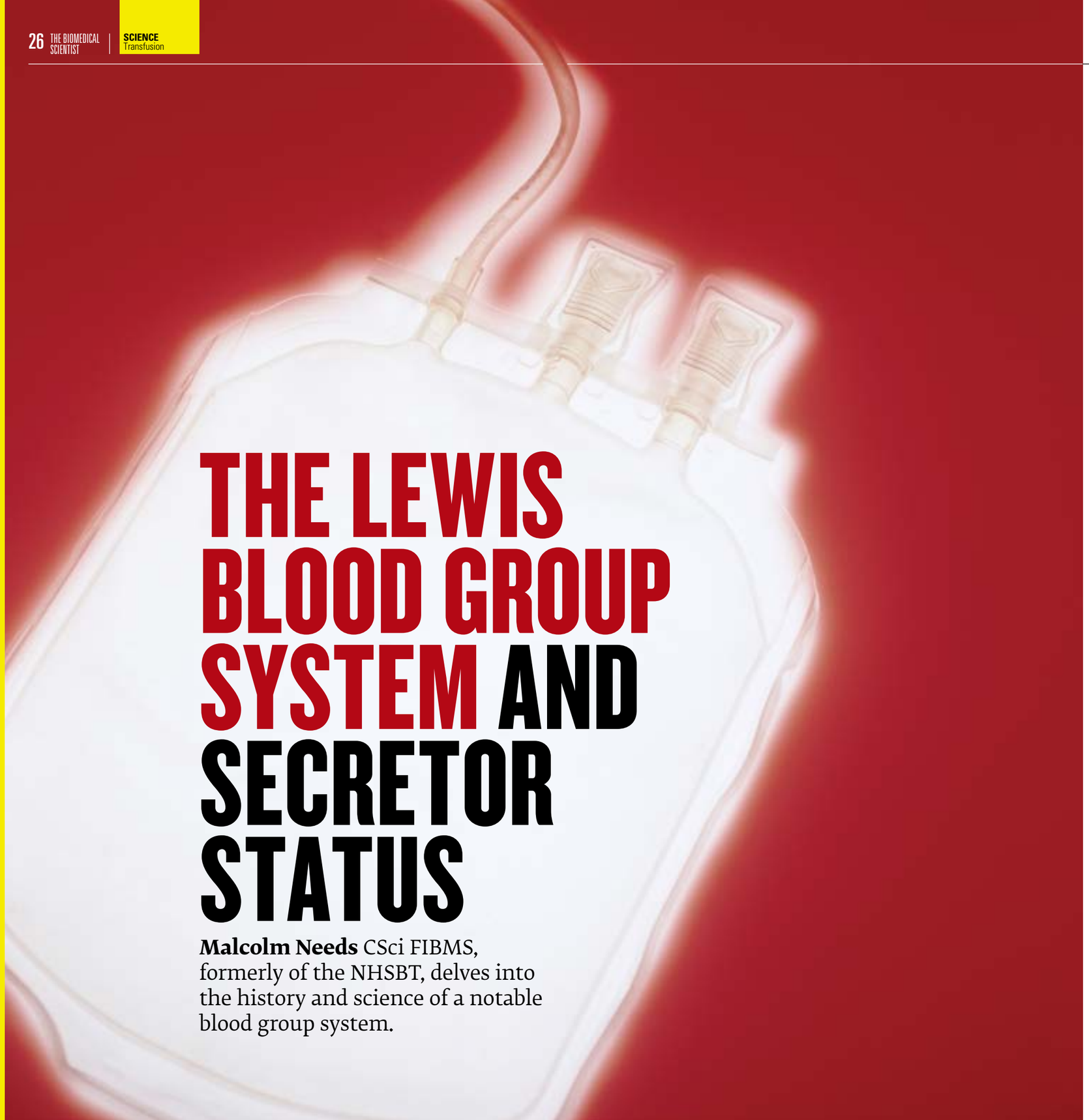

THE LEWIS BLOOD GROUP SYSTEM AND SECRETOR STATUS

Malcolm Needs CSci FIBMS, formerly of the NHSBT, delves into the history and science of a notable blood group system.

Le^a was first described in 1946 by Mourant, when it was named L.

Le^b was first described in 1948 by Andresen.

In 1955, Sneath and Sneath observed that red cells lacking Le^a and Le^b will take up these antigens from plasma containing them. Equally, red cells expressing either Le^a or Le^b will give these up to plasma lacking them. In other words, the antigens were found to be soluble.

