid adenine and guanine (Table 1). The use of uracil-2-C₁⁴ as a precursor (16)
afforded the opportunity of studying the effects of 5-fluorouracil and 5-fluoroorotic acid on its conversion into RNA uracil, DNA thymine, and mixed nucleic acid cytosine. The results (Table 1) show that the conversion of uracil into DNA thymine was inhibited to about the same extent as the incorporation of formate into DNA thymine under the conditions of these experiments, except that there was less inhibition by 5-fluoroorotic acid in the spleen in this case. The conversion of uracil into RNA uracil was inhibited by the fluorinated pyrimidines to a somewhat lesser extent than its conversion into DNA thymine, particularly in the ascites tumor cells. This was also in general true for the conversion of uracil into nucleic acid cytosine.

In the experiments with orotic acid as the precursor, a greater incorporation into the RNA uracil was observed in the liver than in the tumor, in agreement with the results of Hurlbert and Potter (11) and of Heidelberger et al. (16). 5-Fluorouracil and 5-fluoroorotic acid almost completely inhibited the conversion of the precursor into DNA thymine, a result comparable to that obtained when uracil was the precursor. In both cases, the inhibition was greater in ascites cells than in liver. There was considerable, but not complete, inhibition by both drugs of the conversion of orotic acid into RNA uracil, the quantities, of which were again similar to those found with uracil as the precursor. In the experiment with labeled orotic acid as the precursor, cytosine was isolated from DNA and RNA separately, but there was no appreciable difference between the slight inhibitory effect of the drugs on the metabolic conversion of orotic acid into either RNA or DNA cytosine. In general there was a similar inhibition pattern found with orotic acid and uracil as labeled precursors.

When thymidine-H³ was used as a precursor, 5-fluorouracil and 5-fluoroorotic acid produced a stimulation of incorporation into DNA thymine in all tissues relative to the controls. This observation is consistent with the hypothesis that these drugs block the metabolic reaction leading to the de novo formation of the methyl group of DNA thymine, since the utilization of preformed thymidine for DNA thymine biosynthesis would not be blocked. The stimulation observed would be expected from an enhanced utilization and lessened dilution of the preformed thymidine owing to the inhibition of the de novo pathway leading to DNA thymine synthesis.

When tracer amounts of phosphate-P³² were used as the nucleic acid precursor, 5-fluorouracil and 5-fluoroorotic acid inhibited the incorporation into RNA in liver and ascites cells, but not in spleen. Considerable inhibition of the incorporation of P³² into DNA was observed in the drug-treated mice, particularly in the ascites cells. The lack of complete inhibition of this process is in accord with the results of Davidson and Freeman (4), who never obtained an inhibition of more than 50 per cent of the incorporation of P³² into the DNA of Adenocarcinoma 755 with a series of compounds. Although our inhibitions were sometimes greater than 50 per cent, no account was taken in this work of the specific activity of the inorganic phosphate in the tissues, which Davidson and Freeman (4) have shown to be affected by the drug treatment.

Since it was evident from the preceding work and the in vitro experiments (1) that the fluorinated pyrimidines profoundly inhibit the metabolic conversion of formate into the methyl group of DNA thymine, it became of interest to establish an in vivo biochemical dose-response curve for this reaction. Accordingly, the experiment indicated in Chart 1 was carried out. Groups of three mice, bearing Ehrlich ascites carcinomas, were injected intraperitoneally with various doses of 5-fluorouracil and 5-fluoroorotic acid, followed 30 minutes later by formate-C¹⁴. Two hours later the animals were sacrificed, and the DNA thymine was isolated from liver, ascites cells, and, in two cases, the upper part of the small intestine. These specific activities were determined and compared with those obtained from untreated controls. In Chart 1 the logarithm of the dose is plotted against the per cent specific activity against dose.
the in vivo inhibition of this reaction at a dose of 1.25 mg/kg, essentially complete inhibition of the reaction in the ascites cells of fluorouracil-treated mice is found; no inhibition was observed in the liver or intestines of the same animals. 5-Fluoroorotic acid had no significant activity in liver or intestines of the same animals. At a dose of 6.25 mg/kg of 5-fluoroorotic acid, there was considerable inhibition of this reaction in tumors, but not in liver. In general, both 5-fluorouracil and 5-fluoroorotic acid inhibited the conversion of formate into the methyl group of DNA thymine to a greater extent and at a lower dosage in ascites cells than in liver and spleen.

