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Meiotic reversion in an unstable strain of yeast

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SUMMARY

Spontaneous reversions from instability to stability were studied in a mutant homothallic strain of yeast. The mutant strain was characterized by persistent lethal sectoring attributable to the presence of a recessive locus *uns1*. It was found that (1) the meiotic reversion rate is about 140 times higher than the mitotic reversion rate, (2) reversions are much more common in the homozygote *uns1 uns1* than in the heterozygote *UNS1 uns1*, (3) revertant segregants and lethal segregants tend to occur together, and (4) meiotic revertants tend to occur as twin revertants. These results indicate that reversion from unstable to stable results from genetic recombination and that, in meiosis, this recombination involves an unequal exchange at the first division.

1. INTRODUCTION

The dominant lethal damage induced in diploid yeast by radiations can be expressed not only as outright death but also as lethal sectoring. Lethal sectoring is characterized by the sporadic production of clusters of lysing cells among the mitotic progeny of individual irradiated cells. It can be viewed as a form of induced instability, and is of particular interest since at lower doses ($\sim LD_{50}$) it is induced with even greater frequency than is outright death (James & Werner, 1966; James, 1967).

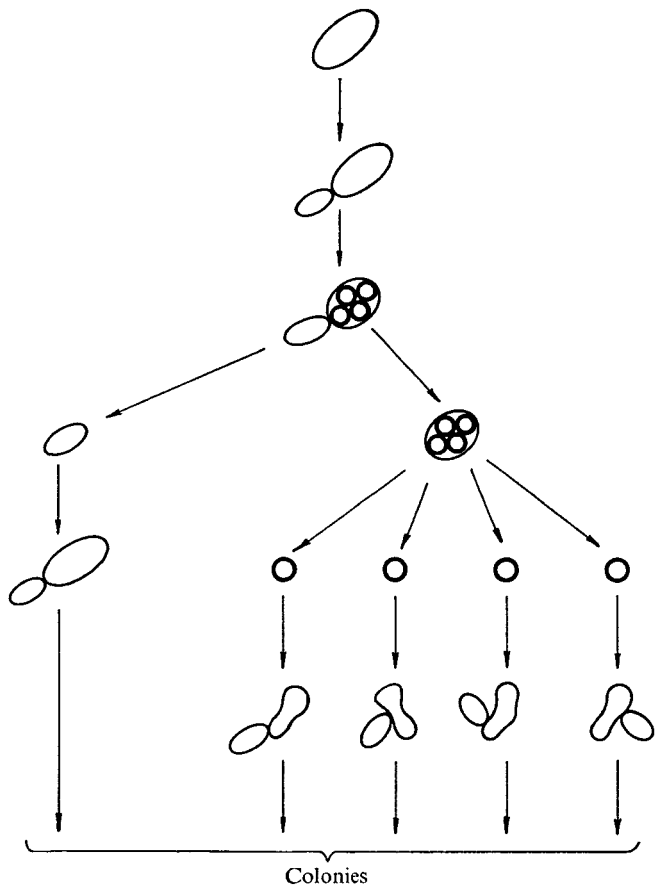
Lethal sectoring tends to diminish in frequency with advancing mitotic generations of an irradiated population, but often it is converted to a fixed or persistent characteristic (James *et al.* 1968). This fixed instability occurs among the meiotic segregants of affected lines and also occurs sporadically during vegetative reproduction. In such strains the propensity to produce lethal sectors may be regarded as a simple mutant characteristic that is open to analysis by routine mating techniques. The results of a recent study of three such strains were consistent with the supposition that the instability results from the presence of recessive chromosomal lesions which are located near each other or near one or more centromeres (James, 1972).

In the present study, the damage responsible for lethal sectoring was further explored using a particular mutant genotype, *uns1 uns1*. Attention was concentrated on spontaneous reversions from instability to partial and complete

stability. These appear with sufficient frequency during both mitosis and meiosis to permit a study of reversion at the level of the single cell rather than at a population level.

2. MATERIALS AND METHODS

The yeast was a strain of *Saccharomyces cerevisiae* (var. *ellipsoideus*). This yeast is homothallic and as such its spores diploidize shortly after germination, yielding lines which are homozygous at all loci except, presumably, at the locus for sex.



Text-fig. 1. The general procedure for determining the genetic constitution of an individual cell as it entered the meiotic phase.

