ANALYSIS OF THE ALBINO-LOCUS REGION OF THE MOUSE. III. TIME OF DEATH OF PRENATAL LETHALS*

LIANE B. RUSSELL AND G. D. RAYMER

Biology Division, Oak Ridge National Laboratory, Oak Ridge, Tennessee 37830

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ABSTRACT

The stage at which homozygotes die was determined for 28 mutations (general symbol c^*) at the albino (c) locus, of which 26 had earlier been found to be probably prenatally lethal. Within each of the mutant stocks, the uterine contents of c^*/c^{ch} females, made pregnant either by c^*/c^{ch} males ("Ex" series) or by c^{ch}/c^{ch} males ("Co" series), were examined between 13 and 17 days postconception. Altogether, 743 females were dissected and 7197 corpora lutea (representing ovulations) counted. In selected stocks, an additional 40 and 13 females were dissected on days seven or nine, respectively.——In each of the 26 presumed prenatally lethal mutants, there was a deficiency of living fetuses in the Ex, as compared with the Co, group. Overall, this deficiency was 23.6% (expectation, 25% c^*/c^*). All meaningful excesses were in numbers either of moles (death shortly before, during, or just after implantation), or of early preimplantation losses. Homozygotes in none of the mutant stocks die between days nine and 19 postconception. Of 24 c-locus mutants known to be deficiencies since they lack the closely linked *Mod-2*, 13 clearly kill before implantation, ten around implantation, and one neonatally. The c and *Mod-2* loci and the region between them are not needed for intrauterine survival.——There are indications that the distinction between early-preimplantation death and implantation death may, in a general way, be related to length of the deficiency.

SPECIFIC-LOCUS mutation-rate experiments (W. L. RUSSELL 1951) yield recoverable mutations involving one (or rarely two) of a number of marked loci. We have recently tested 107 of 119 albino (c-locus) mutants found in experiments that were carried out at our laboratory over the course of several years to study the mutagenic effect of externally administered radiations (RUSSELL, RUSSELL, and KELLY 1979). The mutants were analyzed by origin and by viability, as determined from information obtained in breeding experiments. Among the 107 tested mutants were 28 for which the breeding data indicated that homozygotes were never born and which were therefore presumed to be prenatal lethals. In order to test whether this presumption was correct and to obtain further information on these mutants, we have undertaken a uterine dissection experiment for most of the presumed prenatal lethals and a few other c-locus mutants. Preliminary findings were published in abstract (RUSSELL, DEHAMER and BORMAN 1974). In view of the large number of lethals involved and the

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effort that would be required to carry out detailed embryological studies on each individual one, the present investigation aims primarily to establish broad classifications for time of death of homozygotes and to examine these in the light of other information that has been derived from deficiency and complementation mapping (RUSSELL and DEHAMER 1973; RUSSELL and CACHEIRO 1977).

Two other prenatally lethal *c*-locus mutations have been reported and included in various studies (GLUECKSOHN-WAELSCH, *et al.* 1974). Detailed embryological analyses have been performed for two of these (LEWIS, TURCHIN and GLUECKSOHN-WAELSCH 1976; LEWIS 1978).

MATERIALS AND METHODS

All 28 mutants tested in this experiment originated from crosses in which mice from a genetically uniform wild-type stock, $(101/Rl \times C3H/Rl)F_1$ or $(C3H/Rl \times 101/Rl)F_1$, were exposed to ionizing radiation from an external source and subsequently mated to a multiple-recessive stock that, among other markers, carried chinchilla, c^{ch}. In the case of all but two of the mutants analyzed, the multiple-recessive parent came from the random-bred T stock (*a/a*; *b/b*; c^{ch} *p*/c^{ch} *p*; *d se/d se*; *s/s*); for two mutants (AL, LA), the recessive parent came from the SB stock (*a/a*; *b/+*; c^{ch}/+; *d se*/+ +). The method for detecting the mutants and setting up stocks is described elsewhere (RUSSELL, RUSSELL and KELLY 1979). Almost all the mutants used in the present experiment have been maintained by over 15 generations of backcrossing to our c^{ch}/c^{ch} stock, 2A, which, though not brother × sister inbred, has been kept as a small, closed colony for 30 years.

