CONTROL OF NON-ALLELIC RECOMBINATION IN *NEUROSPORA CRASSA*

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Abstract

Two different *recombination* genes each control both allelic recombination and non-allelic recombination at a number of well-defined places in the genome of *N. crassa*. The dominant gene *rec-3*$^+$ reduces allelic recombination at the *am-1* and *his-2* loci and in the segment between *sn* and *his-2*. The dominant gene *rec-2*$^+$ reduces allelic recombination at the *his-3* locus and in the three separate segments *pyr-3 his-5*, *his-3 ad-3*, and *arg-3 sn*. It is possible that *rec-1*$^+$, which reduces allelic recombination at the *his-1* locus, also reduces non-allelic recombination between *his-2* and *his-3*. The identity of *rec-x* with *rec-3* is very highly probable; the identity of *rec-w* with *rec-2* is also highly probable.

I. INTRODUCTION

It has been shown that the *recombination-3*$^+$ gene, present in the wild strain Emerson A, reduces allelic recombination at the *am-1* (*amination-1*) locus (Catcheside 1966) and at the *his-2* (*histidine-2*) locus (Catcheside and Austin 1971). More precisely, if different *rec*$^+$ genes are in control at the *am-1* and *his-2* loci, they must, with 95% probability, be at loci less than 0·14 centimorgans apart. The *rec-3* locus is in the left arm of linkage group I, proximal to the locus of the *mating type* genes and between the *acr-3* (*acridine-3*) and *arg-3* (*arginine-3*) loci.

An action upon non-allelic recombination between *his-3* and *ad-3* simultaneously with an action on allelic recombination at the *his-3* locus has been found to be characteristic of *rec-w*$^+$ (Angel *et al.* 1970). In this case a large effect on non-allelic recombination was dependent upon the presence of a particular recognition gene (*cog*$^+$) in the region affected. A much smaller effect of *rec-w*$^+$, statistically of doubtful significance, occurred if only the recessive *cog* gene was present. In the case of the *his-1* region, *rec-1*$^+$ causes an insignificant reduction of the *am inos* segment within which the *his-1* locus lies. However, a more careful examination of the *am-1 his-1* and *his-1 inos* segments might disclose an effect. Likewise, *rec-3*$^+$ causes no significant reduction in the *sp am-1* and *am-1 his-1* regions (Smyth 1973). An effect on non-allelic recombination in the neighbourhood of *his-2*, due to *rec-3*$^+$, is reported in this paper.

It will also be shown that *rec-2*$^+$ controls a region close to the one affected by *rec-3*$^+$. The gene *rec-2*$^+$ was first found by Smith (1966) to reduce recombination

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between *pyr-3* (*pyrimidine-3*) and *leu-2*, in linkage group IV, from 23 to 10%. Subsequently, he showed that the whole effect occurred in the *pyr-3 his-5* segment, in which recombination was reduced from about 14% to less than 1% by *rec-2*$^+$, there being no effect on the *his-5 leu-2* segment. Smith (1968) stated that the locus of *rec-2* is in linkage group V, proximal to the *his-1* and *inos* loci and very close to the *am-1* locus. No data were given and it was not known then whether *rec-2* is proximal or distal to *am-1*.

The gene *rec-w*$^+$ reduces allelic recombination at the *his-3* locus and non-allelic recombination in the adjacent *his-3 ad-3* segment of linkage group I (Angel *et al.* 1970). The *rec-w* locus was shown to be in linkage group V and evidence, not reported in that paper, suggested a position proximal to the *inos* locus. The question therefore raised is whether *rec-w* and *rec-2* are the same gene. This paper reports an explicit test which strongly supports the hypothesis of identity and locates *rec-2* between the *spray* and *amination* loci.

II. Material and Methods

The stocks used included those developed for the study of *rec-3* (Catcheside 1966) and of the probable identity of *rec-3* and *rec-x* (Catcheside and Austin 1971). The genes used for testing effects of *rec-3* were 47305 (*am-1*^{2}) and K314 (*am-1*^{6}) at the *am-1* locus, K584 and K612 at the *his-2* locus, K125 at the *arg-3* locus, K83 at the *his-1* locus, and C136 at the *sn* (*snowflake*) locus.

Stocks for locating *rec-2* and *rec-w* were constructed specially, as described in detail in the text. The gene *spray* (*sp*), having an effect on the growth and branching of the mycelium, was used as a marker to define a short segment of linkage group V proximal to *am-1*. The tests for *rec-2*$^+$ and *rec-2* were made using the allele 1298 at the *pyr-3* locus and the allele K553 at the *his-5* locus, both in linkage group V, as markers. Tests for *rec-w*$^+$ versus *rec-w* were made by measuring allelic recombination at the *his-3* locus between K504 and K874, with *cog*$^+$ in the experimental material. The gene *cot-1* (C102, *colonial temperature sensitive*) was present in all stocks used experimentally. Its use allows control of the size of colonies and makes counting of assay plates easier. It is not mentioned in the constitutional formulae of the various stocks, but should be understood to be present even though not mentioned explicitly.

The stock numbers are given in every case to facilitate identification of those used in each cross. The cultural methods employed were the standard ones previously described (Catcheside 1966) with appropriate variations especially in accessory nutrients.

III. Results

(*a*) *Non-allelic Recombination in the* arg-3 his-2 *Segment of Linkage Group I*

Progeny to use for tests of possible effects of *rec-3*$^+$ on the *arg*-3 *his-2* interval were prepared. First, A K584 progeny (11135 and 11137) were isolated from the cross a K584 *rec-1*$^+$ *rec-2 rec-3* × A *rec-1 rec-2 rec-3*$^+$ (3820). Since the locus of *rec-3* is between the *mating type* and *his-2* loci some progeny would be *rec-3* and others *rec-3*$^+$; these were identified by a direct test cross with a K612 *rec-3*. All progeny would be *rec-2* and each would have a half chance of being *rec-1*$^+$. Second, a *arg-3* progeny (11422, 11423, 11425, 11589–11591, 11594–11596, 11599, 11601–11603) were bred from the cross a K125 *rec-1*$^+$ *rec-2 rec-3* (1552) × A *rec-1*$^+$ *rec-2*$^+$ *rec-3*$^+$ (2931). All would be *rec-1*$^+$ and also *rec-3*, since the locus of *rec-3* is between the *mating type* and *arg-3* loci and double recombinants in this region are most unlikely. Each would have a half chance of being *rec-2*$^+$. Crosses between these two sets of stocks were analysed for frequency of recombination between *arg-3* and *his-2* by measuring the frequency of the prototrophs *arg-3*$^+$ *his-2*$^+$, the results being given in Table 1. It is

clear that a large reduction in recombination frequency is correlated with the presence of *rec-3*$^+$ in one parent of a cross. The two sets of frequencies show other variation, especially among those in which one parent was *rec-3*$^+$. These show some indication

