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Mutagenic effect of azathioprine in Drosophila melanogaster.

Azathioprine is a drug extensively used for immuno-suppression and the treatment of neoplasias. Since many of the patients treated with azathioprine are of reproductive age, it is important to evaluate the potential genetic risks associated with the use of the drug. Preliminary mutagenicity studies were carried out with D. melanogaster.

Canton-S males were treated for 24 hours by feeding on 10mg. azathioprine spread on the surface of the usual treacle/semolina medium (10 flies/vial). Treated males were mated to 3 virgin Canton-S females every 3 days, to give a total of 5 broods. The percentage of unhatched eggs was used as an indicator of dominant lethality. The results obtained are shown in Table 1.

Table 1.

	Brood 1		Brood 2		Brood 3		Brood 4		Brood 5	
	% u.h.	No.	% u.h.	No.	% u.h.	No.	% u.h.	No.	% u.h.	No.
Control	13.8	3675	13.8	3824	15.1	3438	15.0	2980	13.2	2173
Treated	15.3	3473	19.1	3627	19.2	3350	19.1	2993	15.8	2305
χ^2	3.1		24.3		20.1		17.8		6.0	

u.h. - unhatched eggs

The ability of azathioprine to cause loss or breakage of chromosomes was tested by treating C(1)RM, y/R(1)2, vf/B^S Y y^+ males as above, and mating to virgin y w^a females with 3 day brood intervals for a total of 4 broods. The progeny were scored for sex, loss of Y^L, loss of Y^S, loss of X or Y and non-disjunction. The results are presented in Table II. The effect of azathioprine on the sex-ratio in rod-X flies was tested by treating C(1)RM, y/y v/B^S Y y^+ males and mating as above.

Table 2.

Series	Total progeny	Male/Female	Complete loss X or Y, %	Loss Y^L, %	Loss Y^S, %	N.D.J. %
Control	14,212	0.863	0.197	0.030	0.060	0.118
Brood 1	8,264	0.908	0.096	0.076	0.076	0.162
2	7,080	0.999	0.141	0.085	0.113	0.198
3	4,847	1.005	0.289	0.247	0.206	0.165
4	2,904	0.971	0.482	0.140	0.070	0.475

Azathioprine induced dominant lethals in Canton-S males in post-meiotic and meiotic broods. In the treated ring-X stock, chromosome breakage, as indicated by partial chromosome loss, is highest in brood 3 (χ^2 = 7.10 for loss of Y^L). In brood 4, the maximum frequency of complete X or Y chromosome loss occurs (χ^2 = 6.89), and this coincides with the highest frequency of non-disjunction (χ^2 = 3.38), indicating that meiotic germ cells are being utilized in this brood. However, it is noted that although peak chromosome loss and non-disjunction coincide in brood 4, the non-disjunction does not account for all the chromosome loss. There was no evidence that preferential loss of the Y^L or Y^S occurred.

Only 4 mosaics were observed amongst 95 exceptional progeny in the treated series, and were subsequently found to be fertile. Only one exchange event was found. Of the 27 progeny with partial chromosome losses in the treated series, 5 were fertile, 2 of which were mosaics. Marker loss in 3 flies was not accompanied by loss of fertility factors.

In brood 3, the ring-X sex-ratio differed significantly from that of its control (χ^2 = 21.12). The rod-X, male/female, sex-ratio was greatest at brood 3, and did not differ significantly from its control (χ^2 = 0.23). From this it can be inferred that much of the sex-ratio shift observed in the progeny of treated ring-X flies can be attributed to breakage of the ring chromosome.

This study demonstrates the genetic activity of azathioprine in D. melanogaster. Tests in mammalian systems are required to evaluate further the mutagenicity of this drug.

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(Moscow) for providing them with D. virilis and D. texana stocks.

References: McReynolds, M. 1967, Genetics 56:527-540; Ohba, S. and F. Sasaki 1968, Proc. Twelfth Internat. Cong. Genetics, Tokyo:156-157; Sims, M. 1965, Nature 207:757-758.