A REVIEW OF INDEPENDENT AND LINKED SEGREGATION IN THE RABBIT

By ROY ROBINSON
St Stephens Road Nursery, Ealing, London

(With Two Text-figures)

(*Received* 23 *August* 1955)

Introduction

There are some forty-four or so reported mutations in the rabbit, and of these only twenty-four have been utilized in published investigations to determine the possible genetic relationships which may exist between them. The primary reason for the difference is undoubtedly the relative inaccessibility of many of the mutations to workers interested in linkage studies. Moreover, several of the genes are semi-lethals of varying severity and involve time-consuming procedures if anything is attempted with them. Of the twenty-four genes which have been used, information is available for ninety-five (32 %) of the 300 possible different combinations. The figure of 300 combinations includes sex, since, for the purpose of linkage studies, maleness has been treated as a dominant gene (symbolized here as ♂; see Appendix for explanation of gene symbols adopted in this paper). The smallness (32 %) of the studied combinations is probably a consequence of several contingencies. Full consideration has not always been given to possible loose linkages (producing a situation where if two genes display linkage, one may be dropped from further study) and the implication of partial sex-linkage has not been appreciated. Finally, it may be that negative results are not invariably considered worthy of publication.

However, at present six groups of linked genes have been detected, labelling six segments of chromosome. Three groups consist of three genes and three groups of two. For one group, adequate data has disclosed that sex differences in crossing-over may occur and that 'interference' may arise with loci situated some distance from each other on the chromosome. Extremely close linkage has been found to exist between the two genes *du–En* and if these are viewed as a unit, the number of effective combinations falls to 276 and the percentage examined rises to 34 %. It may be assumed that approximately one-third of the total number of combinations from 25 loci (with sex) have been tested (albeit inadequately, in some instances).

Much of the information relating to genetic linkage is distributed among numerous papers and hitherto no attempt has been made to collate the material. Nor, indeed, would a simple collation be of special interest. However, with the development of statistical methods enabling data to be pooled from different sources, although consisting of diverse mating types and linkage phases, collation of data with the utilization of such methods enables greater reliability to be attached to statements of supposedly random segregation or to calculated recombination fractions. This paper surveys and statistically combines all cases of simultaneous segregation of two or more genes in the literature known to the author. An attempt has been made to include all the pertinent data.

In spite of a few discordant early determinations of the diploid chromosome number of the rabbit, the more recent examinations have produced general agreement of 44 as the normal complement in germinal tissue (Painter, 1926; Tateishi, 1936; Pincus & Waddington, 1939; MacMillion, 1942; Muldal, 1947; Vara & Personen, 1948; Melander, 1950; Vange 1952). It is to be presumed that the genes of the rabbit will ultimately be assigned to twenty-two linked groups.

PROCEDURE

The statistical technique utilized is based upon the system of scoring data introduced by Fisher (1946); Mather (1951, §19·1; see Carter & Falconer, 1951). This is almost a routine application of the method of maximum likelihood and greatly reduces the tedious algebra often associated with the method, when data from different segregations are combined. A score for each distinguishable phenotype class, m, whose expectation is specified by the recombination fraction p, is obtained by logarithmic differentiation of the expectation. A total score, D, and total amount of information, I, are found by summing over all segregations. The significance of D is conveniently found as $\chi_1^2 = D^2/I$. If D differs significantly from zero, the data must be rescored at the corrected value of p (p initially being taken as 0·5). The standard error of p is, as usual, $I^{-\frac{1}{2}}$.

A portion of the data may be more completely classified by the testing of individuals belonging to one or more phenotypic classes (as in the case of the gene pair r_1–r_2 (Castle & Nachtsheim 1933). This has been incorporated into the analysis by an extension of the principle described by Mather (1951, §19). If m be the expectations on the fuller classification and M be the expectation of the class or classes from which these are chosen, scores and unit amounts of information were computed for the expectation m/M.

Class expectations constructed in ordinary Mendelian terms presume normal viability and complete penetrance of the individual genes. If disturbances of the usual single factor ratios are detected as due to either or both of these factors, this should be taken into account when framing the expectations. Inviability or impenetrant interactions may also occur between the genes under review, and the conventional policy of balancing the two linkage phases to eliminate possible influences of this nature is excluded. A dubious result may be checked for deficient members in one or more classes. For the rabbit data this has been rarely necessary. Following Carter & Falconer (1952) the percentage of the total amount of information contributed by the two dominant genes in coupling has been adopted as an indication of phase balance. Therefore, 50% indicates perfect balance between phases.

Heterogeneity between categories and sources of data may be relatively easily assessed from the attribute possessed by each sample segregation of a χ^2 for one degree of freedom. Both simple and hierarchical grouping may be compiled in the orthodox manner for two-class segregations.

