Clinical and Pharmacological Studies with 5-Iodo-2'-deoxycytidine*

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SUMMARY

The clinical pharmacology of 5-iodo-2'-deoxycytidine (ICDR) has been investigated in twelve patients with advanced neoplastic disorders and compared with that of 5-iodo-2'-deoxyuridine (IUDR).

Studies of the catabolism of ICDR-I131 in four of these patients revealed that between 85 and 98 per cent of this compound was deaminated, with subsequent cleavage of the formed IUDR to 5-iodouracil, which, in turn, was de-iodinated, with the formation of iodide.

Objective evidence of inhibitory effects on various rapidly growing normal tissues was noted after treatment with ICDR and included stomatitis, hair loss, nail changes, and hematopoietic depression similar to that observed after administration of IUDR.

In those patients in whom metabolic studies with ICDR-I131 were performed, and in whom an adequate maintenance of blood levels of IUDR-I131 did not occur, typical signs of toxicity were not seen, and significant antineoplastic effects were not produced. In one patient in whom sustained blood levels of IUDR-I131 resulted from the ICDR-I131 injected, a marked regression of a carcinoma of the vulva was obtained repeatedly on four occasions. Both the antineoplastic effects and the manifestations of toxicity observed in this patient were comparable to those seen after an identical course of therapy with IUDR-I131.

Recent studies with 5-iodo-2'-deoxyuridine (IUDR) (Chart 1) have indicated that, after its metabolic conversion within cells to the 5'-monophosphate derivative and subsequently to the di- and tri-phosphate esters, this antimetabolite interferes with the utilization of the corresponding derivatives of thymidine formed metabolically within cells (13); in addition, IUDR can be incorporated into DNA in place of thymidine (7, 16, 17, 28, 31) (Chart 2). Through these mechanisms, IUDR can markedly inhibit the replication of DNA and the reproduction of cells; also, as do certain other 5-halogenated derivatives of deoxyuridine, IUDR can increase the sensitivity of mammalian cells to radiation injury (1, 3, 5, 9, 10, 15, 18, 35).

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Including those with a variety of substituents in position-5, are readily subject to loss of their sugar components by nucleosidase action, studies of cytidine and deoxycytidine (19, 26, 29) had indicated that these derivatives of 4-aminopyrimidine are resistant to such catabolic alteration. It was postulated, therefore (37), that 5-iodo-2'-deoxycytidine (ICDR) (Chart 1) might escape enzymatic destruction in vivo and might enter cells as such, with subsequent phosphorylation and deamination to form 5-iodo-2'-deoxyuridine 5'-phosphate in situ (Chart 2).

**CHART 1.**—Chemical structure of 5-iodo-2'-deoxycytidine (ICDR), 5-iodo-2'-deoxyuridine (IUDR), and thymidine.

**CHART 2.**—Simplified diagrammatic representation of the probable metabolic sequences and interrelationship of 5-iodo-2'-deoxyuridine (IUDR) and 5-iodo-2'-deoxycytidine (ICDR) and their phosphorylated derivatives.

Much of the initial work bearing on the metabolic fate and utility of ICDR was carried out with a prototype compound, 5-bromo-2'-deoxycytidine (BCDR) (8, 11, 22, 23), since, until recently, the synthesis of ICDR could not be accomplished. Indeed, established methods of iodination of pyrimidines, when applied to deoxycytidine, do not produce ICDR, and this compound did not become available for study until a new procedure for its synthesis was devised by Chang and Welch (6).

The results of the initial pre-clinical studies of the biochemical pharmacology of ICDR have been described (9, 10, 24). The present clinical investigation was conducted to study the pharmacology of ICDR in man; a preliminary report has been presented (4).

**MATERIALS AND METHODS**

**Clinical material.**—Twelve patients with advanced metastatic neoplasms, who required palliation not obtainable by surgery, irradiation, or standard drugs, were included in this study (Table 1). The patients were aware that they were receiving an investigational agent and approved this therapeutic trial.