TABLE 1

PERCENTAGE FREQUENCY OF PROTOTROPHS ARISING FROM RECOMBINATION BETWEEN VARIOUS *arg-3* AND *his-2* STOCKS

a *arg-3* stocks *rec-1*$^+$ *rec-3* (*rec-2* or *rec-2*$^+$)	A *his-2* stocks		
	rec-2 rec-3$^+$ (*rec-1* or *rec-1*$^+$) 11135	*rec-2 rec-3* (*rec-1* or *rec-1*$^+$) 11137	*rec-3* (?*rec-2*) 7560
11422	2·8	6·5	
11601	2·2	5·1	
11595	1·8	4·0	14·3
11423	1·7	6·1	
11594	1·6	6·1	6·7
11590	1·6	3·9	6·2
11589	1·6	4·8	7·8
11591	1·4	5·6	8·0
11596	0·9	5·8	7·3
11599	0·6	4·5	5·8
11602	0·5	4·2	
11603	0·5	4·1	
11425	0·5	3·5	

of values centering around 1·5 and 0·5%, but the separation is not clear cut. If valid, the segregation could be due to an effect of *rec-2*$^+$ versus *rec-2*. Further data have tended to confirm that both *rec-2* and *rec-3* genes control recombination between *arg-3* and *his-2*, but that some of the variation may be due to yet another factor.

TABLE 2

EFFECT OF SUBSTITUTION OF *rec-3*$^+$ FOR *rec-3* ON PERCENTAGE FREQUENCY OF PROTOTROPHS ARISING FROM RECOMBINATION BETWEEN *arg-3* AND *his-2*

a *arg-3 rec-2 rec-3*	A *his-2 rec-2*$^+$ *rec-3*			A *his-2 rec-2*$^+$ *rec-3*$^+$	
	13450	13451	13452	13399	13400
13303	5·6	6·4	3·8	0·4	0·4
13379	3·4	5·2	4·9	0·4	0·4
13382	4·2	5·5	3·1	0·5	0·4

The further experiments included the following:

(1) a K125 *rec-2 rec-3* progeny were bred from the cross a K125 *rec-1*$^+$ *rec-2 rec-3* (1552) × A *rec-1 rec-2 rec-3*$^+$ (3820). Progeny of constitution A K584 *am-1*^{6} *rec-2*$^+$ *rec-3*$^+$ and A K584 *am-1*^{6} *rec-2*$^+$ *rec-3* were bred from 11135 and 11137 crossed, respectively, to a *am-1*^{6} *rec-1*$^+$ *rec-2*$^+$ *rec-3*$^+$ (3696); the locus of *rec-2* is very close to that of *am-1*. Crosses between these selected progeny gave the data summarized in Table 2. They show a large effect due to *rec-3*$^+$.

(2) A K125 *rec-2* rec-*3* (11232, 11518) and A K125 *rec-2 rec-3*$^+$ (11516, 11517, 11519) were bred from the cross a K125 *rec-1*$^+$ *rec-2 rec-3* (1552) × A *rec-1 rec-2 rec-3*$^+$, the *rec-3* versus *rec-3*$^+$ constitution being verified by subsequently breeding in an *am-1* mutant and testing progeny for allelic recombination at the *am-1* locus. a K584 *rec-2 rec-3* (11942, 11948, 11950) and a K584 *rec-2*$^+$ *rec-3* (11943) progeny were bred from the cross a K584 *rec-1*$^+$ *rec-2 rec-3* × A *rec-1*$^+$ *rec-2*$^+$ *rec-3*$^+$ (2931). Data from 19 of the crosses between these two sets of stocks are summarized in Table 3. They show effects on recombination between *arg-3* and *his-2* due to both *rec-2*$^+$ and *rec-3*$^+$, the effects of the latter being much the greater.

TABLE 3

INTERACTION OF *rec-2*$^+$/*rec-2* AND *rec-3*$^+$/*rec-3* ON PERCENTAGE FREQUENCY OF PROTOTROPHS ARISING FROM RECOMBINATION BETWEEN *arg-3* AND *his-2*

	a *his-2 rec-2 rec-3*			a *his-2 rec-2*$^+$ *rec-3*
	11942	11948	11950	11943
A *arg-3 rec-2 rec-3*				
11232	4·3	6·0	4·4	2·9
11518	4·5	—	3·6	3·2
A *arg-3 rec-2 rec-3*$^+$				
11516	2·0	3·2	2·9	0·7
11517	1·7	1·7	1·3	0·8
11519	1·4	1·3	3·1	0·8

(3) Eight each of stocks of the following compositions were bred:

a *acr-3*^{r} *his-2 rec-2 rec-3* (13668a1–a8)
a *acr-3*^{r} *his-2 rec-2*$^+$ *rec-3* (13667a1–a8)
a *acr-3*^{r} *his-2 rec-2 rec-3*$^+$ (13670a1–a8)
a *acr-3*^{r} *his-2 rec-2*$^+$ *rec-3*$^+$ (13669a1–a8)

These were obtained from crosses of a *acr-3*^{r} K612 *am-1*^{2} *rec-3* (10174) and a *acr-3*^{r} K612 *am-1*^{2} *rec-3*$^+$ (10175) to A *rec-1 rec-2 rec-3*$^+$ (3820) and A *rec-1*$^+$ *rec-2*$^+$ *rec-3*$^+$ (2931) in all four possible combinations. The close linkage of the *loci* of *rec-2* and *am-1* assured the constitution of the selected progeny, just as did the location of *rec-3* between the loci of *mating type* and *his-2*.

A stock of A *arg-3 rec-2 rec-3* (11518) was bred from a K125 *rec-1*$^+$ *rec-2 rec-3* (1552) × *rec-1 rec-2 rec-3*$^+$ (3820), the *rec-3* constitution being verified by subsequently breeding to an *am-1* mutant and testing A *arg-3 am-1* progeny for the frequency of allelic recombination at the *am-1* locus. A stock of A *arg-3 sn rec-2 rec-3* (13751) was then bred from the cross 11518 × a *sn rec-2* (13656). The locus of *sn* lies between *arg-3* and *his-2* and so allows the separate examination of the effects of *rec-2*$^+$ and *rec-3*$^+$ on the segments *arg-3 sn* and *sn his-2*. *Snowflake* (*sn*) is a mutant which grows colonially at first and then, after about 3 days, like wild type. It can be scored readily in Petri dish cultures when grown from ascospores by the standard plating procedures. In crosses of 13751 with the a *his-2* stocks, prototrophs (*arg-3*$^+$ *his-2*$^+$) were selected and then classified as *sn* or *sn*$^+$; the relative proportions measured the relative recombination values in the two segments into which *sn* divides the *arg-3 his-2* region.

