GENETICS OF THE Rh-Hr LOCUS IN HUMANS

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An analysis is attempted to throw more light on the inheritance of rhesus factor in humans and the Fisher-Race and Wiener's concepts are respectively evaluated.
It is claimed that the Rh-Hr locus is not comprised of the recombination of C, D, E, c and e genes, much less the help of the auxiliary (d) which merely appears to be a conventional approach derived from an even principle of recombination for a polyhybrid cross.
As for Wiener's rare or common mutants of Rh-Hr in humans and the emergence of different agglutinogens like a sort of genetic proliferation, no such parallel of inheritance has yet been found in experimental plants or animals.
Probably the scarcity of certain genotypes is due to the rare chance of fertilization or embryonic development due to incompatibility between certain mutants of Rh-Hr genes, similar to ABO-Rh incompatibility.

While discovery of the rhesus factor dates back to 1937 (Landsteiner and Wiener), the understanding of its phenotypical variations was first sought by the team of the same workers in 1940-41. Since then, attempts have been made by various investigators to unravel the genetics of ever emerging new mutants of Rh-Hr factor in humans. Various proposals have been presented. Unfortunately none of them has yet proven perfect. Hence, as time passed, Wiener (1943) was the first to propose multiple allele theory for the inheritance of Rh-Hr system. Soon after, Fisher and Race (1946) suggested that the basis of the Rh-Hr inheritance in humans is due to the recombination of three different and main (C, D, E) genes with their respective mutants c, (d), e; (d) being absolutely imaginary and unreal.

Clarke also approved this idea but emphasized that some of their recombinations are very tightly linked like the « supergenes » of butterflies which may very rarely be involved in crossingover (1967). Murray (1944) numbered the Rh-Hr mutants on the basis of the reactions of 8 genes to 6 possible antisera. Sacks et al. (1959) and Rosenfield et al. (1962) named the variants on the basis of the arabic serial numerals. Nijenhuis (1961) differentiated Rh-Hr factors on the basis of the different sites on the Rh-Hr gene. Knox (1966) proposed a decimal system to make the provisional estimate of maximum antigen sites per 100 square units (pattern 1). Conversion of information from one type of nomenclature to another has never been completed fully.

While all of these theories have their individual significance, the following discussion is mainly intended to evaluate the validity of the Fisher and Race and Wiener's concept about the inheritance of the Rh-Hr system in humans. Fisher and Race's different recombinations DCe, DcE, DCE, Dce, (d)Ce, (d)cE, (d)CE, and (d)ce, are supposed to be equivalent to

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Wiener's R^1, R^2, R^z, R^0, r′, r″, r^y, and r, respectively. To clarify the statement, at each step an attempt be made to mention the Rh-Hr genotypes in terms of both the Fisher and Race and Wiener's symbols.

Considering the Hardy-Weinberg hypothesis of 1908, the reciprocal pairs of gametes having

TABLE 1

DDCCEE	1	DDCCEe	2	ddCCEe	2
DDCcEE	2	DDCcEe	4	ddCcEe	4
DDccEE	1	DDccEe	2	ddccEe	2
ddCCEE	1	DdCCEe	4	DDCCee	1
ddCcEE	2	DdCcEe	8	DDCcee	2
ddccEE	1	DdccEe	4	DDccee	1
DdCCEE	2	DdCCee	2	ddCCee	1
DdCcEE	4	DdCcee	4	ddCcee	2
DdccEE	2	Ddccee	2	ddccee	1

any number of genes should be present in equal proportions only if the genes are assorting independently and if all the recombinations are compatible at the time of gametogenesis. Utilizing the Fisher and Race concept of Rh-Hr inheritance based on D,C,E,(d),c,e genes, the frequency of possible recombinations (2^n where n is the number of factors involved) should be equal at the time of gametogenesis. Consequently, if all the recombinations of genes are equally compatible, the frequency of each class of F_2 population should be under the limits of the figures mentioned in Table 1, where the genotypes can be arranged in 27 different orders (Mendel 1865).

The zygotic recombinations of linked genes of a trihybrid cross of F_2 population may also appear to be distributed in 27 different phenotypical classes, if genes are located at distances apart where crossingover may take place with equal frequency between all three different genes and their mutants. However, their cis- and trans- position effects between certain genotypes can alter the frequency of some of the phenotypical classes causing them to be less than 27 or between 27 and 36. Obviously the genotypic recombination of a trihybrid cross cannot exceed 36. (See Table 2).