**Dosage schedules (Table 1).**—Daily doses of ICDR, ranging from 15 to 100 mg/kg, were administered intravenously during a period of 2 hours. Most patients were treated for 5 consecutive days, but in the three individuals with acute leukemia treatment was continued until the manifestations of the toxic effects of the drug prevented the further administration of the compound. One patient (Case 6) has completed four courses of ICDR and also has received one course of IUDR at the same dose (80 mg/kg daily for 5 days), in order to compare the clinical response to, and the metabolism of, the two agents. Intervals of 1 month separated each course of therapy, and she is currently receiving her fifth course of ICDR. In addition, another patient (Case 7) had received IUDR prior to ICDR, in connection with earlier studies of the uracil derivative (5).

Solutions containing from 8 to 12 mg ICDR/ml in 5 per cent dextrose successfully withstood autoclaving; because of lower solubility and much greater thermolability, weaker solutions of IUDR (5 mg/ml), of necessity, were sterile-filtered.

**Clinical and laboratory evaluations.**—During hospitalization patients were examined daily and, after discharge, at least once a week. Evaluations of physical findings included caliper measurements of accessible tumor masses, total body weight, and frequent photographs of lesions. Total and differential leukocyte counts were performed almost daily. Determinations of hematocrit levels, platelet and reticulocyte counts were obtained from 3 to 5 times a week. Hematopoietic suppression was also studied by bone marrow aspiration, both before and after therapy, as well as by the granulocyte response to serial injections of endotoxin (Pyrexal®); this latter test was carried out twice weekly by a method described in detail elsewhere (20). Diagnostic x-ray studies and other routine laboratory determinations were obtained as indicated.

**Metabolic studies.**—ICDR, either nonradioactive or labeled with 1125, was prepared in this laboratory by the method of Chang and Welch (6).

1 The procurement of the costly precursor of ICDR—namely, deoxycytidine—was made possible by a special grant provided jointly by the Connecticut Division and the National Organization of the American Cancer Society.
IUDR was supplied by the Cancer Chemotherapy National Service Center. IUDR-I\(^{125}\) was prepared in the manner described previously (30). Samples of 5-iodocytosine (IC) and 5-iodouracil (IU) were provided by Dr. P. K. Chang of the Department of Pharmacology. Solutions of ICDR for parenteral administration were prepared by dissolving the compound (4–6 gm.) in 500 ml. of warm 5 per cent dextrose in water and autoclaving the solution for 30 minutes. Solutions of ICDR were administered in five daily doses of 80 mg/kg by slow intravenous infusion during a period of 2 hours. When desired, from 8–50 \(\mu\)c. of ICDR-I\(^{125}\) were added to the normal dose of unlabeled compound as a tracer for the metabolic studies. Blood samples (5–10 ml.) were withdrawn by venepuncture both during the infusion and at intervals thereafter; all urine was collected during a period of 72 hours from the time of the infusion.

For the determination of radioactive metabolites of ICDR-I\(^{125}\) in the blood, the samples were counted initially in a gamma-scintillation counter and then acidified with an equal volume of 2 \(\times\) HClO\(_4\). After centrifugation, the proteinaceous residue was extracted 4 times with 1 \(\times\) HClO\(_4\), and the supernatant fractions were pooled. The radioactivity remaining associated with the residue was then determined. The acid extracts were cooled to 0\(^\circ\)C., neutralized with 6 \(\times\) KOH, and centrifuged to remove insoluble KClO\(_4\). After addition of NH\(_4\)OH to give a final concentration of 0.05 \(\times\), the supernatant fractions were applied to columns (1 \(\times\) 10 cm.) of Dowex 1-formate, together with carrier amounts (0.5 \(\mu\)mole) of ICDR, IUDR, and IU. The columns were then washed twice with 5 ml. of water and eluted with 0.007 \(\times\) formic acid, which removed successively ICDR, IC, IUDR, and IU. Usually between twenty and 25 fractions, each of 5-mL volume, were collected during this procedure. The columns were then eluted with 6 \(\times\) formic acid to remove unidentified acidic breakdown products of ICDR, and then with 6 \(\times\) KI to remove iodide. The radioactive peaks were identified by (a) comparison with reference standards (Chart 3), (b) their spectrophotometric characteristics, and (c) paper chromatography, in comparison with known standards, with butanol:water (86:14) used as the solvent system. Distribution of

