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CONTENTS

SOME NEW Rh ANTIGENS: Rh43 TO Rh47

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Introduction

In 1962, Rosenfield et al[1] reviewed the serology of the Rh blood group system and introduced a numerical terminology. Numbers for the antigens Rh1 to Rh21 were assigned in the text of that report; Rh22 to Rh25 were listed in an addendum printed as part of the paper. A number of reports of new Rh antigens were reviewed by Allen and Rosenfield[2] in 1972; in that paper the numbers Rh26 to Rh33 were assigned. In a later review,[3] this time on Rh genetics, Rh34 was named. The term Rh35 seems first to have been used in two textbooks published in 1975.[4,5] When we[6] described the first examples of anti-Rh39 in 1979, we took the opportunity to update the numerical Rh terminology from Rh36 to Rh39.* The next three Rh antigens to be discovered were assigned numbers by the authors first describing them. Rh40 was named by Lewis et al[7] when they showed that the low incidence antigen Tar, which they had described earlier,[8] belongs in the Rh system. Rh40 has now been shown to be the marker antigen for Category VII red cells,[9] a new class in the classification scheme of Tippett and Sanger,[10] for the D+ red cells of persons who can form allo-anti-D. The only known example of anti-Rh41 was named by Svoboda et al[11] in the paper in which that antibody was described. Similarly, in the abstract in which the only example of the definitive antibody was reported,[12] the antigen recognized was named Rh42. Since 1982, responsibility for the assignment of numbers for new Rh antigens has rested with a Working Party on Terminology for Red Cell Surface Antigens of the International Society for Blood Transfusion.

Following meetings of the working party in Budapest in 1982 and Munich in 1984, a report was published[13] that included assignment of the terms Rh43, Rh44, and Rh45. At the 1986 meeting of the working party in Sydney, the terms Rh46 and Rh47 were assigned. The purpose of this review is to describe briefly the places of Rh43 to Rh47 in the Rh system.

Rh43(Crawford)

In 1980, Cobb[14] published an abstract describing a hitherto unrecognized low-incidence antigen, Crawford or Craw. Although the abstract states that the gene that encodes the new antigen segregated independently of *Rh* in a large family studied, reexamination of the pedigree showed that not to be the case. As far as this author is aware, the evidence that associates Craw with the Rh system is somewhat circumstantial and the association has yet to be proved at the genetic level. The first piece

*It should be noted that the references cited are to papers in which the antigens were assigned numbers and not, with the exception of Rh39, to papers in which discovery of the antigens was described.

of evidence that suggested that Craw might be part of the Rh system was that two lots of a licensed anti-D typing reagent gave positive reactions with several known D^u– samples by IAT. The responsible antibody (anti-Craw) in the anti-D was isolated and the antigen defined was shown to be present in a little fewer than one in 1,000 blacks in the southeastern United States.[14] The second piece of evidence to associate Craw with the Rh system was that many but not all Craw + samples found came from persons who had inherited r^S (J. J. Moulds, personal communication, and S. L. Wilkinson and P. D. Issitt, unpublished observations, 1980 and 1981). No consistent pattern of V and VS status on Craw + red cells could be seen. In spite of this somewhat tenuous evidence, Craw was assigned the number Rh43 in 1985.[13]

Rh17(Hr_o), Rh18(Hr), and Rh34

Although the three antigens listed above are not new, mention of some of their characteristics is necessary before Rh44, Rh46, and Rh47 can be described. As early as 1958, Allen and Corcoran[15] recognized that when *D-deletion* homozygotes become immunized, the most potent antibody that they make is often one directed against Hr_o, an antigen present on all red cells of "common" Rh phenotype, eg, R_1R_1, R_2R_2, rr.[16] Sequential adsorption-elution steps can be used to render anti-Hr_o free of anti-e, anti-c, etc. When the blood of Mrs. Shabalala was studied by Shapiro,[17] it was shown that her red cells would adsorb anti-Hr_o from the sera of immunized D-deletion persons but that they left unadsorbed a second antibody that also reacted with all "common" Rh phenotype red cells. The red cells of Shabalala were said to be Hr_o +, Hr–; the antibody not adsorbed by her red cells was called anti-Hr (Mrs. Shabalala herself made anti-Hr/hr^S.) In 1979, when we[6] restudied the antibody made by Mrs. Bastiaan,[18] we showed that D-deletion red cells are Rh:–34, in addition to being Rh:–17,–18. For a number of years, it seemed that the genes *D––*, *Dc–*, and *DC^W–* all fail to encode Rh17, Rh18, and Rh34, and that the immune response in individuals homozygous for those genes involved production of anti-Hr_o, -Hr, and -Rh34 in variable amounts, and sometimes the production of separable antibodies directed against C, c, E, e, f, hr^S, etc, as well. As will become apparent from the descriptions of Rh44, Rh46, and Rh47, the situation is not even that simple!