Each of the two A *arg-3* stocks (11518 and 13751) was crossed with each of the 32 a *his-2* stocks and the results are summarized in Table 4. These show that all values of recombination, in *rec-3* × *rec-3* crosses, are relatively smaller when the A *arg-3* parent is 11518. This particular stock appears often, but not always, to show relatively low frequencies of recombination in crosses to other a *his-2 rec-2 rec-3* stocks. Thus in crosses to a series of sibs of 11137 and 11135 the following percentage frequencies of prototrophic recombinants were observed: 7·85, 6·98, 6·54, 4·22, 3·91, 3·62, 3·34.

TABLE 4

PERCENTAGE FREQUENCIES OF PROTOTROPHS ARISING FROM RECOMBINATION BETWEEN *arg-3* AND *his-2* STOCKS OF KNOWN *rec-2* AND *rec-3* CONSTITUTIONS AND PROPORTIONS OF *snowflake* (*sn*) PROGENY AMONG THE RECOMBINANTS

a *his-2* stocks	A *arg-3* stocks 11518: Frequency of prototrophs (%)	A *arg-3* stocks 13751: Frequency of prototrophs (%)	A *arg-3* stocks 13751: Proportion of *sn*	a *his-2* stocks	A *arg-3* stocks 11518: Frequency of prototrophs (%)	A *arg-3* stocks 13751: Frequency of prototrophs (%)	A *arg-3* stocks 13751: Proportion of *sn*
rec-2 rec-3				*rec-2 rec-3*$^+$			
13608 a1	2·0	3·5	0·43	13670 a1	1·2	1·6	0·87
2	2·9	5·0	0·32	2	1·2	1·7	0·89
3	2·7	4·8	0·37	3	1·3	1·2	0·89
4	2·9	5·5	0·33	4	1·1	1·5	0·87
5	2·2	3·4	0·35	5		1·6	0·84
6	3·1	5·6	0·28	6	1·3	1·1	0·88
7	2·2	4·5	0·35	7	1·3	1·3	0·84
8	3·8	5·4	0·29	8	1·3	1·6	0·86
Means	2·60	4·51	0·34		1·24	1·46	0·87
rec-2$^+$ *rec-3*				*rec-2*$^+$ *rec-3*$^+$			
13667 a1	1·7	3·1	0·19	13669 a1	1·0	0·8	0·81
2	2·6	5·2	0·15	2	0·6	0·7	0·86
3	2·8	4·4	0·22	3	0·6	0·6	0·82
4	2·2	3·9	0·18	4	0·6	0·9	0·85
5	2·1	3·6	0·16	5	0·7	0·7	0·88
6	2·1	3·7	0·20	6	0·8	0·7	0·86
7	2·9	5·0	0·14	7	1·1	0·8	0·92
8	1·2	2·6	0·25	8	0·4	0·7	0·92
Means	2·18	3·73	0·19		0·73	0·73	0·87

The data could be interpreted if there were a recessive gene tending to decrease recombination in the *arg-3 his-2* segment, carried by 11518 and by four of the seven a *his-2* stocks. This supposition is capable of test but results are not yet available. The recessive gene presumed to decrease recombination appears to be unlinked to *cot* (linkage group IV) and to the *mating-type his-2* region (linkage group I).

In the crosses involving A *arg-3 sn rec-2 rec-3* (13751) as one parent, not only are the frequencies of recombination between *arg-3* and *his-2* changed by *rec-2*$^+$ and *rec-3*$^+$, but so also are the proportions of *snowflake* among the prototrophic recombi-

nants. The values of recombination in the *arg-3 sn* and *sn his-2* regions are computed from these data (Table 5, bottom two lines).

TABLE 5

MEAN VALUES OF PERCENTAGE FREQUENCY OF PROTOTROPHS ARISING FROM RECOMBINATION BETWEEN *arg-3* AND *his-2*, ARRANGED TO SHOW VARIATION IN INDIVIDUAL EFFECTS OF *rec-2*$^+$ AND *rec-3*$^+$

Data from	Region	Percentage frequency of prototrophic recombinants				Individual effects on recombination			
		rec-2 / *rec-3*	*rec-2* / *rec-3*$^+$	*rec-2*$^+$ / *rec-3*	*rec-2*$^+$ / *rec-3*$^+$	*rec-2*$^+$ in *rec-3*	*rec-2*$^+$ in *rec-3*$^+$	*rec-3*$^+$ in *rec-2*	*rec-3*$^+$ in *rec-2*$^+$
Table 2	*arg-3 his-2*			4·54	0·41				−4·13
Table 3	*arg-3 his-2*	4·51	1·95	3·06	0·79	−1·45	−1·16	−2·56	−2·27
Table 4 (11518)	*arg-3 his-2*	2·60	1·24	2·18	0·73	−0·42	−0·51	−1·36	−1·45
Table 4 (13751)	*arg-3 his-2*	4·51	1·46	3·73	0·73	−0·78	−0·73	−3·05	−3·00
Table 4	*arg-3 sn*	1·55	1·27	0·71	0·64	−0·84	−0·63	−0·28	−0·07
Table 4	*sn his-2*	2·96	0·19	3·02	0·09	+0·06	−0·10	−2·77	−2·93

Consideration of all the data accumulated (Table 5) shows that both *rec-2*$^+$ and *rec-3*$^+$ act to reduce recombination between *arg-3* and *his-2*. Moreover, to a considerable if not complete degree, each of the *rec* genes acts independently and additively. The indications of some minor interaction, especially in the data of Table 3 (see Table 5, line 2), may be a consequence of heterogeneity among the materials used in respect of genes of minor effect on recombination.

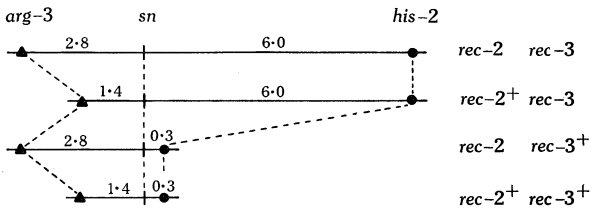


Fig. 1.—Effects of *rec-2*$^+$ and *rec-3*$^+$ on the map of the *arg-3 his-2* segment of linkage group I in *N. crassa*. The *sn* locus is between *arg-3* and *his-2*. The gene *rec-2*$^+$ reduces recombination in the *arg-3 sn* segment from 2·8 to 1·4%; the gene *rec-3*$^+$ reduces recombination in the *sn his-2* segment from 6 to 0·3%.

