VIABILITY OF HOMOKARYOTYPES IN THE TUMOROUS-HEAD STRAIN OF *DROSOPHILA MELANOGASTER*¹

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THE tumorous-head trait in *Drosophila melanogaster* is caused by a third chromosome gene (*tu-3*) showing reduced penetrance. The penetrance can be increased by a sex-linked recessive gene (*tu-1*) controlling a maternal effect (GARDNER and WOOLF 1949), by polygenic modifiers (GARDNER, STOTT and DEARDEN 1952), and by high temperature during an early developmental period (GARDNER and WOOLF 1950). When *tu-1* and *tu-3* are homozygous, the frequency of flies showing an amorphous head growth (defined as penetrance in the tumorous-head literature) in a strain maintained at 25°C will vary from about 20% to over 80% depending on the polygenic background.

Most tumorous-head strains are characterized by chromosomal polymorphism (WOOLF and PHELPS 1960; WOOLF 1965). Two types of third chromosomes are present, symbolized 3A and 3B. They differ because of the presence of the recessive gene *st* (scarlet eyes) and the Payne inversion in the left arm of chromosome 3B. Since chromosome 3B is homozygous lethal, two types of adult flies occur: homokaryotypes (3A/3A) and heterokaryotypes (3A/3B). Chromosome 3B is maintained at a high frequency (over 80%) in laboratory stocks because female heterokaryotypes are more productive (number of adult offspring produced) than female homokaryotypes and because of the greater viability (probability of development from zygote to adult) of female and male heterokaryotypes (WOOLF and CHURCH 1963). The reduced productivity of female homokaryotypes results from a complex genetic system involving chromosome 2 and the left arm of chromosome 3A (WOOLF and KNOWLES 1964; WOOLF, KNOWLES and JARVIS 1964). KNOWLES (1967) has demonstrated that the reduced productivity of homokaryotype females is a function of reduced fecundity, fertility and longevity. Equilibrium formulae were derived by LI (1963) for this situation existing in tumorous-head strains where selection favors the heterokaryotypes but acts differentially in male and female homokaryotypes.

Penetrance is higher in females in tumorous-head strains (GARDNER and WOOLF 1949), females are more apt to show an extreme expression of the abnormality, and heterokaryotypes of both sexes show a higher penetrance (WOOLF and LOTT 1965). Males outnumber females and at high temperature the sex ratio (M/F) increases (GARDNER and WOOLF 1950). It has been proposed (WOOLF and LOTT 1965) that heterosis brought about by heterozygosity for the Payne in-

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version buffers development in the presence of the genetic mechanisms (*tu-1*, *tu-3* and modifiers) producing the abnormal development in the head region. Under this scheme, heterokaryotypes have a better chance of surviving when developmental processes in the head region deviate markedly from the normal, and the greatest mortality occurs among female homokaryotypes since female zygotes have a higher probability of developing abnormally.

Since the productivity of female homokaryotypes can be increased by substituting wild-type chromosomes in place of chromosome 2, experiments were carried out to determine if the relative viability of the homokaryotypes could be increased by similarly changing the genetic background. These experiments demonstrated that the viability of female and male homokaryotypes is influenced by a maternal effect, and wild-type second chromosomes will increase the relative viability of homokaryotypes that have been maternally affected. These experiments also demonstrated that the viability of homokaryotypes is influenced by parental age.

MATERIALS AND METHODS

All experiments were carried out with derivatives of the tumorous-head strain symbolized by tu-h ASU (Woolf, 1965). Unless stated otherwise, the progeny were reared in half-pint milk bottles containing a cornmeal-yeast-agar-molasses-sucrose medium, using propionic acid as the fungicide. All cultures were maintained at 25°C. Live yeast cells were not added to the surface of the medium. Parental females were collected within a 4-hour period following eclosure. They were aged no longer than three days before being used in the experiments. The parental flies (20 to 30 pairs of males and females) were allowed to remain in the bottles for seven days. The flies eclosing over a nine-day period were counted and classified. Multiple replications were made of each mating. The series of experiments were carried out sequentially. Observed values within a series were compared by a chi-square test using a 2×2 contingency table.