THE DATA

Independent loci

Prima facie evidence is presented in Table 1 for the independent segregation of eighty-four pairs of gene combinations for which breeding data is available. The table gives the estimated recombination fraction, with a standard error based upon $p = 0{\cdot}5$, and the degree of phase balance possessed by the pooled data, together with two entries useful for

incorporating future data. That many of the gene pairs are merely 'independent' in a formal sense is shown either by Fig. 1, where the two curves delineate the 5 % limits from random segregation for an effective N ($=I/4$; the number of backcross progeny which would yield the same amount of information as realized from the whole data) or by consulting the closest compatible linkage summarized in Fig. 2. For small or even moderate N, a loose or fairly loose linkage would not be contradicted by the data.

A feature of Fig. 1 is the not unexpected clustering of entries within the 5 % limit curves. With eighty-four observed recombination fractions, we should expect four of the estimates to fall outside these limits by chance alone. Actually, two instances are beyond the lower limit while none exceeded the upper. These are discussed in the succeeding section. In view of the recent theories on the relationship between chromosome map-length and recombination value which suggest the occurrence of recombinants in excess of 0·5, and of the results obtained by Wright (1947), the detection of recombination values beyond the upper curve is of practical concern.

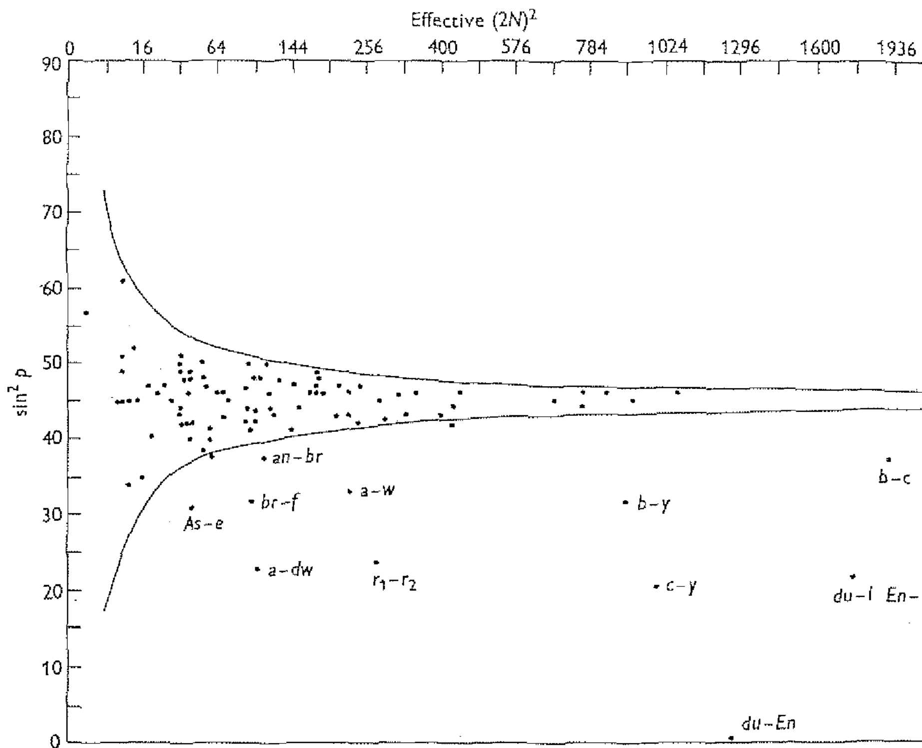

Fig. 1. Distribution of observed recombination fractions for effective sample number ($N=I/4$). Scale transformations are to present the data more perspectively.

Of some interest with experimental data of this nature is that the observations could be subject to two forms of observational bias: (i) an observer may terminate his collection of data at a point where free segregation is supported, and (ii) should the observations yield a significant (or near significant) deviation at some stage of provisional abandonment, the experiment may be continued to ascertain if the deviation is real. The first bias is likely to be at a subconscious level while the second would be conscious. With either,

Table 1. *Quasi-independent loci*

Note. Standard error (s), deviation (D) and total information (I) are computed for $p = 0{\cdot}5$ (see text).