Even more striking is the evidence that the effects of *rec-2*$^+$ and *rec-3*$^+$ are exerted largely, and perhaps entirely, in distinct segments of the *arg-3 his-2* interval. It is fortunate that the locus of *sn* appears to be at or very near the boundary between these segments. This allows the conclusion that *rec-2*$^+$ approximately halves recombination between *arg-3* and *sn*, reducing the value from 2·82 to 1·35%, and has no effect upon recombination between *sn* and *his-2*. Further *rec-3*$^+$ virtually eliminates recombination between *sn* and *his-2*, reducing it by a factor of about 20 from 5·98 to 0·28%; *rec-3*$^+$ may have a slight effect on the *arg-3 sn* region. The effects of *rec-2*$^+$ and *rec-3*$^+$ on the *arg-3 his-2* segment of linkage group I are shown diagrammatically in the maps in Figure 1. The greatly different degrees of apparent action of different

rec$^+$ genes on different segments and indeed, it will be seen, of the same *rec*$^+$ gene on different segments raises intriguing questions as to how these variations of effect arise. However, caution is needed in considering these matters for it is unknown whether the whole segment of action of any of the *rec*$^+$ genes is defined by any of the loci used in these observations.

The actual values quoted must be treated with some caution since, apart from the experimental errors due to sampling and other causes, there are undoubtedly minor heritable differences between the stocks compared and these affect the values calculated. The observed values are reasonably reproducible in experiments conducted at different times. This is illustrated by two instances which contributed most to the variation in the *rec-2 rec-3* data in Table 4:

	Percentage frequency of prototrophic recombinants		Proportion of *sn* among prototrophs	
	Expt 1.	Expt 2.	Expt. 1	Expt. 2
13668a1 × 13751	3·53	3·50	0·451	0·410
13668a6 × 13751	6·05	5·30	0·236	0·235

Determination of whether the effect upon non-allelic recombination between *arg-3 his-2* ascribed to *rec-3*$^+$ is indeed most probably due to this gene may be assessed in the same way that Catcheside and Austin (1971) tested the probable identity of *rec-3* and *rec-x*. In those experiments recombinants were selected in the very short region between *acr-3* and *arg-3* in which the locus of *rec-3* lies. All but three of the 47 selected recombinants previously analysed had been discarded before the new action of *rec-3*$^+$ was found, so fresh isolations were made and all analyses were repeated. The crosses used were the same as before:

10154 a *acr-3*^{r} *rec-3 arg-3 rec-2*$^+$ *am-1*^{2} (9980) × A *rec-3*$^+$ *his-2 rec-2* (7576)

10155 a *acr-3*^{r} *rec-3*$^+$ *arg-3 rec-2*$^+$ *am-1*^{2} (9981) × A *rec-3 his-2 rec-2* (7575)

From these crosses, a *acr-3*^{r} *his-2 am-1*^{2} progeny, recombinant between the loci of *acr-3* and *arg-3*, were selected by plating on medium supplying acriflavin, histidine, and alanine, but not arginine. These progeny were then tested by crossing each isolate in the three following ways:

(1) to A *rec-3 am-1*^{6} to classify for high (*rec-3*) and low (*rec-3*$^+$) frequency of *am-1*$^+$ prototrophs;

(2) to A *rec-3 arg-3* to classify for high and low frequency of recombination in the *arg-3 his-2* region;

(3) to A *rec-x* K612 to classify for high (*rec-x*) and low (*rec-x*$^+$) frequency of *his-2*$^+$ prototrophs.

Consonance of relative values of recombination, whether high or low, in all three tests indicates that the *rec-3* and *rec-3*$^+$ genes are most probably responsible for all three of the effects measured. Altogether, there were 51 isolates from 10154 (Fig. 2) and 59 from 10155; none showed evidence of recombination of the high and low effects on the three characters measured.

From the point of view of measuring non-allelic recombination between *arg-3* and *his-2* it is unfortunate that the test crosses showed a rather low differential between

rec-3$^+$ and *rec-3* progeny, even less than that exhibited by the 11518 crosses in Table 4. In part, the low value in *rec-3* progeny was due to the presence of *rec-2*$^+$ in all of them.

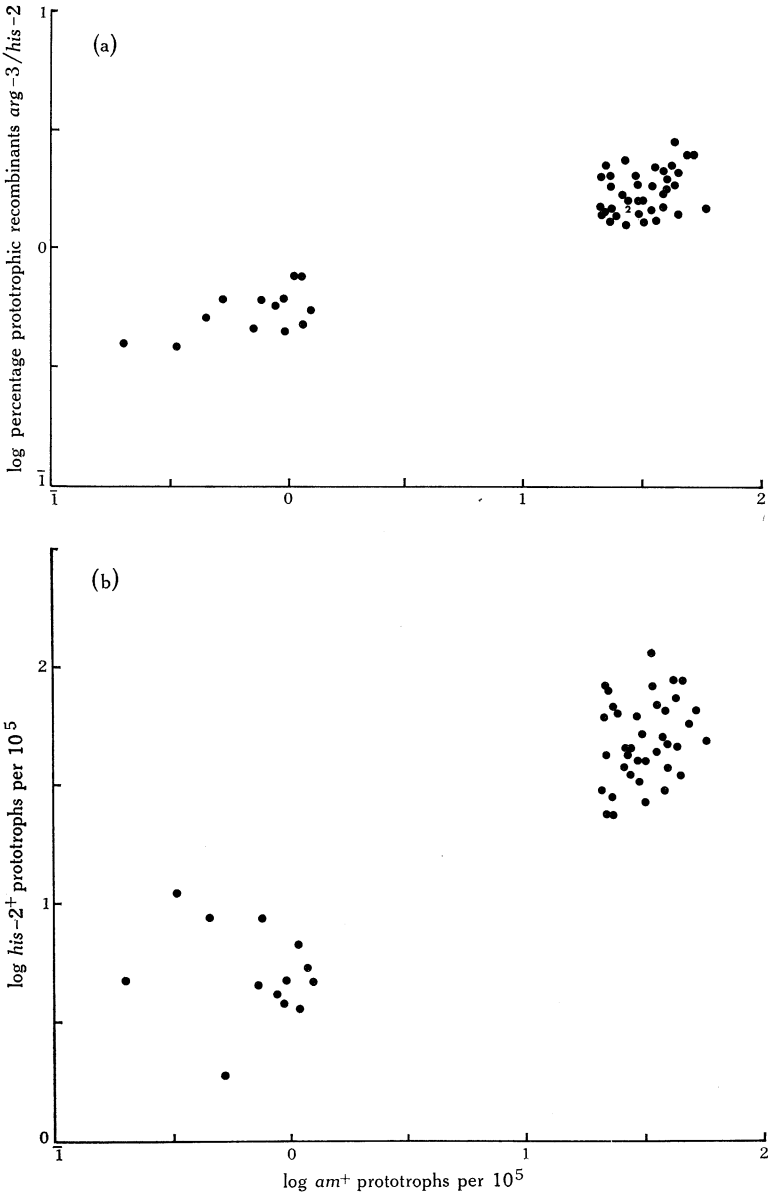


Fig. 2.—Association of recombination characters due to *rec-3* or *rec-3*$^+$ in 51 selected recombinants; (*a*) allelic recombination at *am-1* compared with non-allelic recombination in the *arg-3 his-2* segment; (*b*) allelic recombination compared at the *am-1* and *his-2* loci. The plots are logarithmic.

