does not replicate (that is, there is no evidence of uptake of tritiated thymidine). It seems probable that the radiation injury that responds to anticoagulant therapy is endothelial "damage" and is not dependent on the radiosensitivity or cell-cycle phase of the hepatocytes. Our data support the contention that clinically significant radiation injury does not have to have a cytokinetic basis. The manifestation of radiation damage due to microvascular endothelium injury may be diminished by appropriate systemic anticoagulant therapy.

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Griseofulvin: A Teratogenic Study

Abstract. *Griseofulvin, a fungistatic agent, was administered in oral doses of 125 to 1500 milligrams per kilogram per day to pregnant rats during organogenesis. Evaluation of the offspring from dams treated with the largest doses, 63 and 75 times a therapeutic dose in man, indicated decreased survival rates and a syndrome of malformations.*

Though much is known about griseofulvin's biological actions, its effects on cell division and embryonic development have not been clarified. An intravenous injection of griseofulvin (200 mg/kg), to rats caused disturbances in cell division and maturation in the germinal epithelium of the testes. Mitosis of rapidly dividing cells was transiently arrested at metaphase within 7 hours after administration. Two weeks later testicular histology appeared to be normal (*1, 2*). The fungistatic action of griseofulvin may be due to an interference of nucleic acid synthesis (*3*). Since compounds which block such synthesis have caused teratogenic changes in mammals (*4*), griseofulvin may have teratogenic potential (*1–5*). To investigate this possibility, we performed a reproduction study, using griseofulvin in mature rats.

Groups of 23 to 34 female rats (CAW : CFE SD spf strain) were given either 125, 250, 750, 1250, or 1500 mg/kg per day (*6*). The females were mated with males of proven fertility and then treated orally, from day 6 through 15 after mating, with microsize particles of griseofulvin (*7*) suspended in Tween 80. (Day 0 was defined as the day spermatozoa were detected in the vaginal smear.) On day 21, the dams were killed with an overdose of chloroform, and their offspring were removed. The number of nidation sites and resorptions in each dam was recorded. Approximately one-third of the offspring were examined for soft tissue defects (*8*). The remaining offspring were stained with Alizarin red-S and examined for skeletal defects (*9*).

Dams given 1250 or 1500 mg/kg per day had significantly more resorptions than did the control dams ($P < .01$) (Table 1). The incidence of resorptions, as a percentage of nidation sites, was 5 percent in the controls but 16 percent in the dams given 1250 mg/kg and 64 percent in the dams given 1500 mg/kg. Most resorptions occurred early in pregnancy. The greater number of resorptions in the dams given 1500 mg/kg resulted in a significantly smaller ($P < .01$) average litter size as compared to that in the control group (Table 1).

The body weights of offspring from all groups, except those given 250 mg/kg, were significantly less ($P < .01$) than weights of the controls (Table 1). The weights of the dams given 1250 and 1500 mg/kg were below those of the controls by 13 and 50 percent, respectively.

Skeletal ossification at delivery was retarded about 24 and 48 hours in the offspring of dams given 1250 and 1500 mg/kg, respectively. Offspring growth was commonly reduced in similar studies of other agents (*10*).

Survival rates of the newborns were significantly reduced in all groups, except the one in which the dams were given 250 mg/kg (Table 1). This reduction was related to the dose and was most pronounced in the 1500 mg/kg group where all offspring died within 1 hour after birth.

Somal examination revealed that abnormalities occurred in some pups from four of the treated groups but not in the controls (Table 2). Specifically, one pup from a dam given 250 mg/kg had clubbed feet, no eyes, one gonad, anal atresia, angulated ribs, and deformed skull bones. One pup from a dam given 750 mg/kg had dilated renal pelves. Nineteen of the 222 pups (8 percent) from dams given 1250 mg/kg had tail anomalies (no tails, or shortened or kinky tails), and one pup had exencenphaly. Nine of 90 (10 percent) of the pups from dams given 1500 mg/kg had tail deformities, and one of these pups also had exencephaly.

Table 1. Reproduction data. Rats were treated with griseofulvin daily from day 6 through day 15 after mating. Pups were weighed individually, and the weights were averaged by dose group. Data from treatment groups were compared with data from control groups. Survival rates were determined as follows: (number of pups surviving for 24 hours/number of pups retained for 24 hours) × 100.

Dose per day (mg/kg)	Rats				Litter size*	Pup weight*	24-hour survival rate (%)
	Pregnant rats (No.)	Nidations (No.)	Resorptions (No.)	Resorptions (%)			
None	19	278	14	5.0	13.9 ± 0.7	5.4 ± 0.02	100
125	14	187	3	1.5	13.6 ± 0.7	5.1 ± 0.03†	94
250	19	236	5	2.1	12.2 ± 0.8	5.5 ± 0.02	100
750	24	310	8	2.6	12.6 ± 0.3	5.1 ± 0.03†	93
1250	19	290	48	16.5†	12.7 ± 0.5	4.7 ± 0.04†	80
1500	12	252	162	64.3†	7.5 ± 1.3†	2.4 ± 0.08†	0

* Result is given as the mean ± the standard error of the mean. † Significant differences ($P < .01$) are indicated by a dagger.