Between 1948 and 1951, Grubb and Brendemoen independently observed that the saliva of Le(a+b-) individuals strongly inhibited anti-Le^a, and that the saliva of the majority of Le(a-b+) individuals also inhibited anti-Le^a, but did so less strongly.

In 1963, Mollison *et al* demonstrated that this phenomenon also occurred *in vivo*.

From this it can be seen that:

- Lewis antigens are not intrinsic to red cells.
- They are located on type 1 glycosphingolipids that are adsorbed onto the red cells from the plasma.
- Lewis, therefore, is not strictly speaking, a red cell blood group!

Genotypes and phenotypes and their relationship with the Secretor gene

At a basic level, if you do not inherit a Lewis gene (*LE*, or, as it is now named, *FUT3*), whether you inherit a Secretor gene (*SE*, or, as it is now named, *FUT2*) of not, you will be Le(a-b-). if you do inherit a Lewis gene, but you do not inherit a Secretor gene, you will be Le(a+b-). If you inherit a Lewis gene, and you inherit a Secretor gene, you will be Le(a-b+) (see Table 1).

That having been said, the Secretor gene actually defines whether an individual secretes A, B and/or H Substance (Type 1 A, B and/or H substance) in saliva and other body fluids, rather than directly to do with the Lewis types.

It will be noted that there is no Le(a+b+) shown in Table 1, and the reason for this will be explained below.

The genes

The locus for the gene coding for *LE/FUT3*, has been mapped to 19p13.3.

It was soon realised that there was an interaction between the *LE/FUT3* gene and the *SE/FUT2* gene (see Table 1).

The locus for the gene coding for *SE/FUT2* is also found at 19p13.3, but, although they are mapped to the same chromosome, *LE/FUT3* and *SE/FUT2* segregate independently.

The Lewis carrier molecule

As stated earlier, the Lewis antigens are not an integral part of the red cell membrane, but are plasma soluble molecules. They are also carbohydrate-

LE/FUT3 Genotype	*SE/FUT2* Genotype	Red Cell Lewis Type	ABH Secretor Status
le/le	*se/se*	Le(a-b-)	No
le/le	*SE/se*	Le(a-b-)	Yes
le/le	*SE/SE*	Le(a-b-)	Yes
LE/le	*se/se*	Le(a+b-)	No
LE/LE	*se/se*	Le(a+b-)	No
LE/le	*SE/se*	Le(a-b+)	Yes
LE/le	*SE/SE*	Le(a-b+)	Yes
LE/LE	*SE/se*	Le(a-b+)	Yes
LE/LE	*SE/SE*	Le(a-b+)	Yes

Table 1. The interaction between the *LE/FUT3* gene and the *SE/FUT2* gene, and their influence on the Lewis phenotype.

based molecules, and so, like the A, B and H antigens, they are not direct gene products. The gene products are α-1-4-fucosyltransferase (*LE/FUT3*) and α-1-2-fucosyltransferase (*SE/FUT2*). The *SE/FUT2* direct gene product cannot function, unless the *LE/FUT3* direct gene product is present (rather in the same way that the A and B gene products cannot function, unless the *H* gene product is present and functioning.

A schematic of the two carrier molecules can be seen in Figure 1.

There are six antigens recognised by the International Society of Blood Transfusion (ISBT) within the Lewis Blood Group System. These can be seen in Table 2.

Le^a	Le^b	Le^{ab}
Le^{bH}	ALe^b	BLe^b

Table 2. The antigens of the Lewis Blood Group System.

Lewis phenotype frequencies

The normal figures for Lewis types can be seen in Figure 2; however, for various reasons, such as infancy and pregnancy (see below for explanations), such figures should only be taken as true for individuals from the age of approximately two and upwards, and who are not pregnant.

Lewis antigens in newborns and infants

Most newborn babies type as Le(a-b-) for the first month of their life, as the production of Lewis fucosyltransferase is at very low levels. If they are going on to eventually become Le(a-b+), they will, for a time, type as Le(a+b-), as the production of Lewis fucosyltransferase becomes active before Secretor fucosyltransferase. For a very short time, they may type as Le(a+b+), before they become Le(a-b+). By one year of age, 50% of children express their adult phenotype, and by two years of age, the Lewis phenotype of most children will reflect their *SE/FUT2* and *LE/FUT3* alleles.