Nevertheless, despite the greater sensitivity to experimental error, all of the *rec-3* and *rec-3*$^+$ progeny were distinguishable in showing, respectively, relatively high and

relatively low recombination between *arg-3* and *his-2* [Fig. 2(*a*)]. These results show that, with high probability, the restriction of allelic recombination at the *am-1* and *his-2* loci and the restriction of non-allelic recombination between *sn* and *his-2* are due to *rec-3*$^+$. If genes at different loci were responsible they would be, with 95% probability, less than 0·062 centimorgans apart. Including the 47 examined in previous work, the loci of the genes controlling allelic recombination at the *am-1* and *his-2* must, if different, be less than 0·044 centimorgans apart, with 95% probability. These values are smaller than the frequencies of prototrophic recombinants observed between two alleles at such loci as *am-1*, *his-2*, and *his-3*. It is most reasonable to conclude that the restrictive effects on the three characters are pleiotropic effects of the same gene, *rec-3*$^+$. The evidence then is that *rec-3*$^+$ controls allelic recombination at two different loci and non-allelic recombination in the immediate vicinity of one of them.

(*b*) *Location of* rec-2 *and Its Identity with* rec-w

In the case of *rec-2*$^+$, the evidence to this point is that it controls non-allelic recombination in two different segments, namely *pyr-3 his 5* in linkage group V and *arg-3 sn* in linkage group I. However, there is no evidence of an effect on allelic recombination so far as the loci which bound these segments are concerned, bearing in mind that the *sn* locus cannot be examined.

Preliminary trials confirmed that *rec-2* is close to the *am-1* locus in linkage group V, as reported by Smith (1968). Only one recombinant between *rec-2* and *am-1* was observed among 35 progeny analysed in those of our experiments in which no selection was exercised. Preparations were made to determine whether *rec-2* is proximal or distal to *am-1*. By good fortune, the cross analysed first, A *pyr-3 sp rec-2* × a *am-1*^{6} *rec-2*$^+$, showed that the locus of *rec-2* is between *sp* and *am-1*. From this cross 52 *pyr-3* progeny which were neither *sp* nor *am-1*^{6} were tested for *rec-2* versus *rec-2*$^+$ constitution by crossing to suitable *his-5 rec-2* testers. There were 21 *rec-2* and 31 *rec-2*$^+$. The former arise from recombination between *sp* and *rec-2* and the latter from recombination between *rec-2*$^+$ and *am-1* in the three-point cross *sp rec-2* +/+ *rec-2*$^+$ *am-1*^{6}. The near equality of the two classes is compatible only with *rec-2* lying between *sp* and *am-1* which are linked with only about 5% recombination. In other crosses, in which the character of allelic recombination at the *his-3* locus was also followed, there were 47 *rec-2* and 51 *rec-2*$^+$ recombinants. Pooling these data gives 69 and 82 recombinants, respectively, in the two intervals *sp rec-2* and *rec-2 am-1*.

The observed recombination between *sp* and *am-1* is 5·72±0·42 centimorgans, based on 173 *sp*$^+$ recombinants in a population of 3024 progeny assayed from crosses of the type *sp*+ × +*am-1* plated in the absence of alanine. In crosses of the type *sp rec-2* + × + *rec-2*$^+$ *am-1*, the *sp*$^+$ *am-1*$^+$ progeny comprised 66 *rec-2* and 82 *rec-2*$^+$. This leads to the *sp rec-2* interval being 2·55±0·30 centimorgans and *rec-2 am-1* being 3·17±0·33 centimorgans.

The locus of *rec-w*$^+$, which controls allelic recombination at the *his-3* locus and non-allelic recombination in the adjacent *his-3 ad-3* region, is also near to the *am-1* locus. All stocks so far examined are either *rec-2 rec-w* or *rec-2*$^+$ *rec-w*$^+$. That is, the characters of high or low recombination in the *pyr-3 his-5* and in the *his-3 ad-3* regions keep together. A searching test of identity supports the hypothesis that *rec-w* is the same gene as *rec-2*, *rec-w*$^+$ being the same as *rec-2*$^+$.

The following two stocks were prepared:

(1) A *sp rec-2 rec-w* (13299); the *rec-2* constitution was proved by crossing to a *pyr-3 rec-2*$^+$, selecting *pyr-3 sp* progeny and determining the frequency of non-allelic recombination in a test cross to a *his-5 rec-2* stock; the *rec-w* constitution was proved by crossing to a K874 *cog*$^+$ *rec-w*$^+$, isolating a K874 *sp* progeny and testing these for allelic recombination at the *his-3* locus by crossing to A K504 *rec-w*.

(2) a K874 *cog*$^+$ *pyr-3 rec-2*$^+$ *rec-w*$^+$ *am-1*^{6} (13284), the *rec-2*$^+$ and *rec-w*$^+$ properties being determined by direct tests. The gene *cog*$^+$ was used to ensure that the yields of prototrophs in *rec-w* × *rec-w* crosses were very high.

These two stocks were crossed together (13510) and progeny of the constitution K874 *cog*$^+$ *pyr-3* were selected by plating on SGF supplemented with histidine and uridine. These would all arise from recombination between the *spray* and *amination* loci. The selected recombinants were then analysed for their *rec-2* and

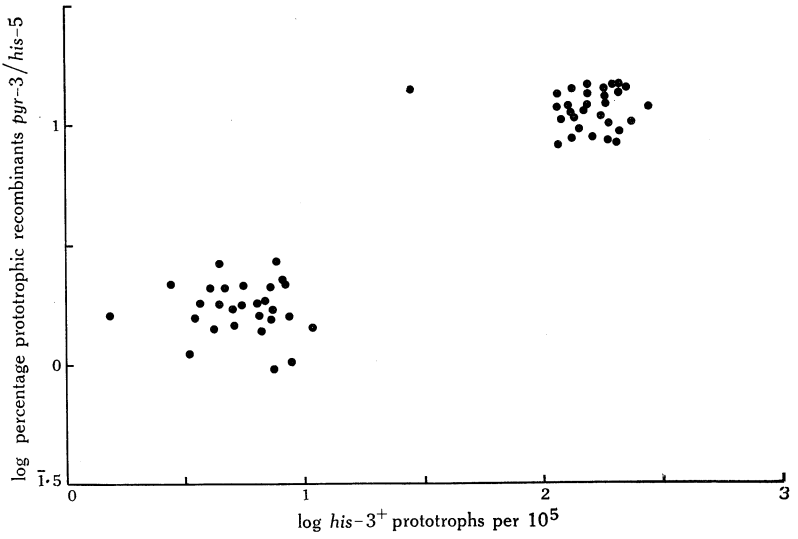


Fig. 3.—Association of recombination characters due to *rec-2* or *rec*-2$^+$ between allelic recombination at the *his-3* locus and non-allelic recombination in the *pyr-3 his-5* segment in selected recombinants. Most carry *cog*$^+$ giving in *rec-2* individuals a high yield of *his-3*$^+$ prototrophs; however, one *rec-2* individual carries *cog*, through recombination with *his-3*, and shows an intermediate frequency of *his-3*$^+$ prototrophs in the test. The plots are logarithmic.

