Rh NOTATION

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The observed serological and genetical facts relating to the Rh system of blood groups are highly complex even when seen in the light of all the simplifying hypotheses proposed by a number of outstanding scientists. It is therefore not to be expected that it will be easy, or even possible, to devise a notation which will cover them completely and at the same time simply.

Two main bodies of theory exist, each associated with a special notation. One theory and system of notation is due to Dr. A. S. Wiener and the other to Sir Ronald Fisher and Dr. R. R. Race. The principal Rh blood-group antigen was discovered by the late Dr. K. Landsteiner and Dr. Wiener (1940) in collaboration. It was subsequently found that a complex system of antigens was involved, and the earliest notation embodying that complexity is due to Dr. Wiener (1943), who by the end of 1943 had set up the main framework of his present system. Soon after this Sir Ronald Fisher, as described below, proposed a second and complementary system of notation. The main object of this paper is, however, to describe the present state of knowledge and its codification, and not to discuss priorities. For comprehensive statements of the facts and theories, including the history of the subject, the reader should consult recent books by Race and Sanger (1954) and by Wiener (1954a, 1954b).

Rh-positive and Rh-negative

In an article in a journal emphasizing clinical medicine it must first be said that it is not necessary for clinicians managing cases of Rh immunization to be able to manipulate a complex notation. The most recondite of the facts and theories are occasionally vitally relevant to the treatment of a case, and here a specialist must in any case be consulted, but it is still as true as it was fifteen years ago that the essential piece of knowledge is whether a mother or a transfusion recipient is Rh-positive or Rh-negative, terms which in clinical use, and in terms of Fisher's notation, should always be regarded as synonymous with "D-positive" and "D-negative" respectively. In terms of Wiener's notation these will be "Rh₀-positive" and "Rh₀-negative" respectively; at this low level of complexity there is obviously little to choose, theoretically or practically, between the two notations. The great majority of immunized persons are D-negative, and, when this is so, any transfusion of the immunized person or of the baby of an immunized woman must be performed by using D-negative blood.

In the treatment of the rare cases where a D-positive mother or recipient becomes immunized it may help to know the theoretical background; but it is much more important to be able to apply a thoroughly reliable direct matching test when selecting blood for transfusing the immunized person or baby with haemolytic disease.

The Rh Antigens

Antigenically, however, the Rh system is much more complex than is implied by the above simple scheme, and comprises in fact about six common entities (C, c, D, E, e, f, in Fisher's notation), and several rare ones, each of which is generally regarded in Great Britain as a separate antigen or haemagglutinin; Wiener, however, calls them "factors" or "partial antigens." Each of them reacts specifi-

cally with a single well-defined antibody or haemagglutinin. While antigenically these entities are distinct, genetically they are invariably transmitted in groups of at least two and usually of three or more. Wiener regards each genetically combined group of antigens as a single antigen and considers that it is transmitted by a single gene, whereas Fisher and Race regard each elementary antigen (or "factor") as the product, probably, of a separate gene.

The Rh Genes and their Arrangement

In order to describe the Rh system any further it is necessary to use some notation, and in this article Fisher's notation is used primarily. The theory and notation were first put forward as a communication from Fisher in a paper by Race (1944), and were subsequently further developed by Fisher and by Race. The primary purpose of Fisher's notation was to provide a distinct designation for each elementary antigen and therefore also for the antibody by which each may be detected, and there was no intention of superseding Wiener's names for the larger genetic units, which were at this stage looked upon as genes. It was only as a result of later investigations that each of the elementary antigens came to be regarded as the product of a separate gene. Taking into consideration all well-established Rh antigens the theory of Fisher and Race, in its genetic aspect, now postulates the existence, on each of the two members of one particular pair of human chromosomes, of a series of four or possibly five loci; to each locus there corresponds a set of two or more alternative or allelomorphous genes. The distances between the loci must be very small compared with the total length of the chromosome. The linear order of the loci is thought to be DCEF; each D locus may be occupied by any one of the allelomorphous genes D, D^u, or d; the C locus by C, C^u, C^w, C^x, c^v, or c; the E locus by E, E^u, E^w, e^x, or e; and the F locus by F or f. A further gene, provisionally called V, certainly belongs to the Rh complex, but it is not yet known whether it is an allele of F and f or whether it corresponds to a fifth locus, the latter hypothesis being the more probable. Thus each individual will have a pair of genes, like or unlike, selected from the D group, a pair from the C group, and so on, giving a genotype represented by two sets of four letters such as, for example, DCEf/Dcef. With the few exceptions mentioned below, each of the genes in the above sense gives rise to a distinct antigen recognized by red-cell agglutination in the presence of a corresponding and distinct antibody. The d and F genes have not been convincingly shown to give rise to antigens. The genes D^u, C^u, c^v, E^u, and apparently e^x give rise to antigens, but none of these is clearly defined in terms of reaction with a single antibody; a given D^u antigen, for instance, will react with certain anti-D sera but not with others, but it is not possible to separate anti-D and anti-D^u components from such sera by absorption; here the term "partial antigen" in the original sense may be justified though the analogy is not complete.