The unstable mutant, *uns1 uns1*, was ultraviolet-induced. Its isolation has been described previously (James, 1972); briefly it was obtained as a recessive segregant from a strain in which dominant lethal sectoring had been induced by treatment with ultraviolet light.

The unstable phenotype conferred by the *uns1* lesion could be recognized by colony morphology, but a sampling procedure was used on occasion to provide specific information about lethal sectoring and growth, i.e. colony diameter after

incubation at 30 °C. Samples of 20–40 single and budding cells from test colonies in logarithmic growth phase were isolated to marked locations on a slab of agar medium and incubated. As soon as possible, the first postisolation buds were removed to new locations. The agar slab was then sealed in a chamber and reincubated for about 24 h, at which time the cells were inspected by means of a microscope. Lethal sectoring was recognized when one of the two separated cells of the postisolation mitotic division failed to divide further or produced only an abortive colony. The diameters of all the colonies were then measured to the nearest 0·01 mm and a mean colony diameter was calculated.

Mean colony diameter often differed between strains, but it was also profoundly affected by the microenvironment of the incubating clones. Consequently, when a reliable comparison of mean diameter of two or more strains was required, the samples were placed on the same agar slab. Even so, the effects of intra-chamber environmental differences sometimes led to small but statistically significant differences in mean colony diameter. These latter effects were ignored in this investigation. Variations in colony diameter within a strain were expressed as standard deviation of items. This value was informative because large variations in colony diameter within a strain provide one indication of the presence of lethal sectoring.

A special technique was required to determine the genotype of individual cells immediately prior to meiosis. The general outline of the procedure is shown in Text-fig. 1. Details of the procedure were as follows: a heavy suspension of washed cells was streaked on an agar slab of sporulation medium to provide conditions conducive to sporulation. At 24 h, washed budding cells from a presporulation medium were individually placed near the day-old growth already present. In a small fraction of instances, the mother cell sporulated while the bud remained stationary and viable. Ascus and bud were removed to the surface of an agar slab containing a complete medium. Within a few hours the bud could be freed from the ascus, whereupon the ascus was transferred to an agar slab containing snail enzyme. After the ascus wall had disintegrated, the freed spores were transferred to an agar slab containing complete medium where they were incubated. The procedure was not particularly efficient since sporulation was poor and buds frequently died on the sporulation medium.

All other procedures were routine and have been published elsewhere (James & Werner, 1966; James *et al.* 1968).

3. RESULTS

The mutant locus, *uns1*, confers extreme instability when homozygous; approximately 20 % of all mitoses initiate lethal sectors when cells are grown on a peptone-yeast–extract–agar medium. The number of cells within a lethal sector varies from one to hundreds, the upper limit being obscured because some cells disintegrate while others continue residual cell division. The progenitor cells of lethal sectors can be either mother cells or buds but are more usually the latter. Cells become enlarged and malformed prior to lysis and, as a result, colonies are ragged in

appearance when viewed under a microscope (see Pl. 1). In contrast, the colonies produced by wild-type or revertant cells are smooth in outline. This difference in colony morphology was particularly advantageous in this investigation since it permitted the unstable phenotype to be recognized without resorting to a single-cell pedigree analysis to detect the presence of lethal sectoring.