### Table 1

**Patients Treated with 5-Iodo-2'-deoxycytidine**

<table>
<thead>
<tr>
<th>Case no.</th>
<th>Age and sex</th>
<th>Diagnosis</th>
<th>Dosage (mg/kg×days)</th>
<th>Tumor response</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>38, F</td>
<td>Hodgkin's disease</td>
<td>15×1</td>
<td>0</td>
</tr>
<tr>
<td>2</td>
<td>56, M</td>
<td>Adenocarcinoma of stomach</td>
<td>40×5</td>
<td>0</td>
</tr>
<tr>
<td>3</td>
<td>64, M</td>
<td>Undifferentiated carcinoma of lung</td>
<td>60×5</td>
<td>0</td>
</tr>
<tr>
<td>4</td>
<td>59, M</td>
<td>Adenocarcinoma of lung</td>
<td>80×5</td>
<td>0</td>
</tr>
<tr>
<td>5</td>
<td>42, F</td>
<td>Epidermoid carcinoma of cervix</td>
<td>80×5</td>
<td>0</td>
</tr>
<tr>
<td>6</td>
<td>57, F</td>
<td>Epidermoid carcinoma of vulva</td>
<td>80×5 Reduction in size of tumor of vulva and inguinal lymphadenopathy</td>
<td></td>
</tr>
<tr>
<td>7</td>
<td>65, F</td>
<td>Adenocarcinoma of colon</td>
<td>80×5</td>
<td>0</td>
</tr>
<tr>
<td>8</td>
<td>67, M</td>
<td>Liposarcoma of gluteal region</td>
<td>80×5</td>
<td>0</td>
</tr>
<tr>
<td>9</td>
<td>45, M</td>
<td>Adrenocortical carcinoma</td>
<td>80×5 100×5</td>
<td>0</td>
</tr>
<tr>
<td>10</td>
<td>42, F</td>
<td>Acute leukemia (blastic crisis of chronic granulocytic)</td>
<td>80×15 Reduction of leukocyte count and splenomegaly</td>
<td></td>
</tr>
<tr>
<td>11</td>
<td>49, M</td>
<td>Acute leukemia (blastic crisis of chronic granulocytic)</td>
<td>80×6 Reduction of leukocyte count</td>
<td></td>
</tr>
<tr>
<td>12</td>
<td>45, M</td>
<td>Acute leukemia (monomyelogenous)</td>
<td>80×8 Reduction of leukocyte count</td>
<td></td>
</tr>
</tbody>
</table>
radioactivity in the urine was determined in a similar manner; thus, 9-ml. aliquots of urine, together with 1 ml. of 0.5 N NH₄OH, were applied to the Dowex columns. Care was taken to elute the ICDR from the column within a few hours, since this compound when adsorbed on Dowex 1-formate decomposed at a rate of 15–20 per cent in 24 hours.

In all three patients with acute leukemia a significant reduction in the total leukocyte count, attributable to the drug, was observed in relation to the administration of ICDR. In one of these patients (Case 10) the decrease in leukocytes (Chart 4) was accompanied by a definite reduction in the size of the spleen (Figs. 5, 6); unfortunately, however, this patient expired before any evidence of improvement of the bone marrow could be detected. Beneficial effects on the bone marrow were not seen in the other two cases by the time the drug had to be discontinued because of toxic manifestations.