Of 28 *c*-locus mutants for which breeding data had indicated prenatal lethality, 26 are included in the present experiment. In addition, we analyzed one neonatally lethal mutant, and one mutant, 20FATw, classified as subvital, in which homozygotes in different sublines die at different stages (RUSSELL, RUSSELL and KELLY 1979). The generalized symbol c^* will be used to indicate the mutant condition at the *c*-locus in each of the 28 stocks tested.

For each stock, parallel matings were made of c^*/c^{ch} females × c^*/c^{ch} males and c^*/c^{ch} females × c^{ch}/c^{ch} males, with females in the two sets of matings being matched for age as nearly as possible, most being between three and six months old. (In the case of mutant 20FATw, all males came from the subvital line, and females either from the subvital or lethal line; since there appeared to be no clear difference between the two types of matings, the results were combined.) Females were checked each morning for vaginal plugs and were sacrificed between days 13 and 17 (with 83% on days 14, 15, or 16) following finding of a plug (plug = day zero). The distribution among these days was roughly the same in all groups. For a subset of mutants, dissections were also made on days seven or nine.

Observations were made of the number of corpora lutea (indicative of ovulations), live fetuses (classified as to eye color), dead embryos (with estimates of age at death), and moles. Moles may be either deciduomata (implantation reactions called forth by dead embryos) or may contain trophoblastic growths and a few undifferentiated embryonic cells (BATEMAN and EPSTEIN 1971). When scored after day 10.5 postconception (pc), these two types can no longer be distinguished. Moles may thus be assumed to represent deaths just before, during, or very shortly after implantation. Embryos that differentiate for a few days beyond implantation, but are already retarded by day 10.5 and disintegrate subsequently, are distinguishable from moles even in advanced pregnancy by having a placenta and membranes (BATEMAN and EPSTEIN 1971). Eye pigment can be recognized from day 11 on.

RESULTS

Results of the uterine dissections are shown in Table 1. The sets of experimental and control matings being compared in each stock have been designated

TABLE 1

Uterine contents and corpora lutea counts in within-stock matings of c-locus mutants of c^{al} and c^{as} types