rec-w characters by two test crosses: (1) To *his-5 rec-2*, the frequency of prototrophic recombination between *pyr-3* and *his-5* being determined by plating on minimal medium and minimal medium supplemented with uridine, so avoiding complexities due to the segregation of two independent *histidine* mutants. Low frequencies (average 1·8%) indicated *rec-2*$^+$ while high frequencies (average 10·7%) indicated *rec-2*. (2) To K504 *cog rec-w*, the frequency of prototrophic recombinants at the *his-3* locus being determined by plating on minimal medium supplemented with uridine and

minimal medium supplemented with uridine and histidine. Low frequencies (average 5·9 per 10^5 spores) indicated *rec-w*$^+$, while high frequencies (average 148 per 10^5 spores) indicated *rec-w*. Although *cog*$^+$ is close to K874, one of the *rec-w* progeny turned out to be *his-3 cog* due to a recombination (see Fig. 3). Such recombinants would be expected with a frequency of about 1 in 40.

The results, from 96 progeny analysed from 13510 and similar crosses, show a concordance of low values or of high values in both tests (Fig. 3 shows the results for the first 58 progeny analysed). This means that it is very likely that *rec-2* is identical to *rec-w* and that *rec-2*$^+$ is identical to *rec-w*$^+$. If they were different they could not be at loci more than 0·176 centimorgans apart with 95% probability. The value of p, the possible separation of *rec-2* and *rec-w* if different loci, is based on the solution of the equation $(1-p/d)^n = 0{\cdot}05$, where d is the probability of recombination (0·0572) between *sp* and *am-1* and n is the number of recombinants (96) between *sp* and *am-1* scored for non-allelic recombination between *pyr-3* and *his-5* and also for allelic recombination at the *his-3* locus. It must be concluded that *rec-2*$^+$ controls non-allelic recombination in three separate segments and in one locus (*his-3*) which defines an end of one of these segments (*his-3 ad-3*). It could of course control recombination in many other sites.

(*c*) *Recombination between* his-2 *and* his-3

The loci of *his-2* and *his-3* are close together in linkage group I. The question of whether the controls due to *rec-3*$^+$ and *rec-2*$^+$, respectively, spread into the segment between the two *his* loci has been examined. Stocks with the *his-2* gene K612 were made of constitutions *rec-2 rec-3*, *rec-2*$^+$ *rec-3*, *rec-2 rec-3*$^+$, and *rec-2*$^+$ *rec-3*$^+$; four of each kind were crossed with a *his-3* stock, A K504 *rec-2 rec-3*. The frequency of prototrophic recombination between *his-2* and *his-3* was determined in each by selective plating. The results are summarized in the following tabulation in which the results of four crosses of each kind are pooled:

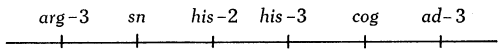
his-2 parent:	*rec-2 rec-3*	*rec-2*$^+$ *rec-3*	*rec-2 rec-3*$^+$	*rec-2*$^+$ *rec-3*$^+$
Prototrophs (%):	0·791±0·040	0·674±0·027	0·732±0·037	0·498±0·027

The effects of *rec-2*$^+$ and *rec-3*$^+$ are quite small and probably insignificant; together they appear to have a mild synergistic effect. However, more extensive data would be needed. The four crosses in each set showed some variation. Nevertheless it can be concluded that neither *rec-2*$^+$ nor *rec-3*$^+$ have any large effect on recombination between *his-2* and *his-3*.

It seems likely that *rec-1*$^+$ regulates recombination between *his-2* and *his-3*. The common *his-3* parent of the crosses was A K504 *rec-1*$^+$ *rec-2 rec-3* (14317), known from its ancestry to be this constitution. The *rec-1* versus *rec-1*$^+$ constitutions of the various *his-2* parents are not known with certainty. Previously, when the segment *his-2 his-3* was examined for a possible effect of *rec-w*$^+$ (= *rec-2*$^+$) differences were observed, but these were unrelated to the presence or absence of *rec-2*$^+$. The crosses examined had as parents three closely related *his-2* stocks all of constitution *rec-1 rec-2* and four *his-3* stocks, respectively one each of *rec-1 rec-2*$^+$ and *rec-1*$^+$ *rec-2*$^+$ and two of *rec-1*$^+$ *rec-2*. Of the 12 crosses, the three with the *his-3 rec-1 rec-2*$^+$ stock as one parent all showed about 6% of prototrophic recombinants, while the other nine

crosses all showed much smaller values, usually under 1%. The difference is correlated with the absence and presence of *rec-1*$^+$ and further data confirm this correlation. It is not technically possible to test in great depth the association between recombination in the *his-2 his-3* segment and allelic recombination at the *his-1* locus because all three markers have the same nutritional requirement.*

In linkage group I, the major controls of recombination are known over the segment between *arg-3* in the left arm and *ad-3* in the right arm (Fig. 4). Acting together *rec-1*$^+$ *rec-2*$^+$ *rec-3*$^+$ reduce recombination in this interval to about a fifth, from 39·4 to 8·1 centimorgans. Notably five-eighths of the residual recombination is in the two extreme segments.



			rec-2	rec-3	rec-1	rec-2	rec-2	
rec-1	rec-2	rec-3	5·6	12	12	2·6	7·2	Total 39·4
rec-1$^+$	rec-2$^+$	rec-3$^+$	2·7	0·6	1·5	0·9	2·4	Total 8·1

Fig. 4.—Map of the *arg-3 ad-3* segment of linkage group I showing the *rec* genes which control each of the recognizable segments of recombination and the quantitative effects of substitution of a *rec*$^+$ for a *rec* gene.

