Comparative Study of the Toxicologic Effects of 7-Deazaadenosine (Tubercidin) and 7-Deazainosine

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SUMMARY

Differences were found between the toxicologic effects of tubercidin and those of 7-deazainosine which were consistent with the idea that 7-deazainosine requires conversion into anabolites of tubercidin in order to exert biologic effects. In rodents treated parenterally, and in dogs treated orally, tubercidin was 6- to 20-fold more toxic than 7-deazainosine. Severe local reactions occurred only in rats treated with tubercidin. In contrast, necrosis of the walls of the intrahepatic bile ducts and of the myocardium was found only in rats treated with 7-deazainosine. Pulmonary edema, focal necrosis of hepatic parenchyma, and generalized lymphoid depression were observed after either drug. After treatment of dogs with tubercidin, pneumonia, renal tubular necrosis, and gastrointestinal toxicity were severe, whereas hepatotoxicity was slight and infrequent. Only tubercidin caused atrophy of the Islands of Langerhans.

In view of the lack of local and renal toxicity, 7-deazainosine may offer therapeutic advantages over tubercidin provided that hepatotoxicity is not a limiting factor.

INTRODUCTION

TU exerted marked cytotoxicity in vitro (1, 14), and inhibited the growth of several tumors in vivo (14). Because of its marked cytotoxicity, the drug was considered worth testing for possible clinical anticancer activity (14).

In this laboratory, DI was found to be active in vitro on Sarcoma 180 but not on S. faecalis, a microorganism sensitive to TU (2, 3). In mice and rats, DI was less toxic than TU (2, 12, 16). Since in vitro DI was converted into 7-deazaadenylic acid upon incubation with sensitive, but not with insensitive, cells, it was suggested that this conversion may be a prerequisite for activity in vivo (4, 13). Consequently, the possibility was considered that the requirement for metabolic activation of DI might result in a more favorable selective tissue toxicity of this compound than that of TU. The comparative study of the toxicologic effects of TU and DI is the subject of the present report.

MATERIALS AND METHODS

Mice, weighing 17—22 gm, were obtained from the Roswell Park Memorial Institute breeding colony. The Sprague-Dawley CD Charles River rats weighed 150—200 gm. Adult mongrel dogs of both sexes were used. The quarantine procedures adopted, the design followed for the toxicity tests, and the methods used in the biochemical and hematologic studies have been reported previously (10, 11). Since in dogs only biochemical parameters of hepatic and renal function, and glycemia levels, were significantly changed as a result of drug treatments, only these data are shown in detail. DI was initially prepared by Dr. A. Bloch of this Department and was then provided, together with TU, by the Upjohn Co. through the courtesy of Dr. C. G. Smith. TU was dissolved in 1% HCl solution, and the pH was then adjusted to about 6 by the addition of a 1% NaOH solution. DI was dissolved in saline (pH about 5). All the solutions were prepared shortly before use.

RESULTS

Toxicity in Mice

The LD₅₀'s of TU and DI in DBA/2 Ha and Swiss mice by the i.p. route are shown in Table 1. At doses within the LD₅₀ range, death was delayed and occurred over an extended period of time. For instance, Swiss mice died 7—85 days after treatment with a single dose of 6 mg/kg of TU. At autopsy, massive peritonitis was observed in mice treated with TU but not in those treated with DI.

Toxicity in Rats

Course of Intoxication. The LD₅₀'s of TU and DI in rats are shown in Table 1. Tu was more toxic than DI i.p. or s.c. but not p.o. The LD₅₀ of DI was similar regardless of the route of administration. At doses in the LD₅₀ range, death occurred 3—12 days after single or repeated treatments with DI by all routes and s.c. or p.o. with TU. Rats treated with TU i.p. died 17—30 days or 6—60 days after single or repeated doses respectively, with massive peritonitis.

This investigation was supported in part by a research grant (CA 04130) from the National Cancer Institute, USPHS.

The abbreviations used are: TU, tubercidin or 7-deazaadenosine; DI, 7-deazainosine; LD₅₀, median lethal dose; AP(P), serum alkaline phosphatase; SGOT, serum glutamic oxaloacetic transaminase.

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Toxicologic Effects of 7-Deazainosine

Table 1

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<tr>
<th>Animals used</th>
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<th>Route of administration</th>
<th>No. of successive daily doses</th>
<th>LD50b, b (mg/kg/day)</th>
<th>19/20 confidence limits (mg/kg/day)</th>
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Lethal effects of tubercidin and 7-deazainosine in rodents.