Loci	p	s	D	I	Phase balance	References
a–An	0·58	0·08	+14	172	100	55
a–As	0·50	0·17	0	36	?	53
a–b	0·46	0·03	−46·5475	1308·0124	100	37, 38, 43, 47
a–br	0·51	0·06	+ 2	276	?	25
a–c	0·47	0·04	−27·2229	813·7749	100	5, 9, 12, 26, 28, 42
a–d	0·51	0·02	+25·9947	3455·6572	83	12, 19, 38
a–e	0·50	0·02	−15·0656	3922·3256	60	12, 19, 26, 42, 43, 44, 47
a–En	0·49	0·02	− 4	2680	73	12, 19
a–f	0·47	0·05	−14	438·6557	100	17
a–H	0·55	0·04	+34	724	95	22, 29
a–H_6	0·49	0·08	− 2	148	100	54
a–r_1	0·51	0·02	+14·6775	1800·0230	0	13, 14, 34, 38
An–c	0·59	0·05	+40	448	100	55
An–d	0·61	0·08	+16	148	14	55
An–e	0·57	0·19	+ 2	28	100	55
An–En	0·58	0·08	+12	152	100	55
An–H	0·43	0·06	−18	244	?	29
An–sa	0·52	0·06	+ 4	272	100	54
An–v	0·45	0·05	−20	424	100	54
As–c	0·50	0·18	0	32	?	53
ax–H	0·33	0·13	−10	60	?	29
b–d	0·45	0·03	−65·3368	1189·3482	78	38, 40
b–e	0·52	0·04	+13·5560	688·1112	3	12, 43, 44, 47
b–En	0·54	0·04	+26	692	100	12
b–f	0·61	0·16	+ 4·0001	37·3338	0	17
b–r_1	0·47	0·03	−40·4390	1356·4614	13	34, 38, 40
b–v	0·55	0·04	+28	544	0	12
b–wa	0·42	0·07	−17·1120	214·6686	100	40
br–c	0·52	0·11	+ 2	84	?	25
br–d	0·43	0·05	−28	376	?	25
br–En	0·51	0·03	+10	1212	?	25
br–H_6	0·47	0·03	−28	944	100	54
c–d	0·53	0·04	+15·5562	519·3323	35	9, 12, 51
c–e	0·50	0·03	− 4·4410	1095·5550	14	9, 12, 26, 37, 42, 45, 47
c–En	0·47	0·05	±12	446	?	12
c–H	0·46	0·06	−10	276	?	29
c–H_6	0·52	0·07	+ 4	168	100	54
c–l	0·53	0·04	+26·0002	829·7792	25	1, 9, 12
c–r_1	0·51	0·04	+10·2251	734·2247	0	13, 14, 34, 40
c–sa	0·55	0·07	+11·5558	209·7804	100	51
c–v	0·53	0·11	+ 2·8890	93·9998	0	12, 37
c–δ	0·47	0·04	−17·3325	514·538	47	1, 9, 51
d–e	0·48	0·02	−66·6666	3019·5564	99	9, 12, 19, 44
d–En	0·52	0·02	+82	4140	100	12, 19
d–f	0·55	0·08	+ 7·5567	151·1130	0	17
d–H	0·55	0·05	+22	420	91	22
d–H_6	0·42	0·08	−14	180	100	54
d–l	0·32	0·16	− 7·5553	40·8894	0	9
d–r_1	0·52	0·03	+26·4513	1438·7936	0	13, 14, 34, 38, 40
d–sa	0·57	0·08	+11·5564	160·0020	0	51
d–v	0·43	0·04	−40	574	100	12
d–wa	0·44	0·08	− 9·3323	154·6686	0	40
d–δ	0·41	0·07	−22·0004	233·275	75	9, 51
e–En	0·51	0·06	+24	3032	100	12, 19
e–f	0·48	0·04	− 7·9970	508·4508	0	17
e–H	0·49	0·04	− 4	600	91	22, 29
e–H_6	0·50	0·06	0	288	100	54
e–l	0·54	0·03	+39·3335	980·8894	58	9, 12
e–r_1	0·51	0·03	+ 8·00016	890·6696	0	13, 14, 34
e–t	0·46	0·08	− 6·4446	143·7776	10	12, 37
e–δ	0·50	0·17	+ 0·0003	34·6610	0	9
En–f	0·49	0·05	− 5·9999	357·9982	100	17
En–H	0·48	0·02	−40	1720	100	22
En–H_6	0·50	0·07	0	196	0	54
En–r_1	0·45	0·03	−50	980	100	13

Table 1 (*cont.*)

Loci	p	s	D	I	balance	References
En–v	0·53	0·05	+10	328	100	12
f–r_1	0·47	0·04	−19·9955	688·0086	0	17
f–r_2	0·38	0·07	−23·5542	190·2246	0	17
f–v	0·53	0·09	+ 5·7792	229·3363	0	17
H–H_6	0·37	0·06	−30	228	?	29
H–sa	0·57	0·08	+10	148	?	29
H–v	0·42	0·12	− 6	76	?	29
H_6–r_2	0·58	0·05	+30	330	100	54
H_6–r_3	0·52	0·05	+ 8	472	100	54
H_6–v	0·55	0·05	+20	416	100	54
l–r_1	0·45	0·08	− 7·5546	151·1090	0	14, 34, 40
l–v	0·44	0·03	−98	1756	0	12
l–♂	0·50	0·14	− 0·0003	47·9880	100	9
r_1–r_3	0·53	0·12	+ 2·6658	70·6037	0	24
r_2–r_3	0·76	0·15	+10·7931	42·1590	0	24
r_1–v	0·44	0·05	+19·5545	350·2242	0	13, 14, 34
r_1–wa	0·70	0·39	+ 1·3334	6·6666	100	40
r_1–y	0·62	0·14	+ 6	52	100	13
s–♂	0·51	0·04	+ 6	708	100	50
sa–♂	0·55	0·08	+ 8·0002	157·3294	0	51