Besides chromosomal sets each consisting of four genes, one at each hypothetical locus, there exists, as shown by Race *et al.* (1954), a very rare type of set or genetical unit consisting solely of D, in which it is assumed that a chromosome segment, comprising the C, E, and possibly F loci, has been deleted. Wiener, Gordon, and Cohen (1952) have described a set which is apparently equivalent to c and D without a detectable gene at the E locus; no investigation with anti-f appears to have been done; a deletion of the E locus would be compatible with the order DCE.

According to Wiener's hypothesis only one locus on each chromosome is responsible for the Rh blood groups. This locus can be occupied by any one of a large number of allelomorphous genes. These genes are, as we have seen, the equivalents of groups of four of Fisher's genes. Each of Wiener's genes is given a symbol containing the letters R, r, or $\mathbb{R}$ followed by an index. The synonymy between the systems is shown in Table I. The second column of this table is explained in a later paragraph. It will be observed that R corresponds to the presence of D, r to that of d, and

R to that of D^u . The index ¹ or ² shows the presence of C; ² or ² shows the presence of E, while ^z or ^y indicates the presence of both C and E. The index ^{1w} or ^{2w} shows that C^w is present; Wiener regards the last as composed of two factors, equivalent to the ordinary C "partial antigen" together with something additional; this is because he supposes that all anti-C (or anti-rh') sera inevitably react with the C^w antigen or factor; most of them do so react, behaving as though they were a mixture of anti-C and anti- C^w ; but he does not appear to realize that certain anti-C sera

TABLE I.—*Rh Chromosomes So Far Described, Showing Fisher's Notation, the Standard Abbreviated British Notation, and the Latest Form of Wiener's Notation. (Based on a Table in "The Distribution of the Human Blood Groups," by A. E. Mourant, Blackwell Scientific Publications, Oxford, 1954)*

Fisher's Notation	Abbreviated British Notation	Wiener's Notation
CDE	R_z	R^z
cDE	R_2	R^2
CdE	R_y	r^y
cdE	R_1	R^1
CDe	R_2^p	R^0
cDe	R_1^p	r^p
Cde	r	r
C^w dE	R_y^w	—
C^w Dc	R_2^w	R^{1w}
C^w dE	R_1^w	r^{1w}
CdDe	—	—
cdDE	—	—
CdDe	—	—
CD ^u E	R_z^u	—
cD ^u E	R_2^u	R^2
CD ^u e	R_1^u	R^1
cD ^u e	R_0^u	R^0
C^w D ^u e	—	—
cDE ^u	—	—
cDE ^w	—	—
cder	—	—
cD-	—	R^{0u}
-D-	—	R^{0z}

exist which do not react with C^w , and that C^w is thereby shown not to carry the full complement of antigenic properties conferred by the normal C gene.

The factors or "partial antigens" are given names corresponding to those of the genes but with the letter h after the R, r, or R^z , and with certain of the indices dropped to form suffixes. The antibodies are named after the factors—for example, anti-Rh₀.

The facts so far brought forward are fairly adequately explained either by Fisher's theory or by Wiener's. The latter, however, does not fully account for the allelomorphism within the genetical units, which is such that no chromosome, for example, carries more than one representative of the set C, C^w , c, etc. There is no question but that allelomorphism of this type is important, and the real alternative to a series of four or five genes set out in linear order along a chromosome appears to be a single complex "gene" with multiple reactive atom groups not in linear order but limited in number and in kind so that there can be only one group of the C class, one of the D class, and so on. The latter idea is not, however, part of the hypothesis put forward by Wiener himself.