RESULTS

Effect of wild-type second chromosomes on the viability of homokaryotypes when both parents are heterokaryotypes: In order to distinguish homokaryotypes from heterokaryotypes, a strain was used with the recessive gene *h* (hairy) substituted in the left arm of chromosome 3A. Except for this recessive gene (position 26.5) and small adjacent regions, the genetic background of this strain is similar to that of the tu-h ASU strain (WOOLF, KNOWLES and JARVIS 1964). This strain is symbolized by 1; 2; *h* 3A/3B, where 1 and 2 represent the first and second chromosomes from the tu-h ASU strain. Wild-type second chromosomes were substituted by first mating *M-5*; *Cy/Pm*; *ru h D^s st ri In(3R)C e l(3)e/3B* males with 1; 2; *h* 3A/3B females. Selection was made in later generations for flies that were 1; *Cy/Pm*; *h* 3A/3B. The chromosomes with Curly (*Cy*) and Plum (*Pm*) were then replaced with wild-type second chromosomes from the *H^s/In(3R)C Sb e l(3)e* laboratory stock. This was accomplished by mating 1; *Cy/Pm*; *h* 3A/3B females with *H^s/In(3R)C Sb e l(3)e* males. F₁ males of the type 1; *Cy/+*; *h* 3A/*In(3R)C Sb e l(3)e* were backcrossed to 1; *Cy/Pm*; *h* 3A/3B females. Male and female progeny with the chromosomes 1; *Cy/+*; *h* 3A/3B were mated together to produce the desired strain 1; +; *h* 3A/3B. This strain differs from the

1; 2; *h* 3A/3B strain by the presence of wild-type second chromosomes (symbolized by +) and probably the fourth chromosomes which were not controlled.

Series 1: The following matings were made: (1) ♀♀ 1; 2; *h* 3A/3B × ♂♂ 1; 2; *h* 3A/3B, and (2) ♀♀ 1; +; *h* 3A/3B × ♂♂ 1; +; *h* 3A/3B. The results are presented in Table 1. The total frequency of male and female homokaryotypes was slightly less (27.1% *vs.* 25.3%) when the parents possessed wild-type second chromosomes. It is concluded that these wild-type second chromosomes do not increase the viability of homokaryotypes when the parental flies are both heterokaryotypes. In each case, the observed frequency of homokaryotype (hairy) offspring was less than the expected Mendelian frequency of 33.3%.

The influence of a maternal effect on the frequency of homokaryotype offspring: *Series 2:* Reciprocal matings were made between flies of the karyotypes 1; 2; *h* 3A/*h* 3A and 1; 2; *h* 3A/3B. The expected Mendelian ratio of hairy and non-hairy offspring was 1:1 in each case. When the mothers were homokaryotypes, the observed frequency of homokaryotypes in the offspring was 21.1% ($n = 1722$). A frequency of 45.2% ($n = 4667$) was observed for these types when the mothers were heterokaryotypes (Table 1). The difference between these two frequency values (21.1% *vs.* 45.2%) is highly significant and suggests the influence of a maternal effect on the viability of homokaryotype offspring.

Series 3: A maternal effect is also manifested when the parental flies have wild-type second chromosomes from the *H³/In(3R)C Sbel(3)e* laboratory stock (Table 1). Only 33.1% ($n = 3500$) of the offspring were homokaryotypes when the mating was ♀♀ 1; +; *h* 3A/*h* 3A × ♂♂ 1; +; *h* 3A/3B, while the frequency of homokaryotypes resulting from the reciprocal mating (♀♀ 1; +; *h* 3A/3B × ♂♂ 1; +; *h* 3A/*h* 3A) was 45.8% ($n = 5662$). The difference between these frequency values (33.1% *vs.* 45.8%) is highly significant.