	a	*An*	*As*	*ax*	*b*	*br*	*c*	*d*	*du*	*dw*	*e*	*En*	*f*	*H*	H_6	*l*	r_1	r_2	r_3	*s*	*sa*	*v*	*w*	*wa*	*y*
An	35																								
As	17																								
ax																									
b	45		37																						
br	38																								
c	43	41	15			29																			
d	47	34			44	40	42																		
du																									
dw																									
e	47		13		42		44	46																	
En	46	34			42	44	41	47			39														
f	41				18			34			41	40													
H	43	38		25			38	40			42	45													
H_6	34					44	35	35			38	36		37											
l							43	19			44														
r_1	45				45		43	45			43	44	42			34									
r_2													36		40										
r_3						41											27	20							
s																									
sa		38					36	34						34											
v		40			42		30	42			34	39	32	27	40	45	39								
w																									
wa								34									>0								
y																	23								
♂							41	37			17					22				43	34				

Fig. 2. Extent of quasi-independent linkage tests. The entry within each cell is the closest linkage compatible with the observed data; obtained by subtracting 1·96s from 0·5 and multiplying by 100.

the total variation would appear to be smaller than expected by chance, the larger deviates being eliminated. The present compendium of quasi-independent loci lends itself to an examination for over-homogeneity of the observations. The total χ^2 of 73·77 for the eighty-four pairs of genes is well within the 5% distribution (61–111) about the mean χ^2 for this number of degrees of freedom, using the A_3 approximation of Rao (1952, p. 222). Indeed, the same approximation converting χ^2 to a normal deviate (0·7728) gives $P = 0{\cdot}44$–$0{\cdot}43$.

An illustration of a suggestive linkage being openly followed up occurs in the literature. Castle (1920) reported a possible linkage between the pair *d*–*En* ($0{\cdot}3855 \pm 0{\cdot}055$) which was not sustained by subsequent data (Castle, 1926, 1934*b*). The total segregation scarcely differs from that expected from independent segregation, and the amount of heterogeneity between the four groups of data tabulated by Castle is not significant ($\chi^2_3 = 7{\cdot}42$; $P = 0{\cdot}10$–$0{\cdot}05$).

Additional to the estimated recombination fraction, Table 1 lists both D and I scored at $p = 0{\cdot}5$, so new data can be combined without the inconvenience of searching over old records. It would be useful if new material could be accumulated whenever possible either to increase the precision of the independence or to reveal a linkage. In the latter event, of course, all the segregations must be rescored at the estimated value of p.

Castle & Law (1936) state that recombination occurs with such frequencies as to indicate free assortment of *sa* from the following ten loci, c, l, e, f, r_1, r_3, a, En, b and H_1, without, however, giving the data upon which these conclusions are based. Castle (personal communication 25 January 1955) regrets that the experimental evidence has not been preserved and is not available.

Castle (1926) mentions that the linkage phase of *c*–*En* was unknown, although of one type, producing the cross-over values of 0·53 or 0·47. For this reason the gene pair is omitted from Fig. 1; while the lower cross-over value is used for Fig. 2. It is possible that the loci represented by *s* in Table 1 is in fact *du*; direct evidence on this point is not available. Castle's (1926) extensive review of linkage experiments embodies most of his previous notes on joint segregation data (Castle, 1920, 1921, 1924*a*, *b*). The information of Castle (1929*c*) is included with that of (1934*a*) and that of (1933*b*) in (1936). The data presented by Castle & Keeler (1933) on *H*–*r* could not be utilized, since these authors pooled segregations involving the two rexoid genes r_1 and r_2.

Possible linkage

Aside from the established linkages, three other gene pairs deserve further consideration. All are formally significant, but one is associated with considerable heterogeneity.

Knopfmacher (1942) records twenty-one cross-over young in a sample of fifty-seven, a recombination of $0{\cdot}3684 \pm 0{\cdot}0662$, for the pair H–H_6. The observed deviation is barely significant, and since the sample number is small, could easily be due to chance.

Castle (1926) has tabulated a series of six groups of segregations involving the two genes l and v which together yield a recombination value of $0{\cdot}4442 \pm 0{\cdot}0237$. The deviation from free segregation is significant ($\chi^2_1 = 5{\cdot}47$; $P = 0{\cdot}02$–$0{\cdot}01$), and the heterogeneity between groups is negligible ($\chi^2_5 = 2{\cdot}781$; $P = 0{\cdot}80$–$0{\cdot}70$); the data are thus consistent. In spite of this, Castle was cautious in postulating linkage between the pair of genes. He correctly points out that v might be expected to exhibit linkage with the genes *du* or *En* (as these are known to be linked to l) if v indeed resides in the same chromosome as l. However, the data available merely invalidate the suggestion that the three genes could

two smaller linkages ($0{\cdot}5758 \pm 0{\cdot}025$). If interference is general in the chromosomes of the rabbit (as appears probable on the evidence of the first linkage group) the expected recombination value for *v–En* may not differ appreciably from the estimated. The interrelationships of these three genes evidently merits further investigation.