TABLE 2

DCE/DCE	R^zR^z	1	DCE/dcE	R^zr''	2	DcE/dce	R^2r	2
DCE/DCe	R^zR^1	2	DCe/dCe	R^1r'	2	Dce/dcE	R^0r''	2
DCE/DcE	R^zR^2	2	DcE/dCE	R^2r^y	2	dCE/dCe	r^yr'	2
DCe/DCe	R^1R^1	1	Dce/Dce	R^0R^0	1	Dce/dce	R^0r	2
DCE/Dce	R^zR^0	2	DCE/dce	R^zr	2	dCE/dcE	R^yr	2
DCe/DcE	R^1R^2	2	DCe/dcE	R^1r''	2	dCe/dCe	r′r′	1
DCE/dCE	R^zr^y	2	DcE/dCe	R^2r'	2	dCE/dce	r^yr	2
DCe/Dce	R^1R^0	2	Dce/dCE	R^0r^y	2	dCe/dcE	r′r″	2
DcE/DcE	R^2R^2	1	DCe/dce	R^1r	2	dCe/dce	r′r	2
DCE/dCe	R^zr'	2	DcE/dcE	R^2r''	2	dcE/dcE	r″r″	1
DCe/dCE	R^1r^y	2	Dce/dCe	R^0r'	2	dcE/dce	r″r	2
DcE/Dce	R^2R^0	2	dCE/dCE	r^yr^y	1	dce/dce	r r	1

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While the Ortho study (1961) has provided statistical data for 36 possible genotypic recombinations in a nonreciprocal proportion, the probability of these genes being assorted independently or linked at distances apart is eliminated. However, if these genes are linked as explained by Morgan (1910) or as units of various supergenes as proposed by Clarke (1967) remains to be determined.

Linkage as explained by Morgan applies to two loci rather than any two particular alleles (Li 1961). Therefore, if " D ", " C " and " E " genes are located on separate loci, their respective alleles " (d) ", " c " and " e " should also be separated from each other. Moreover, the proportion of alternate alleles should remain constant if all the recombinations are compatible at the time of gametogenesis or zygote formation. According to this Mendelian principle the frequency of " DCE " recombination should be equal to " (d)ce ". As a result, the zygotes DCE/DCE and (d)ce/(d)ce should also be equal to each other. Unfortunately the Ortho statistical study (1961) shows that the flow of any reciprocal zygotes for Rh-Hr inheritance is not in equal proportion. For instance, (d)ce/(d)ce is about 15.1020 while DCE/DCE is only 0.0006. Therefore, the mystery of compatibility between certain recombinations against the incompatibility of others, has to be investigated counting upon the Rh-Hr blood types of the children from the marriages outlined in experiments 1 and 2.

In both of these experiments an equal number of couples should be studied separately as well as collectively. As a result, if there is compatibility between all the recombinations, and the Rh-Hr locus is at all comprised of three different D-C-E genes, the children from experiments 1 and 2 should be distributed in proportion of one-to-one from each set of couples as none of the parents can produce other than their parental gametes because of their homozygous genotypes. For example, couples with genotypes (DCE/DCE × DCe/DCe) and (DCe/DCe × dce/dce) should have DCE/DCe and DCe/dce children respectively and in equal proportion. And if they are not in equal proportion this discrepancy may probably be due to the fact that the gene " D " has not been yet known to possess its alternate allele " (d) ". While anti-(d) serum is not yet reported, it is possible that the locus for allele (d) may be empty. Absence of an alternate allele (d) as the mutant of " D " is unique though possible, but rules out the possibility of Mendelian inheritance with respect to " D ".

However, if these genes are linked, experiment No. 3 (test crossing) should disclose it. Persons heterozygous for three genes can only be of 4 different categories, viz.: DCE/dce, DCe/dcE, DeE/dCe and Dce/dCE. Any of them engaged in mating with a homozygous recessive should have children of 8 different genotypes but in different proportions, because of linkage. The parental recombinations in each case should be 50% or more than 50%, and their double crossovers the least. For instance, in a cross of 3-1 (DCE/dce × dce/dce), where the parental recombinations of the heterozygous parent is " DCE " and " dce ", the double crossovers are (DcE/dce × dCe/dce) which are the least in quantity. In 3-III, where the parental recombination is (DcE/dCe × dce/dce) the double crossovers are (DCE/dce × dce/dce) which is the parental recombination of 3-I. However, the single crossovers of both of them are DCe, Dce, dcE, and dCE, which have to be reciprocally equal with ± differences. Therefore, at least 50% children from the categories (3-I) and (3-III) should be (DCE/dce and dce/dce) and (DcE/dce and dCe/dce) respectively. Suppose the parental recombination in each case, viz., (3-I, 3-II, 3-III and 3-IV), is only 50% with single crossovers between D-C and C-E as 24% each, and the double crossovers only 2%. Calculating the linkage values based on this supposition it is noteworthy that whatever the genotypes of the parental recombination and the double cross-