Series 4: The frequency of homokaryotype offspring was relatively similar in Series 3 and 4 when the female parents were 1; 2; *h* 3A/3B and 1; +; *h* 3A/3B (45.2% and 45.8%), respectively. However, the frequency of homokaryotype offspring produced by homokaryotype females was 21.1% (Series 2) when the parents and offspring possessed second chromosomes from the tu-h ASU strain, and 33.1% when the parents and offspring had wild-type second chromosomes (Series 3). A mating was made to determine whether the wild-type second chromosomes increase the frequency of homokaryotype offspring by modifying the maternal effect in the female parent, or by increasing the viability of the homokaryotype offspring that have been maternally affected. Females of the type 1; 2; *h* 3A/*h* 3A were crossed with 1; +; *h* 3A/3B males. Even though the female parents were 2/2, the observed frequency (Table 1) of homokaryotype offspring was 31.9% ($n = 1381$), which is relatively similar to the value (33.1%) obtained when the parents and offspring were +/+ . It is concluded that the viability of maternally affected homokaryotypes is increased when they are homozygous or heterozygous for the wild-type second chromosome, and the + chromosomes in 1; +; *h* 3A/*h* 3A females (Series 3) have no influence on maternal effect activity.

Series 5: Further evidence for a maternal effect and the role of wild-type second chromosomes is shown by reciprocal matings involving 1; +/2; *h* 3A/3B flies.

TABLE 1
Results of matings involving homokaryotypes and heterokaryotypes

	Offspring						Total
	Parents	Replications	Females		Males		
			Hetero-karyotypes	Homo-karyotypes	Hetero-karyotypes	Homo-karyotypes	
<i>Series 1</i>							
♀ 1; 2; <i>h</i> 3A/3B × ♂ 1; 2; <i>h</i> 3A/3B	5	770	320	1077	367	2534	27.1% (24.5 — 29.0)
♀ 1; +; <i>h</i> 3A/3B × ♂ 1; +; <i>h</i> 3A/3B	5	1088	378	1174	389	3029	25.0% (22.4 — 28.2)
<i>Series 2</i>							
♀ 1; 2; <i>h</i> 3A/ <i>h</i> 3A × ♂ 1; 2; <i>h</i> 3A/3B	10	586	133	772	231	1722	21.1% (13.5 — 27.0)
♀ 1; 2; <i>h</i> 3A/3B × ♂ 1; 2; <i>h</i> 3A/ <i>h</i> 3A	11	1215	871	1342	1239	4667	45.2% (33.8 — 52.7)
<i>Series 3</i>							
♀ 1; +; <i>h</i> 3A/ <i>h</i> 3A × ♂ 1; +; <i>h</i> 3A/3B	9	1210	542	1133	615	3500	33.1% (15.1 — 39.0)
♀ 1; +; <i>h</i> 3A/3B × ♂ 1; +; <i>h</i> 3A/ <i>h</i> 3A	9	1576	1331	1495	1260	5662	45.8% (38.9 — 50.6)
<i>Series 4</i>							
♀ 1; 2; <i>h</i> 3A/ <i>h</i> 3A × ♂ 1; +; <i>h</i> 3A/3B	9	475	201	466	239	1381	31.9% (24.6 — 40.6)
<i>Series 5</i>							
♀ 1; +/2; <i>h</i> 3A/ <i>h</i> 3A × ♂ 1; +/2; <i>h</i> 3A/3B	5	810	342	926	406	2484	30.1% (27.5 — 33.3)
♀ 1; +/2; <i>h</i> 3A/3B × ♂ 1; +/2; <i>h</i> 3A/ <i>h</i> 3A	5	997	889	1132	1023	4041	47.3% (45.2 — 50.4)

The frequency of homokaryotype offspring was 30.1% ($n = 2484$) when the mother was a homokaryotype as compared to 47.3% ($n = 4041$) when the mother was a heterokaryotype (Table 1). The observed frequency (30.1%) of maternally affected homokaryotype offspring is near the value expected, based on the previous results, because of the large number of offspring homozygous and heterozygous for segments of the wild-type second chromosome.

