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California. The effect of 5 fluorouracil  
on *Drosophila melanogaster*.

The compound 5 fluorouracil (FU) has a marked toxic effect on the larvae of *Drosophila*. This effect is primarily characterized by the failure of the larvae to develop into the pupal stage.

Under normal circumstances a first instar

larva will pupate in 4 or 5 days, but when such a larva is fed FU, it will remain in the first or second instar stage for as long as 10 days before death eventually occurs. Experiments were designed to determine if FU is incorporated into RNA and/or if FU, in its deoxy-nucleotide form, inhibits the methylating enzyme, thymidylate synthetase.

*Drosophila* larvae were fed or injected with FU and at the same time fed or injected with thymidine in varying concentrations, the objective being to see if a reversal of the toxic effect would occur. There was no reversal of the toxic effect at any FU/TdR ratio, either in feeding or injection experiments.

In other experiments larvae were fed 5-FU-2-C<sup>14</sup> and their nucleic acids were extracted (Kilgore and Painter, 1964, *Biochem. J.* 92:353-357). Following alkaline hydrolysis, paper chromatography was used and a highly significant amount of radioactive FURP was identified. Further evidence for the involvement of FU in RNA metabolism was obtained by feeding the radioactive FU to either males or females, allowing mating, then collecting and analyzing the eggs. When the males were fed the labeled compound no significant radioactivity was detected in the eggs. When the females were fed the C<sup>14</sup> containing compound a significant amount of radioactivity was recovered in the eggs. The results thus parallel the difference in RNA concentration found in the sperm and the egg.

While results of these experiments indicate that part of the toxic effect of FU may be a consequence of its incorporation into RNA, other strong possibilities exist. Metabolic derivatives of FU, such as alpha-fluoro-beta-alanine, alpha-fluoro-beta-ureidopropionic acid or alpha-fluoro-beta-guanidopropionic acid, might be responsible for the toxicity. Additional experiments are needed to test this possibility.

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by disruptive selection.

Scharloo, Hoogmoed and Ter Kuile (1967 and *D.I.S.* 41:96) showed that disruptive selection practised on fourth veinlength in a cubitus interruptus mutant (*ci*<sup>D-G</sup>) causes the appearance of bimodal frequency distributions. Analysis of the

phenotypic variability suggested different mechanisms for the bimodality in the disruptive lines with random mating (*D*<sup>R</sup>) and negative assortative mating (*D*<sup>-</sup>). Further analysis revealed that in the *D*<sup>R</sup> line the polymorphism is based on a genetic switch mechanism on the second chromosome. Flies with an extreme long 4th vein are homozygous for a plexus allele and flies with an extreme short vein are homozygous for a factor which seems to be composed of two genes in close proximity and is located 2-4 map units to the left of plexus. This factor causes, in the absence of *ci*<sup>D</sup>, an interruption of the 4th vein and the second cross-vein. One of its component genes causes the interruption of the 4th vein, the other component which causes the cross vein interruption seems to reveal its presence only in combination with the first one. Flies without *ci*<sup>D-G</sup> but homozygous for both the "low" and "high" factors have a complete fourth vein but lack the cross vein.

Polymorphism in the *D*<sup>-</sup> line, however, is based on a developmental switch mechanism. Substitution of chromosomes of the *D*<sup>-</sup> line in other stocks showed that the genetical differences between the extreme flies are small. Bimodality was still present in lines inbred from the *D*<sup>-</sup> line for 20 generations in which selection for low and high expression did not have any effect. Direct evidence for a threshold mechanism in the development of the fourth vein was obtained by temperature experiments. In contrast with the linear relation between temperature and expression in the base population, this relation is markedly-non-linear in the *D*<sup>-</sup> line and in inbreds obtained from it. There seems to be a marked facilitation of response in the range of expression values between the two modes of the frequency distribution.