No objective evidence of antineoplastic effects was noted in any of the other patients. Although some claimed relief of symptoms, particularly pain, this could have been related to other factors.

Toxic manifestations.—The toxic manifestations observed with ICDR were identical with those of IUDR and were primarily exhibited in rapidly proliferating normal tissues by stomatitis, hair loss, and hematopoietic depression. The prevalence of these manifestations in this series of patients treated with ICDR was similar to that previously encountered in a group of patients receiving IUDR at the same dosage levels (3). Because IUDR has been most difficult to obtain, a direct comparison of the toxicity of the two agents was possible in only one patient. In this woman (Case 6) the degree of stomatitis, hair loss, and nail changes (Figs. 7, 8) were similar after treatment with ICDR or IUDR, each given in intravenous doses of 80 mg/kg daily for 5 days, and the degrees of tumor regression were comparable; the patterns of depression in the numbers of peripheral leukocytes caused by each course of therapy were remarkably similar (Chart 5).

The myelosuppressive effects of ICDR were studied by peripheral blood counts, evaluation of the marrow granulocyte reserves in response to endotoxin stimulation (Pyrexal® test), and bone marrow aspirations. Leukopenia occurred in approximately half of the nonleukemic patients; with the dosage levels of the drugs employed, the degree of leukopenia was better correlated with the clinical status of the patient (liver metastases, recent weight loss, and protein depletion) than with the

RESULTS

CLINICAL OBSERVATIONS

Tumor inhibition.—In this series objective evidence of repeated tumor regression was observed in only one patient, a 59-year-old woman with carcinoma of the vulva (Case 6), in this individual four courses of treatment with ICDR and one with IUDR were given. Successive marked reductions in the size of the large primary mass in the vulva were noted (Figs. 1–4) with concomitant regression of metastatic inguinal nodes. In addition, each course of therapy resulted in striking improvement with respect to manifestations of local irritation and pain, as well as an increase in appetite and gain of weight. The clinical response to each compound was similar, but differences were observed in the levels of drug found in the blood; the products of catabolism of the two agents excreted in the urine will be discussed in a later section.

We are grateful to Drs. John McL. Morris and Gilles D. Hurteau, of the Department of Gynecology, for their participation in the clinical care of this patient.
total amount of drug administered. The response of the bone marrow to endotoxin stimulation, as reflected by the peripheral granulocyte count, frequently permitted a reliable prediction, before therapy, with respect to the effect of the drug on the total leukocyte count (Chart 6). The Pyrexal® test was often a more sensitive index than were peripheral leukocyte counts in the detection of a compromised marrow (Charts 6, 7). Moderate thrombocytopenia without hemorrhagic manifestations was transiently present in two patients with carcinoma (Cases 5, 7), but severe depressions in the levels of thrombocytes, which occurred in all three patients with acute leukemia, were the limiting factor with respect to the continuation of therapy with ICDR; the platelet counts returned to normal levels within 2–3 weeks after the discontinuation of therapy (Cases 11, 19). No significant alterations in the reticulocyte counts were observed. Reduction of cellularity was the predomi-

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**Chart 5.** Response of the total leukocyte count in Case 6 after each of two separate courses of therapy, one with 5-ido-2'-deoxycytidine (ICDR) and one with 5-ido-2'-deoxyuridine (IUDR); both drugs were given at identical doses of 80 mg/kg daily for 5 days.

**Chart 6.** Case 5. Response of the total leukocyte count during course of therapy with 5-ido-2'-deoxycytidine (ICDR) (upper graph). Maximal absolute granulocyte response after administration of 0.1 mg of endotoxin (Pyrexal®) (lower graph). Note that abnormal granulocyte response (under 3,000 cells per cu. mm.) accurately predicted the occurrence of severe leukopenia before the start of therapy when the total leukocyte count in the peripheral blood was above normal limits (over 5,000 cells per cu. mm.).

