

Lateral reading 2

UNSTABLE METHOTREXATE RESISTANCE IN HUMAN SMALL CELL CARCINOMA ASSOCIATED WITH DOUBLE MINUTE CHROMOSOMES (Curt GA *et al. N Engl J Med* 1983;308:199–202)

Patients who become resistant to anti-neoplastic drugs may do so for various reasons, for example, because of an upset in the membrane transport mechanism. More interestingly, there may be a mutation of the gene coding for the target protein such that raised levels are produced—technically gene amplification—and therefore the drug is inadequate to perform its function. This may happen with methotrexate and when it does the drug resistance is stable because the amplified genes are copied as chromosomal DNA and passed to both daughter cells during mitosis. On the other hand, and this is the most interesting point of all, the amplified genes may be situated in small pieces of DNA called double minute chromosomes. These lack centromeres and do not segregate at mitosis and they therefore tend to become lost. This happens when the drug is stopped.

The authors describe a patient with a small cell lung carcinoma who was treated with methotrexate and became resistant to it. The cultured cell line initially showed a large number of double minute chromosomes, but during serial passage of this line in the absence of the drug a progressive loss of resistance was observed in association with loss of the minute chromosomes. In other words, the drug resistance was unstable and reversible. The therapeutic possibilities relating to these observations are obvious.

CYTOGENETIC ABNORMALITIES IN DUPUYTREN'S DISEASE (Sergovich FR *et al. Letter. N Engl J Med* 1983;308:162–3)

Chromosome abnormalities (see their table for details) were found in the diseased palmar fascia compared with the unaffected palmar skin in a substantial proportion of patients with Dupuytren's disease. The pattern of the abnormalities was similar to that described in various malignant growth disorders. The importance of the letter is to show that the occurrence of chromosomal abnormalities, which were non-random in Dupuytren's disease, is not of itself an indication of

potential malignancy, for Dupuytren's disease is eminently a benign condition.

MATERNAL TRANSMISSION IN HUNTINGTON'S DISEASE (HD) (Myers RH *et al. Lancet* 1983;i:208–10)

Women with late onset (aged 50 or over) HD are much more likely to have inherited the major gene from an affected mother than from an affected father, but on the other hand early onset HD is associated with paternal transmission. However, contrary to what is expected in autosomal dominant transmission (equal parental sex distribution) there is a disproportionate number of late onset cases inheriting HD from an affected mother compared with early onset cases inheriting the disease from the father.

The authors suggest 'modifiers', but because of the disproportion it is argued that some of these cannot be of chromosomal origin, and the suggestion is made that they may be mitochondrial and thus confined to the female. These will be transmitted to the unaffected females in the population, as will the unlinked chromosomal modifiers to both sexes, but all will be 'switched off' unless the major gene is present.

This is a most complicated paper but it is important in demonstrating that modifying genes are not just 'thought up' by geneticists to explain a difficult problem, but that they actually exist. Since consanguinity increases as we go back in time, does this mean that the modifiers more frequently 'met up' with the major gene than at present?

(Note: there are references to four papers on HD from *J Med Genet*.)

PROSPECTS FOR PREVENTION (Doll R. *Br Med J* 1983; 286:445–53)

It was Joshua Lederberg who defined genetics as 'anything interesting' and my excuse for including Doll's paper is that it *is* interesting, and it emphasises, particularly for the non-medical reader of this Journal, how vastly more important the environment is than heredity in relation to disease and how much can be done in a few generations to alter things for the better for the whole population. On the other hand, genetic improvement is only for a relatively few unfortunate families, but here antenatal screening has many new techniques and these are well summarised in the paper.

THE GENETICS OF SYSTEMIC LUPUS ERYTHEMATOSUS (Hughes GRV, Batchelor JR. *Br Med J* 1983; 286:416-7. Fielder AHL *et al.* *Br Med J* 1983; 286:425-8)

Autoimmune mechanisms play a key part in the pathogenesis of SLE and therefore significant associations with HLA antigens are to be expected. These have been found, as well as evidence of familial factors, the most important being an increased frequency of auto-antibodies in otherwise healthy relatives of SLE patients. In addition to the HLA associations the papers report likely complement deficiencies, but these are difficult to assess because of the heterogeneity of the disease, for example, the symptoms and signs can occur in Sjögren's syndrome and after the ingestion of certain drugs.

From a practical point of view the question raised is whether treatment with complement has a role in the management of the individual patient.