*Median lethal dose.

*bCalculated according to Litchfield and Wilcoxon (8).

Following treatment with either drug, moderate losses of body weight were noted. In a few animals jaundice was observed 20–40 days after treatment. On Days 2–4, diarrhea was profuse in rats given TU p.o. In animals injected s.c. with TU, severe local reactions were followed occasionally by loss of hair and ulceration.

No leucopenia was noted in rats 3, 6, 9, or 13 days after the beginning of treatment with 5 consecutive daily i.p. doses of 0.5–1.0 mg/kg of TU or 4–6 mg/kg of DI (5 animals per group).

Pathologic Effects of Tubercidin. Autopsy was performed on 69 rats treated with single or 5 consecutive daily doses in the LD50 range or higher. The findings were similar in animals treated by the same route with single or repeated equitoxic doses.

Five days after the beginning of i.p. treatment, peritonitis was evident in all the animals, pleural effusion in some. By the 20th day after treatment, massive abdominal adhesions were noted causing intestinal obstruction. Mottled livers with round edges were present. These changes were also seen in rats autopsied as late as 120 days. Following s.c. injections, clear pleural effusion and hemorrhagic lesions on the lung were noted in almost all the rats which died. Severe local reactions were also seen. After p.o. administration, the intestines appeared dilated, edematous, hemorrhagic and full of opalescent fluid. Pleural effusion was found in many cases. No peritonitis was seen after s.c. or p.o. administration.

Except for the effects related to the local toxicity, the histologic study did not reveal any major qualitative difference attributable to the route of administration.

Pulmonary edema was seen in the majority of the rats, which were autopsied 2 days after the end of treatment. In the liver 1–2 days after the end of treatment, loss of glycogen was evident, and a few foci of necrosis were present. Mitotic figures were seen in the parenchyma of 70–80% of the rats at Days 3–8. One to 5 days after repeated p.o. or s.c. doses, liver necrosis was more severe than after i.p. injections, and large amounts of fat were present. Forty-two days after i.p. injections, biliary proliferation, increased cellularity in the portal tracts, and a few foci of necrosis were present in 12 of 25 rats and were correlated with the severity of adhesions in the portal fissure. Pyknosis of lymphocytes was noted in rats sacrificed 2 days after the end of i.p. treatment. Evidence of regeneration was seen 2 days later. No consistent renal lesions were noted. Except for secondary effects related to peritonitis, no signs of toxicity were observed in other organs.

Pathologic Effects of 7-Deazainosine. Autopsy was performed on 76 rats treated with doses in the LD50 range. The peritoneal reactions were slight and not associated with adhesions. No skin reactions occurred after s.c. administration.

Since the histologic study of tissues did not reveal any qualitative difference attributable to the route of administration, only the observations made in rats treated i.p. will be described in detail.

Pulmonary edema was seen in 3 of 12 rats 2–4 days after single injections.

In the liver of 6 rats sacrificed 1 day after single doses, only swelling of parenchymal cells was noted. In the 21 animals sacrificed 2–4 days after treatment, the parenchymal cells were small and contained fat, and some foci of necrosis were present. Early necrosis of the epithelium was seen in the larger intrahepatic bile ducts 2 days after treatment. Two to 6 days later, necrosis of the wall of the intrahepatic bile ducts was seen in 10 of 12 rats (Fig. 1), and the surrounding inflammation involved the whole portal tract including the walls of the blood vessels. In no instance were these changes observed in
the common bile duct. In rats given repeated doses, parenchymal changes were similar, but only minor alterations in the bile duct epithelium were seen. Hepatotoxicity was more severe in rats treated p.o. or s.c. Small foci of inflammation were noted in the liver of only 3 of 19 rats sacrificed 42 days or more after treatment.

Pyknosis in thymus and spleen lymphocytes was seen in rats sacrificed 1 day after single doses and was maximal 1–3 days later. At this time, some necrosis of hematopoietic cells was noted. Early regeneration of lymphoid tissue was seen in some rats on Day 4. Marked recovery of lymphoid tissue and bone marrow occurred in the majority of the animals by Day 8. In rats autopsied 4 days after the end of treatment with 5 daily doses, the lymphoid depression remained severe.