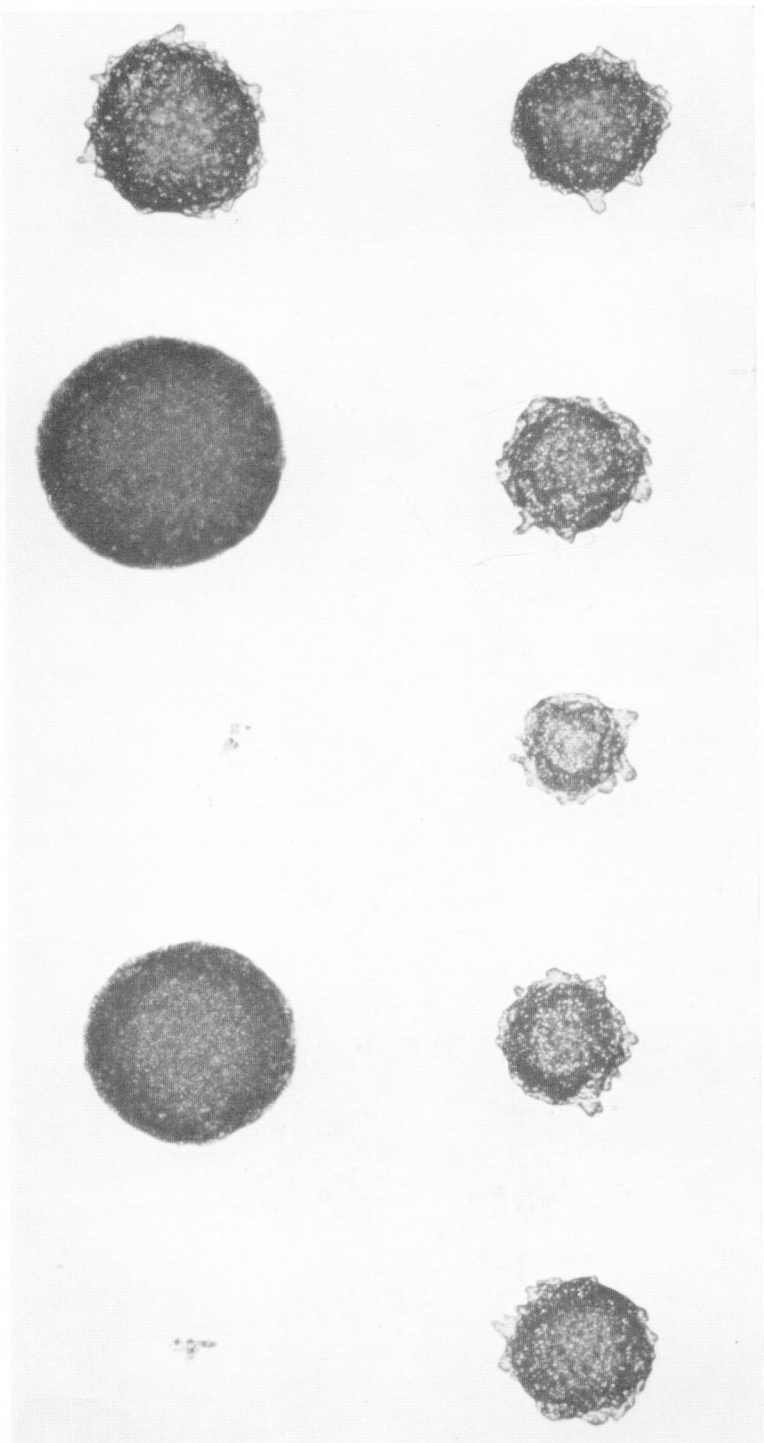
Table 1. *The distributions of tetrad phenotypes produced by sporulating cultures which were either heterozygous or homozygous for a recessive mutation conferring instability*

UNS1 uns1 Tetrad phenotypes*				No.	*uns1 uns1* Tetrad phenotypes				No.
S	S	s	s	215	s	s	s	s	324
S	S	s	—†	22	s	s	s	—	28
S	—	s	s	3	s	s	—	—	10
S	S	—	—	8	s	—	—	—	2
S	s	s	s	1	S	S	s	s	23
					S	S	s	—	1
					S	—	s	s	1
					S	S	—	—	4
					S	s	s	s	1
		Total		249					394

* S, smooth colony outline. s, ragged phenotype of *uns 1*.
† Non-germinating spore or abortive colony.

The sporulating heterozygote, *UNS1 uns1*, was reversion-resistant, whereas the sporulating homozygote, *uns1 uns1*, was reversion-prone. The difference in behaviour of the two genotypes is demonstrated by the data of Table 1. These are the segregation data accumulated from 25 cultures of the heterozygote and 23 cultures of the homozygote, each culture being derived from a single cell. There were no revertant spore colonies among 249 segregations of the heterozygote, and the only exception to a regular 2:2 (smooth to ragged) segregation was an apparent forward mutation or gene conversion in one segregant of a single ascus. In contrast, more than 7 % (30/394) of the segregations of the homozygote included the smooth colonies expected of revertants. These were distributed rather uniformly among the 23 test cultures. The presence of non-germinating spores prevented a complete analysis of segregation, but with one or possibly two exceptions, the revertants appeared as twin segregants.

The existence of twin segregants (Table 1) could be considered an indication that reversion occurred during mitoses prior to sporulation. On the other hand, two facts were consistent with the supposition that the revertants were meiotic in origin. First, the frequency of revertants tended to be constant among sporulating cultures and second, four of the eight lethal spores accompanying the revertants were unusual, they germinated to produce abortive colonies, an indication that they, as well as the revertants, had undergone a genetic change. A test of this possibility will be considered later.



