CORRESPONDENCE

This department is for the publication of informal communications that are of interest because they are informative and stimulating, and for the discussion of controversial matters. The mandate of this JOURNAL is to disseminate information relating to leprosy in particular and also other mycobacterial diseases. Dissident comment or interpretation on published research is of course valid, but personality attacks on individuals would seem unnecessary. Political comments, valid or not, also are unwelcome. They might result in interference with the distribution of the JOURNAL and thus interfere with its prime purpose.

HLA-DQ Molecules may be Products of an Immune Suppression Gene Responsible for *Mycobacterium leprae*-specific Nonresponsiveness

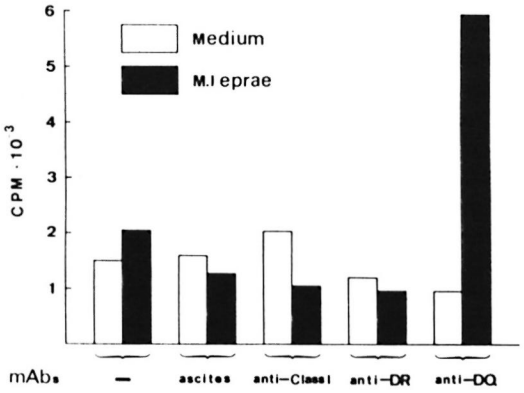
TO THE EDITOR:

HLA-DQw1 was found to be associated with lepromatous leprosy in several populations ([3, 12]). The increasing evidence for suppressor-T (Ts) cells in lepromatous leprosy ([1, 8, 10]) suggests that this association and the HLA-linked control of susceptibility to lepromatous leprosy may be due to an immune suppression (Is) gene ([2, 9, 11]). Based on the observation that helper-T-cell responsiveness could be restored by anti-DQ antibodies, Sasazuki and his co-workers have put forward the hypothesis that DQw1 molecules may be the products of an HLA-DQw1-associated Is gene, which might also be the explanation for the association between DQw1 and lepromatous leprosy ([5, 11]). To test this hypothesis, we studied 18 lepromatous leprosy patients who were nonresponsive to *Mycobacterium leprae* antigens.

Proliferative assays. Peripheral blood mononuclear cells (PBMC) of 18 lepromatous leprosy patients were isolated as described previously ([4]). The diagnosis of all patients used for this study was based on regular clinical examination, lepromin skin test, and skin-biopsy histology by Dr. D. L. Leiker, Department of Dermatology, University Hospital of Amsterdam, Amsterdam, The Netherlands. A standard lymphocyte proliferation assay was performed in which the soluble *M. leprae* preparations CD67.11 (kindly provided by Dr. R. J. W. Rees, IMMLEP *M. leprae* bank, London; 2.5 μg/ml) or Dharmendra lepromin (Dh.1: 60) (kindly provided by Dr. R. C. Good, Centers for Disease Control, Atlanta, Georgia, U.S.A.) were added to 10^5 PBMC in flat-bottomed, 96-well, microtiter plates (Greiner, Federal Republic of Germany). After incubation in a fully humidified 5% CO_2-air mixture for 5 days at 37°C, 1.0 μCi ^{3}H-thymidine (^{3}H-TdR) was added to each well. After a further 16 hr, the cultures were collected on glass-fiber filters using a semi-automatic sample harvester, and ^{3}H-TdR incorporation was counted by liquid scintillation.

Monoclonal antibodies (mAbs). The murine mAbs used in this study were B9.12.1 (anti-HLA class I monomorphic, IgG2A, gift of B. Malissen); B8.11.2 (anti-DR monomorphic, IgG2b, gift of B. Malissen); SPVL3 (anti-DQ monomorphic, IgG2a, gift of H. Spits); IIB3 (anti-DQw1, DQw4, IgG2b, gift of F. Koning); IVD-12 (anti-DQw3, IgG1, gift of R. C. Giles); HU-11 (anti-DQw1, gift of M. Aizawa); and HU-18 (anti-DQw3, IgG2b, gift of M. Aizawa). All mAbs consisted of mouse-derived ascites. All mAbs are described in reference [7] except for HU-11 and HU-18 (see [6]).