Slight changes were seen in the intestinal epithelium of rats sacrificed 1–4 days after single treatments. Small areas of inflammation with a few necrotic fibers were seen in the hearts of 6 of the 12 rats sacrificed 4–8 days after single doses. No such lesions were found in rats treated repeatedly.

Toxicity in Dogs

Course of Intoxication. The toxic effects caused by TU and DI were studied in 55 dogs (Table 2). TU was more toxic p.o. than i.v. The toxicity of DI was similar by either route. In dogs treated i.v. with DI, a sharp increase of lethality occurred as a consequence of a relatively small increase of dosage. Neither drug caused major cumulative toxicity.

The toxic effects of TU consisted of vomiting and bloody diarrhea, both of which occurred in all but 1 of the dogs which eventually died, and were more severe after p.o. treatment. Anorexia was noted in half of these dogs. Losses of body weight up to 35% of the initial weight were observed in the lethally intoxicated animals. Severe multiple skin ulcerations developed in the proximal part of the forelegs and under the axilla in 3 of 7 dogs which survived 3 weeks or more after i.v. treatment with 2–5 mg/kg.

The toxic signs caused by DI were similar to those elicited by TU except that no skin ulcerations were noted. Jaundice developed in 5 of 11 dogs which survived a course of 10 i.v. treatments with 4–6 mg/kg. In 1 dog this sign became evident 1 week after the end of treatment.

Hematologic and Blood Biochemical Changes. The changes caused by TU were studied in 17 dogs treated repeatedly i.v. and in 7 of the 8 dogs treated p.o. with 0.5–4.0 mg/kg; those caused by DI were studied in 15 dogs treated i.v. with doses of 2–6 mg/kg and in 5 dogs treated repeatedly p.o. (Table 2).

After treatment with TU, hemoconcentration occurred in most of the dogs, and its severity was related to the severity of the toxic effects caused by TU and DI was similar to those elicited by TU except that no skin ulcerations were noted. Jaundice developed in 5 of 11 dogs which survived a course of 10 i.v. treatments with 4–6 mg/kg. In 1 dog this sign became evident 1 week after the end of treatment.

Hematologic and Blood Biochemical Changes. The changes caused by TU were studied in 17 dogs treated repeatedly i.v. and in 7 of the 8 dogs treated p.o. with 0.5–4.0 mg/kg; those caused by DI were studied in 15 dogs treated i.v. with doses of 2–6 mg/kg and in 5 dogs treated repeatedly p.o. (Table 2).

After treatment with TU, hemoconcentration occurred in most of the dogs, and its severity was related to the severity of the toxic effects caused by TU and DI was similar to those elicited by TU except that no skin ulcerations were noted. Jaundice developed in 5 of 11 dogs which survived a course of 10 i.v. treatments with 4–6 mg/kg. In 1 dog this sign became evident 1 week after the end of treatment.
the bloody diarrhea and vomiting. Granulocytosis developed in 8 dogs treated i.v. and reached values higher than $20 \times 10^3$ cells per cu mm in 5 of them. Reticulocytopenia was noted in 6 of the 9 dogs which died after i.v. treatment and in a dog given 1 mg/kg X 8 p.o. After DI the hematologic changes were similar to, but less frequent than, those seen after TU. In addition, thrombocytopenia to levels below $100 \times 10^3$/cu mm was observed in a dog treated with 5 mg/kg i.v. which was sacrificed on Day 15.

After i.v. treatment with TU, prolongation of prothrombin time was significant in 4 dogs, the greatest being that noted in Dog No. 2 (Table 3). SGOT activity was increased only slightly in Dog No. 3 and in 3 other cases, whereas AP(P) activity remained unchanged. Slight hypoglycemia was observed in Dog No. 2 and in 3 other animals; hyperglycemia was seen terminally only in Dog No. 3. Marked elevation of BUN was accompanied by an increase of the inorganic phosphorus level and was seen in 8 of the 9 dogs which died after i.v. treatments and in the dog given 1 mg/kg X 8 p.o. No significant changes occurred in the 8 dogs which survived after i.v. treatment with 2–5 mg/kg. Except for hemococoncentration, no change occurred in 6 of the 7 dogs treated p.o.

After treatment with DI, marked prolongation of prothrombin time was noted in 13 dogs, and it was more than 60 sec in 3 dogs which also developed jaundice. The data obtained in 1 of these dogs (No. 4) are shown in Table 3. In most cases this prolongation was the 1st change to become evident. Among the animals treated i.v., this sign was accompanied by significant increases of AP(P) and/or SGOT activity in each dog, except in 1 which died on Day 6. Prolongation of prothrombin time without increases in the activity of the 2 enzymes also occurred in the dogs treated p.o.