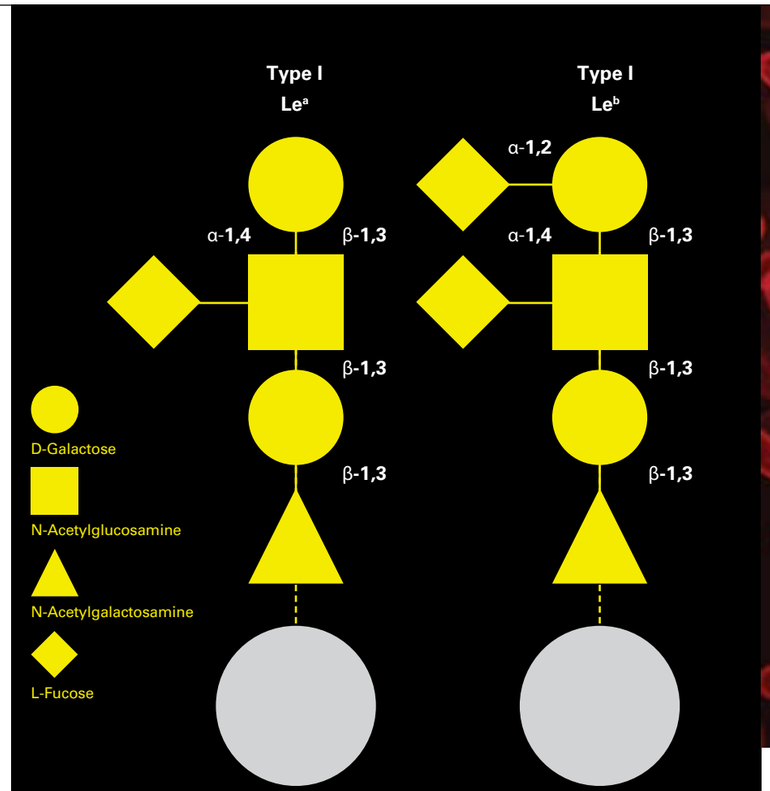

Figure 1. The Le^a and Le^b Antigen Carrier Molecules (Note that these carrier molecules are NOT an integral part of the red cell membrane) (after Race and Sanger).

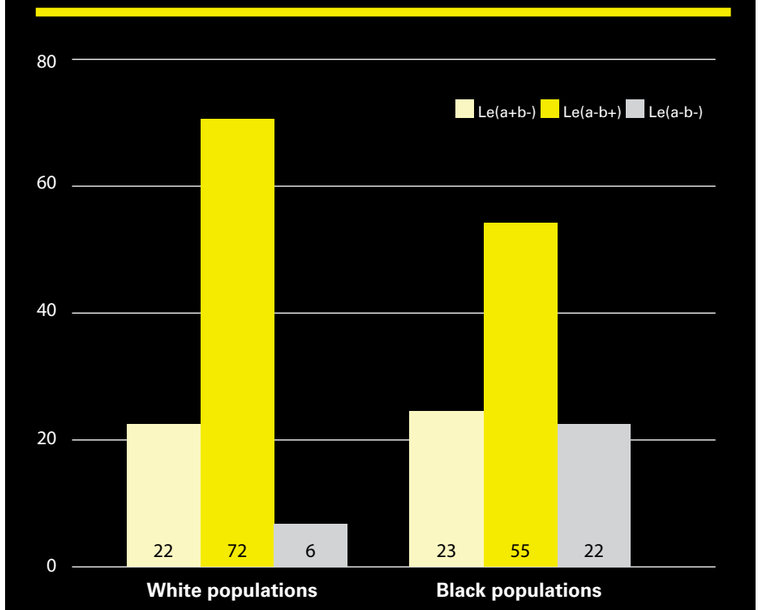

Figure 2. Lewis phenotypes[8].

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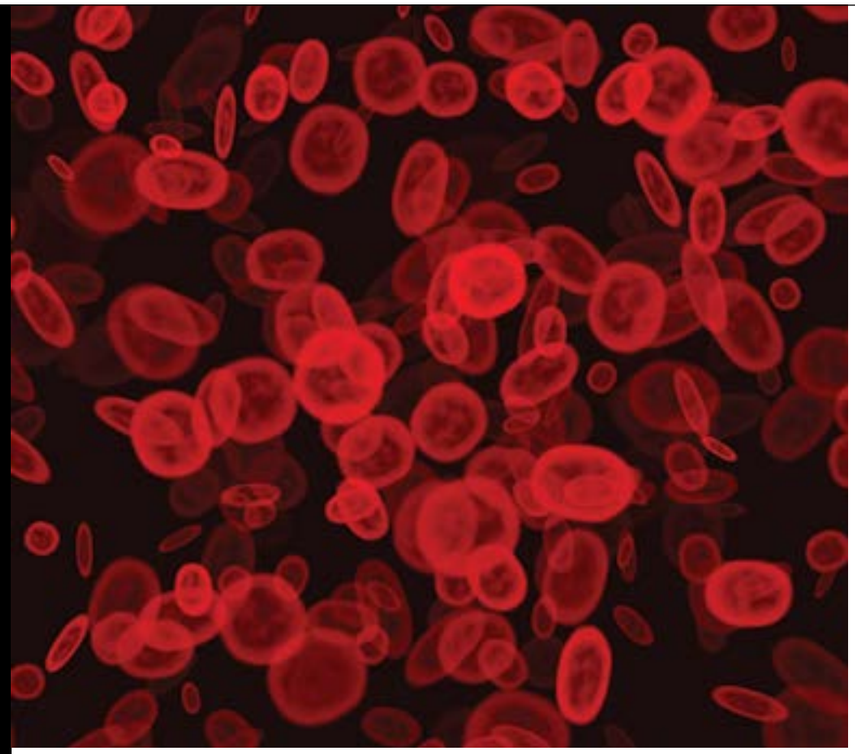