The data brought together by Pickard (1941) are suggestive that linkage could exist between the genes *b* and *wa*, as this deviation from random segregation is significant for the total ($\chi^2_1 = 6{\cdot}66$; $P < 0{\cdot}01$). However, this suggestion is vitiated by considerable intergroup heterogeneity, whether scored for $p = 0{\cdot}5$ ($\chi^2_3 = 11{\cdot}439$; $P < 0{\cdot}01$) or for the estimate $p = 0{\cdot}369$ ($\chi^2_3 = 23{\cdot}210$; $P < 0{\cdot}01$). The matings given by Pickard are reproduced in Table 2, whence it may be seen that the first mating is causing the discrepancy. If this is ignored both the appearance of linkage ($\chi^2_1 = 1{\cdot}364$; $P = 0{\cdot}30$–$0{\cdot}20$) and heterogeneity ($\chi^2_2 = 2{\cdot}009$; $P = 0{\cdot}50$–$0{\cdot}30$) disappear. Pickard, on the basis of the third mating, concluded that the two genes are inherited independently. In view of the heterogeneity these loci are not included in the analysis of the foregoing section. Except for the first mating, the individual gene ratios are not appreciably disturbed in spite of impenetrance being feasible for some *wawa* zygotes. The closest compatible linkage value of Fig. 2 was obtained from the last three segregations.

Table 2. *Segregation of genes* b *and* wa (*Pickard*, 1941)

C = coupling, I = intercross and B = backcross for the respective genes.

Mating	*BWa*	*Bwa*	*bWa*	*bwa*	χ^2_1
CII	15	0	2	5	14·726
CBB	5	1	3	6	0·099
CII	38	15	13	6	0·008
CII	8	2	4	1	3·266

Established linkages

Six linkage groups have been determined thus far in the rabbit; these are usually designated in the order of discovery. Table 3 summarizes the recombination fraction yielded by the combined data. A sex difference in crossing-over occurs in a segment of one chromosome and 'genetic interference' may be associated with the same chromosome segment.

The first linkage group is composed of three genes, *b*, *y* and *c*, and provides evidence for a sex differentiation in recombination frequency. The sex difference is significant for the intervals *b–c* and *c–y*, crossing-over occurring more frequently in females than in males. A similar tendency is manifested by the pair *b–y*, but the difference is small and not significant.

The possible appearance of genetic interference is suggested by the data on the three genes pooled for both sexes. The order of the loci would seem to be *b–y–c* on the criterion of relative recombination fractions. However, the sum of the two smaller fractions significantly exceeds that observed between *b–c* (difference $0{\cdot}0606 \pm 0{\cdot}0216$; $d/s = 2{\cdot}79$, $P < 0{\cdot}01$). Stevens (1936) proposed measure of the coincidence fraction (c) confirms that the proportion of double cross-overs is significantly less than expectation ($c = 0{\cdot}6579 \pm 0{\cdot}1174$; $c/s = 2{\cdot}91$, $P < 0{\cdot}01$). The tri-coupling data of Castle (1936) are utilized for computing the coincidence.

When the data for the sex of the F_1 parent are considered separately, those for the male are in sharp contrast to the female both regarding distance of the genetic map length (Table 4) and particularly for the value of the coincidence. The difference between realization and expectation is closely similar for both sexes (♂ difference $0{\cdot}0657 \pm 0{\cdot}0552$ compared with ♀ $0{\cdot}0543 \pm 0{\cdot}0237$), and the non-significance of the male sex most probably reflects the smaller sample size (109 individuals or 12% of the pooled data). However, fitting the relevant sex recombination value in the formula for c, we obtain for females $c = 0{\cdot}5509 \pm 0{\cdot}0161$ and for males $c = 2{\cdot}088 \pm 0{\cdot}6036$. Since c is the ratio of observed proportion of double cross-overs to the expected, the figure of 2·088 discloses that the number observed is surprisingly in excess of chance occurrence (highly significantly so). The apparent inconsistency introduced by the data contributed by the male parent is disturbing. Clearly the male observations could be due to chance or these may be preliminary indications of a fundamental difference of chiasmata distribution for the two gametogenesis. The lower recombination values for the male sex for this segment of chromosome suggests at first sight fewer chiasmata in the region, a suggestion not immediately compatible with the abundance of double cross-overs. However, since it is the distribution as well as the frequency of chiasmata which probably determines recombination, the suggestion may have no support in fact.

