Induced Dominant Lethals in Female Mice

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The dominant lethal (DL) assay combining relative simplicity with relevance seems particularly suited for the routine testing of potential mutagens. To its best advantage this assay should be used as a *specific* test system; its relevance is certainly not increased when it is attempted to 'integrate' it into procedures that are designed for different purposes than mutagenicity testing.

BATEMAN has presented all the aspects of the usual assay in males that are of theoretical and practical importance [1]. Treatment of females was considered to be less suitable for general purpose, mainly because of the possible interference of a variety of non-genetic factors with oogenesis, ovulation, fertilization and implantation [2]. On the other hand, oocytes entering metaphase I and progressing to metaphase II with ovulation, are particularly susceptible to the induction of DL [7]. Similar to spermatocytes, and in contrast to the earlier stages of spermatogenesis, the post-dictyotene oocytes are not subject to germinal selection before fertilization.

In order to demonstrate that the increase in number of dead embryos following pre-fertilization treatment of the females (i.e. dominant lethals) is due to genetic causes, a variety of criteria have to be considered [4]. Although it is most important to define the stage(s) of oogenesis that is affected by given treatment, it is not possible, for practical purposes, to precisely time the treatment in relation to the meiotic cycle. Since the particularly sensitive first meiotic division comprises a period of only a few hours, it seems sufficient to determine the time of ovulation. Some investigators synchronized ovulation by treating the females with gonadotrophin [3, 6]. In our view, this procedure has disadvantages mainly because it brings about superovulation.

Our own studies [5] have indicated that it is sufficient to time ovulation by careful observation of the oestrus cycle only. Groups of about 30 females treated at late pro-oestrus and oestrus are mated in a 3:1 ratio with untreated males of the same age and breed. 15.5 hours later, presence of a vaginal plug is ascertained and only those females that have copulated are examined 14 days later for the presence of corpora lutea, and living and dead implants. By this means, dominant lethals may be found to be induced in the germ cells of female mice in a reproducible manner and under standard laboratory conditions, provided that single dose treatment is timed with regard to late pro-oestrus and oestrus. This technique may prove a convenient and valid measure of genetic effects on the female gamete, i.e. on mature oocytes.

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References

[1] A. J. BATEMAN, *The Dominant Lethal Assay in the Mouse*, this issue.
[2] A. J. BATEMAN and S. S. EPSTEIN, *Dominant Lethal Mutations in Mammals*, in: *Chemical Mutagens, Principles and Methods for their Detection*, vol. 2 (Ed. A. Hollaender; Plenum Press, New York–London 1971), p. 541–568.
[3] R. G. EDWARDS and A. H. GATES, *Timing of the Stages of the Maturation Divisions, Ovulation, Fertilization and the First Cleavage of Eggs of Adult Mice treated with Gonadotrophins*, J. Endocr. *18*, 292–304 (1959).
[4] W. M. GENEROSO, *Chemical Induction of Dominant Lethals in Female Mice*, Genetics *61*, 461–470 (1969).
[5] L. MACHEMER and R. HESS, *Induced Dominant Lethals in Female Mice: Effects of Triaziquone and Phenylbutazone*, Experientia *29*, 190–192 (1973).

[6] G. RÖHRBORN and I. HANSMANN, *Induced Chromosome Aberrations in Unfertilized Oocytes of Mice*, Humangenetik *13*, 184–198 (1971).

[7] L. B. RUSSEL and W. L. RUSSEL, *The Sensitivity of Different Stages in Oogenesis to the Radiation Induction of Dominant Lethals and other Changes in the Mouse*, in: *Progress in Radiobiology* (Eds. J. S. Mitchell, B. E. Holmes and C. L. Smith; Oliver and Boyd, London 1955), p. 187–192.