Rh44(Nou)

In 1969, Salmon et al[19] described an individual (Madame Nou) who was homozygous for a new *D-deletion* gene, *$D^{IV}(C)$–*. It was shown that the gene makes D, Go^a, and a weak form of C. In 1981, Perrier et al[20] described a study that included tests against the red cells of Madame Nou that suggested that some antibodies made by *D-deletion* homozygotes might recognize a high-frequency antigen or antigens in addition to Hr_o, Hr, and Rh34. Later in the same year, Habibi et al[21] published the definitive study. It was shown that although *$D^{IV}(C)$–* does not make Hr_o or Hr, it does make a very common antigen, the antibody to which is present in a minority of sera from immunized *D-deletion* homozygotes. Table 1 shows the results of the tests described by Habibi et al[21] in which they used antibodies made by D-deletion individuals and red cells of D-deletion and Rh_{null} phenotypes. The antibodies were adsorbed onto and eluted from R_2R_2 red cells to free them of separable anti-e. They were then used in titration studies against the red cells of ten persons with common Rh phenotypes, and four who were D––/D––, two who were Dc–/Dc–, Madame Nou ($D^{IV}(C)$–/$D^{IV}(C)$–), and one who was Rh_{null}. As the results in Table 1 show, five of the eluates contained only anti-Hr_o/Hr, since they reacted with all common phenotype red cells but not with those of D-deletion or Rh_{null} phenotypes. The fact that the red cells of Madame Nou failed to react with these antibodies confirmed that *$D^{IV}(C)$–* does not make Hr_o or Hr. The two eluates that did react with the red cells of Madame Nou (numbers 1 and 4 in Table 1) clearly contained another antibody defining an antigen made by *$D^{IV}(C)$–* but not by the other *D-deletion* genes. Since it was known by then that *$D^{IV}(C)$–* makes Go^a (Rh30), Rh33, and Rh45 (for references, see next section) it was possible that the additional antibody was directed against one of those antigens. Adsorption studies quickly eliminated that possibility. The antibody activity in both eluates was adsorbed to exhaustion using red cells of common Rh phenotypes that were Rh:–30,–33,–45. The same eluates were adsorbed with $D^{IV}(C)$–/$D^{IV}(C)$– red cells until they no

Table 1. Titer scores of eluates from R_2R_2 red cells from antibodies made by D-deletion homozygotes in tests against red cells of deletion phenotypes (from Habibi et al)[21]

Test red cells	Antibody made by						
	D––/D––				Dc–/Dc–		$D^{IV}(C)$–/$D^{IV}(C)$–
	1	2	3	4	5	6	7
Common Rh phenotypes (10 samples)	65–72	8–13	21–41	34–42	35–47	26–35	34–39
Dc–/Dc–	0	0	0	0	0	0	0
Dc–/Dc–	0	0	0	0	0	0	0
$D^{IV}(C)$–/$D^{IV}(C)$–	55	0	0	13	0	0	0
D––/D––	0	0	0	0	0	0	0
D––/D––	0	0	0	0	0	0	0
D––/D––	0	0	0	0	0	0	0
D––/D––	0	0	0	0	0	0	0
Rh_{null}	0	0	0	0	0	0	0

longer reacted with those cells. After absorption with the $D^{IV}(C)-/D^{IV}(C)-$ red cells, the eluates reacted with all cells of common Rh phenotype, showing that the anti-Hr_o/Hr and additional antibody in the eluates were separable. Thus it was clear that the new antigen, Nou (later given the designation Rh44),[13] is made by all common *Rh* genes (red cells of common Rh phenotypes adsorbed the anti-Hr_o/Hr and anti-Rh44 activity)[13] and by *$D^{IV}(C)-$* (the red cells of Madame Nou adsorbed anti-Rh44 but not anti-Hr_o/Hr), but not by *D*–– or *Dc*– (red cells from persons with those genes were non-reactive with the two eluates that contained anti-Rh44), Table 1.