Meiotic reversion of a cell of genotype *uns1 uns1*. Each column consists of four segregant spore colonies and, at the top, the colony of the bud produced at the mitosis immediately preceding meiosis. On the right is a normal segregation. On the left is a reversion segregation consisting of two revertant and two abortive colonies.

(*a*) *Complete and partial reversion*

The two revertant spore colonies from any one segregation of a sporulating homozygote were apparently identical. In contrast, the revertant spore colonies from different segregations were sometimes phenotypically fully revertant, S, and sometimes partially revertant, S′.

Data leading to the above conclusions were obtained from a detailed examination of individual revertant spore colonies, as follows: All the revertant spore colonies (14 pairs) from eight different cultures, each of which was derived from a single homozygous recessive cell, were sampled to provide information on growth behaviour. From the summarized data (Table 2), it was clear that the cells from the two revertant spore colonies of each segregation were similar if not identical in mean colony diameter.

Table 2. *The mean colony diameter (mm) of the twin revertants obtained by sporulating eight cultures of the homozygote*, uns1 uns1

Culture no.	...	1				2	3	4		5		6		7	8
Revertant no.	...	1	2	8	3	4	5	7	9	6	11	13	14	10	12
Spore col.*															
no. 1		0·37†	0·38	0·27	0·26	0·26	0·32	0·37	0·35	0·23	0·21	0·35	0·21	0·35	0·33
no. 2		0·38	0·37	0·26 (0·40)‡	0·28	0·33	0·36	0·37	0·37	0·24	0·23	0·37	0·23	0·33	0·35
Resample§		0·51	0·48	0·30	0·29	0·30	0·48	0·47	0·48	0·31	0·29	0·45	0·27	0·47	0·46
Phenotype‖		S	S	S′	S′	S′	S	S	S	S′	S′	S	S′	S	S

* Sampled for comparison of spore col. no. 1 *vs.* spore col. no. 2.
† Standard deviation of items varied between 0·02 and 0·06.
‡ Two non-overlapping distributions.
§ Sampled for comparison of revertants from different segregations.
‖ S, wildtype; S′, partial revertant.

Differences between pairs in growth rate are implied by these data but were confirmed from a comparison of mean colony diameters in which one revertant from each of the fourteen pairs was resampled on a single agar slab. The diameters (see Table 2) fell into either of two groups. In one, S, diameters ranged from 0·45 to 0·51 mm, in the other, S′, they ranged from 0·27 to 0·31 mm. The two types appeared with about equal frequency. There may have been differences between revertants within these two classes but the data were insufficient to demonstrate this.

Complete and partial revertants differed not only in mean colony diameter but also in frequency of lethal sectoring. The accumulated frequency among clones classed as S was 0·004 (2/452), a value comparable to that of wild-type. The frequency among clones classed as S′ was much higher, being 0·03 (7/247). The manner of lethal sectoring was also different from that of *uns1*: sectors were all single cells rather than clusters of lysing cells, and these cells were all buds, whereas in the case of *uns1* the progenitor of a lethal sector was not infrequently a mother cell.

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(b) The site of reversion

Most if not all reversions occurred at the original mutant locus rather than as suppressor mutations at some other locus.

To obtain this information, revertant no. 2 (Table 2) was crossed to wild-type and the resultant hybrid was subjected to tetrad analysis. If reversion was the result of a suppressor mutation at an independent locus, then five out of six segregations would be expected to include one or two unstable segregants. In fact, none of 75 segregants from 19 asci were of this phenotype.

Table 3. *The mean colony diameter of hybrids (revertant × revertant, and revertant × wild-type) and of their segregants; valid comparisons: between hybrids, and between segregants within hybrids*

Cross ...	2 × 1			2 × 5			2 × 7			2 × 9			2 × 18		
Hybrid* ...	0·62			0·63			0·52			0·61			0·59		
Tetrads† ...	1	2	3	1	2	3	1	2	3	1	2	3	1	2	3
	0·47	0·45	0·45	0·50	0·48	0·48	0·46	0·46	0·45	0·44	0·43	0·44	0·42	0·40	0·40
	0·46	0·45	0·44	0·48	0·48	0·46	0·46	0·45	0·42	0·43	0·43	0·43	0·41	0·39	0·39
	0·46	0·44	0·44	0·48	0·47	0·45	0·33	0·32	0·32	0·43	0·42	0·42	0·41	0·39	0·38
	0·45	0·43	0·43	0·47	0·46	0·45	0·32	0·32	0·31	0·42	0·42	0·42	0·40	0·38	0·38