Experiment No. 1

Homozygous Dominant Recombinations vs. Each of the 8 Possible Homozygous Recombinations

Parents					*Children*	
DCE/DCE	(R^zR^z)	×	(R^zR^z)	DCE/DCE	DCE/DCE	(R^zR^z)
DCE/DCE	(R^zR^z)	×	(R^1R^1)	DCe/DCe	DCE/DCe	(R^zR^1)
DCE/DCE	(R^zR^z)	×	(R^2R^2)	DcE/DcE	DCE/DcE	(R^zR^2)
DCE/DCE	(R^zR^z)	×	(R^0R^0)	Dce/Dce	DCE/Dce	(R^zR^0)
DCE/DCE	(R^zR^z)	×	(r^yr^y)	dCE/dCE	DCE/dCE	(R^zr^y)
DCE/DCE	(R^zR^z)	×	($r'r'$)	dCe/dCe	DCE/dCe	(R^zr')
DCE/DCE	(R^zR^z)	×	($r''r''$)	dcE/dcE	DCE/dcE	(R^zr'')
DCE/DCE	(R^zR^z)	×	(rr)	dce/dce	DCE/dce	(R^zr)

Experiment No. 2

All of the 8 Possible Homozygous Recombinations vs. Homozygous Recessives

Parents					*Children*	
DCE/DCE	(R^zR^z)	×	(rr)	dce/dce	DCE/dce	(R^zr)
DCe/DCe	(R^1R^1)	×	(rr)	dce/dce	DCe/dce	(R^1r)
DcE/DcE	(R^2R^2)	×	(rr)	dce/dce	DcE/dce	(R^2r)
Dce/Dce	(R^0R^0)	×	(rr)	dce/dce	Dce/dce	(R^0r)
dCE/dCE	(r^yr^y)	×	(rr)	dce/dce	dCE/dce	(r^yr)
dCe/dCe	($r'r'$)	×	(rr)	dce/dce	dCe/dce	($r'r$)
dcE/dcE	($r''r''$)	×	(rr)	dce/dce	dcE/dce	($r''r$)
dce/dce	(rr)	×	(rr)	dce/dce	dce/dce	(rr)

Experiment No. 3

Test-Cross Like (Heterozygous) Individuals in all Possible Cis- and Trans- Position for D-C-E Genes vs. Homozygous Recessives

I.	DCE/dce	(R^zr)	×	(rr)	dce/dce
II.	DCe/dcE	(R^1r'')	×	(rr)	dce/dce
III.	DcE/dCe	(R^2r')	×	(rr)	dce/dce
IV.	Dce/dCE	(R^0r^y)	×	(rr)	dce/dce
V.	DCe/dce	(R^1r)	×	(rr)	dce/dce
VI.	Dce/dCe	(R^0r')	×	(rr)	dce/dce
VII.	DcE/dce	(R^2r)	×	(rr)	dce/dce
VIII.	Dce/dcE	(R^0r'')	×	(rr)	dce/dce
IX.	dCE/dce	(r^yr)	×	(rr)	dce/dce
X.	dCe/dcE	($r'r''$)	×	(rr)	dce/dce
XI.	Dce/dce	(R^0r)	×	(rr)	dce/dce
XII.	dCe/dce	($r'r$)	×	(rr)	dce/dce
XIII.	dcE/dce	($r''r$)	×	(rr)	dce/dce
XIV.	dce/dce	(rr)	×	(rr)	dce/dce

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PROCEDURE TO CALCULATE LINKAGE VALUES BASED ON BACK-CROSS TESTING FROM EXPERIMENT NO. 3