It should be added that Wiener may rightly claim, in his early and fundamental work on the genetics of the Rh blood groups, to have shown that the serological phenomena could not be determined by a number of separately segregating gene pairs, whether on separate chromosomes or loosely linked on one chromosome with the occurrence of frequent cross-overs. He does not appear, however, in any of his papers written before 1944, to have referred specifically to the possibility of linkage of any kind; and he certainly did not mention the alternative of very closely linked genes; it was Fisher who first suggested this as a possible explanation of the genetics of the Rh groups. Wiener (1939), however, referring to a similar hypothesis at one time applied to the ABO groups, has stated, "Cases of 'complete linkage,' such as the one postulated by Furuhashi, are ordinarily considered by geneticists as multiple effects of a single gene."

The Genotypes

Whichever system is used, the symbols for the genotypes arise directly from those of the genes or combinations of genes. In neither case is there any ambiguity of gene or genotype notation; and at the level of complexity represented by the six genes—C, c, D, d, E, e—and of their eight possible combinations, there is little to choose between them. For reasons which will be stated later Fisher's notation is thought by those who use it to give the more complete expression of the genetical situation, but it is somewhat awkward to express in speech. For this as well as other reasons many, if not most, blood-group workers continue to use Wiener's notation or a variant of it as a convenient "shorthand," in certain contexts, for the CDE notation. It has already been said that Fisher's notation was not intended to supersede but to supplement that of Wiener; and it is right to add that, when Dr. Race and the late Dr. G. L. Taylor found that certain antigenic combinations, for which they had previously proposed other symbols, were identical with combinations independently identified and named by Dr. Wiener, they adopted his symbols.

The symbols at present used by Wiener differ more from those originally proposed than do the ones in common use in Britain, and from the former have been derived symbols for such other entities as the phenotypes. The various changes and elaborations, which some workers have found difficult to follow, have been necessitated by the attempt to stretch the single system of notation to cover the whole of the admittedly complex serological and genetical facts. There is undoubtedly an advantage, for those who are constantly doing blood-grouping work, in having a command of, at least, the British "shorthand" notation in addition to Fisher's notation, but many younger workers in fact use only the latter.

The Antibodies

The names of the principal antibodies are shown in both notations in Table II. In naming these, and in expressing the reactions between red cells and sera, Fisher's notation

TABLE II.—*Principal Rh Antibodies*

Fisher's Notation	Wiener's Notation
Anti-D	Anti-Rh ₀
"-C	"-rh'
"-C ^w	"-rh ^w
"-c	"-hr'
"-E	"-rh ^z
"-e	"-hr ^z
"-f	"-hr

has the great advantage that (allowing for the fact that the existence of anti-d has not been clearly proved) the genotype formula of any blood is a direct expression of the antisera with which it reacts.

The Phenotypes

It is in naming phenotypes that both notations meet their greatest difficulties. Wiener has devised consistent systems for phenotypes of bloods tested with anti-C, -D, and -E (anti-rh', -Rh₀, and -rh^z), for those tested with these and anti-c (anti-hr') in addition, and for those also tested with anti-e (anti-hr^z). With Fisher's notation it is often convenient to express a phenotype in terms of the "most probable genotype," while I have described (Mourant, 1949) a method of using the CDE symbols which is adaptable, and is completely comprehensive at the level of complexity now under consideration—that is, so long as only two allelomorphs are considered at each of Fisher's loci. From the point of view of simple convenience the CDE notation here seems to demand rather less effort of memory and it is, once again, a full expression of the serological reactions.

In order to express a phenotype by Mourant's method the reactions relating to the products of the genes at the C locus are first considered. If the blood has been tested with anti-C alone and the result is positive, a single C is written. If the result is negative, cc is written, whether or not the blood has been tested with anti-c, since a negative result with anti-C implies the presence of two c genes. If

the blood has been tested with both anti-C and anti-c and both give positive results, Cc is written. If the result with anti-c is negative, CC is written, and this can be done even in the absence of a test with anti-C. The D and E systems are treated similarly (but of course no tests with the hypothetical anti-d can be done). If, however, both of the sera for a particular system were unavailable (for example, Ee) the statement of results (for example, Ccdd) would make this quite clear.