Cross ...	2 × 10			2 × 17			2 × wild-type			2 × 8			2 × 3		
Hybrid ...	0·60			0·61			0·61			0·58			0·61		
Tetrads ...	1	2	3	1	2	3	1	2	3	1	2	3	1	2	3
	0·49	0·48	0·05	0·54	0·52	0·52	0·36	0·36	0·37	0·40	0·39	0·40	0·40	0·38	0·36
	0·47	0·48	0·04	0·54	0·52	0·51	0·36	0·34	0·34	0·40	0·39	0·40	0·38	0·37	0·34
	0·47	0·48	0·03	0·53	0·51	0·51	0·34	0·31	0·31	0·23	0·23	0·22	0·24	0·37	0·23
												(0·39)‡			
	0·47	0·48	0·03	0·48	0·50	0·50	0·34	0·31	0·31	0·23	0·22	0·22	0·23	0·37	0·22

Cross ...	2 × 4			2 × 6			2 × 16			2 × 20		
Hybrid ...	0·57			0·56			0·60			—		
Tetrads ...	1	2	3	1	2	3	1	2	3	1	2	3
	0·34	0·34	0·32	0·47	0·47	0·46	0·37	0·37	0·36	0·46	0·46	0·45
	0·32	0·33	0·30	0·46	0·43	0·44	0·36	0·35	0·36	0·45	0·43	0·43
	0·20	0·19	0·21	0·26	0·28	0·26	0·35	0·35	0·34	0·24	0·25	0·24
	0·19	0·18	0·19	0·25	0·24	0·26	0·35	0·35	0·34	0·24	0·23	0·20
												(0·41)‡

* Standard deviation of items varied between 0·02 and 0·04.
† Standard deviation of items varied between 0·02 and 0·08.
‡ Two non-overlapping distributions.

Thereafter, revertant no. 2 was crossed to each of the other 13 revertants. From 10 to 20 asci from each hybrid were dissected. Again, none of the 599 segregants from 152 asci displayed the unstable phenotype of *uns1*.

Confirmation of phenotypes was obtained by sampling the hybrids and 12 segre-

gants of three asci from each hybrid (Table 3). All the hybrids were essentially free of lethal sectoring, the accumulated frequency being 0·002 (1/406). The segregants from hybrids involving only 'complete' stables were indistinguishable from each other with the exception of those from revertant no. 2 × revertant no. 7. These produced an obvious 2:2 segregation for colony diameter. The reduced diameter of the associated hybrid suggests that one of the parental cells was mutant for growth rate, but the mating was not repeated.

All the segregants from crosses involving partial revertants had the phenotypes of either complete or partial revertants. The mean frequency of lethal sectoring among those classed as complete revertants, S, was 0·002 (5/1978). The mean frequency of lethal sectoring among those classified as S′ was 0·07 (32/460); all but three were daughter buds and all but three were single cells. The frequency of lethal sectoring in one revertant, no. 6, was excessive, being 0·14 (12/88).

It is evident from Table 3 that S′ tended to revert to S. Two segregant spore colonies contained cells of both phenotypes; they produced clear bimodal distributions for colony diameter. Further, one ascus from the cross revertant no. 2 × revertant no. 3 produced four complete-revertant segregants, and all 12 segregants from another cross (revertant no. 2 × revertant no. 16) were complete revertants.

The fourteen original revertants represented a minimum of 10 independently-occurring complete or partial reversions. From the combined data, it was evident that reversions usually occurred at or near the original mutant lesion, though the data were insufficient to disprove the presence of a dominant suppressor in any one instance.

(*c*) *Meiotic reversion*

The fact that revertants were present among the segregants of sporulating homozygotes but absent from the segregants of sporulating heterozygotes (Table 1) did not, in itself, provide incontrovertible evidence that revertants of the segregating homozygote were meiotic in origin. Some or all of them might have been produced in mitoses preceding sporulation, where, as heterozygotes, they would have had a selective advantage over homozygous cells both in growth rate and in ability to sporulate. Nevertheless, the indication of meiotic reversion was considered sufficiently strong to warrant a direct test.

