THE LEWIS SYSTEM*

Mogens Hauge, M.D.**

In 1946, Mourant detected a new antibody which seemed to define an antigen of red cells having no relation to the ABO, MN or Rh blood group systems. This discovery opened a fascinating new chapter in serological and biochemical genetics. The antibody was denoted anti-Le^a, and the red cell antigen with which it was supposed to react was denoted Le^a. Family studies indicated that the characteristic was recessive - something new to serological genetics - but the accumulation of inexplicable facts forced a reconsideration of the theory.

Family studies based on the use of suitable anti-Le^a sera and red cells have produced results supporting the theory that the Le^a red cell character behaves like a Mendelian recessive character. A few exceptions appear, but the theory is still essentially correct. It should be stressed, however, that we are determining only to a limited extent the effects of the true Lewis genes in this way.

The main steps leading to the synthesis of the Lewis system, the ABH secretor system, and the ABO system are worth restating as they support the entire logical structure. First, Grubb, a Swedish serologist, was able to show that Le (a+) red cells belong to ABH non-secretors, and that Le (a—) red cells belong to ABH secretors in almost all instances. These statements still hold true, with extremely few exceptions.

The second step was the discovery that 90 per cent of unrelated Swedes had Le^a substance in their saliva. The relationship of this characteristic with the supposed red cell Lewis group is as follows : Le (a+) individuals are strong secretors of Le^a substance; Le (a-) individuals in most cases, secrete Le^a substance, but more weakly.

The third step was the finding of Le^a substance in the *serum* of Le (a+) individuals and the absence of such a substance in Le (a-) individuals. The relationship is summarized as follows :

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* From the Institute of Human Genetics, Copenhagen, Denmark.
** Director, Institute of Human Genetics, Copenhagen, Denmark.

Red cell reaction	Serum	Saliva
Le (a+)	always contains Le^a substance	always contains great amounts of Le^a substance
Le (a—)	contains very little or no Le^a substance	sometimes contains small amounts of Le^a substance sometimes none.

Finally, it could be demonstrated in various ways that the Le^a antigen of the red cells could be removed and red cells without the Le^a antigen could, irrespective of the individual's genotype, take up Le^a substance from the serum. Thus the Lewis antigen in the red cell cannot be considered to be determined directly by genetics, but is, rather, passively *acquired*. This system is not comparable to other blood group systems and is more like a combination of a serum group system and a secretor system.

The time had now come to reconsider a theory first suggested by Grubb in 1951, but which had not been accepted at that time because of lack of factual support. Evidence in support of the theory came in the demonstration of the transformation of the Lewis groups of the red cells and the presence of the Lewis antigen in serum and saliva. Careful family studies, combining the investigation of ABH blood groups and secretion, Lewis secretion and the so-called Lewis «blood groups», mainly carried out by Cepellini, proved Grubb's original theory to be largely correct.

Perhaps the main lead to a new concept was the lack of any kind of association between ABH secretion and the Lewis system according to saliva studies. The only association discovered was that between ABH secretion and the presence or absence of Le^a antigen or substance on the red cells.

The true Lewis locus contains two alleles, Le and le. The Le gene is dominant and controls the presence of Le^a substance in the saliva. There is no evidence of genetic linkage between the Le-le locus and Se-se locus, but they do interact in some ways. Possible interactions are shown in the following chart.

The amount of Le^a substance in the serum is much higher when ABH is no tsecreted (provided the individual has the Le gene) and explains the reactions of the red cells. The amount is high enough to make the red cells acquire the Le^a character.

	Saliva		
	presence of ABH	Le^a	Red cell reactions
SeSe LeLe SeSe Lele Sese LeLe Sese Lele	+	+ Les	Le (a—) (a— b+)
sese LeLe sese Lele	—	+ Les	Le (a+) (a+ b—)
SeSe lele Sese lele	+	— nL	Le (a—) (a— b—)
sese lele	—	— nL	Le (a—) (a— b—)

One new point—inconsistent with the older theory of the recessivity of the Le^a red cell character—is that Le (a+)∼Le (a+) matings would occasionally produce Le (a—) children. If the parents were sese Lele and sese Lele, 25 per cent of the children would be sese lele. Such families have been reported.

The Le-le locus does not seem to be closely linked with the Se-se locus, and may even be on a separate chromosome. The Lutheran and ABO loci also appear to be some distance from the Le-le locus.

To sum up, the effect of the three loci mentioned does not seem to be to synthesize slightly different macromolecules, but rather to determine the serological and genetic specificity of the macromolecules. The final product, the detectable antigen, is attained after a series of metabolic steps which are controlled by the loci mentioned here. The place of Le^b in the system is controversial. It is known that two types of anti-Le^b sera exist, increasing the complexity of the situation, even more so because Grubb worked with one type and Cepellini with another, although this was not apparent in the main phase of their work.

The so-called antigen Le^b was thought to be a product of the interaction between genes from different loci. It is probably not determined by an allele at the Le-le locus. When more facts are established, the whole system may be found to look quite different than we think today. The Le^b antigen can be accommodated in the picture given here, but only with some difficulty.