Test for meiotic drive: The data presented in Table 1 are compatible with a maternal effect hypothesis. They are also compatible with a meiotic drive hypothesis, i.e., more spermatozoa are recovered with the 3B chromosome than the *h* 3A chromosome because of some force operating during meiosis. This latter hypothesis was tested by making reciprocal matings between *bw; st* (*bw* = brown eyes) and 1; 2; *h* 3A/3B flies. If meiotic drive were the explanation, there should be more scarlet offspring from the mating ♀♀ *bw; st* × ♂♂ 1; 2; *h* 3A/3B than from the reciprocal mating. This was not observed. Among the progeny a 1:1 ratio was expected of scarlet (*bw/2; st/3B*) and non-scarlet (*bw/2; st/h* 3A) offspring. There was a deficiency of scarlet offspring in each case, but the difference between the observed frequencies [38.1% ($n = 2417$) when the male parent was a heterokaryotype, and 36.1% ($n = 1503$) when the female parent was a heterokaryotype] is not significant ($0.30 > P > 0.20$). It is concluded that the reduced frequency of homokaryotypes among the offspring of female homokaryotypes and male heterokaryotypes is not caused by meiotic drive. The reduced frequency of scarlet offspring among the progeny of these crosses is likely a function of their genotype (interaction of *st/3B* with genetic background).

The influence of parental age on the frequency of homokaryotype offspring: Homokaryotypes develop more slowly than heterokaryotypes. For example, in Series 2 (Table 1), for the mating ♀♀ 1; 2; *h* 3A/*h* 3A × ♂♂ 1; 2; *h* 3A/3B, the frequency of homokaryotype offspring was 17.7% ($n = 933$) during the first half of the nine-day counting period and 25.1% ($n = 789$) during the second half. Experiments were designed to determine if the reduced frequency of maternally affected homokaryotypes is due to a loss of a certain proportion of these karyotypes rather than an extreme reduction in developmental rate, so that less eclose during the limited nine-day counting period. These experiments were also designed to test for any parental age effect on the frequency of homokaryotype offspring. Twenty 1; 2; *h* 3A/*h* 3A females and 20 1; 2; *h* 3A/3B males were placed in each of ten vials. Every 24 hours, the parental flies were transferred to a new vial. The same experimental procedure was used for heterokaryotype females and homokaryotype males. All progeny eclosing in each vial were classified. The number of days the parents were transferred and the results are shown in Table 2. The frequency of homokaryotype offspring in all vials was 40.9% ($n = 16,692$) when the parental flies were ♀♀ 1; 2; *h* 3A/3B × ♂♂ 1; 2; *h* 3A/*h* 3A. The frequency of these karyotypes in all vials resulting from the reciprocal mating was 14.0% ($n = 1469$). It is concluded that the reduced frequency of maternally affected homokaryotypes is due to a loss of these karyotypes under the given environmental conditions and not to a severe reduction in the rate of development.

TABLE 2

Influence of age of parents on frequency of homokaryotype offspring

♀ ♀ 1; 2; h 3A/h 3A × ♂ ♂ 1; 2; h 3A/3B			♀ ♀ 1; 2; h 3A/3B × ♂ ♂ 1; 2; h 3A/h 3A		
Age (X)	Offspring eclosing	% Homo-karyotype (Y)	Age (X)	Offspring eclosing	% Homo-karyotype (Y)
1	26	0.0	1	461	47.3
2	54	37.0	1	1069	52.9
3	40	10.0	3	1352	51.1
4	95	28.4	4	1289	44.8
5	72	23.6	5	1267	42.7
6	75	20.0	6	1274	44.4
7	102	20.6	7	1174	38.2
8	115	12.2	8	1221	38.5
9	170	10.6	9	847	40.8
10	156	10.3	10	1017	34.7
11	170	12.4	11	949	39.8
12	123	9.8	12	959	39.0
13	115	7.8	13	795	41.9
14	77	7.8	14	650	35.8
15	17	0.0	15	614	34.5
16	39	5.1	16	652	33.4
17	23	1.3	17	518	27.2
18	..	..	18	584	27.6
Total	1469	14.0	Total	16,692	40.9
Total offspring: 1469			Total offspring: 16,692		
Percent homokaryotypes: 14.0			Percent homokaryotypes: 40.9		
b_1 = Regression coefficient = -1.1961			b_2 = -1.1781		
S_b = 0.4186			S_b = 0.1465		
a_1 = Y-intercept = 23.5235%			a_2 = 50.8921%		
S_a = 4.2891			S_a = 1.5860		
H_0 : $\beta_1 = 0$ $t = -2.86$ $0.02 > P > 0.01$			H_0 : $\beta_2 = 0$ $t = 8.04$ $P < 0.01$		