This test was accomplished in the manner illustrated diagrammatically in Text-fig. 1. Essentially, it consisted of determining the genotype of a premeiotic cell by demonstrating the genotype of the mitotic bud produced immediately prior to meiosis.

The results were unequivocal in demonstrating a high incidence of meiotic reversion. Typical results are illustrated in Pl. 1 and summarized data are presented in Table 4. Although revertant and non-revertant bud colonies and spore colonies were easily distinguished by microscopic examination, the phenotypes were confirmed by sampling, a procedure that permitted the revertants to be classified as complete or partial.

Five features of the data are of particular interest: (1) Both complete and

partial revertants were produced during meiosis. (2) The frequency of meiotic reversion was extraordinarily high, being 7% (11/152). (3) With one exception, revertant meiotic segregants were accompanied by lethal segregants. The exceptional revertant was, in fact, atypical – mean colony diameter was approximately one-third that expected of revertants. The frequency of abortive colonies among lethal segregants (not shown in Table 4) was much higher among meiotic revertant segregations than among non-revertant segregations, 10/20 *vs.* 8/59. (4) There

Table 4. *The phenotypes of meiotic segregants and of the premeiotic cells producing them*

4-spored asci						3-spored asci				
Pre-meiotic bud colony	Segregants*				No.	Pre-meiotic bud colony	Segregants			No.
s	s	s	s	s	28	s	s	s	s	70
s	s	s	s	—†	11	s	s	s	—	22
s	s	s	—	—	4	s	s	—	—	6
s	S	S	—	—	3	s	S	—	—	2
s	S	—	—	—	1	s	S′	S′	—	1
s	S′	S′	—	—	2	s	S′	—	—	1
s	(S)‡	s	s	s	1					
S′	S′	S′	s	s	1	S′§	S′	S′	S′	1
S′ & s	S′	S′	S′ & s	s	1	S′ & s‖	S′	S′	S′	1

* S, wildtype; S′, partial revertant; s, phenotype of *uns1*.
† Non-germinating spore or abortive colony.
‡ The growth rate of this revertant was subnormal.
§ Cells were homozygous for the partial revertant.
‖ The revertant was heterozygous as determined by sporulation.

was a strong tendency for revertant segregants to appear as twin revertant spores. This was true in five of 11 instances and the data were compatible with this in five other instances. The only exception was the atypical revertant mentioned above. (5) The data relating to the four mitotic revertants (those instances in which cells of the premeiotic bud colony were not unstable) were unusual. In two spore colonies, the locus under test was apparently unstable since the colonies contained both revertant and non-revertant cells. Further, one of these mitotic revertants, though heterozygous, apparently produced three revertant segregants from a 3-spored ascus. In addition, one revertant bud was judged to be homozygous for partial reversion.

(*d*) *Mitotic reversion*

Mitotic reversion occurred sporadically among the cells of genotype *uns1 uns1*, though with a frequency that was about 140 times lower than that of meiotic reversion.

An estimate of the rate of reversion was obtained by a direct method involving

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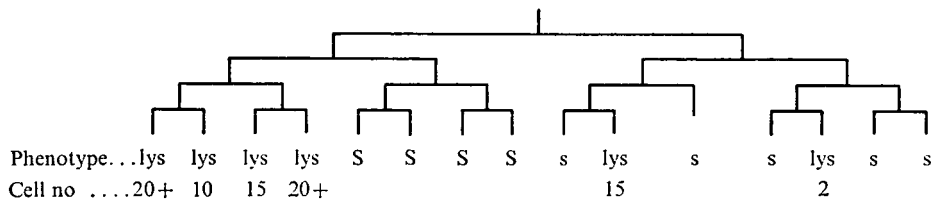
pedigree analysis. The mitotic products of individual cells were separated and the frequency with which one of these produced a stable colony was recorded.

To date, one revertant has been found among 1818 mitoses, a frequency of 0·0005. The pedigree in which this revertant was found is shown in Text-fig. 2 and is of interest. The mother cell could be classified as unstable at isolation because the progeny of its first bud produced ragged colonies and lethal sectors. However, the second bud was a stable revertant. Thereafter the mother cell became the progenitor of a large lethal sector. The coincident appearance of a lethal sector and a revertant cell is suggestive of a genetic interaction similar to that postulated to occur during meiotic reversion. It is evident, though, that lethal sectoring can occur independently of reversion.