(*d*) *Coincidence of Recombination*

Since recombination in different segments of the linkage maps is under the control of the same genes, it is worth examining whether there is any competition between different segments for the occurrence of recombination. The following stocks were prepared and crossed together in complementary pairs: (1) a *cog*$^+$ *ad-3 his-5 rec-2* and A *his-3 cog*$^+$ *pyr-3 rec-2*; (2) a *cog*$^+$ *ad-3 his-5 rec-2*$^+$ and A *his-3 cog*$^+$ *pyr-3 rec-2*$^+$. Spores from the crosses were plated at convenient dilutions on selective media containing respectively the following supplements: (i) none, (ii) adenine, (iii) uridine, (iv) adenine and uridine. The second and third allow the growth of prototrophic recombinants arising in the *pyr-3 his-5* and *his-3 ad-3* intervals respect-

TABLE 6

CONCURRENCE OF RECOMBINATION IN DIFFERENT SEGMENTS

Segment with recombination	*rec-2* × *rec-2*		*rec-2* × *rec-2*$^+$	
	Expt. 1	Expt. 2	Expt. 1	Expt. 2
his-3 ad-3	6·6±0·5	6·8±0·5	0·73	0·68
pyr-3 his-5	17·0±1·3	17·3±1·3	0·42	0·54
Both (*a*) observed	1·5±0·1	1·3±0·1	0·026	0·008
(*b*) expected	1·1±0·1	1·2±0·1	0·0025	0·002
Difference	+0·3±0·2	+0·1±0·2	+0·024	+0·006

* Further studies show that the locus controlling recombination between *his-2* and *his-3* is not *rec-1*.

ively, the first allows the growth of prototrophic recombinants which have arisen simultaneously in both intervals, while the fourth provides an estimate of the total spores assayed. The results (Table 6) show no evidence of an interaction such as might be expected if there were a limited amount of *rec-2*$^+$ substance or of some other substance whose production was limited by *rec-2*$^+$. Recombination in the two segments examined occurs independently, coincident recombination in both segments occurring as frequently as would be expected in the absence of competition. Indeed there is some indication of a possible concurrence of recombination in the two intervals considered, but this is not established. The "excess" might be due to the occurrence of a few pseudo wild progeny.

IV. Discussion and Conclusions

In recent years, a number of genes have been reported to affect the frequency of recombination at particular loci (presumably by conversion) or between loci. The evidence reported in this paper shows that the genes may control the frequencies of these two events simultaneously, the dominant allele reducing recombination. Genes at two different loci (*rec-2* and *rec-3*) control both allelic and non-allelic recombination simultaneously. Whether this is always the case is not known. In part this is due to presently uncontrollable genetic modifiers which alter the actual values measured. One of these genetic factors, probably a recessive, has been indicated above. In the presence of such variation, small effects of the *rec* genes considered would be difficult to establish. Secondly, small effects on non-allelic recombination may be virtually lost in the experimental errors due to sampling and growth conditions. Thirdly, effects on allelic recombination in loci which flank regions in which non-allelic recombination is altered by *rec* genes may be difficult or impossible to study for special reasons. In some cases, e.g. *sn*, only one mutant allele is known. In other cases, e.g. *arg-3*, *ad-3*, and *pyr-3*, crosses between alleles are virtually sterile. Sometimes a few ripe spores are obtained but, since prototrophic recombinants have a great selective advantage in nearly sterile crosses, the absence of an observed difference is not conclusive evidence of no effect.

Before reviewing the individual effects of *rec-2*$^+$ and *rec-3*$^+$, consideration of the synonymy of each is required. When two different characters, each genetically determined, are discovered independently it may later be realized that both are due to the same genes at the same locus. Adjustment of nomenclature then becomes essential.

The *rec-3* and *rec-3*$^+$ genes were defined by an effect on allelic recombination at the *am-1* locus, while the *rec-x* and *rec-x*$^+$ genes were defined by similar effects at the *his-2* locus. It has now been shown (Catcheside and Austin 1971 and this paper) with a high degree of probability that *rec-x* is the same gene as *rec-3* and that *rec-x*$^+$ is the same gene as *rec-3*$^+$. Actual identity is impossible to prove, but it is most unlikely that *rec-3* and *rec-x* are different. For the future, the locus will be named *rec-3*, *rec-x* being relegated to synonymy. The *rec-3*$^+$ gene differs from the *rec-3* gene in (1) reducing allelic recombination at the *am-1* locus by a factor of about 20, (2) reducing allelic recombination at the *his-2* locus by a factor of about 8, and (3) reducing non-allelic recombination in the *sn his-2* segment by a factor of about 20. Non-allelic recombination in the *sn his-2* segment is virtually eliminated by *rec-3*$^+$, the residual recombination being about 0·3%. This effect is of great interest since it suggests that

an event of recombination might run through the centromere, for *his-2* is in the right arm of linkage group I (Perkins 1972) and *sn* is in the left arm. The effect observed could be wholly in the centromere to *his-2* segment. Admittedly, there is some evidence (Table 5) of a small effect of *rec-3*$^+$ on the *arg-3 sn* segment, but this might be due to a separate control segment, a possibility not capable of resolution. Moreover, there are uncontrolled variations in the data, so small apparent effects should be treated cautiously.

The nomenclature of *rec-2* is more complex. The *rec-2* and *rec-2*$^+$ genes were defined by the effect on non-allelic recombination between *pyr-3* and *leu-2* (Smith 1966), the effect later being found to be due wholly to changes in the *pyr-3 his-5* segment (Smith 1968). The *rec-w* and *rec-w*$^+$ genes were defined by the effect on allelic recombination, at the *his-3* locus, between the alleles K504, K26, and K874 (Catcheside and Austin 1969). Evidence presented in this paper shows, with high probability, that *rec-2* and *rec-w* are the same gene, while *rec-2*$^+$ and *rec-w*$^+$ are the same. For the future the locus will be named *rec-2*, *rec-w* being relegated to synonymy. Two other locus names must be added to this synonymy. One, *rec-5*, is simple to dispose of since it was used (Catcheside 1968) alternately for *rec-w* before it was realized that the effect on the *his-3* locus could be due to a *rec* gene already known (Catcheside and Austin 1969). The other, *rec-4*, was defined by Jha (1967) on the basis of effects manifested in allelic recombination at the *his-3* locus between the alleles K492 and K474, though it was also shown that certain stocks of K504 and K874, known to be *rec-w*, were also apparently *rec-4*. The dominant *rec-4*$^+$ reduced yields from crosses between particular alleles about threefold. The linkage relationships of *rec-4* were never established. Because of the apparently smaller effects of *rec-4*$^+$ the possibility that it was different from *rec-w*$^+$ was entertained. Fairly extensive experiments in which the *rec-w* versus *rec-w*$^+$ and *rec-4* versus *rec-4*$^+$ constitutions of numerous stocks were determined have failed to separate *rec-w* and *rec-4* as two loci. The experiments could not be pursued further, because the *rec-4* testers were female sterile, as were many of the progeny to be tested. It is unlikely that *rec-4* is not *rec-2*.

Jha (1969) has also proposed another dominant gene, *rec-6*$^+$ which, in association with *rec-4*$^+$, causes a greater reduction in prototroph frequency than does *rec-4*$^+$ alone, the action of *rec-6*$^+$ when present with *rec-4* being uncertain. He also states that *rec-6*$^+$ reduces prototroph frequencies only when a particular *his-3* allele (K504) is in the cross and not when another *his-3* allele (K492) is used. We have not been able to substantiate these results and much further work is required on this effect. It cannot be disputed that in this case, as in others, there are accessory genetic factors which modify the degree of activity of *rec*$^+$ and *rec* genes, but their mode of inheritance and of action is presently quite obscure.