Table 3. *Summary of established linkages*

Linkage group	Loci	p	Effective N	References
I	*b–c*	0·3566 ±0·0110	1912	12, 21, 40
	b–y	0·2819 ±0·0144	908	21
	c–y	0·1353 ±0·0112	992	21, 39
II	*du–En*	0·00166±0·0012	1178	6, 12, 20, 46
	du–l	0·1349 ±0·0082	1750	12
	En–l	0·1316 ±0·0074	2097	12
III	r_1–r_2	0·1625 ±0·0243	268	21, 24
IV	*a–dw*	0·1472 ±0·0375	101	25
	a–w	0·2890 ±0·0306	225	52
V	*br–f*	0·2828 ±0·0453	99	25
	An–br	0·3684 ±0·0444	114	54
VI	*As–e*	0·2624 ±0·0678	42	53

Group II also is composed of three genes, *du*, *En* and *l*, the first two contributing one of the closest linkages known in rodent genetics. Until recently the accepted order of the three genes has been *du–En–l* on the basis of the observed recombination fractions. However, Rifaat (1954) has suggested that the order may be *En–du–l*. It is correctly stated that the solitary cross-over animal reported by Castle (1926) must have arisen by a double cross-over by the former arrangement but by a single cross-over by the latter. Rifaat's biometrical analysis indicates how difficult it is to decide unambiguously between different alternative explanations in certain circumstances. The question of precise order may not often arise in practice, since the closeness of the linkage between *du–En* is such that the two genes segregate as a unit in crosses (cf. Castle, 1932).

The map alinement of the loci constituting group IV has not been ascertained. These may be distributed in the order *a–dw–w*, in which case the recombination value between *dw–w* may be approximately $0{\cdot}1418 \pm 0{\cdot}0484$; or in the order *dw–a–w*, whence the recombination value may be in the region of $0{\cdot}4362 \pm 0{\cdot}0484$. The linear arrangement of the three genes forming group V is unsettled. If the order is taken as *br–f–An*, the crossing-over

a value of somewhat under 0·6512 ± 0·0634 may be expected. The latter cannot be ruled out *a priori*. Additional data to clarify the positions of the genes in the two groups are desirable.

Discussion

If a simple mechanical explanation of the formation of chiasmata is postulated as a means of holding together the chromosomes at diplotene, and assuming one chiasma per bivalent, every graduation of recombination fraction may be expected approaching a limit of 0·5. If the frequency of chiasma formation is greater than unity (as is likely), then a satisfactory relationship between chromosome map length and observed recombination value must be obtained. Relatively elementary assumptions can engender quite intricate analyses (Owen, 1949; Carter & Robertson, 1952), several of which feature a conclusion that two loci may reside in a common chromosome though displaying a recombination fraction even a little beyond 0·5, a line of reasoning which prepares us not to accept apparent evidence of independence uncritically.

Table 4. *Sex differences in recombination values*

Loci	Sex	p	Effective N	References
b–c	♂	0·2830 ± 0·0263	364	12, 21
	♀	0·3737 ± 0·0123	1544	12, 21
		0·0907 ± 0·0266**		
b–y	♂	0·2661 ± 0·0423	109	21
	♀	0·2841 ± 0·0160	799	21
		0·0180 ± 0·0452		
c–y	♂	0·0827 ± 0·0264	109	21
	♀	0·1439 ± 0·0124	799	21
		0·0612 ± 0·0291*		
du–l	♂	0·1344 ± 0·0131	677	12
	♀	0·1361 ± 0·0105	1073	12
		0·0017 ± 0·0168		
En–l	♂	0·1588 ± 0·0096	1452	12
	♀	0·1356 ± 0·0135	645	12
		0·0232 ± 0·0166		

* Significant. ** Highly significant.

Recent examinations of the chromosomes of the rabbit have confirmed Painter's (1926) early determination of 44 as the diploid number. Muldal (personal communication 5 June 1950) has suggested a mean chiasma frequency per bivalent of 1·3. No data are available on the frequency distribution of chiasmata per bivalent. However, for the purpose of genetic linkage studies, two provisional deductions may be derived from this value. First, on the assumption that each chiasma roughly corresponds to 50 cross-over units, the average length of chromosome map may be of the order of 65 units. Secondly, 22 chromosomes, with a mean chiasmata frequency of 1·3 for each, indicate a total of approximately 50·5 chromosome segments.

The thoroughness of investigation of genetic linkage relationships is clearly a function of the number of genes available for study; and of the competition offered by other facets of formal genetic work for time and facilities. Carter & Falconer (1951) have discussed how, by suitably building up stocks of animals containing groups of apparently independent genes, linkage investigation can be appreciably systematized so that a few crosses can yield information on the possible location of a new mutation upon a range of chromosome

segments or whole chromosomes. Ideally, of course (and probably ultimately), one such cross would suffice, provided sufficient marking genes can be combined in a single stock which do not display phenotypic interactions (of viability or epistasis). Even when the purely genetical technique is appropriately organized, there still remains the question of efficiency of the statistical analysis employed. The efficiency would appear to be divisible into three parts: (1) relative efficiency (unit amount of information) of the type of cross to be employed; (2) detection of spurious linkages (if twenty gene pair segregations are simultaneously considered, one would be expected to exceed the 5% level by chance; affinity phenomenon in laboratory stocks, Wallace, 1953); and (3) the onset of diminishing returns for detecting loose linkages or establishment of complete independence (the elimination of possible linkages approaching 0·5 varies as the reciprocal of the root of the sample number).