Sporulation and segregation of the revertant showed it to be heterozygous (*UNS1 uns1*).



Text-fig. 2. Mitotic reversion in the pedigree of a cell of genotype *uns1 uns1*. At each division, the line on the left represents the mother cell. 'lys' refers to the lysed cells of a lethal sector.

4. DISCUSSION

Several distinct if unconventional features of the reversion process at a genetic site in yeast have been uncovered by this study: (1) The frequency of meiotic reversion is at a high level of 7 %. (2) This frequency is more than 100 times that of mitotic reversion. (3) Meiotic reversions are more frequent among cells homozygous for the mutant locus than among heterozygous cells. (4) Meiotic revertant segregants, and perhaps mitotic revertants also, tend to be accompanied by lethal segregants. (5) Meiotic revertant segregants tend to occur as twin revertants.

An excessively high frequency of wild-type revertants among the segregants of homozygotes for particular mutant characteristics has been noted in several organisms. The classical example is that of Bar eye in *Drosophila* (Sturtevant, 1925). Here, reversion was found to result from unequal crossing over in a region of duplication. Other instances of meiotic reversion in *Drosophila* (Lewis, 1941; Judd, 1964), maize (Laughnan, 1949) and *Ascobolus* (Paszewski & Surzycki, 1964) have been similarly interpreted. In yeast, a disparity between meiotic and mitotic reversion frequencies has been found by Magni and co-workers at several specific loci (see Magni & Sora, 1969). These workers, having noted an association of meiotic reversion with frame-shift mutation and with recombination of outside markers, have also attributed meiotic reversion to unequal crossing over. In *Neurospora crassa*, reversions of isoleucine–valine mutants occur during meiosis with frequencies as high as 10 % (Bausum & Wagner, 1965). Here again, unequal

crossing over has seemed the most likely mechanism, though the manner in which outside markers segregate is unexpected. In *Salmonella* a comparable phenomenon, termed 'selfing', has been attributed to reverse mutation under the influence of a transducing fragment (Demerec, 1963).

In the present study, the association of meiosis with reversion suggests, as did most of the examples quoted above, an involvement of genetic recombination. Here the possibility is strongly reinforced by the coincident occurrence of meiotic revertant segregants and lethal segregants within a tetrad. Indeed, it is difficult to conclude otherwise than that reversion is a gain–loss event in which genetic material is acquired by one segregant at the expense of another. But, whether the revertant segregants are the recipients of the gain or of the loss is not obvious.

It is possible to construct models based on either unequal crossing over or non-disjunction to explain reversion at the *uns1* locus. However, neither is entirely satisfactory in view of the information presently available.

Unequal crossing over could either restore or partially restore the original constitution of a chromosome, depending on the location of the exchange. In either instance, the extent of damage in the homologue might be increased sufficiently to cause death. The initial lesion may be pictured as a deletion covering more than one locus but it is evident that a duplication would equally suit the purpose. In the case of deletion, the model requires that a degree of genetic redundancy be normal in the region of unequal crossing over. However, to explain the occurrence of twin meiotic revertants, it is necessary to postulate either that two identical exchanges occur at the 4-strand stage or that exchange occurs at a 2-strand stage. Neither postulate is attractive.

In some respects a model based on nondisjunction is preferable. Thus, if the instability of the homozygous recessive genotype, *uns1 uns1* were caused by tetrasomy ($2n+2$), then nondisjunction at the first meiotic division would lead to two segregant types, one which would contain the normal chromosome complement, $2n$, and thus be revertant, and one which would contain four extra chromosomes, $2n+4$, and might be lethal. The low frequency if not absence of revertants among the segregants of the heterozygote ($2n+1$) would also be accounted for by this type of aneuploidy. It is difficult to explain the existence of partial revertants with this model. Nevertheless, an interpretation based on non-disjunction has been strengthened by a recent investigation (James, 1972) of three independently induced unstable lines, one of which was the strain under study here. The results indicated that different loci were involved since the dihybrids were normal or nearly so. Segregants of the dihybrids were of only two types, parental ditype and non-parental ditype. Taken at face value, these segregation data implied that the lesions responsible for lethal sectoring are either tightly linked to different centromeres or involve whole chromosomes.

It will be possible to answer many of the questions relating to lethal sectoring and, in particular, to reversion, when the responsible lesions are located within the genetic apparatus of the cell. In the meantime, the phenomenon of meiotic reversion provides one method of investigating such loci.

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