	Parental recombination	Single crossingover		Double crossingover		Single crossingover		Parental recombination
	$\frac{DCE}{dce}$ 25%	$\frac{Dce}{dce}$ 12%	$\frac{DCe}{dce}$ 12%	$\frac{DcE}{dce}$ 1%	$\frac{dCe}{dce}$ 1%	$\frac{dcE}{dce}$ 12%	$\frac{dCE}{dce}$ 12%	$\frac{dce}{dce}$ 25%
3-I Parents: DCE/dce × dce/dce		D with c & d with C		12 + 12 + 1 + 1	= 26			
		C with e & c with E		12 + 12 + 1 + 1	= 26			
		D with e & d with E		12 + 12 + 12 + 12	= 48			
	$\frac{DCe}{dce}$ 25%	$\frac{DcE}{dce}$ 12%	$\frac{DCE}{dce}$ 12%	$\frac{Dce}{dce}$ 1%	$\frac{dCE}{dce}$ 1%	$\frac{dce}{dce}$ 12%	$\frac{dCe}{dce}$ 12%	$\frac{dce}{dce}$ 25%
3-II Parents: DCe/dcE × dce/dce		D with c & d with C		12 + 12 + 1 + 1	= 26			
		C with E & c with e		12 + 12 + 1 + 1	= 26			
		D with E & d with e		12 + 12 + 12 + 12	= 48			
	$\frac{DcE}{dce}$ 25%	$\frac{DCe}{dce}$ 12%	$\frac{Dce}{dce}$ 12%	$\frac{DCE}{dce}$ 1%	$\frac{dce}{dce}$ 1%	$\frac{dCE}{dce}$ 12%	$\frac{dcE}{dce}$ 12%	$\frac{dCe}{dce}$ 25%
3-III Parents: DcE/dCe × dce/dce		D with C & d with c		12 + 12 + 1 + 1	= 26			
		c with e & C with E		12 + 12 + 1 + 1	= 26			
		D with e & d with E		12 + 12 + 12 + 12	= 48			
	$\frac{Dce}{dce}$ 25%	$\frac{DCE}{dce}$ 12%	$\frac{DcE}{dce}$ 12%	$\frac{DCe}{dce}$ 1%	$\frac{cdE}{dce}$ 1%	$\frac{dCe}{dce}$ 12%	$\frac{dce}{dce}$ 12%	$\frac{dCE}{dce}$ 25%
3-IV Parents: Dce/dCE × dce/dce		D with C & d with c		12 + 12 + 1 + 1	= 26			
		c with E & C with e		12 + 12 + 1 + 1	= 26			
		D with E & d with e		12 + 12 + 12 + 12	= 48			

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overs may be, the linkage values in each case are the same. In other words, in all of them the centimorgan units between D-C, C-E and D-E, are 26, 26 and 48 respectively. Therefore, by such an experimentation in vivo, we can calculate linkage values in any population which also have to be uniform. If not, the D-C-E genes are not linked but are probably united in the form of ' supergenes ' as expected by Clarke.

Linkage values between D-C and C-E genes separately can also be calculated from the data in vivo from categories 3-V through 3-X. 3-XI through 3-XIV should segregate in 1 : 1 ratio, a simple Mendelism.

In fact, such an experimentation is not only a theoretical proposition but is also a practical one which should occur very frequently if the genotypes of the children for such marriages are carefully studied. Such an observation must come quite close to our proposed experimental findings.

In terms of the multiple allele theory of Wiener (1943) and Wiener and Landsteiner (1943), the Rh-Hr mutants must first be investigated for their chemical or physical mutation. Unfortunately, Wiener has never emphasized this point. However, if they are chemical mutants, some of them could certainly be expected to be frequent and others rare (Wiener and Hyman 1948). It may, therefore, be anticipated that the rare continue to decrease as time passes — a process which ultimately should result in elimination of certain genotypical classes as occurred with the Rh negative factor in chimpanzee (Wiener 1965).

The other possibility could be that some of the so-called Rh-Hr mutants may be the result of physical alteration. Probably, some of them could be comprised of unbreakable genetic contents, while other could possibly be made of loose genetical units which could be severed at times, yielding new genotypes. Such a possibility of mutation or crossingover resulting in an inheritable unit has already been demonstrated by Steinberg (1965). Incidentally, this is against the principle of regular crossingover established by Morgan et al. in 1915. Based on such a breakage of Rh-Hr gene and formation of various segments at molecular level, the proliferation of certain mutants is more feasible. Consequently, a new agglutinogen (Wiener 1961 and 1970, Wiener and Socha 1971) can be formed at each new regular or irregular exchange. Multiple alleles, therefore, may not be all chemical mutants but some of them (if not all) appear to be physical alterations of the Rh-Hr breakable genes.