In this context, it is proposed to use the term precision to designate the concept of the sample discrediting a linkage strength below a certain magnitude. Precision in these terms is of importance during the initial stages of establishing markers for the known chromosomes of probable number of chromosome segments. If precision is defined as the limit of a deviation (d) from random segregation at the 5% level of significance and I the total amount of information from all matings, we have

$$d = \frac{1{\cdot}95996}{\sqrt{I}},$$

as the maximum deviate compatible with the information yielded by the data. Clearly, precision implies that all linkage values below $0{\cdot}5-d$ are formally excluded by the sample information. Study of the formula for d (by inserting, for example, $I = 4N$, the amount of information for backcrosses) reveals that the curve plotted against sample number (N) is a typical hyberbola reaching the zero value of d only at infinity. The lower curve of Fig. 1 simulates the curve in spite of the scale transformations. The issue to be made is that the labour involved in collating data is subject to diminishing returns and beyond a certain point must be considered unrewarding. As yet, no satisfactory intrinsic point on the curve has been discovered by which a non-arbitrary decision may be made to terminate collection of data. Two curves are shown in the figure (and the formula above does not exclude values above 0·5) in view of chromosome length/map length relationship theories which result in curves where the recombination fraction may exceed 0·5.

However, the sheer unprofitable nature of tabulating data solely to obtain a high precision can be circumvented, in some measure at least, by making collection of data on independent segregation additional to other formal genetic work, such as the testing out of a new mutation which also involves the simultaneous segregation of 'known independent genes' or in the formation of inbred lines segregating at two or more loci, functioning both as an 'allele repository' and as a source of linkage data. The ease by which a scoring technique, based upon logarithmic differentiation of the expectation, can be utilized to combine data should encourage the collection of material in this manner. For the expenditure of a little extra effort in fore-planning useful information can be gathered and which is probably accumulating. Such information, compactly presented as new independent data in the style of Carter & Falconer (1952) if other work prevents immediate analysis, would be of considerable value for future collations.

SUMMARY

The published data on possible genetic linkage in the rabbit are surveyed and combined by the aid of maximum-likelihood scores to provide estimates of (i) closest linkage compatible with the apparent random segregation and (ii) the recombination fraction where random segregation is contradicted.

I am indebted to Dr Paul B. Sawin, Mr J. C. Sandford and Miss Ivy C. Robertson for assistance with bibliographical material and to Dr D. S. Falconer for kindly reading the manuscript.

REFERENCES

(1) Assheton, R. (1910). *Guy's Hosp. Rep.* **64**, 313–42.
(2) Carter, T. C. & Falconer, D. S. (1951). *J. Genet.* **50**, 307–23.
(3) Carter, T. C. & Falconer, D. S. (1952). *J. Genet.* **50**, 399–413.
(4) Carter, T. C. & Robertson, A. (1952). *Proc. Roy. Soc.* B, **139**, 410–26.
(5) Castle, W. E. (1905). *Publ. Carneg. Instn*, no. 23.
(6) Castle, W. E. (1919). *Publ. Carneg. Instn*, no. 288, pp. 4–28.
(7) Castle, W. E. (1920). *Science*, **52**, 156–7.
(8) Castle, W. E. (1921). *Science*, **54**, 534–636.
(9) Castle, W. E. (1922). *Publ. Carneg. Instn*, no. 320.
(10) Castle, W. E. (1924*a*). *Proc. Nat. Acad. Sci., Wash.*, **10**, 107–8.
(11) Castle, W. E. (1924*b*). *Proc. Nat. Acad. Sci., Wash.*, **10**, 486–88.
(12) Castle, W. E. (1926). *Publ. Carneg. Instn*, no. 337, pp. 3–47.
(13) Castle W. E. (1929*a*). *J. Hered.* **20**, 193–9.
(14) Castle, W. E. (1929*b*). *Z. indukt. Abstamm. u. VererbLehre*, **52**, 53–60.
(15) Castle, W. E. (1929*c*). *J. Exp. Zool.* **53**, 421–54.
(16) Castle, W. E. (1932). *Publ. Carneg. Instn*, no. 427, pp. 3–13.
(17) Castle, W. E. (1933*a*). *J. Hered.* **24**, 81–6.
(18) Castle, W. E. (1933*b*). *Proc. Nat. Acad. Sci., Wash.*, **19**, 947–50.
(19) Castle, W. E. (1934*a*). *J. Exp. Zool.* **67**, 105–14.
(20) Castle, W. E. (1934*b*). *J. Exp. Zool.* **68**, 377–91.
(21) Castle, W. E. (1936). *Proc. Nat. Acad. Sci., Wash.*, **22**, 222–5.
(22) Castle, W. E. & Keeler, C. E. (1933). *Proc. Nat. Acad. Sci., Wash.*, **19**, 98–100.
(23) Castle, W. E. & Law, L. W. (1936). *J. Hered.* **27**, 235–40.
(24) Castle, W. E. & Nachtsheim, H. (1933). *Proc. Nat. Acad. Sci., Wash.*, **19**, 1006–11
(25) Castle, W. E. & Sawin, P. B. (1941). *Proc. Nat. Acad. Sci., Wash.*, **27**, 519–23.
(26) Castle, W. E., Walter, H. E., Mullenix, R. C. & Cobb, S. (1909). *Publ. Carneg. Instn*, no. 114.
(27) Fisher, R. A. (1946). *Amer. Nat.* **80**, 568–78.
(28) Hurst, C. C. (1905). *J. Linn. Soc.* **29**, 283–324.
(29) Knopfmacher, H. P. (1942). Thesis, Brown University.
(30) MacMillion, T. M. (1942). *Bull. Pittsburgh Univ.* **38**, 289–93.
(31) Mather, K. (1951). *The Measurement of Linkage in Heredity*, 2nd ed. London.
(32) Melander, Y. (1950). *Hereditas, Lund*, **36**, 335–41.
(33) Muldal, S. (1947). *Rep. Innes Hort. Instn*, **38**, 22–3.
(34) Nachtsheim, H. (1929). *Z. indukt. Abstamm. u. VererbLehre.*, **52**, 1–52.
(35) Owen, A. R. G. (1949). *Proc. Roy. Soc.* B, **136**, 67–94.
(36) Painter, T. S. (1926). *J. Morph. Physiol.* **43**, 1–43.
(37) Pap, E. (1921). *Z. indukt. Abstamm. u. VererbLehre.*, **26**, 185–270.
(38) Parkhurst, R. T. & Wilson, W. K. (1933). *J. Hered.* **24**, 35–9.
(39) Pease, M. S. (1928). *Verh. V. Intern. Kongr. Vererbungswissenschaft*, **2**, 1153–6.