Moderate hypoglycemia occurred in 2 dogs treated with 6–10 mg/kg p.o., and hyperglycemia in 1 treated with 5 mg/kg/day i.v.

As indicated by the observations made in 2 dogs (data not shown), prolongation of prothrombin time up to 66 sec and increases of SGOT activity up to 158 units/ml were not necessarily followed by death and were reversible upon discontinuation of treatment. To evaluate this point further, 2 dogs were treated i.v. with 6 injections of 6 mg/kg, a dose which had been lethal to 4 of 4 dogs when given 10 times. Data obtained in 1 of these 2 animals (Dog No. 5) are shown in Table 3. Both of the dogs showed a prolongation of prothrombin time on the day of the last injection and an increase of AP(P) activity a few days later. Dog No. 5 also showed an increase of SGOT activity. In this dog return of these functional parameters to normal levels occurred ultimately. The other dog was recovering and was sacrificed for pathologic study 8 days after the end of treatment.

No abnormal changes were noted in 3 dogs treated i.v. with 4 mg/kg/day for 10 days and in 2 dogs treated i.v. with 2 mg/kg/day for 20 days.

Pathologic Effects of Tubercidin. The pathologic changes were studied in 13 dogs treated i.v. and in 7 dogs treated p.o. Intestinal hemorrhages and/or pneumonia were observed in all

### Table 3

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<th>Prothrombin time (sec)</th>
<th>AP(P) (mg %)</th>
<th>P (mg %)</th>
<th>SGOT (units/ml)</th>
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Effects of intravenous administration of tubercidin and 7-deazainosine in mongrel dogs.  
AGiven daily except during weekends.  
BCounted from the day of the first injection.  
C$AP(P)$, alkaline phosphatase; $P$, inorganic phosphorus; SGOT, serum glutamic oxaloacetic transaminase (1 unit is the amount of enzyme which will cause a change in $OD_{340}$ of 0.001 per min per cm light path at 25°C in a system coupling the transaminase reaction to malic dehydrogenase and measuring the rate of disappearance of DPNH at 340 nm. See Reference 10).
the dogs which died during, or shortly after, the end of treat-
ment. After p.o. administration, diffuse gastrointestinal hem-
orrhages were the predominant effect seen.

In the mucosa of the stomach of 4 dogs treated p.o. with
1—5 mg/kg, edema was associated with surface necrosis. Intes-
tinal mucosa changes were generally maximal in the ileum and
varied from blunting of villi to total necrosis of mucosa and
submucosa.

Histologic changes in the liver ranged from a slight loss of
normal vacuolation of parenchymal cells to the presence of fat
and small areas of necrosis. The extent of the lesions was not
directly correlated with the changes of the parameters of
hepatic function seen prior to death.

Pancreatic lesions were seen in 2 dogs treated i.v. with 4
mg/kg for 10 days and in 3 dogs treated p.o. with 1—5 mg/kg
which died 3—5 days from the beginning of treatment. These
lesions consisted of a reduction in cellularity or complete loss
of cells in the Islands of Langerhans. Marked hyperglycemia
was observed terminally in Dog No. 3, in which the pancreatic
lesion was most severe.

Histologic evidence of severe renal tubular necrosis was
found in 6 of 7 dogs which died after i.v. treatments. Early
renal necrosis was seen in the 2 dogs treated p.o. with 4 of 5
mg/kg which died on the 3rd day. No lesions were found in
the 6 dogs treated i.v. which recovered and in 5 animals
treated p.o. with doses lower than 4 mg/kg.

Severe generalized lymphoid depletion was observed in most
of the intoxicated dogs. Slight reduction in cellularity of the
bone marrow was also seen. The presence of giant cells in the
germinal epithelium of the testis was noted only in Dog No. 3.

**Pathologic Effects of 7-Deazainosine.** The pathologic effects
caused by repeated administration of DI were studied in 12 of
the 17 dogs which had been treated i.v., and in the 5 dogs
which had been treated p.o. At autopsy, pneumonia was found
in 2 dogs treated i.v. Hemorrhages were noted in the viscera
of 4 dogs. Jaundice was seen in 5 dogs. The liver was frequently
pale, occasionally with scattered red patches as, for example,
in Dog No. 4. The liver was slightly granular in 2 dogs treated
with 5 mg/kg/day.