Later in this review, the probable antithetical relationship between Rh46 and Rh32 will be described. In addition, it is possible that two new antibodies currently under study (see summary) define antigens antithetical to Rh33 and Rh9(C^X). For this reason, it is important to appreciate that Rh44 cannot be antithetical to any low-incidence antigen (Go^a, Rh33, Rh45) made by *$D^{IV}(C)-$*. Instead, Rh44 is encoded by all common *Rh* genes and by *$D^{IV}(C)-$*. Madame Nou is immunized and her serum contains at least anti-Hr_o and/or anti-Hr (see Table 1). G. L. Daniels (personal communication 1986) has pointed out that her serum might also contain an antibody that defines an as yet unrecognized, low-incidence antithetical partner to Rh44. Studies to investigate such a possibility have not yet been reported.

Rh45(Riv)

The first known example[22] of anti-Riv (later assigned the designation anti-Rh45)[13] caused mild hemolytic disease of the newborn. The antibody was made by a Cuban woman who, like her Cuban husband, came from a family with known black admixture. When Mrs. Riv was delivered of her second child, it was found that the red cells of the infant had a positive DAT. The maternal serum and an eluate made from the cord blood red cells contained an antibody that reacted strongly with the red cells of the infant's father but not with other samples (the maternal anti-Le^a played no role in the HDN and will not be considered further). Rh phenotyping tests on the red cells of the mother, her husband, and the infant at first appeared to exclude the husband from paternity. Based on the most simple interpretation of such tests, the trio appeared to be *R^or* (mother), *$R^{1W}R^1$* (husband), *R^or* (child). However, there was no other evidence to exclude the husband from paternity, and the fact that his red cells carried the same low-incidence antigen as those of the child, as defined by the antibody in the maternal serum, made an exclusion highly unlikely. Additional phenotyping studies yielded the results shown in Table 2. As can be seen, the father had passed an *Rh* gene making Go^a and Rh33, and a very weak form of C, to his child. The child did not inherit the paternal gene that encodes C^w. The lower portion of Table 2 shows a genetic interpretation of the family.

Tests on the maternal serum showed the presence of anti-Go^a and the antibody defining Rh45. Separation of anti-Go^a from anti-Rh45 was accomplished by adsorption with Go(a+), Rh:–45 red cells. The maternal serum did not contain anti-C^w or anti-Rh33; later studies showed that the couple's first child had also inherited the paternal *$D^{IV}(C)-$* that encodes Go^a, Rh33, and Rh45, but not C^w. Tests on the eluate made from the cord blood red cells showed the presence of strong anti-Rh45 (4+ IAT reactions with all red cells from persons known to have inherited *$D^{IV}(C)-$*) and weak anti-Go^a (1+ IAT reactions with Go(a+), Rh:–45 red cells). Thus, it seemed that the mild HDN (the infant recovered without transfusion) was caused predominantly by anti-Rh45, with anti-Go^a playing only a minor role despite the fact that both antibodies gave 4+ IAT reactions when the maternal serum was tested.

A number of red cell samples from persons who had inherited *$D^{IV}(C)-$* were available for testing. The maternal serum was adsorbed free of anti-Go^a and was then shown to react strongly with the red cells of Madame Nou *($D^{IV}(C)-/D^{IV}(C)-$)* and with those of individuals genetically *$D^{IV}(C)-/r$*, *$D^{IV}(C)-/R^2$*, and *$D^{IV}(C)-/R^o$*.