(40) PICKARD, J. N. (1941). *J. Genet.* **42**, 215–22.
(41) PINCUS, G. & WADDINGTON, C. H. (1939). *J. Hered.* **30**, 515–18.
(42) PUNNETT, R. C. (1912). *J. Genet.* **2**, 221–38.
(43) PUNNETT, R. C. (1915). *J. Genet.* **5**, 37–50.
(44) PUNNETT, R. C. (1924). *J. Genet.* **14**, 231–40.
(45) PUNNETT, R. C. (1926). *J. Genet.* **17**, 217–20.
(46) PUNNETT, R. C. (1928). *J. Genet.* **20**, 247–60.
(47) PUNNETT, R. C. (1930). *J. Genet.* **23**, 265–74.
(48) RAO, C. R. (1952). *Advanced Statistical Methods in Biometric Research.* New York.
(49) RIFAAT, O. M. (1954). *Heredity*, **8**, 107–16.
(50) ROBINSON, R. (1951). *Nature, Lond.*, **168**, 300.
(51) ROBINSON, R. (1953). *J. Hered.* **44**, 95–6.
(52) SAWIN, P. B. (1934). *J. Hered.* **25**, 477–81.
(53) SAWIN, P. B. & GLICK, D. (1943). *Proc. Nat. Acad. Sci., Wash.*, **29**, 55–9.
(54) SAWIN, P. B., GRIFFIN, M. A. & STUART, C. A. (1944). *Proc. Nat. Acad. Sci., Wash.*, **30**, 217–21.
(55) SLEEPER, H. A. (1940). Thesis, Brown University.
(56) STEVENS, W. L. (1936). *J. Genet.* **32**, 51–64.
(57) TATEISHI, S. (1936). *Zool. Mag., Tokyo*, **48**, 617–24.
(58) VARA, P. & PERSONEN, S. (1948). *Acta obstet. gynec. scand.* **27**, 215–48.
(59) VENGE, O. (1952). *LantbrHogsk. Ann. Uppsala*, **19**, 233–43.
(60) WALLACE, M. E. (1953). *Nature, Lond.*, **171**, 26.
(61) WRIGHT, M. E. (1947). *Heredity*, **1**, 349–54.

APPENDIX

A list of gene/loci symbols used in this paper with a brief note on nomenclature and characteristic expression.

Symbol	Designation	Character
a	non-agouti	coat colour
An	antigen A	human blood antigen
As	atropinesterase	enzyme system
ax	ataxia	behaviour
b	brown	coat colour
br	brachydactylia	digit abnormality
c	albinism	coat colour
d	dilute	coat colour
du	Dutch spotting	white spotting
dw	dwarf	body size
e	yellow	coat colour
En	English spotting	white spotting
f	furless	coat texture
H	blood group	blood
H_6	blood group	blood
l	long hair	coat texture
r_1	French rex	coat texture
r_2	German short hair	coat texture
r_3	Normandy rex	coat texture
s	white marked	white spotting
sa	satin	coat texture
v	Viennese white	white spotting
w	wide band	coat colour
wa	waved	coat texture
y	yellow fat	enzyme system
♂	male	sex