Complementation group*	Mutant	Number of females†	Average number per female of: Corpora lutea	Live embryos Eye pigm.	Live embryos No pigm.	Dead embryos‡	Moles	Preimpl. loss§	Diagnosis‖
	$1DThW_b$	Co 10	9.5	8.1	—	0.2	0.4	0.8	
		Ex 10	8.5	5.5	0	0.1	1.9	1.0	imp
A′	23DVT	Co 16	9.5	7.8	—	0	0.9	0.9	
		Ex 17	9.8	5.2	0	0.1	2.6	1.8	imp
	$3YPS_D$	Co 12	9.6	6.4	—	0.1	1.5	1.6	
		Ex 15	9.7	4.2	0	0	3.1	2.4	imp
	11DSD	Co 24	10.4	6.8	—	0.0	1.9	1.6	
		Ex 22	10.5	5.4	0	0.1	3.3	1.7	imp
	$1FDFoHr_c$	Co 14	9.9	6.4	—	0.1	2.2	1.2	
		Ex 23	9.6	5.4	0	0.1	1.0	3.0	pre
	$1FR60H_b$	Co 12	10.0	6.3	—	0.2	2.1¶	1.4	
		Ex 10	9.7	5.2	0	0	0.4	4.1	pre
	$9FR60H_b$	Co 25	9.0	6.6	—	0.1	1.3	1.0	
		Ex 23	9.3	5.2	0	0.1	1.4	2.6	pre
	$14FR60H_b$	Co 12	8.8	6.4	—	0.1	1.4	0.8	
		Ex 9	8.9	5.0	0	0.1	0.7	3.1	pre
B	$4FR60H_d$	Co 15	10.9	7.8	—	0.2	1.1	1.9	
		Ex 17	10.9	6.2	0	0.1	3.1	1.5	imp
	$5FR60H_g$	Co 15	9.0	6.2	—	0.1	1.8	0.9	
		Ex 15	9.3	4.6	0	0.1	3.1	1.5	imp
	4PB	Co 11	10.2	5.8	—	0.1	2.5	1.8	
		Ex 12	9.3	4.6	0	0.1	1.8	2.8	pre
	3R60L	Co 10	10.0	7.4	—	0.0	1.2	1.4	
		Ex 21	9.3	4.3	0	0.1	1.7	3.1	pre
	2R145L	Co 10	10.4	7.9	—	0.2	1.0	1.3	
		Ex 12	10.1	5.0	0	0.1	1.5	3.5	pre
	3R145L	Co 12	9.3	6.6	—	0	2.4	0.3	
		Ex 10	11.7	5.0	0	0	2.0	4.7	pre
C	20FATw	Co 12	10.3	6.8	—	0.1	0.9	2.4	
		Ex 17	10.2	4.4	1.7	0.1	1.1	3.0	neo
	19DTR	Co 17	10.5	6.7	—	0.2	1.2	2.4	
		Ex 17	10.5	6.5	0	0.1	2.4	1.5	imp
	10FR60L	Co 14	9.1	6.4	—	0.0	1.1	1.6	
		Ex 14	9.3	5.1	0	0.2	1.0	2.9	pre
	68G	Co 14	8.4	5.1	—	0.3	1.1	1.9	
		Ex 15	8.7	4.4	0	0.1	2.5	1.7	imp
	146G	Co 10	9.6	7.2	—	0.4	1.2	0.8	
D		Ex 8	9.3	4.9	0	0.0	1.4	3.0	pre
	202G	Co 7	8.4	6.3	—	0.3	0.6	1.3	
		Ex 8	9.3	4.4	0	0.9	2.9	1.1	imp

TABLE 1—Continued

Complementation group*	Mutant	Number of females†		Average number per female of: Corpora lutea	Live embryos Eye pigm.	Live embryos No pigm.	Dead embryos‡	Moles	Preimpl. loss§	Diagnosis‖
	24R145L	Co	12	11.3	8.0	—	0.0	0.7	2.6	
		Ex	14	10.1	6.0	0	0.1	2.7	1.3	imp
	7R250H	Co	12	9.9	6.0	—	0.0	1.9	2.0	
		Ex	17	9.1	5.2	0	0.1	2.9	0.9	imp
	39SAS	Co	11	10.1	6.3	—	0.1	1.1	2.6	
		Ex	15	11.0	5.4	0	0.2	0.9	4.5	pre
	26DVT	Co	11	8.7	5.5	—	0.3	1.5	1.4	
F		Ex	10	10.2	4.8	0	0.1	1.2	4.1	pre
	$12FR60H_b$	Co	12	8.9	4.8	—	0.1	1.9	2.2	
		Ex	13	8.1	4.0	0	0.2	0.7	3.2	pre
	$2YPS_J$	Co	10	10.2	6.4	—	0.1	2.4	1.3	
		Ex	10	10.0	5.1	0	0.1	4.0	0.8	imp
?	AL	Co	10	9.9	7.0	—	0.0	0.7	2.2	
		Ex	9	9.2	5.0	0	0.0	2.4	1.8	imp
	LA	Co	4	7.8	5.3	—	0.0	0.5	2.0	
		Ex	6	8.7	6.3	1.3	0.0	1.0	1.3	neo

* RUSSELL, DEHAMER and BORMAN 1974; RUSSELL and CACHEIRO 1977. Mutants in groups B, E, D are deficient for *Mod-2*; those in group F are deficient for *Mod-2* and *sh-1*.

† Co = control mating, c^{ch}/c^{*} ♀ × c^{ch}/c^{ch} ♂. Ex = experimental mating, c^{ch}/c^{*} × c^{ch}/c^{*} ♂.

‡ Died after day nine.

§ Computed as the difference between corpora lutea and total.

‖ pre = early preimplantation loss. imp = death just before, during, or very soon after implantation. neo = survival to term or later (see text).