During this study[22] and those in Paris on the blood of Madame Nou,[20,21] it was noticed that *$D^{IV}(C)-$* encodes Rh33 in addition to Go^a(Rh30) and Rh45(Riv). The Paris workers (C. Salmon, personal communica-

Table 2. Extended Rh phenotyping studies on the red cells of members of the Riv family*

Family member	Rh phenotype
Mrs. A.R. (Mother)	D+, C–, c+, E–, e+, C^w–, Go(a–), Rh:–33,–45. Lack of C proved by adsorption-elution studies.
Mr. S.R. (Father)	D+, C+, c–, E–, e+, C^w+, Go(a+), Rh:33. Positive for the new Rh antigen defined by the maternal antibody, ie, Rh:45. Lack of c proved in adsorption-elution studies.
A.R. (Infant)	D+, C– in direct tests, c+, E–, e+, C^w–, Go(a+), Rh:33,45. Presence of weak C and lack of C^w proved in adsorption-elution studies. Presence of Rh45 confirmed by recovery of anti-Rh45 from the DAT+ cord blood red cells.
Genetic interpretations of above phenotypes	
Mrs. A.R. (Mother)	*R^o/r*
Mr. S.R. (Father)	*$R^{1W}/D^{IV}(C)-$*
A.R. (Infant)	*$R^o/D^{IV}(C)-$*

**Note:* Some of these data included in poster but not abstract of reference 22.

tion 1982) found that red cells from persons with $D^{IV}(C)-$ also reacted with a serum used there that was thought to contain only anti-Rh32. In Cincinnati (S. L. Wilkinson and P. D. Issitt, unpublished observations 1982) and in London (P. Tippett and C. Lomas, personal communication 1982) those red cells were non-reactive with all available examples of anti-Rh32. This discrepancy, which may indicate the presence of yet another low-incidence antigen made by $D^{IV}(C)-$, has not yet been resolved.

The gene $D^{IV}(C)-$ is thus unique in that it encodes at least three rare Rh antigens, Go^a, Rh33, and Rh45. The red cells of the father of infant Riv are also unique in that they carry C^W (made by his R^{1W} gene) in addition to Go^a, Rh33, and Rh45.

Rh46(Sec)

The $\bar{\bar{R}}^N$ gene was first described by Rosenfield et al[23] in the now famous Charlie By. family. The gene encodes such a weak form of C that the presence of that antigen can be overlooked if the pe on on whose red cells it is present has a paired R^{-z} gene. Some years after $\bar{\bar{R}}^N$ had been described, Chown et al[24,25] reported that, in addition to its other actions, $\bar{\bar{R}}^N$ encodes the low-incidence antigen Rh32. There are now a fair number of antibodies known, that have been made by individuals who seem to be genetically $\bar{\bar{R}}^N\bar{\bar{R}}^N$; what may have been the first recognized example (Sec) was mentioned briefly by Chown et al[26] in 1972. The examples most fully studied in our laboratory were in the sera Coul (kindly supplied by Dr. Salmon from Paris) M-J.F. (kindly supplied by Ms. Mary Anne McDowell from Columbus, Ohio) and V.Q. (kindly supplied by Mr. W. Michael Tregallas from Scottsdale, Arizona). At the 1986 Sydney meeting of the ISBT working party, Dr. Phillipe Rouger mentioned that the Paris workers have a paper in press, describing many examples of this antibody; these authors have not yet seen that paper.

The antibody, that was named anti-Rh46 in Sydney reacts with all red cells of common Rh phenotype, and with many of unusual phenotype (Shabalala-type; Dc(e)/Dc(e), Rh:33; DC^Xe/DC^Xe; etc). It does not react with D-deletion or Rh_{null} red cells or with those from persons homozygous for $\bar{\bar{R}}^N$. Anti-Rh46 differs from anti-Hr_o/Hr by failing to react with the red cells of $\bar{\bar{R}}^N$ homozygotes that appear to be Hr_o+, Hr+. The authors presume, but do not know for sure, that differentiation between anti-Rh44 and anti-Rh46 has been made on the basis of adsorption studies. If $\bar{\bar{R}}^N$ encodes Hr_o, Hr and Rh44, it would be expected that red cells from an $\bar{\bar{R}}^N$ homozygote would adsorb to exhaustion a serum from an immunized D-deletion individual that contained all three antibodies (see section on Rh44 and Table 1). The red cells of $\bar{\bar{R}}^N$ homozygotes do not, of course, adsorb anti-Rh46.