The results of these experiments led to the conclusion that the frequency of homokaryotype offspring decreases with parental age, regardless of the karyotype of the female parent (Table 2). For each type of mating the relationship between age and percent appears to be linear (Figure 1). A regression analysis was carried out ignoring the fact that the percentages were based on different values of n . Both regression coefficients deviate significantly from zero, but they do not deviate significantly from each other ($1.00 > P > 0.90$), indicating that the rate of decrease with age is not influenced by the karyotype of the female parent. The regression coefficient and Y-intercept for the data when the female parent is a homokaryotype are $b_1 = -1.1961$ and $a_1 = 23.52\%$, respectively. These statistics for the data obtained from the reciprocal mating are $b_2 = -1.1781$ and $a_2 = 50.89\%$. In the latter case, it is of interest that the Y-intercept approaches the expected Mendelian value of 50% even if the data for the first several days are left out of the calculations.

FIGURE 1.—Regression analysis of influence of karyotype of parents and parental age on frequency of homokaryotype offspring.

DISCUSSION

The literature contains many references to maternal effects in *Drosophila*. Studies with tumorous-head strains have led to the discovery of three, perhaps four different maternal effects. The maternal effect involved in the tumorous-head abnormality has been the object of extensive investigations (GARDNER and WOOLF 1949; GARDNER 1959; HANSEN and GARDNER 1963; JOHNSON and GARDNER 1965). The genome of tumorous-head strains was instrumental in the discovery of a maternal effect which influences the development of the male genital disc (WOOLF 1966). This maternal effect, which is also due to a sex-linked gene, was encountered when males from the tumorous-head strain were backcrossed to females with different attached-X chromosomes. KNOWLES (1967) discovered that the fertility of homokaryotype females, as defined by the percentage of eggs developing to the adult stage, is influenced by a maternal effect. This fertility maternal effect is controlled largely by a genetic mechanism in chromosome 2. The present study has shown that the maternal effect influencing the viability of homokaryotype offspring is attributable to a genetic system involving the left arm of chromosome *h* 3A. These experiments do not rule out, however, an interaction involving regions in the right arm of chromosome 3 or other chromosomes, with the threshold for maternal effect expression being reached when the left arm of chromosome *h* 3A is homozygous. Definitive experiments have not been carried out to determine what genetic relationship exists, if any, between the fertility and viability maternal effects. The strong role of the second chromosome for the fertility maternal effect suggests that they are at least partially independent.

Conclusive experiments have not been carried out to determine if the responsible genetic mechanism in the left arm of chromosome *h* 3A is a single gene or

consists of polygenes grouped in one region or scattered along the arm. In a preliminary experiment, a 3A chromosome was synthesized with the left arm replaced from roughoid (0.0) to past thread (42.0) with a segment from a chromosome with *ru h th st cu sr e^s ca*. A strain was synthesized with *ru h th* 3A/3B chromosomes, chromosome 1 from the tu-h ASU strain, and uncontrolled second and fourth chromosomes. Flies of this strain are homozygous for *tu-1* and *tu-3*. When reciprocal matings were made, 43.2% ($n = 1065$) of the offspring were homokaryotypes when the female parent was *ru h th* 3A/*ru h th* 3A. The frequency of homokaryotype offspring was 45.2% ($n = 2277$) when the female parent was a heterokaryotype (*ru-h th* 3A/3B). The difference is not significant ($0.30 > P > 0.20$). These results show that the recessive gene for hairy (*h*), by itself, is not responsible for the results given in Table 1. Females from this strain of the type *ru h th* 3A/3B were backcrossed to 1; 2; *ru h D^s st ri In(3R)C l(3)e*/3B males for five generations, in order to incorporate an increased amount of the genome from the tu-h ASU strain. Reciprocal matings then demonstrated the presence of maternal effect activity. Homokaryotypes female parents produced 38.6% ($n = 1125$) homokaryotype offspring. Heterokaryotype female parents produced 44.4% ($n = 3193$) homokaryotype offspring. The difference is highly significant. Although these results plus those presented in Table 1 could be explained by some alternative hypothesis, the overall observations suggest that (1) polygenes distributed along the length of the 3A chromosome produce the maternal effect and *ru h th* 3A/*ru h th* 3A females lack a substantial number of these genes; or, (2) the responsible region is right of 42.2 and viability of the homokaryotypes is increased because of the segment from roughoid to past thread and/or wild-type second chromosomes. Additional experiments are needed to determine the genetic basis for the maternal effect.