The gene *rec-2*$^+$ reduces non-allelic recombination in the *pyr-3 his-5* region at least 10-fold. There is no effect on the frequency of allelic recombination at the *his-5* locus (Smith 1966) nor, probably, at the *pyr-3* locus, though crosses between *pyr-3* alleles are very infertile. Observed values for the alleles KS16 and 37301 were $46{\cdot}9 \pm 11{\cdot}9$ prototrophs per 10^5 in *rec-2* × *rec-2* and $44{\cdot}1 \pm 11{\cdot}1$ in *rec-2* × *rec-2*$^+$. Also *rec-2*$^+$ reduces non-allelic recombination in the *arg-3 sn* region. Allelic recombination cannot be examined at the *sn* locus and whether *rec-2*$^+$ has any effect at the *arg-3* locus is not known due to infertility of the crosses.

Smith (1966) observed that there was a reduction due to *rec-2*$^+$ in the frequency (0·115) of allelic prototrophic *his-5*$^+$ recombinants bearing the less frequent proximal flanking marker to a little under half the frequency (0·26) found in crosses homozygous for *rec-2*. He considered that this could not be accounted for by the increase in non-allelic recombination between *pyr-3* and *his-5*, which would require an increase from 1% in *rec-2*$^+$ crosses to 19·8% in crosses homozygous for *rec-2*. Such an increase would be 1·7 times greater than the total increase he observed between *pyr-3* and *leu-2*. Our data, as will be shown below, show an increase in recombination between *pyr-3* and *his-5* (from 1·8 to 23·3%) of about the right order required to account for the effect of *rec-2*$^+$ on recombination at the *his-5* locus as indirect.

Finally, *rec-2*$^+$ affects allelic recombination at the *his-3* locus and non-allelic recombination in the *his-3 ad-3* segment. The degree of effect due to the absence of *rec-2*$^+$ is dependent on whether the gene *cog* or *cog*$^+$ is present between *his-3* and *ad-3* (see Angel *et al.* 1970, writing *rec-2* for *rec-w*). Whether any effect occurs in the *ad-3* locus cannot be determined since crosses between *ad-3* alleles are quite sterile. There appears to be little or no spread of the effect of *rec-2* into the *his-2 his-3* region.

The frequency of the events controlled by the *rec*$^+$ genes is worthy of closer consideration. In the *pyr-3 his-5* segment our data tend to show even higher frequencies of recombination in *rec-2* × *rec-2* crosses than are suggested by Smith's data (1966), though these have not been published fully. In *rec-2* × *rec-2* crosses, the prototrophic recombinants between *pyr-3* and *his-5* average 11·64%, so that the recombination value would be 23·3%. In *rec-2*$^+$ × *rec-2* crosses, the corresponding values are 0·92% prototrophs and 1·84% recombination value. In both sets of data, there are considerable variations, certainly over a range in which the upper values are twice the lower ones. It is fairly certain that the variations have a genetic basis, since small groups of related material run to high values, while other groups run to relatively low values. Nevertheless, it can be said that the absence of *rec-2*$^+$ from a cross commonly means an increase of about 21·5 centimorgans in the "length" of the *pyr-3 his-5* segment from the value of 1·8 centimorgans found in the presence of *rec-2*$^+$. Each meiotic cell in which a crossing over between *pyr-3 his-5* occurred would produce an equal number of recombinant and non-recombinant spores. Therefore the observed increase means the occurrence of an event leading without fail to crossing over between *pyr-3* and *his-5* in 47% of the meiotic cells in *rec-2* × *rec-2*, as compared with about 3·6% in *rec-2*$^+$ × *rec-2*, material.

Work in recent years has tended to show that allelic recombination ("conversion") and non-allelic recombination ("crossing over") are different manifestations of one common mechanism. Further, it has been shown that half of the tetrads in which allelic recombination by conversion has occurred show correlated crossing over between flanking markers, while the other half do not. Thus, it could be inferred that tetrads which manifest crossing over in a given segment represent only half of those in which an event, with a half chance of leading to crossing over, has occurred in the designated segment. We conclude that in *rec-2* × *rec-2* crosses an event of this kind is initiated in about 94% of meiotic cells, compared with about 7% in *rec-2*$^+$ × *rec-2* crosses. Thus the action of *rec-2*$^+$ is to prevent the occurrence of a precursory event of recombination in the great majority of cells, actually 87% using the above values. By similar arguments, *rec-2*$^+$ prevents similar events in the *his-3 ad-3* segment in 26% of

meiotic cells and in the *arg-3 sn* segment in 12% of cells. Collectively, considering only these segments, *rec-2*$^+$ would remove an average of half a chiasma from all meiotic cells. Likewise, *rec-3*$^+$ prevents a similar precursory event in the *sn his-2* region in about 40% of meiotic cells, while *rec-1*$^+$ apparently has a similar action in the *his-2 his-3* segment in about 40% of cells. In other words, events with these chances of occurrence in meiotic cells in these particular regions are virtually prevented by the *rec*$^+$ genes. By any standards these are major actions in the apparent control of recombination and can hardly be regarded as "fine" controls of recombination as Simchen and Stamberg (1969) have argued. The observations are consistent with the control of an event percursory to, or initiatory of, the occurrences which may lead to crossing over or to conversion and essential to these phenomena.

The evidence now is that genetic recombination is organized so that individual events occur, with varied probability, in short segments of the chromosomes. These segments have a fixed initial point and a variable terminus; the direction of occurrence is therefore determined. The frequency of recombination in the segment, whether crossing over or conversion or both, is controlled by *rec*$^+$ genes, such as those studied in this paper. Such control can be understood if there were a gene (the *recognition* gene) at which, for example, a specific endonuclease could nick a DNA chain and so start a sequence of reactions leading to recombination. The function of *rec*$^+$ would be to produce a compound which either protects the recombination initiation gene from being nicked or is a regulator of the gene specifying the endonuclease. Each kind of recognition gene (*cog*), and variants of it, are situated at several to many scattered places in the genome. For example, the *rec-2*$^+$ and *rec-3*$^+$ data predict two kinds of *cog* gene. The type associated with *rec-2*$^+$ is present in the *arg-3 sn*, *his-3 ad-3*, and *pyr-3 his-5* regions; the type associated with *rec-3*$^+$ occurs in the *sn his-2* and *sp am-1* regions. How many other duplicates of these two types of *cog* gene occur elsewhere in the genome cannot be estimated from present evidence. Nor can the number of different classes of *cog* gene and corresponding *rec* gene loci be estimated.

Although the recognition genes (*cog*) could be the sites of action of specific endonucleases this is not a necessary or exclusive interpretation. It is possible that they may be sites of failure of replication of DNA at the premeiotic mitosis. In this case the function of *rec*$^+$ genes could be to decrease failure of replication locally, the *cog*$^+$ genes being more liable to failure in the absence of a *rec*$^+$ gene. However, it is not obvious how the *rec* genes could show specificity in such a situation.

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