Each of the phenotype symbols of Wiener, in cases where tests with four or five antisera have been performed, is in general derived from that of the commonest genotype in each phenotype, but in roman not italic letters, with the R or r followed by an h and with numerical indices reduced to suffixes thus: Rh₁Rh₁ derived from R¹R¹, becoming thus a symbol for the antigens present. In certain cases, however, in order to show what tests have been done the symbol is based on that of a genotype other than the commonest in the phenotype—for example, Rh₂Rh₀ in place of Rh₁Rh₂ if tests have been done with anti-hr" (anti-e). (The distinction made between R¹R² and R²R⁰ by anti-f is, of course, not relevant in this connexion.) In Table III—based in part on Table 9 of Wiener's (1954b) book—Rh and CDE notations are given for each of the 18 phenotypes distinguishable by means of tests with anti-C, -D, -E, -c, and -e.

We have seen, however, that the Rh system is now known to include many more than six genes in Fisher's sense, while the number of complex genes in Wiener's sense (see Table I) is very considerable indeed. Fisher's system of notation is sufficiently broad-based to incorporate all these, whereas *ad hoc* methods, such as the use of gothic characters, have had to be devised in order to bring even a part of the known chromosome combinations within Wiener's notation.

Mourant's phenotype notation concisely expresses the results of tests with a small number of sera, while, on the other hand, it is easily extended to include F and f, and will no doubt also be able to bring in V when the genetical relationships of the latter are better understood. It needs some simple *ad hoc* conventions, related to the range of tests performed, in order to cover the rarer genes and antigens such as C^w and D^u. Wiener's notation, however, would become quite unmanageable if an attempt were made to use it for phenotypes at these levels.

In its existing form and up to the level of complexity involving clear-cut positive and negative reactions with anti-C, -D, -E, -c, and -e, Wiener's whole system of notation is, in fact, completely logical and self-consistent, but to those who are accustomed to Fisher's notation it appears most cumbersome. Those who have at different times attempted to teach the two notations state that their students understand Fisher's notation much more readily than Wiener's.

Medico-legal Application

In medico-legal work Fisher's notation relates genotypes directly to serological reactions and so presents the court

with a simpler train of reasoning. Moreover, so long as the paternity of only a single child is in dispute, and its siblings or half-siblings are not also under consideration, it is possible and completely legitimate to consider, and to set before the court, the evidence for each of the loci of the CDE system separately as though they were independent blood-group systems. This manner of regarding the facts may indeed occasionally imply that if a man is to be the father of a given child he must be of a rare genotype. For example, if both mother and child are of the unambiguous genotype cde/cde and the father is of the phenotype CcDEe then he can only be the father if he is of the very rare genotype CDE/cde rather than the common genotype CDE/cDE, which is included in the same phenotype. When, however, such a situation arises it will be presumably necessary to state that the existence of paternity demands that the man be of a rare genotype, in whatever notation it may be expressed.

Another difficult situation would arise if the prosecution attempted to deny an exclusion of paternity on the plea, based on the hypothesis of separable closely linked genes, that the accused man had contributed a cross-over chromosome to the child—for example, that a man known to be CDe/cde had contributed Cde. This legal situation could arise only if his genotype were known from independent evidence, such as the Rh groups of his parents. It should, however, be sufficient defence to show that, if crossing over exists at all, it is exceedingly rare and hitherto demonstrable only, if at all, by population surveys, which integrate the results of cross-overs taking place over thousands of years.

The Genetical Background

We have up to this point considered mainly the relative convenience of the systems of notation. Each system is, however, associated with a genetical theory, and these we must now consider. Wiener regards his notation and his genetical theory as inevitably interlocked, while Fisher's genetical theory can be examined and could even be disproved without necessarily affecting his notation.

Fisher's genetical system arose from a consideration of the apparent separate allelomorphism of C and c within the larger Rh complex, and it explains other similar allelomorphisms since discovered. Single Rh genes with multiple serological effects do not necessarily explain these allelomorphisms, though they can, as we have seen, be made to do so by the postulation of a series of discrete reactive groups of atoms on the gene, with a limited possibility of substitution for each group.

