subtyping and suggest that the telomeric border of the ancestral hemochromatosis-susceptibility haplotype goes as far as D6S105 or even beyond. This work is highly relevant to any discussion of the localization of the hemochromatosis gene and clarifies the uncertain points raised in the French study.

MARK WORWOOD, M. TEVFIK DORAK, AND RUMA RAHA-CHOWDHURY
Department of Haematology, University of Wales College of Medicine, Heath Park, Cardiff

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Reply to Worwood et al.

To the Editor:

We were quite surprised to read the letter of Worwood et al. concerning criticisms leveled at our article. Two statements within the letter require rebuttal; one concerns the mundane issue of publishing, while the other concerns the essence of our own work, which represents a continuing effort extending over the past decade.

First, Worwood et al. reproach us for not making reference to the interesting work of Jazwinska and her collaborators, which appeared in the August 1993 issue of the *Journal*. With respect to the temporality of publishing an article (of which we would expect Worwood et al. to be cognizant), our original submission and the subsequent, multiple modifications of our article far preceded the appearance of the Jazwinska et al. paper. Indeed, we had knowledge of this publication only after the second resubmission of our modified manuscript, which occurred in September 1993. We are well aware of the fact that the possibility of a D6S105 allele existing in linkage disequilibrium was promulgated in abstract form to the small community of researchers studying hemochromatosis (we refer to the Congress on Hemochromatosis, in Jerusalem, May 1993); however, the inclusion of this unmapped marker (or any one of many available CA-repeat polymorphisms mapping to 6p) within our study merely as corroborative evidence was considered a risky investment and a deviation from our focused approach of analyzing well-defined and mapped markers falling immediately within or telomeric of the major histocompatibility complex proper. This brings us to our second point.

The results that we have recently published in the *Journal* are the balance of work performed from 1988 to 1992. We considered as a point of departure the solid genetic results that supported the possibility that *HFE* would fall within a narrow physical window, generally ≤ 1 Mb (~ 1 cM) from the *HLA-A* locus. We chose a direct line of characterization and study and, within the HLA class I region, focused on only those RFLP markers that had, for the most part, been physically mapped by our laboratories. The results that have accrued from our efforts define a 350-kb *HFE* linkage-disequilibrium zone extending from I.82, located 100 kb centromeric of *HLA-A*, to the *HLA-F* locus.

The association of *HFE* with a D6S105 allele has been recently confirmed among our French patient population. In view of our published data, this association generally poses a difficult problem with respect to interpretation, since the D6S105 locus is not within proximity of *HLA-A*. To our knowledge, the exact physical localization of D6S105 is not known and may, in fact, be 1,000–3,000 kb telomeric of the *HLA-A* gene. This distance is incompatible with the extreme rarity of crossovers between HFE and *HLA-A*, unless one considers recombination supression, based on physical map anomalies within the region as described by members of our team.

It seems to us that in the absence of the exact physical mapping of D6S105, much caution must be exercised during the interpretation of association or linkage results. For the moment, we must await the positioning of D6S105, followed by the reconciliation of these data with our own published mapping results.

J. YAOUANQ, M. CHORNEY, J. Y. LE GALL, V. DAVID, AND P. PONTAROTTI
Laboratoire de Biochimie Médicale B
Faculté de Médecine de Rennes
Rennes

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