Perhaps the most exciting aspect of Rh46 is the possibility that it may have some sort of antithetical relationship to Rh32. $\bar{\bar{R}}^N$ encodes the rare antigen Rh32; persons who are genetically $\bar{\bar{R}}^N\bar{\bar{R}}^N$ have red cells that are Rh:32,–46. Although there is no complete agreement as yet about the exact nature of the red cell membrane structure that carries the Rh antigens, there is some good evidence[27–33] that the component is (are) a non-glycosylated polypeptide(s). It is not at all unreasonable to suppose that the same amino acid substitution(s) that give(s) rise to the rare antigen Rh32, result(s) in the absence of Rh46. Individuals homozygous for $\bar{\bar{R}}^N$ would then have Rh32 on both polypeptides on which that antigen is carried, and would have Rh:–46 red cells. When exposed to Rh:46 red cells by transfusion or pregnancy, such individuals might be expected to mount an immune response to that antigen. It seems that this describes exactly the circumstances in which anti-Rh46 has been made. It is also entirely possible that the same amino acid substitution(s) that result(s) in the presence of Rh32 cause(s) a steric rearrangement of the polypeptide so that C and e become less available to complex with their antibodies. A characteristic of the presence of $\bar{\bar{R}}^N$ is that the individual's red cells carry reduced levels of e and difficult-to-detect C if the paired gene does not make those antigens. As mentioned in the summary, it is possible that two other antibodies currently under study are to Rh33 and $Rh9(C^X)$ what anti-Rh46 is to Rh32.

In considering possible antithetical relationships in the Rh system, it must be remembered that such relationships are not totally straightforward all the time. When common *Rh* genes are considered, *C* and *c*, and *E* and *e* behave as pairs of alleles so that C and c, and E and e appear to be antithetical pairs of antigens. Exceptions are seen. The genes *D*–– and *D··* do not make C, c, E, or e. The genes *Dc–*, DC^W- and $D^{IV}(C)-$ do not make E or e. The gene r^S makes both c and some C or C^G. For a review of different interpretations, see reference 34.

Rh47(Dav)

The antigenic products of *D*–– and *D··* are similar enough that before 1978 it was difficult to distinguish between presence of the genes. This problem was overcome when Contreras et al[35,36] showed that *D··* encodes the low-incidence antigen Rh37(Evans), while *D*–– does not. In 1982, Daniels[37] showed that *D··* is somewhat like $D^{IV}(C)-$ in that it makes an antigen of very high incidence that is not made by *D*–– or *Dc–*. Table 3 lists some of the results presented by Daniels.[37,38] As can be seen, of 25 sera from immunized D-deletion individuals, each of which contained anti-Hr_o and/or anti-Hr (reactions with red cells of common phenotypes), 21 failed to react with D-deletion and D··/D·· red cells. This of course confirmed that *D··* does not make Hr_o or Hr. The other four sera, one each from immunized D––/D––, D––/–––, Dc–/Dc–, and DC^W-/DC^W- individuals, reacted

Table 3. Reactions of sera from immunized *D-deletion* homozygotes in tests against red cells of deleted Rh phenotypes (from Daniels)[37]

Phenotype of antibody-maker	Number of sera giving these reactions	Test red cells			
		Normal Rh phenotype	D−−/D−−	D··/D··	Rh_{null}
D−−/D−−	15	+	0	0	0
D−−/D−−	1	+	0	+	0
D−−/−−−	1	+	0	+	0
Dc−/Dc−	2	+	0	0	0
Dc−/Dc−	1	+	0	+	0
DC^W−/DC^W−	2	+	0	0	0
DC^W−/DC^W−	1	+	0	+	0
D^{IV}(C)−/ D^{IV}(C)−	1	+	0	0	0
D··/D··	1	+	0	0	0