The linear order of genes postulated by Fisher carries, however, the further implication that crossing over should be possible between the loci. Such crossing over has never been demonstrated directly and convincingly in family studies, and this is one of the strongest arguments put forward against the theory. Fisher and Race have, however, shown that the relative frequency of rare combinations such

TABLE III.—*Symbols of the Phenotypes**

Reactions with Antisera					Phenotype Notation		Commonest Genotype (in European Populations)	
Anti-C Anti-rh'	Anti-D Anti-Rh ₀	Anti-E Anti-rh"	Anti-c Anti-hr'	Anti-e Anti-hr"	CDE	Rh	CDE	Rh
+	+	+	+	+	CcDEe	Rh ₂ Rh ₀	CDe/cDE	R ¹ R ²
+	+	+	+	+	CcDEE	Rh ₂ Rh ₀	CDE/cDE	R ² R ²
+	+	+	+	+	CCDEe	Rh ₂ Rh ₁	CDE/CDe	R ² R ¹
+	+	+	+	+	CCDEE	Rh ₂ Rh ₂	CDE/CDE	R ² R ²
+	+	+	+	+	CcDee	Rh ₁ rh	CDe/cde	R ¹
+	+	+	+	+	CCDee	Rh ₁ rh ₁	CDe/CD _e	R ¹ R ¹
+	+	+	+	+	ccDee	Rh ₂ rh	cDE/cde	R ²
+	+	+	+	+	ccDEE	Rh ₂ Rh ₂	cDE/cDE	R ² R ²
+	+	+	+	+	CcDee	Rh ₀	CDe/cde	R ⁰
+	+	+	+	+	CcddEe	rh ₁ rh	Cde/cdE	r ¹ r ¹
+	+	+	+	+	CcddEE	rh ₁ rh"	CdE/cdE	r ¹ r ¹
+	+	+	+	+	CCddEe	rh ₁ rh'	CdE/Cde	r ¹ r ¹
+	+	+	+	+	CCddEE	rh ₁ rh ₁	CdE/CdE	r ¹ r ¹
+	+	+	+	+	Ccdee	rh/rh	Cde/cde	r ¹ r ¹
+	+	+	+	+	CCdee	rh/rh'	Cde/Cde	r ¹ r ¹
+	+	+	+	+	ccddEe	rh"rh	cdE/cde	r ² r ²
+	+	+	+	+	ccddEE	rh"rh"	cdE/cdE	r ² r ²
+	+	+	+	+	ccdee	rh	cde/cde	rr

* Partly based on Wiener (1954a, Table 9). The Rh notation is that used by Wiener, which differs in certain respects from that in common use in Britain.

as CDE and Cde in the British population can be explained if they have resulted from rare cross-overs—the first in individuals of the common genotype CDe/cDE and the second only in these with certain rare genotypes. On the whole the distribution of Rh chromosomes throughout the world is compatible with such rare crossing over. The combinations in which the f gene is found are strongly in favour of crossing over having occurred, and the same appears to be true of V.

When Fisher first proposed the genetical theory associated with his name relatively few cases had been discovered of combinations of a number of closely linked genes having closely related effects, and these cases were not widely known, but examples of similar sets of genes have now been found in a great many kinds of organism—especially in micro-organisms but also in *Drosophila*. In these various lowly creatures very numerous matings can be made and crossing-over frequencies of the order of 1 in 1,000 can be and have repeatedly been observed and measured. Such low frequencies, if they occurred in the Rh system in man, would demand inordinate numbers of tests for their detection. Several species of animals, especially cattle and domestic poultry, have systems of blood-group genes somewhat resembling the Rh system in man. In these, however, not only have no cross-overs been found until recently, but there is little or no clear-cut allelomorphism of the CC^wc type. For such systems the evidence in favour of a genetic mechanism of the type supported by Wiener is much stronger than it is in the case of the human Rh system. Recently, however, Amos, Gorer, and Mikulska (1955) have not only demonstrated the existence of a system of blood-group antigens in the mouse genetically similar to the Rh system in man, but by virtue of examining the offspring of very numerous matings have actually detected crossing over within the system.