**Chart 7.** Case 7. Response of the total leukocyte count during course of therapy with 5-ido-2'-deoxycytidine (ICDR) (upper graph). Maximal absolute granulocyte response after administration of endotoxin (Pyrexal®) (lower graph). Note that the granulocyte response was abnormally low (under 2,000 cells cu. mm.) from the 6th to the 15th day after initiation of therapy, the period of expected leukopenia. The failure of the peripheral total leukocyte count to fall below normal limits (under 5,000 cells per cu. mm.) suggests that, in this patient, this determination was a less sensitive index of myelosuppressive effective than was the Pyrexal test.
nant change seen in the smears of bone marrow aspirates obtained shortly after the 5-day period of therapy. The manifestations of hematopoietic toxicity were completely reversible within 3–4 weeks after the initiation of therapy.

In addition to stomatitis, varying degrees of anorexia, nausea, and diarrhea sometimes occurred during or after the period of treatment; however, these were only questionably related to therapy.

CHART 8.—Rate of disappearance of total radioactivity in the blood after the intravenous infusion, during a 2-hour period, of 80 mg. of 5-iodo-2′-deoxycytidine (ICDR) (containing I¹²⁵) per kg.

As with IUDR, gastrointestinal manifestations were always mild, although diarrhea was somewhat more frequent in the present series of patients than in that in which IUDR was administered (3).

Loss of hair was encountered in approximately half of the patients treated with ICDR and was comparable in extent to that seen with IUDR in the same dosage range. In two patients (Cases 6, 7) nail changes consisting of transverse ridges and discolorations were observed (Figs. 7, 8). This interesting lesion of another rapidly growing dermal appendage has been reported during treatment with 5-fluorouracil (36) and has been observed by us after therapy with IUDR.

A metallic taste, probably related to the presence of catabolically released free iodide formed from ICDR, was reported by a few patients during the infusions. Three individuals evidenced manifestations frequently associated with mild iodism; these consisted of periorbital edema, acneform dermatitis, and parotid enlargement with pain.

CLINICAL PHARMACOLOGY

Blood levels.—The rates of disappearance of I¹²⁵ from the blood of the four patients are shown in Chart 8. In Case 6 significant levels of radioactivity were found as late as 48 hours after the infusion. The critical point, however, is the form in which this radioactivity is available. In Cases 4 and 6, ICDR was rapidly eliminated from the circulation, whereas it persisted for a longer time in the other patients (Chart 9). Extensive conversion of ICDR to IUDR was evident (Chart 10), and, in Case 6, significant levels of this compound were maintained for 12 hours. As can be seen in Table 2, however, the larger proportion of the radioactivity was in the form of IU and iodide. It is important to emphasize that 5-iodocytosine was not found in any sample and that from 15 to 30 per cent of the total radioactivity in the blood was bound to protein.

Urinary excretion.—Between 95 and 102 per cent of the administered radioactivity was recovered in the urine during a period of 72 hours after the infusion. The rates of urinary excretion of total I¹²⁵ are shown in Chart 11; that of Case 6 was somewhat slower than in the other three patients, but the difference was not especially marked. During the first few hours, deoxyribonucleosides accounted for a considerable proportion of the excreted radioactivity, but in the later stages iodide predominated (Chart 12). Table 3, which presents the complete excretion data for the 72-hour pe-
period, shows that there is considerable variation in
the extent to which the different metabolites ac-
cumulate.