Although it might be argued that, since the drugs and precursors were injected intraperitoneally and thus came in direct contact with the tumor cells, it is not justifiable to consider these results as in vivo evidence for selective action on tumor cells, it may be pointed out that with 5-fluoroorotic acid no such wide differential was found between tumor cells and liver as that observed with 5-fluorouracil. This mode of administration was selected, because these drugs do not prolong the life of mice bearing the Ehrlich ascites tumor when injected at other sites.

It next became desirable to extend these studies to a third dimension and determine the duration of effect in various tissues. To make the experiment practical, it was limited to a consideration of liver and ascites cells at a single dose of 5-fluorouracil. The dose selected was 25 mg/kg, which is the effective dose most commonly given daily in tumor-screening experiments (14). In Chart 2 the per cent specific activities of DNA thymine as compared with that of the untreated controls is plotted against time. The drug was administered intraperitoneally at zero time; at the number of hours afterward shown on the chart, formate-C\textsuperscript{14} was injected, and the animals were sacrificed 2 hours later. It will be observed that the metabolic conversion of formate into the methyl group of DNA thymine in the tumor cells was essentially completely inhibited for 12 hours and rose to only 22 per cent of the controls at 24 hours. On the other hand, in liver the inhibition was never complete and rose to 42 per cent of the controls at 12 hours and 112 per cent at 24 hours. The initial dip in the liver curve probably reflected a delay in absorption. Thus, it is evident that, at least at this dose, 5-fluorouracil exerted an effect of longer duration on this biosynthetic reaction in ascites cells than in liver. This represents a still further example of the selective action of fluorouracil against tumor cells. This finding is similar to that of LePage et al. (18), who found a longer duration of azaserine inhibition of de novo purine biosynthesis in tumor cells than in spleen.

During the course of these investigations the riboside and deoxyriboside of 5-fluorouracil, 5-fluorouridine, and 5-fluoro-2'-deoxyuridine were synthesized by Duschinsky et al. (6). These compounds have been screened against various tumors, and the results will be reported elsewhere (13). In mice bearing the Ehrlich ascites tumor, both ribosides, whose structures are shown in Chart 3, are more effective than 5-fluorouracil in increasing the life span of the animals.

In view of the demonstration that 5-fluorouracil is converted into acid-soluble nucleotides of various levels of phosphorylation (2) and that deoxyfluorouridylic acid is also produced (1), it seemed likely that these nucleosides should also inhibit the metabolic conversion of formate into the methyl group of DNA thymine to a greater extent and at a lower dosage in ascites cells than in liver and spleen.

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methyl group of DNA thymine. Accordingly, dose-response experiments were carried out in vivo under conditions comparable to those described in Chart 1. The results are shown in Chart 4.