with all red cells of common phenotype and with the D··/D··, but not with other D-deletion, nor with Rh_{null} red cells. It was apparent that these sera contained additional antibody activity that defined an antigen present on D··/D·· but not on D−−/D−− red cells. Since *D··* encodes Rh37, it was necessary to show that the additional antibody was not anti-Rh37. This was accomplished by adsorption studies. Red cells of common Rh phenotypes that were Rh:−37 adsorbed all antibody activity from the sera. D··/D·· red cells adsorbed all activity for red cells of that phenotype and left the anti-Hr_o/Hr unadsorbed. In other words, the newly defined antigen Dav, later assigned the term Rh47 (ISBT working party, Sydney 1986, report not yet published), is encoded by all common *Rh* genes (red cells of common phenotypes adsorb anti-Hr_o/Hr and anti-Rh47) and by *D··* (red cells from an individual homozygous for that gene adsorb anti-Rh47 but not anti-Hr_o/Hr). Rh47 is not made by *D−−* (red cells from individuals homozygous for that gene are nonreactive with the sera that contain anti-Rh47) and probably not by *Dc−* or *DC^W−* (one example each of anti-Rh47 made by *Dc−* and *DC^W−* homozygotes). As expected, Rh47 is not present on Rh_{null} red cells. Daniels[37] also showed that a serum that contained anti-Hr_o and/or anti-Hr and anti-Rh47 still reacted with D^{IV}(C)−/D^{IV}(C)− red cells after it had been adsorbed with D··/D·· red cells until it no longer reacted with such cells. This showed that anti-Rh47 was different from anti-Rh44 (ie, anti-Rh47 removed, serum still reactive with Rh:44 (Nou) red cells). In the report Daniels says that "anti-Nou" (now anti-Rh44) "may contain anti-Dav" (now anti-Rh47). The above test seems to suggest that the serum that contained anti-Hr_o and/or anti-Hr and anti-Rh47 also contained anti-Rh44 (anti-Nou). That is, the serum rendered free of anti-Rh47 by adsorption with D··/D·· red cells still reacted with Rh:44 (D^{IV}(C)−/D^{IV}(C)−) cells, although *D^{IV}(C)−* is known not to make Hr_o or Hr.

The study of Daniels[37] also showed that Rh37(Evans) and Rh47(Dav) are not antithetical since both are encoded by *D··*. G. L. Daniels (personal communication, 1986) has pointed out that the serum of an immunized *D··* homozygote may contain an as yet unrecognized antibody to a low incidence antithetical partner of Rh47, in addition to its known anti-Hr_o and/or anti-Hr content.

Other Possible "New" Rh Antigens

As described, Rh44, Rh45, Rh46, and Rh47 seem to be established as distinct Rh system antigens; more work is required for Rh43 to achieve a similar status. We are aware that a number of additional sera that may contain antibodies to still more "new" Rh antigens are currently under intense scrutiny in different laboratories around the world. Our own current investigations involve a number of such sera. We are studying three examples of an antibody that may define a very common antigen that bears an antithetical relationship to Rh33, similar to the relationship between Rh46 and Rh32. In addition, we are investigating possible heterogeneities of both anti-Rh29 and the D−−/D−− phenotype. The antibody made by C.M., as described in an abstract by Mougey et al,[39] might recognize an antithetical partner of Rh9(C^X). We have also heard of one other low-incidence antigen that may be a part of the Rh system. As can be seen from the above descriptions of Rh44, Rh46, and Rh47, it is now very difficult to be certain that an apparently new antibody to a very common Rh antigen is different from those directed against Hr_o, Hr, Rh29, Rh34, Rh39, Rh44, Rh46, and Rh47, already characterized. Careful adsorption studies are essential and even then the adsorbed sera must be tested against very rare, red cell samples, such as those from *D^{IV}(C)−*, *D··* and *$\bar{R}^N$* homozygotes. If work currently in progress shows that some of these antibodies do indeed define additional Rh antigens, another review similar to this one will be prepared.

Finally, in addition to the assignment of new Rh numerical terms, two numbers have been declared obsolete. The ISBT working party has agreed (Sydney, 1986) that because the genes that encode their production are known not to reside at the *Rh* locus, the antigens previously called Rh25(LW) and Rh38(Duclos) will not be considered part of the Rh system. The numbers Rh25 and Rh38 will be retired and will not be reassigned to new antigens. Their re-use for different antigens would obviously cause confusion. Since their production is also controlled by genes[40–42] at a locus independent of *Rh,* the antigens LW^b(Ne^a) and LW^{ab} will not receive Rh numbers.

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STIMULATION OF ANTIBODY FOLLOWING ^{51}CHROMIUM SURVIVAL STUDIES

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Abstract

The survival of red blood cells (RBCs) radiolabeled with ^{51}chromium (^{51}Cr) is a reliable method for predicting transfusion compatibility. Approximately 1.0 ml of ^{51}Cr tagged RBCs is infused into the patient and samples are drawn at predetermined intervals post infusion to determine RBC survival. Red cells used for the study are usually incompatible with the patient's