Griseofulvin and Human Spermatogenesis. (25212)

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Griseofulvin, a fermentation product of several species of Penicillium, has been shown to have marked inhibiting effects on morphogenesis of many fungi. Brian(1) has reported upon the *in vitro* activity of griseofulvin against 51 species of fungi and Campbell(2) has surveyed successful use of the antibiotic as an agricultural fungicide and its failure to produce toxicity in mammals under these conditions. As the therapeutic use of griseofulvin has shifted from the agricultural field to possible treatment of intractable fungal diseases in the human, legitimate emphasis has been placed upon the possible toxic effects of the drug. For example, recent studies in England(3) in which enormous doses of griseofulvin (up to 2 g/kg) were administered intraperitoneally to rats showed no overt reactions. However, histologic examination of the testicular tissue in these animals disclosed severe damage to germinal epithelium, and in many cases, complete necrosis of the testes. While we were aware that these effects were obtained in the rat only with rather overwhelming doses, we were interested in the possibility that, in lower concentrations, and in the human, a reversible inhibition of spermatogenesis could be produced. Our interest was stimulated further by preliminary clinical studies (4) which indicated that at dose levels of one to 2 g daily, griseofulvin was most effective against certain fungal infections in the human and did not produce unpleasant side effects.

Methods. We were fortunate in having access to a group of 14 men, inmates of an eastern penitentiary, who volunteered to take the drug for a period of 3 months at a level of 2 g daily. The latter dose, at present, is considered to be at least twice that necessary to produce remission of most of the fungal infections in the human which respond to this therapy. The 14 individuals were in the age group of 23-47 years (mean age 33), their physical condition was good, and they were living under similar rigid conditions of diet, exercise etc. Testicular biopsies were obtained from each during a short control period in which 2 semen specimens were examined, the second after 3 days of continence, to establish their level of semen quality. Thereafter, the griseofulvin was taken orally at the daily level of 2 g for a period of approximately 3 months. During this time, semen specimens were examined at weekly intervals, emphasis being placed upon ejaculate volume, sperm count, and sperm motility and morphology. A second testicular biopsy was obtained from 8 of the men at the end of the experimental period.

Results. Table I presents the mean counts/cc, total sperm counts and the mean readings of the spermatozoa morphology expressed as percentage of normal forms. The first control semen specimen examined was obtained after undetermined periods of continence, although in most of the 14 individuals this period was at least 2 weeks. The high mean sperm counts found in the first specimen may be accounted for on that basis. The second control semen specimen was obtained after only 3 days of continence (3 days after the first specimen) and should be considered as more representative than the first. Nevertheless, the mean sperm count figures for these 14 men both in the control specimens and thereafter during the entire course of the study, represent a population of high potential fertility. None of the 14 individuals in the study could be considered as an infertile individual and most were above average normal in all factors of semen quality. Motility readings are not recorded in the Table but without exception, they were good initially in controls and showed no serious deviation in any individual. Mean sperm counts showed a degree of fluctuation throughout the 12 week course of therapy but none that could be considered as outside the normal range of variation. Indeed, all aspects of semen quality, including sperm morphology, remained at a remarkably constant level. As would be expected from the

TABLE I. Average Semen Quality of 14 Men, at Weekly Intervals during 3 Month Period of Griseofulvin Intake.

	Semen specimen #	Ejaculate vol (cc)	Sperm count/cc —in millions—	Total sperm count	% normal forms
Control	1	3.42	228	780	79
"	2	2.84	185	527	78
	3	3.20	100	320	84
	4	3.30	175	577	84
	5	3.42	180	615	82
	6	2.91	134	389	81
	7	3.10	111	341	79
	8	3.10	117	363	83
	9	2.50	128	320	80
	10	3.48	130	452	81
	11	3.18	130	413	80
	12	2.74	123	337	79
	13	3.38	152	513	81

Semen specimens #3-13 produced at weekly intervals after intake of griseofulvin (2 g daily) was begun.

data on semen quality (Table I) the testicular biopsies did not show significant changes. Only 8 of the 14 individuals who had been on the griseofulvin for 3 months consented to the second biopsy. Attention was given to tubal size, patterns of spermatogenic activity, sperm production, condition of the peritublar connective tissue and number and functional appearance of the Leydig cells. In all these respects, the histologic condition of the testes appeared to be unaffected by treatment with griseofulvin. Both before and after the period of treatment the histologic picture of the biopsies obtained from the men in this series was, in each instance, within the recognized range of normality.

Summary and conclusions. Daily administration of 2 g of griseofulvin to 14 normal men for 3 months did not produce significant changes in semen quality or in histology of the testes of 8 of the individuals.

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Antibody Production in Neonatal Chickens Following Injection of Adult Cells Mixed with Antigen *in vitro*.* (25213)

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Neonatal animals commonly exhibit an impaired immune response. They succumb easily to infection by pathogenic agents and do not respond, or react only poorly, to stimulation with non-living bacterial or protein antigens. Inability to produce circulating antibody following antigenic challenge appears to be a consistent feature among different species. Interspecies, interstrain, and individual variations, however, are characteristic of interactions between neonatal animal and transferred, viable lymphoid cells stimulated *in vivo* or *in vitro* with antigen(1-4). The variable reactivity of the chimera, *i.e.* the neonate containing transferred, stimulated, adult homologous lymphoid cells has been interpreted as representing a homograft reaction by Sterzl, Trnka, and co-workers(3,5), and the inadequacy or immaturity of the neonatal environment by Dixon and Weigle(1,8) and by Nossal(4). Our studies which confirm those of Trnka and Riha(2,3) demonstrate that antibody produc-

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