There remain a few facts which, at first sight at least, might be regarded as weighing against Fisher's theory. One of these is the "position effect" demonstrated by Race *et al.* (1951) whereby, for instance, by the use of empirically selected antisera, quantitatively different expressions of the genes C and E can be demonstrated according to whether they are present in the genotype CDE/cDe or in CDe/cDE, though the total complement of genes is the same in each case. Such a "position effect" was, however, already known in a number of systems of proved closely linked genes in other organisms; and it was indeed the knowledge of the existence of this effect elsewhere that led Race and his colleagues to search for and to find it in the Rh system.

The existence of the isolated D gene of enhanced activity, though explicable on Fisher's theory by a deletion of the C and E loci, is not entirely favourable to that theory, since deletions, especially in the homozygous form in which -D- was first found, are usually lethal, whereas no suggestions of abnormality of the germ plasma have been found in any of the -D-/-D- persons examined. Wiener's theory, on the other hand, allows considerable freedom in the combinations of "factors" which may be determined by a single "gene." However, even on this theory there must be some rather big difference between this "gene" which he calls R^{ox} and the other genes of the Rh system, and something like a deletion or loss of active chemical groups must be involved. Moreover, on Fisher's theory, it is the C and E loci which are deleted without the D, in conformity with other facts which point to the linear order being DCE.

Most of the facts which help to discriminate between the two theories arise from highly specialized genetical investigations: they are, on the whole, more readily and completely explained by Fisher's theory than by Wiener's. Either theory accounts about equally well for the greater part of the observed facts, including nearly all those encountered in clinical investigation. To the minds of most people, however, Fisher's notation appears much more convenient than that of Wiener, and is to be recommended for this reason even if the validity of the genetical theory associated with it be disputed. It may be mentioned that the current gene

and genotype notation for certain complex blood group systems in cattle includes a separate symbol for each antigen present, as does Fisher's Rh notation, despite the fact that some workers, whilst using this notation, adopt a genetical hypothesis similar to that supported by Wiener for the Rh system.

Other systems of Rh notation are outside the scope of this article. It should, however, be mentioned that Strandkov (1949) proposed a notation which was a compromise between those of Fisher and Wiener; while Ford (1956) on the basis of Fisher's theory, has suggested a modification which brings the genetical notation into line with modern genetical practice. If it and the corresponding notations for other blood-group systems are generally adopted by geneticists it will be necessary for blood-group workers to be familiar with it and perhaps ultimately to use it for routine clinical purposes.

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Preparations and Appliances

VARIABLE-SPEED MOTOR-DRIVEN SYRINGE FOR CONTINUOUS INJECTION

Dr. RONALD A. BOWEN, of St. Bartholomew's Hospital, London, writes: Drugs such as trimetaphan ("arfonad"), noradrenaline, and suxamethonium are commonly given by continuous intravenous drip, a method having certain disadvantages. Firstly, the volume of diluent is large. Again, intravenous infusions are notoriously liable to fluctuation in rate. A third objection is the necessity for frequent counting of drip rates and the difficulty of altering the rate without a great deal of adjustment. If a syringe containing a concentrated solution of the drug is driven by an electric motor and variable gear these objections are overcome.

A prototype of the apparatus described was home-made from ex-W.D. parts. It was used by myself and colleagues in the department of anaesthesia for two years without trouble, after which it was decided to produce a commercial model. The present apparatus consists of a synchronous electric motor driving a stepless variable gear. This in turn rotates a threaded rod. Mounted on the rod and located by a guide is a metal platform. Within this is a split nut whose halves are held in contact with the thread of the rod by spring pressure. As the rod rotates, the platform is moved forwards. A small button mounted on it contacts the piston of a syringe. The halves of the split nut may be separated by a catch, allowing the platform to be moved to any position on the rod. The stepless variable gear transmits the drive by friction and permits the platform to be stopped or to be driven at any speed up to 2 mm. a minute. Slip does not occur, as the power required is small. The speed is indicated by the position of a pointer on an engraved dial. A 20-ml. syringe is held in a spring carrier, which holds it rigidly and permits rapid replacement. An adaptor and a length of fine nylon tubing connect the syringe to a needle.