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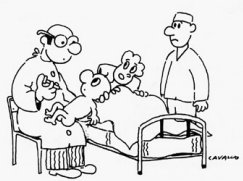

"Early to detect,
Early to apprise,
Makes prediction feasible, cost-effective, and wise."

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way. In these familial cases, typing for HLA is probably, in terms of cost-to-benefit ratio, not worth pursuing except for excluding DR2+ (DQB*0602) individuals, that have a very low risk of becoming diabetics. However, what is to be done for the sporadic cases, which account for the remaining 45,000?

In sporadic cases, as opposed to familial cases, it has been shown that the above immunological reactivities have a low predictive value. Consequently, for the moment, if we want to select a high risk group, we must rely mainly on genetic markers or on a combination of genetic markers and immunological reactivities. This is a multifactorial disease, but among the several loci involved HLA is the most relevant and indeed the only locus whose involvement has been demonstrated beyond doubt. Unfortunately, the disease-predictive value of HLA, *when taken alone*, is very limited. The proportion of the general population that can be considered at risk because possessing at least one susceptibility associated DQA/DQB heterodimer is about 50% (in Italy).[1] Therefore, HLA typing *per se* would enable the exclusion of 50% of the general population from further consideration and even this with some reservation, since a small proportion of patients do not possess any susceptible heterodimers. Obviously, this is not worth doing as a general population screening unless coupled with the definition of other risk factors.

Let us consider the only additional risk factors for which extensive information is available, i.e. ICA antibodies. It has been shown that in a school-age population only 30% of the individuals found positive for ICA eventually develop the disease.[2] If we assume that all of them possess at least one susceptible heterodimer, HLA typing would permit following the ICA titre in half of the individuals and to reach about 50–60% disease prediction among them. If we ask whether such a combined screening is worth performing, the answer would again probably be negative because of another problem, i.e. the relatively high cost of HLA typing as compared with its advantages. However, if other predictive genetic factors are defined and if the cost of HLA typing is reduced, cost and benefits may in the not so distant future reach a realistic balance. At present, none of the available HLA typing methods appears to meet the requirement of cost-effectiveness for mass screening. Attempts at an automation of genornic typing are under way and the future development in this field depends on its outcome.

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HLA-DQ Typing for prediction of IDDM? Some 'Yes' people

Roberto S. Accolla and Giovanna Tosi
Institute of Immunology and Infectious Diseases, University of Verona, Italy

There is ample debate on the need and/or usefulness of HLA-DQ typing in the population for assessing the risk of IDDM. Those who do not consider it is worth performing wide and indiscrimate HLA DQ typing stress the scarce prediction value in conjunction with the still relatively high cost of molecular typing as arguments which should dissuade enthusiastic expectations.

However, our personal opinion is that with the introduction of new and cheaper procedures for HLA-DQ molecular typing such as DEIA,[1] focusing on the assessment of the complete DQB1 and DQA1 genotype through haplotype segregation studies in families, a picture is emerging that justifies, if not the enthusiasm at least a more attentive reconsideration of the issue. In a recent analysis of 51 IDDM patients, their parents, and geographically matched normal controls without family history of IDDM, we found that the combination of two 'susceptible haplotypes' for DQB1 Asp-57 and DQA1 Arg-52 was found in about 40% of IDDM patients and in none of the normal controls. If HLA-DQ genes play a role in the pathogenesis of IDDM because of the self antigen presenting function of their products, then it is reasonable to assume that the more DQ α-β susceptible heterodimers are formed the higher is the risk of contracting the disease. Table 1 shows the results in terms of relative risk for disease depending upon the number of possible susceptible heterodimers which may be formed both *in cis* and *in trans* configuration: 4 (two full susceptible haplotypes), 2 (one full susceptible haplotype and either a DQB1 or a DQA1 susceptible allele in the other haplotype), 1 (one DQB1 and one DQA1 susceptible allele either *in cis* or *in trans*), and 0. At least for the group of 4 susceptible heterodimers the relative risk is so important that in itself it may represent (if confirmed in a larger sample of patients and normal controls) a parameter of high prediction for onset of IDDM. By focusing attention on a restricted population at risk (first, family members of IDDM patients; second, a small population within an area of high incidence of disease), young healthy individuals with the corresponding genotype will be detected. We propose that these 'susceptible homozygous' individuals should be seriously considered as a group of choice for preventive therapeutic trials even in the absence of other classical serological markers such as ICA antibodies against GAD, etc.