¶ Omitting two ♀ ♀ who had a total of 12 moles, this figure is 1.3.

"Ex" (c^{*}/c^{ch} females × c^{*}/c^{ch} males) and "Co" (c^{*}/c^{ch} females × c^{ch}/c^{ch} males), respectively. "Ex" matings are expected to produce one-fourth c^{*}/c^{*} and "Co" matings are not expected to yield any c^{*}/c^{*}. Half the conceptuses in each case are presumed to be c^{*}/c^{ch}, and the genotype of the mother is the same (c^{*}/c^{ch})—thus providing controls for any possible deleterious effects of the mutation in the heterozygous state.

Altogether, 743 females were dissected and 7197 corpora lutea (representing ovulations) counted. The "preimplantation-loss" category is calculated as the difference between corpora lutea and total implants (live and dead fetuses, and moles) and can include nonfertilized eggs along with embryos failing to evoke an implantation reaction.

It may be noted that Ex and Co females within a given stock (all of them c^{ch}/c^{*}) are similar with respect to average number of corpora lutea (the within-stock difference being greater than 1.0 in only three of the 28); but that different stocks vary considerably in this respect. The average control number of living fetuses also varies with the stock, and females in the F complementation group are among the worst producers. Since the genetic backgrounds of most mutants are roughly similar, the between-stock differences may be indicative of heterozygous effects of the mutations.

In each of the 26 prenatally lethal mutants listed in Table 1, there is a deficiency of living embryos in the Ex group, as compared with the Co group. Overall, this deficiency is 23.6% (expectation, 25%), with 21 of the 26 stocks having reductions of >15%. On comparing Ex and Co matings, it may be noted that in none of the mutant stocks was there a significant excess of embryos dying after day nine pc. All meaningful excesses were in numbers either of moles, or of preimplantation losses. All of the living fetuses observed, except in the case of mutants 20FATw and LA, had pigmented eyes of either the c^{ch}/c^{ch} (broad iris ring) or c^{ch}/c (narrow ring) type. We therefore conclude that in the 26 presumed prenatally lethal *c*-mutant stocks investigated, homozygotes die either early enough so as not to cause an implantation reaction or around the time of implantation (just before, during, or just after). These two broad classes are indicated by "pre" and "imp," respectively, in the last column of Table 1.

Although the dominant-lethal-test experience indicates that implantation and early preimplantation deaths can be distinguished even when uterine dissections are made during the last week of the gestation period (BATEMAN and EPSTEIN 1971), it seemed nevertheless desirable to gather direct evidence on this point in the present investigation. Accordingly some B- and D-group females from stocks classified as implantation lethals (4FR60H_d, 11DSD, 19DTR, 68G, 202G) and from others classified as early preimplantation lethals (1FDFoHr$_c$, 39SAS) were dissected on day seven or day nine of pregnancy (Table 2). In comparing Ex matings, the proportion of corpora lutea represented by implants was about 88% in the former group, but only 66% in the latter. The difference is highly significant ($P < 0.0001$), confirming the diagnosis of early preimplantation death. Within the presumed early preimplantation lethals, a comparison of Ex and Co matings leads to the same conclusion ($P < 0.01$). Further in keeping with this conclusion is the finding, for the day nine group, that the proportion of moles is significantly lower ($P = 0.03$) in the presumed early-preimplantation than in the implantation lethals.

Fetuses with nonpigmented eyes were found in two stocks, 20FATw and LA, where they constituted about 28% and 21% of living implants, respectively. Such presumed c^*/c^* fetuses appeared to be normal in mobility and external appearance even in some uteri dissected as late as 16 days pc. Immediately post-

TABLE 2

Early dissections in within-stock matings of c-locus lethals

		Implantation lethals*			Early preimplantation lethals*		
Days pc	Type of mating†	Corpora lutea	Implants/ corp. lut.	Moles/ corp. lut.	Corpora lutea	Implants/ corp. lut.	Moles/ corp. lut.
7	Co			—‡	56	0.86	—
7	Ex	198	0.88	—	104	0.66	—
9	Ex	54	0.91	0.43	62	0.66	0.24

* Classification based on dissections made during last week of pregnancy (see Table 1). Mutants from B and D complementation groups (see text).