Tumorous-head strains are maintained in various laboratories in the United States. The only one tested for the maternal effect influencing viability is 1; 2; *h* 3A/3B, which was derived from tu-h ASU. Since genetic divergence has occurred among tumorous-head strains (WOOLF 1965) for polygenes affecting traits such as female productivity, the frequency of aspermia, and the tumorous-head abnormality, it is not unlikely that one or more of the strains lack the viability maternal effect. For example, the responsible genetic system should be selected against in any strain, such as tu-h Phil, which has lost chromosomes 3B. However, it is noteworthy that the maternal effect influencing the viability of homokaryotypes has manifested itself throughout the history of the 1; 2; *h* 3A/3B strain at Arizona State University. This strain has been propagated by selecting each generation parental flies showing some expression of the tumorous-head abnormality.

Maternal age effects have been well studied for meiotic events. PARSONS (1962) has reviewed the literature and presented, in addition, two cases that are measures of developmental stability: variability of egg length and sterno-pleural chaeta number asymmetry. The relationship between the frequency of homokaryotype offspring and parental age observed in this study may indicate that homokaryotypes are more sensitive than heterokaryotypes to physiological changes in eggs

theoretically brought about by advancing maternal age. However, because of the way the experiments were designed, an influence of paternal age has not been eliminated. Additional experiments are needed to clarify which parent is responsible for the effect, to determine the nature (one gene or many) and location of the responsible genetic mechanism, and to determine what internal and external factors influence this effect.

The data in Table 1 (Series 2) verify further that the sex ratio in tumorous-head strains favors males (56.1%, $n = 6389$). These experiments have also demonstrated that the sex ratio is decreased (49.1%, $n = 9162$) when wild-type second chromosomes are present (Series 3, Table 1). A genetic analysis of sex ratio in tumorous-head strains is under investigation. The data in Table 1 (Series 2) also support the observations of WOOLF and LOTT (1965) that in the absence of the maternal effect, the frequency of karyotypes can be ranked in the following order: male heterokaryotypes > male homokaryotypes > female heterokaryotypes > female homokaryotypes, although in this study there was little difference between the frequencies of female heterokaryotype and male homokaryotypes. The rankings are changed in the presence of the maternal effect and/or wild-type second chromosomes.

Studies with tumorous-head strains have demonstrated clearly the role of genetic background on fitness traits associated with chromosomal polymorphism (WOOLF, KNOWLES and JARVIS 1964). The evolution of the systems influencing viability of homokaryotypes, as well as the evolution of the complex genetic systems influencing other important traits such as sex ratio, fecundity, fertility and longevity of females and aspermia in these laboratory strains remains enigmatic.

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SUMMARY

The viability of homokaryotypes ($h\ 3A/h\ 3A$) in the 1; 2; $h\ 3A/3B$ strain is influenced by a maternal effect. When reciprocal crosses are made between homokaryotypes and heterokaryotypes, a lower proportion of homokaryotypes eclose when the karyotype of the mother is 1; 2; $h\ 3A/h\ 3A$ than when she has the karyotype 1; 2; $h\ 3A/3B$. The maternal effect is dependent on a genetic mechanism involving at least the left arm of Chromosome $h\ 3A$. The proportion of maternally affected homokaryotypes eclosing is increased if they possess wild-type second chromosomes. These wild-type second chromosomes have no influence on viability in the absence of the maternal effect. Regardless of the karyotype of the mother, the proportion of homokaryotypes eclosing is also influenced by the age of the parents, which may reflect an increased sensitivity of homokaryotypes to physiological changes in eggs resulting from advancing maternal age.

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