Histologic evidence of liver changes were noted in all 17 dogs
studied. Parenchymal necrosis was present in the livers of Dog,
No. 4 and 7 other dogs treated with 10 doses of 4—6 mg/kg
i.v. or 6—10 mg/kg p.o.; the animals were autopsied 4—17 days
after the beginning of treatment. The necrosis ranged from
focal to massive and was associated with accumulation of fat
and inflammatory cells. In each of these dogs, except one,
increases of SGOT or AP(P) activity, or of prothrombin time,
had been observed. In contrast to this acute picture, in a dog
treated with 5 mg/kg/day X 10, which was sacrificed 70 days
after treatment, the architecture of the liver was grossly dis-
turbed (Fig. 2). Prothrombin time and AP(P) and SGOT activi-
ties had returned to normal levels in this dog at the time of
sacrifice. In 6 of the 8 other dogs, sacrificed 14—53 days after
the beginning of treatment with 4—6 mg/kg, there was some
irregularity of architecture, and the parenchymal cells were
evernumously enlarged (Fig. 3). No fat was found in frozen sec-
tions stained with oil red O. Although some glycogen was
demonstrated in these cells in paraffin-imbbed sections, the
amount observed did not seem to account for the enormous
vacuoles seen. Further steps were not taken to identify the
substance present.

Hemorrhages and small amounts of necrosis were found in
the gastrointestinal mucosa of 4 of the 5 dogs treated p.o. No
pancreatic lesions were seen.

Renal lesions consisted of protein exudate in the glomerular
space in 5 dogs, with tufting of glomerular loops and capsular
adhesions in 2. Severe tubular necrosis with hemorrhage was
noted only in 1 dog, treated i.v. with 6 mg/kg, which died on
the 14th day.

Lymphoid depression was observed in 8 dogs; it was very
severe in 4. A slight depression of bone marrow was seen in 3
dogs. Atrophy of the germinal epithelium of the testis was
found in the 7 male dogs studied.

**DISCUSSION**

Both quantitative and qualitative differences were noted be-
tween the toxicity of TU and that of DI. In rodents the i.p.
or s.c. lethal doses of TU were 6- to 20-fold smaller than those of
DI, but in rats they were comparable p.o. The reduced lethal-
ity of TU by this route may be related, at least in part, to the
absence of peritonitis. In dogs, lethal doses of TU were 6-
fold smaller than those of 7-deazainosine p.o. but not i.v.
Severe local toxicity caused by TU was not seen after
equitoxic doses of DI. Nevertheless, this difference did not
seem to be in each case the major cause for the quantitative
differences in lethality seen between TU and DI. For example,
in rats treated s.c. or p.o., and in dogs treated p.o., the time of
death following LD50’s of either drug was comparable in spite
of the major differences in local toxicity observed.

Both in rats and dogs, the LD50’s of DI and the time of
death were independent of the route of administration. This
observation suggests that comparable drug levels are reached
at critical target tissues following administration by any route.
Since hepatotoxicity was seen in each case, the hypothesis that
DI is activated primarily in the liver should be considered.

Qualitative differences in toxicity were also noted. In rats,
selective necrosis of the walls of intrahepatic bile ducts was
causd only by DI. It is likely that this effect requires relatively
high concentrations of active drug in order to become evi-
dent, because it was seen only after administration of single
doses in the LD50 range or higher. The fact that this effect did
not occur after repeated doses in the LD50 range or higher
indicates that it was not necessarily related to the lethal action
of DI. Necrosis and inflammation in the myocardium were also
seen only after single lethal doses of DI. However, the possibil-
ity cannot be excluded that toxic changes of cardiac function
may be related to early death in cases in which no pathologic
evidence of myocardial damage was seen. Both drugs may
affect the cardiovascular system or the smooth muscles similarly
to adenosine and some of its derivatives (6, 9). However,
preliminary in vitro tests on isolated rabbit jejunum indicated
that TU caused transient depression of spontaneous motility
only at concentrations about 50-fold greater than those re-
quired for adenosine to elicit comparable effects; DI had no
activity (unpublished data).