† See footnote to Table 1.

‡ Moles and living implants not distinguished in day-seven dissections.

TABLE 3

Distribution of c-locus lethals by radiation history and stage of death

Radiation history of mutant		Stage of death of homozygote			
Germcell stage exposed	Type of radiation	Early pre-implantation*	Implantation*	Neonatal†	Untested
Spermatogonia	X or γ	4	6	4‡	2
	neutrons	1	2	2	
Postspermatogonia	X or γ	0	3	0	
	neutrons	2	0	0	
Oocytes	X or γ	1	0	1 + 1§	
	neutrons	5	2	0	

* See Table 1.
† See RUSSELL, RUSSELL and KELLY 1979. No uterine dissection data except as indicated.
‡ Uterine dissection data available for three of these mutants: LA, see Table 1, this paper; 65K–112K (cluster) and 14CoS (ERICKSON, GLUECKSOHN-WAELSCH and CORI 1968).
§ Subvital mutant 20FATw (Table 1). Homozygotes in some sublines occasionally survive past weaning (RUSSELL, RUSSELL and KELLY 1979).

natal deaths had been noted in the breeding of both of these stocks (RUSSELL, RUSSELL and KELLY 1979); and in one line of 20FATw, some deaths occur even later than that. (In the case of 20FATw, the matings in the present experiment were either within the subvital line or between the subvital and the lethal line. No matings within the lethal line were available, and that line is now extinct.) Uterine dissections for other neonatally lethal albinos, namely Oak Ridge mutants 65K-112K and 14CoS, and Harwell mutant 3H (ERICKSON, GLUECKSOHN-WAELSCH and CORI 1968), indicate that those mutants, like LA and 20FATw, have normal or near-normal viability, at least until very late in pregnancy.

Table 3 groups all *c*-locus lethals by radiation history and stage of death of the homozygote. Since even 3,622,814 observations (RUSSELL, RUSSELL and KELLY 1979) yielded only 36 *c*-lethal mutants altogether, most comparisons that can be made do not attain statistical significance. Some of the differences are, however, suggestive. For example, the proportion of early-preimplantation lethals (presumably the most extreme class of mutants) is 57.1% in the neutron-irradiated groups, but only 25% in X or γ ray groups ($P = 0.057$); it is 53.3% in offspring of irradiated oocytes and postspermatogonial stages, but only 26.3% in offspring of spermatogonia (difference, however, not significant). On the other hand, the proportion of neonatal lethals (presumably the least extreme of the lethal groups) is higher following spermatogonial irradiation (31.6%) than following irradiation at other stages (7.1%).

DISCUSSION

We have studied the prenatally lethal mutations at the *c*-locus in considerably greater detail than those at the *d* (dilute) and *se* (short-ear) loci with respect to time of death (L. B. RUSSELL 1971). Interestingly, there is a developmentally significant gap in death time between the neonatal and prenatal lethals, with none of the latter group dying between days nine and 19 pc. The prenatal lethals

can, however, rather clearly be further divided into at least two subgroups with regard to when loss of homozygotes occurs relative to implantation. This subdivision cuts across the earlier established delimitation of B- and D-complementation groups, *i.e.*, both B and D contain both implantation and early-preimplantation lethals and are thus presumably further divisible.

Detailed embryological studies have been performed for two *c*-locus prenatal lethals, namely, the radiation-induced Harwell mutations c^{6H} and c^{25H}, both of which are deficiencies (ERICKSON, EICHER and GLUECKSOHN-WAELSCH 1974). Presumed c^{25H}/c^{25H} embryos die preimplantation (LEWIS 1978). Homozygous effects of c^{6H} are first detectable on day 6.5 pc, and all c^{6H}/c^{6H} embryos are dead by day eight pc (LEWIS, TURCHIN and GLUECKSOHN-WAELSCH 1976). Another small deficiency (L. B. RUSSELL 1971) whose effect has been studied in embryological detail, our radiation-induced *se*-locus lethal 5RD300H, also was found to kill on about day eight pc (DUNN 1972). On the other hand, some well-known lethal alleles of spontaneous origin, which are not known to be deficiencies, initiate their effects well before implantation (MCLAREN 1976). The distinction between pre- and early postimplantation death thus does not in itself clearly distinguish between deficiencies and point mutations.

