# THE DETECTION OF ANTIGENS WITH AN ABNORMAL GENETIC DETERMINATION

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Since the pioneer work of Little, it is generally believed that all members of the $F_1$ between two pure lines of animals possess all the antigens of the parent lines, and no more. This, if true, is explicable on the one gene-one antigen theory of Haldane (1933) provided all the genes concerned are autosomal. This theory has been a useful guide to action, but it seems in danger of becoming a dogma, and I wish to suggest the need for a systematic search for exceptions to it. This search will be easiest in mice. Such a search is made possible by the technique of skin grafts developed by Medawar and his colleagues.

I symbolize pure lines by letters $A$, $B$ and so on, the progeny of $A♀ \times B♂$ by $AB$, and so on. $A♀ \rightarrow BA♂$ means a graft of skin from an $A$ female to a male whose mother was $B$ and whose father was $A$, and so on.

The failure or success of grafts to grow is most readily detected when the skin colour of donor and host is different. I therefore suggest that $F_1$ hybrids be made between pure lines in such a way that, as far as possible, the colour of the $F_1$ differs from that of both parents. If a graft between two stocks fails, there is a presumption that the donor possesses an antigen which is absent in the host. I think that the prospects of success might be considerably increased if one or more of the pure lines tested were derived from a subspecies other than *Mus musculus musculus*.

If the graft $A \rightarrow BA♂$ breaks down, this could be due to the fact that $BA♂$ lacks an antigen determined either by a gene in an X-chromosome from $A$ or a cytoplasmic or milk factor from $A$. In the former case the graft $A \rightarrow BA♀$ should take, in the latter it should break down. The converse case, a breakdown of $A♂ \rightarrow BA♀$ but not of $A♂ \rightarrow BA♂$, would suggest a Y-borne antigenic gene in the $A$ line. This is most unlikely, as it would lead to the breakdown of $A♂ \rightarrow A♀$ grafts, which has never been observed. Thus a study of $A♂ \rightarrow BA♂$ and $A♂ \rightarrow BA♀$ grafts would detect any of these types of antigenic determination. In any particular case it is easy to predict additional results. Thus if $A$ carried an X-linked antigen absent in $B$, not only would $A \rightarrow BA♂$ fail, but $AB \rightarrow BA♂$ and $BA♀ \rightarrow BA♂$ would fail.

Much more interesting is the possibility of the formation of hybrid antigens, that is to say, the possibility that $AB$ or $BA$ possesses an antigen found in neither $A$ nor $B$. Billingham, Brent & Medawar (1953) have shown that by injecting minced tissues of $A$ into $B$ embryos, the graft $A \rightarrow B$ is often made possible. If we call these $B$ individuals on which $A$ grafts will take $B(A)$, then if hybrid antigens are formed the graft $AB \rightarrow B(A)$ or $BA \rightarrow B(A)$ will probably break down, though $A \rightarrow B(A)$ does not.

Hybrid antigens have been found in species hybrids (Irwin, 1947) and in *Drosophila melanogaster* by Fox and his colleagues (e.g. Fox & White, 1953). Filitti-Wurmser, Jacquot-Armand, Aubel-Lesure & Wurmser (1954) have found a hybrid protein (so far not known to be antigenic) in *Homo sapiens*. The genes which co-operate to form a hybrid antigen or protein have so far always proved to be approximately allelomorphic, though

as in Chovnick & Fox's (1953) case, they may prove to be pseudo-alleles. Miller (1954) found that one of Irwin's hybrid antigens was produced by the interaction of two apparently allelomorphic genes. It is possible, however, that the relation of the Lewis antigens and the secretor factor in man may show interaction between different loci. It is certainly too early to state as a general principle that the presence of an antigen in a tissue is never determined by the interaction of genes at two different loci. None of the studies on mouse tumours demonstrate the absence of hybrid antigens. They show that $AB$ mice have all the antigens of $A$ and all those of $B$. They do not show that they have no others in addition.

If $n$ pure lines are available, it is not necessary to make all the $n(n-1)$ possible matings to demonstrate the presence or absence of sex-linked or milk-determined antigens. Such a scheme as $A \times B$, $B \times C$, $C \times D$, $D \times E$, or $A \times B$, $A \times C$, $A \times D$, $A \times E$ would be sufficient. For if $A$ and $E$ differ by a sex-linked gene, then one of the crosses $A \times B$, $B \times C$, $C \times D$ or $D \times E$ will differ by this gene, and so on. However, as many crosses as possible should be made in a search for hybrid antigens.

If any exceptions are found to the 'one-autosomal gene, one-antigen' theory, it is of course entirely possible that they may prove to be due to some other cause than those suggested. Thus a cytoplasmic factor and a milk factor could only be distinguished by fostering experiments, a hybrid antigen could be due to the interaction of a gene and a cytoplasmic or milk factor, and so on.

However, I suggest that a systematic search for exceptions should be undertaken. A negative result would place the generally accepted theory on a much more secure foundation. A positive result would either add to the small stock of sex-linked genes and milk factors known in mice, disclose a new method of determination of antigens, or conceivably a mechanism of graft resistance which did not depend on antigens. Moreover, further work on the nature of a hybrid antigen, were one discovered, would probably be easier with mice than with pigeons.

When I wrote in 1933, the existence of hybrid antigens was doubtful, and some workers believed that the X-chromosome of the mouse carried very few genes. Moreover, the only method for the demonstration of a hybrid antigen in $AB$ was the exhaustion of the serum of an animal immunized against $AB$ cells by a mixture of cells from $A$ and $B$, and a subsequent test of the exhausted serum on $AB$ cells. This method is practicable with erythrocytes, but much harder with other cells. New prospects of disproving the theory enunciated in 1933, or of giving it additional support, are therefore open.

Unfortunately, no facilities for such work exist here. I suggest that it be undertaken by workers elsewhere.

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