In dogs, TU, but not DI, caused severe gastrointestinal tox-
icity and atrophy of the Islands of Langerhans. Moreover, renal tubular necrosis and pneumonia were seen in most of the dogs lethally intoxicated with TU, whereas only 1 of the dogs treated with DI had renal tubular necrosis and 2 had pneumonia. In some cases, DI, but not TU, caused renal glomerular damage. Severe and consistent parenchymal liver damage was caused by DI but not TU.

The renal injury caused by TU seemed to be more readily reversible than the hepatic damage caused by DI. In fact, no kidney histopathology related to previous drug injury was observed in dogs, which were sacrificed 25—109 days after treatment with doses of TU in the LD_{50} range. In contrast, hepatic damage was found in animals, completely recovered in terms of functional signs, which were sacrificed 42—70 days after treatment with comparable doses of DI. During 20-day treatments, neither compound caused delayed effects qualitatively different from those observed during or after subacute courses.

The differences observed between the toxicity of TU and that of DI may be related to a requirement for metabolic activation of DI. Indeed a correlation was apparent between the inhibitory activity of DI on Sarcoma 180 cells in culture and the formation of 7-deazaadenylic acid after incubation of DI with homogenates from these cells and, on the other hand, between the lack of inhibitory activity on S. faecalis and the lack of such metabolic transformation by S. faecalis extracts (2, 4). Recently, inosine kinase activity was demonstrated in cell-free extracts of Ehrlich ascites cells (15). Thus it is conceivable that tissue sensitivity to DI is related either to in situ formation of 7-deazaadenylic acid, which is also a metabolic product of TU (3), or to exposure to TU and/or derivatives formed from DI in other sites, such as the liver. However, the toxicologic differences between TU and DI may also reflect different patterns of drug disposition. For example, it was found that, in dogs, 0.25% of the TU injected i.v. is excreted in urines within 24 hours, in contrast to the 25% of DI which is excreted within the same period of time (16).

Some of the toxicologic effects of TU and DI described in this report are not necessarily unique for these compounds among purine riboside derivatives. For example, 2-fluoroadenosine (F. S. Philips, personal communication) caused severe local toxicity in rats and both pancreatic and hepatic changes in dogs which were quite comparable to those elicited by TU. Moreover, in dogs, 2-fluoroadenosine also induced hyperglycemia or hypoglycemia, which were correlated with pancreatic and adrenal injury. No renal damage was observed, however, in rats, this adenosine analog caused myocardial lesions similar to those seen in animals treated acutely with DI. It is apparent that purine riboside derivatives may have common, as well as different, pharmacologic features. The differences seen among some of these active derivatives in terms of major toxicologic effects need not reflect basic differences in intracellular mode of action (3, 5), but may be the consequence of specific pharmacodynamic characteristics.

The fact that cytotoxic purine riboside derivatives can exert different toxicologic effects in vivo suggests the possibility that therapeutic advantages may be provided by new compounds of this type. For instance, DI may offer therapeutic advantages with respect to TU by virtue of the fact that it does not cause severe local or renal toxicity. Indeed local cytotoxicity in and around veins, and renal tubular toxicity, were among the major side effects of TU in man (7). In the case of DI, however, hepatotoxicity was severe in animals and may constitute a substantial limitation during the clinical trial of this compound.

ACKNOWLEDGMENTS

The authors are indebted to Mrs. L. Loth, Mrs. G. Stein, and Mr. J. Stachowicz for their proficient assistance in the course of this investigation. The interest in this work of Drs. A. Bloch and C. A. Nichol is gratefully acknowledged.

REFERENCES

E. Mihich, C. L. Simpson, and A. I. Mulhern


Fig. 1. Necrosis of the wall of a large intrahepatic bile duct associated with a heavy infiltration of the portal tract in a rat sacrificed 4 days after a single i.p. dose of 24 mg/kg of 7-deazainosine. Inflammatory cells included many polymorphonuclear leucocytes. H & E, × 125.

Fig. 2. Fatty cysts and fibrosis with distortion of architecture in the liver of a dog treated with 5 mg/kg/day of 7-deazainosine for 10 days which was sacrificed on Day 70.

Fig. 3. Grossly swollen liver parenchymal cells in a dog sacrificed 28 days after the beginning of 10 consecutive daily p.o. treatments with 4 mg/kg of 7-deazainosine. H & E, × 200.
Toxicologic Effects of 7-Deazainosine
Comparative Study of the Toxicologic Effects of 7-Deazaadenosine (Tubercidin) and 7-Deazainosine

E. Mihich, C. L. Simpson and A. I. Mulhern