Analysis of the *c*-locus now indicates that known deficiencies, like point mutations, can kill at a variety of developmental stages. At least 24 of the Oak Ridge *c*-locus lethals are known to be deficiencies by virtue of the fact that they lack the closely linked *Mod-2* locus (RUSSELL, DEHAMER and BORMAN 1974; DEHAMER 1975; BERNSTINE, RUSSELL and CAIN 1978, and unpublished for mutant AL). Similarly, the two prenatally lethal *c* mutants induced at Harwell, c^{6H} and c^{25H}, are *Mod-2* deficiencies (ERICKSON, EICHER and GLUECKSOHN-WAELSCH 1974). Of these 26 Df(*c Mod-2*)'s, 13 kill before implantation, 12 (namely, ten Oak Ridge lethals and the two Harwell lethals) at or shortly after implantation, and one (the E-group cluster 65K-112K, see RUSSELL, RUSSELL and KELLY 1979) as late as birth.

The last of these indicates that it is possible for an embryo carrying a homozygous deficiency of at least 1 cM in length to survive throughout full morphogenesis and fetal growth. Complementation studies (RUSSELL and DEHAMER 1973; RUSSELL, DEHAMER and BORMAN 1974; GLUECKSOHN-WAELSCH *et al.* 1974) have shown presumed double absence of the *c* locus to be compatible with adult survival. (Since there is no *a priori* reason against assuming that the standard *c* allele is an intragenic null mutant, the *c/c* genotype could not be considered to provide critical evidence on this subject.) The double absence of *Mod-2* allows postnatal survival (RUSSELL, DEHAMER and BORMAN 1974; BERNSTINE, RUSSELL and CAIN 1978), though with reduced vigor (L. B. RUSSELL, unpublished) and inability to reproduce (LEWIS, TURCHIN and WOJTOWICZ 1978). It may be concluded (1) that neither *c* nor *Mod-2* nor the region between them is needed for intrauterine survival, and (2) that the other Df(*c Mod-2*) mutants that die before, or just after, implantation lack genetic material outside this region.

It may be noted that a complementation map suggested by GLUECKSOHN-WAELSCH *et al.* (1974) shows 65K and 112K as not involving the *Mod-2* locus. However, of the set of mutants shown on that map, only three (not including 65K, 112K) had been analyzed for MOD-2 dosage (ERICKSON, EICHER and GLUECKSOHN-WAELSCH 1974). The latter authors suggested that mitochondrial malic enzyme might be essential in embryonic development, a conclusion that must now be revised on the basis of our MOD-2 determinations in the *c* locus lethals (RUSSELL, DEHAMER and BORMAN 1974; DEHAMER 1975; BERNSTINE, RUSSELL and CAIN 1978).

There are indications that the distinction between implantation and early-preimplantation death may, in a general way, be related to length of the deficiency. For example, only 25% of the X- or γ-ray-induced lethals, but 57% of the neutron-induced lethals kill at early preimplantation. Although this difference is only on the borderline of statistical significance, it is in the direction expected on the supposition that the high-LET-produced lesions are bigger. Further, it is of interest that all three of the mutations in the A′-complementation group, which are not deficient for markers flanking *c*, kill during or shortly after implantation. And, conversely, three of our deficiencies that are large enough to be cytologically visible (RUSSELL and CACHEIRO 1977) all kill well before implantation. Similarly, the cytologically visible deficiency c^{25H} (MILLER *et al.* 1974), though originally reported to kill "soon after implantation" (GLUECKSOHN-WAELSCH *et al.* 1974), is now known to cause its developmental arrest in three- to six-cell embryos (LEWIS 1978).

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