Table 2. Somal examinations of rat pups. The number of offspring examined and the frequency of skeletal (S) and visceral (V) abnormalities are shown. The incidence of major malformations in the Carworth CFE strain rat used in these experiments was less than 0.5 percent.

Griseofluvin (mg/kg)	Rats examined (No.)			Major abnormalities	
	Total	Skeletal	Visceral	Total	Type
None	264	183	81	0	
125	190	130	60	0	
250	231	161	70	1	S and V
750	302	209	93	1	V
1250	242	168	74	20	S
1500	90	65	25	9	S

While the incidence of resorptions increased by 50 percent when the dose was raised from 1250 to 1500 mg/kg, the incidence of malformations between the two treated groups increased only 2 percent. These changes suggest that 1500 mg/kg approaches the limit of fetal tolerance.

Since under specific conditions griseofulvin disrupts spermatogenesis in rats (*1, 2*), we performed other experiments to evaluate the effects of long-term administration on male and female fecundity.

In one study, we treated a group of males orally with 1500 mg/kg per day during spermatogenesis for 63 days and mated them with untreated females. The males were then killed, and the testes were removed and examined histologically. On day 14 after mating, the dams were killed and examined for a dominant lethal effect. Testicular histology, the number of nidation sites, the number of resorptions, and embryonic viability were normal.

The results show that, at high doses, griseofulvin affected embryonic development but not spermatogenesis. This difference is not surprising and has several possible explanations, of which three stand out. First, spermatogenesis and embryonic development both involve rapidly dividing cells, yet tissue differentiation characterizes only the latter. Second, enzyme induction may have occurred in males and not in females because the males were treated for a longer period. Last, the testes were not removed until 2 weeks after treatment, a delay which may have allowed them to return to normal if treatment had resulted in a transient change (*2*).

In another study, we segregated 100 male and 100 female rats into controls and 50-, 100-, and 250-mg/kg groups. Males were treated for 63 days and then mated with females that had been treated for 14 days. Males were treated until the end of the 3-week mating period, whereas females were treated until they were killed. About 40 of the females were killed on day 14 after mating; the remainder were killed when the offspring reached 21 days of age. Rates of conception, litter sizes, pre- and postnatal mortality, body weights of offspring, and somal development were normal in all groups.

From the results of these two studies, male and female fecundity appears to be unaffected.

From each group, 14 or 15 (F_1) male and female pups were reared to maturity and mated with members from the same group. On day 21, females were killed, and the number of resorptions and nidations, the conception rates, the litter sizes, and the numbers of viable F_2 offspring were all normal.

The results obtained by others giving griseofulvin intravenously cannot be correlated with those we obtained since we gave the drug orally. Our results can be correlated with those obtained in humans by MacLeod and Nelson (*11*). In their experiment, 14 men were given daily doses of 2000 mg of microsize griseofulvin for 3 months. After treatment, sperm counts and histological examination of testicular biopsies indicated that griseofulvin exerted no adverse effects on spermatogenesis.

From the results of our study we can conclude that (i) compared to controls, pregnant rats treated orally with high doses of griseofulvin have more malformed offspring, (ii) offspring from those dams which were treated with high doses have decreased pre- and postnatal survival rates, and (iii) griseofulvin given to male rats daily for 63 days in oral doses up to 1500 mg/kg does not adversely affect spermatogenesis.

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6. These doses were approximately 6, 12, 38, 63, and 75 times the human dose, based on a daily dose of 1 g of microsize (*7*) griseofulvin for a 50-kg person.
7. The average particle diameter was 3 μm. More than 90 percent of the particles were less than 5 μm in diameter.
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Meiosis in Triploid All-Female Fish (Poeciliopsis, Poeciliidae)

Abstract. *Prior to meiosis in triploid gynogenetic all-female forms of* Poeciliopsis, *the chromosome number of the nucleus of the triploid oogonium is raised endomitotically to hexaploid. Recombination does not occur; instead, a triploid ovum with a genetic complement identical to that of the mother is produced by two conventional meiotic divisions. Sperm from a sympatric gonochoristic (bisexual) species stimulates the ovum to develop, but paternal genes are not incorporated into the zygote. This is the first cytologically verified case of natural endomitosis in the egg production in fish.*

The existence of natural populations of unisexual vertebrates raises questions about the evolutionary potential of these animals, both as individuals and as parts of unisexual-bisexual complexes with their gonochoristic (bisexual) relatives. To understand the evolutionary potential of unisexual forms, the sources of their genetic variability must be determined; this in turn requires an understanding of the meiotic mechanisms of these forms.

One mode of reproduction used by unisexual vertebrates is gynogenesis, that is, the development of an ovum after stimulation by a sperm but without fusion of the male and female pronuclei. This results in offspring genetically identical to the mother (matroclinous inheritance). Natural populations of gynogenetic vertebrates have been identified in teleost fishes (*1–4*) and salamanders (*5*). The viviparous genus *Poeciliopsis* (Poeciliidae: Cypri-