Comparison with metabolism of IUDR.—In Case
6, the metabolism of IUDR-1135 (50 μc.), adminis-
tered in the same way as ICDR at a dose level of
80 mg/kg, was studied. The curves for blood levels
and excretion of total radioactivity were virtually
superimposable, but there were marked differences
in the levels of IUDR in the blood; these, although
initially lower after the administration of ICDR,

![Chart 10](chart10.png)

![Chart 11](chart11.png)

**TABLE 2**

<table>
<thead>
<tr>
<th>Time† (hours)</th>
<th>Percentage of radioactivity</th>
<th>Iodide</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>5-Iodouracil</td>
<td>Iodide</td>
</tr>
<tr>
<td></td>
<td>Case 4</td>
<td>Case 6</td>
</tr>
<tr>
<td>0</td>
<td>10</td>
<td>13</td>
</tr>
<tr>
<td>2</td>
<td>19</td>
<td>13</td>
</tr>
<tr>
<td>4</td>
<td>20</td>
<td>15</td>
</tr>
<tr>
<td>8</td>
<td>21</td>
<td>32</td>
</tr>
</tbody>
</table>

* Details of determinations are given in the text.
† The end of the 2-hour infusion is referred to as hour 0.

**TABLE 3**

<table>
<thead>
<tr>
<th>Compound</th>
<th>Percentage of total radioactivity</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Case 4</td>
</tr>
<tr>
<td>ICDR</td>
<td>11.1</td>
</tr>
<tr>
<td>IUDR</td>
<td>11.6</td>
</tr>
<tr>
<td>5-Iodouracil</td>
<td>22.8</td>
</tr>
<tr>
<td>6 N-formate fraction</td>
<td>13.4</td>
</tr>
<tr>
<td>Iodide</td>
<td>41.0</td>
</tr>
</tbody>
</table>

* Details of determinations are given in the text.
were subsequently sustained (as IUDR) for a longer period (Chart 13).

DISCUSSION

Investigations of IUDR in patients with advanced neoplastic disease have demonstrated that this potent inhibitor of cellular replication is capable occasionally of causing marked regressions of solid tumors and of increasing the sensitivity of tissues to the injurious effects of radiation (3). These effects have been observed, even though only a small proportion of the cells in human neoplasms in vivo are in the DNA-synthesizing phase of their growth cycle and the time of exposure of these cells to IUDR is limited essentially to the %-hour period of intravenous infusion and for 2 hours thereafter. These observations suggest that phosphorylation of IUDR inside the cell not only prevents its egress but, in addition, enables the cell to maintain an adequate concentration of the analog for subsequent inhibition of both the biosynthesis and the utilization of the phosphorylated derivatives of thymidine, as well as for incorporation of IUDR into DNA. Thus, a single daily administration of IUDR to mice bearing neoplasms was as efficacious as were three divided doses (21). Very marked increases in the amount of IUDR incorporated into the DNA of Ehrlich ascites tumor cells in vivo occurred when both the total amount of IUDR injected and the frequency of administration were increased (31).

It is clear that the optimal conditions for the clinical evaluation of IUDR remain to be elucidated. Although continuous intravenous infusions of IUDR have been administered for several days, the obvious limitations of these dosage schedules spurred the search for derivatives with greater metabolic and chemical stability. Since cytosine-containing compounds appeared to be more resistant than the corresponding derivatives of uracil to cleavage by nucleosidases in vitro (14), studies of BCDR and ICDR were initiated in animals (8—11, 33) as soon as these compounds became available. Although studies in the rat have shown that BCDR is more stable metabolically than 5-bromo-2'-deoxyuridine (23, 25), investigations in man have not been equally encouraging (22). Corresponding studies with ICDR in mice and rats indicated that, although the compound is rapidly metabolized by the mouse (8, 10), catabo-
lism is much slower in the rat (18, 24). The first metabolic alteration can be attributed to a nucleoside deaminase, present to a variable degree in mammalian tissues, which converts ICDR directly to IUDR before phosphorylation can occur (18). On the other hand, because of certain notable advantages of ICDR over IUDR (namely, its greater solubility and sufficient thermostability so that solutions can be sterilized by autoclaving), and because species differences in enzyme patterns are encountered frequently, the present clinical trials of the deoxycytidine derivative were conducted. These studies have shown that human subjects differ in their capacity to maintain blood levels of IUDR derived from injected ICDR; consequently, investigations of various normal and malignant tissues for deaminase activity are underway. Rapid disappearance of ICDR from the blood should not be taken necessarily to imply that rapid deamination is occurring, since the evidence from urinary excretion studies, in which unchanged ICDR was excreted during the 48-hour period after administration, suggest that sequestration of the compound by the tissues is an important factor. It is significant that, in those patients in whom metabolic studies with ICDR-I are done and in whom an adequate maintenance of blood levels of IUDR did not occur, significant antineoplastic effects were not produced and such typical signs of toxicity as stomatitis and alopecia were not evident; in addition, hematopoietic depression was not observed in the two patients without blood dyscrasias. On the other hand, in the patient in whom sustained blood levels of IUDR resulted from the ICDR injected, a marked regression of a carcinoma of the vulva was obtained repeatedly on four occasions; furthermore, the manifestations of toxicity observed in this patient were comparable to those seen after an identical course of therapy with IUDR.