Therefore, if all the 8 prominent mutants of rhesus factor (R^0, R^1, R^2, R^z, r, r′, r″, r^y) are absolutely unalterable, the children from experiments 1, 2 and 3 should segregate accordingly. If not, some of the Rh-Hr mutants are either fragile and can break in unpredictable fashions or they are affected by some sort of compatibility/incompatibility between certain genotypes at the time of zygote formation or the embryonic development. While the first category of incompatibility which is at the conception level may not be discovered at all, the second possibility similar to the formation of distorted embryos for homozygous yellow coat color in mice (Hadorn 1955) may be studied by blood typing in the aborted embryos in humans. Another example of similar nature can be cited from the ABO-Rh compatibility/incompatibility (Emery 1970). As a result, the abundance of certain genotypes against the rareness of others can be investigated in light of the factors mentioned above.

However, if all the above methods fail to yield the expected results, it becomes necessary to evaluate Fisher and Race's concept of D, C, E and their respective mutants c, (d), e as different linked genes, or Wiener's hypothesis of rare or common alleles of rhesus factor in humans.

Consequently, it appears as if the linear arrangement of D, C, E, (d), c, e genes (Fisher and Race) in the form of ' supergenes ' (Clarke) has the firm or loose union of linear segments of Rh-Hr genes at molecular level acting in the form of multiple alleles (Wiener).

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RIASSUNTO

Genetica del Locus Rh-Hr nell'Uomo

Viene effettuata un'analisi al fine di chiarire il meccanismo ereditario del fattore rhesus nell'uomo e vengono prese in considerazione le due diverse concezioni di Fisher e Race e di Wiener.
Si sostiene che il locus Rh-Hr non si compone dei geni C, D, E, c, e, meno che mai del gene ausiliare (d), il quale sembra essere nient'altro che un risultato convenzionale dell'applicazione di un semplice principio di *ricombinazione per un incrocio poliibrido.*
Quanto ai mutanti comuni e rari della concezione di Wiener, con diversi agglutinogeni che ne emergono in una sorta di proliferazione genetica, non è stato finora trovato un parallelo nelle piante e negli animali.
È probabile che la scarsità di certi genotipi sia dovuta a difficoltà di fecondazione o sviluppo embrionale per motivi di incompatibilità fra certi mutanti Rh-Hr, analogamente a quanto avviene per l'incompatibilità ABO-Rh.

RÉSUMÉ

Génétique du Locus Rh-Hr chez l'Homme

Une analyse est effectuée afin d'éclairir le mécanisme héréditaire du facteur rhésus chez l'homme et les deux conceptions différentes de Fisher-Race et de Wiener sont considérées.
On indique que le locus Rh-Hr ne se compose pas des gènes, D, C, E, c, e et sourtout pas du gène auxiliaire (d) qui ne semble être que le résultat conventionnel d'une application d'un simple principe de recombinaison pour un croisement polyhybride.
En ce qui concerne les mutants connus et rares de Wiener, avec différents agglutinogènes qui en dérivent par une sorte de prolifération génétique, aucun parallèle n'a jusqu'à présent été trouvé chez les plants ou les animaux.
Il est probable que certains génotypes soient rares à cause des difficultés de fertilisation ou développement embryonnaire résultant d'une incompatibilité entre certains mutants Rh-Hr, ainsi qu'il arrive pour l'incompatibilité ABO-Rh.

ZUSAMMENFASSUNG

Vererbung des Locus Rh-Hr beim Menschen

Untersuchung zur Klärung des Erbmechanismus des Rh-Faktors beim Menschen. Erörterung zweier verschiedener Auffassungen nämlich von Fisher u. Race und von Wiener.
Es wird behauptet, dass im Locus Rh-Hr weder die Gene C, D, E, c, e vorhanden sind und noch weniger das Hilfsgen (d), das scheinbar nichts anderes ist als das konventionelle Resultat der Anwendung eines einfachen Rekombinationsprinzips auf eine polyhybride Kreuzung.
Wiener hingegen denkt an gewöhnliche und seltene Mutanten mit verschiedenen Agglutinogenen, die daraus in einer Art Erbproliferation hervorgehen; doch hat sich bisher weder bei den Pflanzen noch bei den Tieren eine Parallele dazu gefunden.
Möglicherweise erklärt sich die Seltenheit gewisser Genotypen mit Schwierigkeiten bei der Befruchtung oder während der Embryonalentwicklung durch Inkompatibilität gewisser Rh-Hr-Mutanten, ähnlich wie die Rh-ABO-Inkompatibilität.

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