With our method the relative cost for full HLA-DQ typing is in the range of 100 US dollars per individual, which is not cheap, but is likely to be further reduced. This cost is certainly not higher than other sophisticated serological analyses. Maybe 'the cost is worth the candle'.

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Table 1. *IDDM correlates with the number of susceptible DQ heterodimers an individual can potentially assemble*

Number of susceptible heterodimers	IDDM (51)		Controls (52)		Pc	RR
	n	%	*n*	%		
4	20	39.2	0	0	4.4×10^{-6}	68.3
2	24	47.0	11	21.1	0.04	3.2
1	4	7.8	16	30.8	0.03	0.2
0	3	5.9	25	48.1	12×10^{-5}	0.07

LESSONS FROM IMMUNOTHERAPY IN OTHER AUTOIMMUNE DISEASES

Organ-specific immunotherapy: dermatological experience is more than skin-deep

M.W. Greaves
St John's Institute of Dermatology, UMDS St Thomas's Hospital, London

Dermatologists have been using systemic immunotherapy in the treatment of autoimmune dermatological disorders, especially pemphigoid and pemphigus, for upwards of thirty years. However, the extent to which undoubted benefits are due to immunosuppression or to anti-inflammatory of cytostatic actions is still unclear. Synthetic corticosteroids are the most widely used because of their speed of action, but their long-term toxicity has prompted routine coadministration of a non-steroid immunosuppressive, usually azathioprine, to obtain a 'steroid-sparing' benefit.[1] Azathioprine, which is metabolized to 6-mercaptopurine, also caused bone marrow suppression. With this caveat, azathioprine in dosage 2.5 mg kg^{-1} day^{-1} remains both safe and effective and is the most widely used immunosuppressive in autoimmune blistering disorders. Cyclophosphamide, which has been used for the same indications and with the same precautions, is sometimes used as alternative.[2]

As a result of immunopathological studies, evidence that the pathogenesis of the skin lesions of psoriasis involves an immune reaction between activated CD4 T lymphocytes and an autoantigen on external antigen (e.g. a bacterial antigen or super antigen) or a combination of these is now highly persuasive.[3,4] Accordingly, systemic cyclosporin (which has a specific suppressive action on cytokine-driven T cell activation due mainly to inhibition of synthesis of interleukin-2[5] is now increasingly used in the treatment of severe psoriasis.[6] Low dosage cyclosporin (no more than 5 mg kg^{-1} body weight day^{-1}) is normally prescribed. Anxiety about effects on renal function preclude use in patients with laboratory (glomerular filtration rate) evidence of impaired kidney function which should be regularly monitored by determination of the serum creatinine.[7] Similar strict monitoring of the blood pressure is also advised Although cyclosporin is not curative and relapse occurs after withdrawal, there is no evidence of rebound as experienced after withdrawal of systemic steroids. Under appropriate circumstances, low dose cyclosporin can be given continuously for up to 2 years, but in the longer term, the possible effects on renal function are being studied in a multicentre international investigation.

The onset of other complications, including provocation of cancer (especially of the skin in patients likely to have received previous ultraviolet phototherapy) and lighting up of latent infections, including tuberculosis, remain major concerns. Unfortunately, cyclosporin does not work topically and it is unlikely that the above guidelines will be relaxed in the foreseeable future. The use of other systemic immunosuppressants with a similar mode of action to cyclosporin (including FK506) has been reported[8] but there is no evidence at present of an improved therapeutic index in terms of renal function impairment or other side effects.

Cyclosporin now has an established place in management of patients with recalcitrant severe psoriasis, especially those with intolerance of methotrexate and other cytostatics. There is no doubt that other congeners with an improved risk-benefit ratio will widen the dermatological indications for this form of immunotherapy.

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