The cytotoxic effects of ICDR observed in this study resembled those seen with IUDR at similar dosage levels in a previous series (3); as discussed previously, these included stomatitis, hematopoietic suppression, and loss of hair. It also would appear from these studies that the myelosuppressive properties of ICDR lack specificity for leukemic cells. Thus, although a definite depression of the total leukocyte count was observed in all three cases with leukemia and a regression of splenomegaly was noted in one, marked thrombocytopenia was induced in these patients by the drug, and this effect on bone marrow already compromised by leukemic infiltrations made it necessary to discontinue therapy with ICDR.

A study of the catabolic fate of ICDR in these patients revealed that between 85 and 98 per cent of this compound was deaminated, with subsequent cleavage of the formed IUDR to 5-iodouracil, which, in turn, was de-iodinated, with the formation of iodide. A similar sequence of metabolic events was observed in mice (10, 24). Although no marked differences were observed in the total amounts of ICDR which escaped deamination, a considerable variation was observed in the rate at which this occurred. Analogous conclusions regarding the degradation of ICDR in rodents and in man have been reached by Kriss et al. (22, 24).

Finally, it should be emphasized that it was not the purpose of this study to determine the ultimate clinical value of ICDR, but to study its pharmacology in man. Further studies with ICDR and IUDR, to determine their relative clinical utility, are in progress.

ACKNOWLEDGMENTS
We are grateful to Mrs. Barbara Livingston, R.N., and to Mr. Thomas Collins for competent technical assistance.

REFERENCES
Figs. 1-4.—Regression of carcinoma of the vulva observed in Case 6 after treatment with 5-iodo-2'-deoxyuridine (ICDR).

Fig. 1.—Before therapy; Fig. 2, 2d week after initiation of drug; Fig. 3, 3d week; Fig. 4, 4th week. The tumor began to escape from the inhibitory effects of ICDR at the end of the 8th week and grew rapidly during the 6th week. Subsequent courses of therapy with ICDR or, in one instance, with 5-iodo-2'-deoxyuridine (UDR), resulted in similar reductions in size of the primary mass. Both drugs were given at doses of 80 mg/kg daily for 5 days.
FIGS. 5, 6.—Reduction in size of the spleen in a patient with chronic granulocytic leukemia in blastic crisis (Case 10). Fig. 5, before and Figure 6, after treatment with 5-iodo-2′-deoxyctydine (ICDR).
Figs. 7, 8.—(Case 6). Toxic manifestations observed after treatment with 5-iodo-2'-deoxycytidine (ICDR). The degree of stomatitis (Fig. 7) and the changes in the nails (Fig. 8) were identical to those seen after a similar course of 5-iodo-2'-deoxyuridine (IUDR). Both drugs were given at doses of 80 mg/kg daily for 5 days.
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