Restoration of PBMC's proliferative immune response by mAb. At the start of the culture described above, 0.05 ml Iscove's modified Dulbecco's medium (IMDM) with mAb was added. All mAbs were filter-sterilized through 0.22-μm filters (Gelman Instrument Co., Ann Arbor, Michigan,



THE FIGURE. Restoration of PBMC's proliferative immune response to *M. leprae* by anti-DQ mAb from one nonresponder lepromatous leprosy patient. PBMC were in a concentration of 10^5 cells per well. Results are expressed as the mean cpm × 10^{-3} of triplicate cultures (^{3}H-thymidine incorporation). Standard errors did not exceed 20%. Ascites was SPO2; mAbs are described in text.

U.S.A.), and tested in a concentration of 1:200.

All PBMC from 18 lepromatous leprosy patients were unresponsive to *M. leprae* per se (left two rows in The Table). To test whether this antigen-specific unresponsiveness is regulated via an HLA Is gene product, we performed blocking studies using various mAbs against HLA antigens. Whole PBMCs were cultured with or without *M. leprae* antigen in the presence of various mAbs for 6 days. As shown in The Figure, such cells from patient W2 showed a significant response when mAb against HLA-DQ (SPVL3) was added at the start of culture but the response could not be restored by mAbs against HLA class I, DR (The Figure), DQw3 (mAb IVD-12), and two DQw1 mAbs—Hu-11 and IIB3 (data not shown). The results were repeatable, that is, the *M. leprae*-specific response could be restored in only 1 out of 18 lepromatous leprosy patients.

We and others (T. Sasazuki and T. Ottenhoff, personal communications) have observed that anti-DQ mAb could abolish *M. leprae*-specific suppression, indicating that HLA-DQw1 may be the product of an Is gene for *M. leprae*. We observed restoration of the response only with mAb SPVL3 (reactive with a nonpolymorphic determinant on DQ molecules) and not for anti-DQw1 mAbs (HU-11 and IIB3, data not shown). This could be due to the polymorphism of DQ molecules (DQ typing of patient W2 is DQw3 and DQw7) and to the different specificities/affinities of the anti-DQ mAbs. However, because the phenomenon was observed so infrequently, it seems unlikely to us that this observation can explain the association between HLA-DQw1 and lepromatous leprosy. Therefore, we have undertaken a more complete study of the restriction and regulation by HLA products of *M. leprae*-specific suppressor-T-cell clones.

THE TABLE. *Restoration of peripheral blood mononuclear cells' specific proliferative response to* M. leprae[a] *from 1 out of 18 lepromatous leprosy patients by anti-DQ mAb.*

Patients		^{3}H-TdR incorporation (cpm)			
	Anti-DQ[b]	−	−	+	+
	M. leprae[c]	−	+	−	+
B		1845	1853	1440	2335
C		1050	1190	670	650
D1		585	485	498	558
D2		973	825	518	863
E		1023	1228	843	1225
F1		520	303	380	500
F2		850	765	840	1608
H1		198	343	163	445
H2		1340	703*	663	523*
K		1398	1408	1155	1480
L1		85	70	60	225
L2		643	738	2195	2120
M		1640	1700*	1615	1493*
N		1865	1595*	1408	1155*
S		548	675*	6315	800*
T.T		1350	1485*	2115	1378*
W1		3105	2835	2480	2698
W2		1503	2078	983	5975

[a] Results are expressed as the mean counts per minute (cpm) of triplicate cultures. Standard errors did not exceed 20%.

[b] SPV-L3, which is directed against a monomorphic determinant on molecules.

[c] CD67.11 or Dharmendra lepromin (indicated by *) in final concentrations of 2.5 μg/ml and 1:60 dilution, respectively.

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Interpretation of Published Papers on Controlled Clinical Trials

To the Editor:

Although the major (international) leprosy journals subject all research papers submitted to their editors to careful peer review, it still behooves leprologists to read critically those that are published. This is especially true for all clinical trial papers, whether dealing with the chemotherapy of leprosy or the treatment of reactions. There are a number of good reasons, including the following: a) Some papers may not be scientifically quite satisfactory, yet they contain important data, so that their findings warrant checking by others using correct methodology. The responsibility borne by the referees and, ultimately, by the editor for publishing such communications is considerable. b) The editor and referees may consider that a strongly held heterodox view should be published so that the scientific world may study the evidence (or lack of it) in its favor. c) The editor and referees may be subject to current bias and not recognize