Lewis Type of the recipient prior to the bone marrow/stem cell transplantation	Lewis Type of the bone marrow/stem cell transplantation	Lewis Type of the recipient after successful bone marrow/stem cell transplantation
Le(a-b-)	Le(a-b-)	Le(a-b-)
Le(a-b-)	Le(a+b-)	Le(a-b-)
Le(a-b-)	Le(a-b+)	Le(a-b-)
Le(a+b-)	Le(a-b-)	Le(a+b-)
Le(a+b-)	Le(a+b-)	Le(a+b-)
Le(a+b-)	Le(a-b+)	Le(a+b-)
Le(a-b+)	Le(a-b-)	Le(a-b+)
Le(a-b+)	Le(a+b-)	Le(a-b+)
Le(a-b+)	Le(a-b+)	Le(a-b+)

Table 3. Lewis Types of recipients and donors of bone marrow/stem cell transplantation, and the resultant recipient Lewis Type following successful transplantation.

Lewis antigens in pregnancy

It has been known for many years that pregnant women may become transiently Le(a-b-) and may even produce Lewis antibodies. It was originally thought that pregnant women produced less Lewis glycolipid, but it is now thought that this is not so. Hammar *et al* put forward the theory that the increased incidence of the Le(a-b-) phenotype during pregnancy may be a result of increased concentration of plasma lipoproteins during pregnancy. In pregnant women, the ratio of lipoprotein to red blood cell mass increases more than four-fold, so that much more Lewis glycolipid is attached to plasma lipoprotein than is available for the red blood cell surface.

The Le(a+b+) phenotype in adults

In truth, in almost every case of the phenotype Le(a-b+), a small amount of Le^a antigen can, in fact, be detected.

The frank Le(a+b+) phenotype in Polynesian adults is, however, quite common (~40%). This is due to a weak or mutated Secretor status.

Lewis phenotypes following transplantation

As has been mentioned above, Lewis antigens are not produced as an integral part of the red cell membrane, but are adsorbed onto the red cell membrane. In 1986 and 1987, Myser *et al* and Needs *et al* independently observed that the Lewis antigens always remain of the recipient type after bone marrow transplantation.

Following successful bone marrow/stem cell transplantation all red cell antigens that are integral to the red cell membrane (*i.e.* are produced in the bone marrow) change from that of the recipient, to that of the donor, although, of course, these are sometimes identical. However, those that are not integral to the red cell membrane (i.e. are produced remote from the bone marrow) remain as the antigen type of the recipient. These include the soluble A, B and H antigens, the Lewis antigens and the antigens within the Chido/Rodgers Blood Group System.

In the case of the Lewis antigens, the final Lewis phenotypes can be seen in Table 3.

Lewis antibodies

IgM anti-Le^a is more frequent than IgG. IgG anti-Le^a can cause a haemolytic transfusion reaction, albeit very rarely and self-limiting, as the Le^a antigen elutes from the transfused red cells and the anti-Le^a is then inhibited by this eluted antigen.

Anti-Le^a has only been reported once as causing mild HDFN.

IgM anti-Le^b is more frequent than IgG. IgM and IgG anti-Le^b were thought to be clinically benign, but there has been a recent report of an acute haemolytic transfusion reaction due to anti-Le^b.

There has been one (dubious) report of mild HDN caused by anti-Le^b.

There is some evidence that Lewis antibodies may be involved in renal transplant rejection, but the evidence is slight and the theory controversial. IBMS

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To see the references, view the article online at **thebiomedicalscientist.net**