At the very small doses employed in this experiment, both nucleosides completely inhibited the methylation reaction in the tumor cells. In the case of 5-fluorouridine there was no inhibition of thymine biosynthesis in the livers at these dose levels. However, in the ascites cells there was complete inhibition at 5 mg/kg and very little inhibition at 0.05 mg/kg of 5-fluorouridine. When the inhibitory effects of 5-fluorouracil and 5-fluorouridine are compared, it is found, from Charts 1 and 4, that this metabolic reaction occurred in the tumor cells to an extent of 30 per cent of the controls at a dose of 0.5 mg/kg, whereas, with an equimolar dose of fluorouracil (0.25 mg/kg), the specific activity of the DNA thymine was 65 per cent of the controls. Therefore, the riboside of 5-fluorouracil was somewhat more effective than the free base in inhibiting this reaction in vivo. With 5-fluoro-2'-deoxyuridine, there was a 50 per cent inhibition in liver of the conversion of formate into DNA thymine at all three doses, and complete inhibition in the tumor cells, even at 0.05 mg/kg. Thus, with the two nucleosides there was some selective action on the tumor, at least as compared with liver, and the 5-fluoro-2'-deoxyuridine has been demonstrated to be an extraordinarily potent inhibitor of DNA thymine formation in vivo. It is also the most powerful inhibitor of the series in vitro (1).

DISCUSSION

It is evident from the foregoing that 5-fluorouracil and 5-fluoroorotic acid are powerful inhibitors of certain processes of both RNA and DNA pyrimidine nucleic acid biosynthesis and exert a somewhat selective effect on tumor cells. Moreover, these compounds, as well as 5-fluorouridine and 5-fluoro-2'-deoxyuridine, completely inhibit the conversion of formate into the methyl group of DNA thymine in Ehrlich ascites tumor cells in vivo. As indicated from the P32 experiments, this block is sufficient to inhibit appreciably the process of DNA biosynthesis in vivo. However, the experiments with labeled thymidine clearly show that DNA biosynthesis can occur in the presence of fluorinated pyrimidines, provided that exogenous preformed thymidine is supplied. This is further evidence for the location of the block at the reaction leading to the formation of the methyl group of DNA thymine. Because the utilization of exogenous thymidine is not blocked by these drugs, one might predict that they would show greater tumor-inhibitory activity in animals maintained on a diet free of nucleic acids and their precursors.

It has been previously demonstrated (2) that 5-fluorouracil and 5-fluoroorotic acid are incorporated into ribonucleic acid. Now it has been shown, in addition, that these drugs inhibit various processes of ribonucleic acid biosynthesis. With the data now at hand it is not possible to determine which of these biochemical effects is responsible for the tumor-inhibitory properties of this series of compounds, or whether both are required. The in vivo results reported here are in complete agreement with the findings obtained in vitro in glycolyzing suspensions of Ehrlich ascites cells reported in an accompanying paper (1) and serve to strengthen the conclusions drawn from that work. Since interpretation of the results and the localization of the metabolic block(s) produced by the fluorinated pyrimidines must take into account both in vivo and in vitro experiments, detailed discussion of this subject will be given in the next paper (1).

SUMMARY

1. The effects of 5-fluorouracil and 5-fluoroorotic acid on nucleic acid biosynthesis in livers, spleens, and Ehrlich ascites carcinoma cells have been studied in vivo in mice
2. These drugs inhibited the conversion of uracil-2-C14 and orotic-6-C14 acid into DNA thymine, RNA uracil, and, to a lesser extent, into nucleic acid cytosine. The inhibition was usually greater in spleen and ascites tumor cells than in liver.
3. The conversion of formate-C14 into the meth-
yl group of DNA thymine in spleen and tumor was completely inhibited by 5-fluorouracil and 5-fluoroorotic acid. In vitro dose-response curves in this reaction indicated that there was some selective action of fluorinated pyrimidines on the tumor cells. 5-Flourouridine and 5-fluoro-2'-deoxyuridine were more potent inhibitors of this reaction than the free fluorinated pyrimidine bases.

4. The incorporation of phosphate-P32 into DNA was inhibited by 5-fluorouracil and 5-fluoroorotic acid. However, these compounds were ineffective in blocking the conversion of labeled thymidine into DNA thymine. This is further evidence that the drugs block the reaction involving the formation of the methyl group of DNA thymine.

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Studies on Fluorinated Pyrimidines: IV. Effects on Nucleic Acid Metabolism in Vivo

Peter B. Danneberg, Betty Jo Montag and Charles Heidelberger


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