ADVANCES IN TISSUE TYPING (Joysey VC. In: Lachman PJ, Peters DK, eds. *Clinical immunology*. Chap 17. Oxford: Blackwell, 1982)

HLA associated diseases are frequently in the news, but before accepting them as proven it is important to appreciate the many pitfalls in tissue typing, and these are well set out in the chapter. In the 1960s agglutinating techniques were used but the reproducibility was not good and owing to cross-reactions the patterns were extremely complex. Currently, the ability of the antibody to cause cell death assessed by the use of stains (the NIH test) is used, but here it is necessary to add complement and though the principle is simple it is easy to get the wrong answer, and a knowledge of the nature of the cross-reactions

is essential for reliable results. Other points are: (1) Lymphocytes need accurately separating from platelets, since the latter contain HLA-A, -B, and -C antigens and therefore may weaken the reaction of the antibodies.

(2) If test cells are homozygous for a particular antigen, they will have double the amount of that antigen as compared with heterozygotes. Because of this, homozygous B7 cells, for example, will react strongly to anti-B7 but (because of cross-reactivity) they will also react to anti-B27. It is thus difficult to decide whether the cells have both B7 and B27 or a double dose of B7.

(3) It is also essential to test lymphocytes with serum from the *same* population as that from which the donor was drawn. This is because different racial groups have widely different antigen frequencies and specificities, and consequently a serum may appear monospecific when tested on one population and yet be shown to possess extra specificities when tested on another.

When monoclonal antibodies have been perfected, these will greatly help to solve the above problems.

IMMUNOGENETICS OF SPONTANEOUS ABORTIONS IN HUMANS (Gill TJ. *Transplantation* 1983;35:1-6)

I am intrigued by reversals of view among the Establishment. Not so long ago my juniors clearly thought I had no immunological knowledge because I transfused my renal failure patients and this showed the nadir of ignorance in relation to transplantation. Now the position is reversed for it has been demonstrated that transfusion benefits transplantation, though the reason is not clear. We have a somewhat similar situation in relation to spontaneous abortions. One might think that when husband and

TABLE 3 Prevalence of shared antigens at different HLA loci in couples having habitual abortions and in normally fertile couples (controls).

Reference*	Aborters			Controls		
	HLA-A	HLA-B	HLA-D/DR	HLA-A	HLA-B	HLA-D/DR
Lauristen <i>et al</i> ⁸⁰	12/29	6/29	10/12 ^a	22/35	11/35	2/12 ^a
Komlos <i>et al</i> ⁷⁵	11/22	8/20	ND ^b	3/7	1/7	ND
Gerencer <i>et al</i> ^{77 78}	20/45	17/45	ND	20/79	20/79	ND
Schacter <i>et al</i> ^{76c}	21/39	9/39	ND	4/17	2/17	ND
Taylor and Faulk ⁷⁴	4/4	3/4	3/4	ND	ND	ND
Beer <i>et al</i> ⁷³	9/10	3/10	4/10	2/16	0/16	4/16
Amar <i>et al</i> ⁷⁹	9/21	5/21	— ^d	7/21	6/21	— ^d
Total	86/170	51/168	17/26	58/175	40/175	6/28
Frequency ^e	0.50	0.30	0.65	0.33	0.23	0.21

*Negative reaction between parents in mixed lymphocyte culture.

^bND not done

^cIn mothers having children with neural tube defects, prevalence of shared HLA-A = 14 of 21 (0.67) and HLA-B = 8 of 21 (0.38).

^dThere was no mixed lymphocyte response by husbands' lymphocytes stimulated by wives' lymphocytes.

^eSignificance of the difference from controls at the different loci (χ^2 test): HLA-A, $p < 0.005$; HLA-B, $p > 0.05$, and HLA-D/DR, $p < 0.005$.

*The numbers following the authors' names refer to the references in the Gill paper.

(This table is reprinted by courtesy of the author and the editor of *Transplantation*.)

Editorial

wife differ with regard to their HLA antigens, spontaneous abortions would be more likely than when they are similar, but the story is that the reverse is the case and transfusion of heterologous white cells is beneficial to recurrent aborters.

The paper discusses this in detail but one has difficulty (at least I have) in assessing the author's opinion. However, the findings in table 3 of the paper seem to indicate that shared antigens at certain HLA loci are more common in habitual aborters than in controls but other shared antigens are not. As usual "more work is required" but the matter is of great interest.

A further puzzle concerns ABO incompatibility between mother and fetus. There is a large body of evidence showing that this predisposes to abortion but, as Gill points out, the trophoblast does not express ABO antigens, nor do the naturally occurring IgM anti-A and anti-B cross the placenta. Group O mothers are said to be more liable to abort because some of their anti-A and anti-B is of the IgG class, but though these *will* cross the placenta there will be no antigens for them to attack.

The paper is an 'overview' and covers a wide field which is only touched on here.

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