be a reflexion of the interplay between (i) the relative abundance of the different Y-chromosome types in the ancestral African population, (ii) the number of migrants of each type giving origin to modern non-African populations, and (iii) genetic drift after they migrated out of Africa. In this context, one possible explanation for the unusually high frequency of the XY275G (*low*) allele in the Portuguese population is that it may have been introduced by migrating farmers from the Fertile Crescent during the Neolithic transition (Cavalli-Sforza et al. 1993), given the XY275G (*low*) allele's relatively high frequency already demonstrated in an Asiatic-Indian population (Spurdle et al. 1992). Further investigation of the XY275 polymorphism, along with other autosomal and mitochondrial polymorphic markers, in Middle Eastern and Mediterranean individuals (both southern Europeans and northern Africans) would certainly be very informative.

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Haplotypes in Linkage Disequilibrium with the Hemochromatosis Gene

To the Editor:

We have read with interest the paper by Yaouanq et al. (1994), in which they describe an HLA-A3 haplotype and suggest that it may be the ancestral haplotype in which the first mutation causing genetic hemochromatosis (GH) occurred. This study used HLA-A serotypes, RFLP analyses of i82 and 6.7, and a *Hin*dIII polymorphism of the HLA-F locus with a very low PIC. According to the authors, the telomeric limit of the ancestral haplotype was less precisely defined because of the weak informativeness of the HLA-F polymorphism. We are surprised to find that the authors neither cite the very strong association of GH with the more telomeric locus D6S105 nor use this CA-repeat polymorphism in their analysis. The results of the analysis of D6S105 were published by the Australian group, as an abstract in 1992 (Lee et al. 1992), and, in full, in the *Journal* last year (Jazwinska et al. 1993). Our findings were reported at the Fourth International Conference on Hemochromatosis and Clinical Problems in Iron Metabolism, held in Jerusalem in April 1993. The full paper has now appeared (Worwood et al. 1994). Both studies have shown that allele 8 of D6S105 is associated with GH as strongly as is HLA-A3.

Using HLA-A RFLP analysis and PCR analysis of D6S105, we have described a hemochromatosis-specific genotype (Worwood et al. 1994). Taking advantage of the recessive nature of GH, we examined homozygous genotypes of the HLA-A and D6S105 loci in unrelated patients (n = 42) and controls (n = 376). We took this approach, first, because it was not possible to assign haplotypes in the unrelated control population and, second, to avoid the haplotypes of HFE carriers in the normal population. As well as the significant associations with HLA-A3 and D6S105-8, homozygosity for both of these alleles was found in 21.4% of patients with GH but was not observed in controls (χ^2 = 63.7; relative risk = 214; 95% CI = 26–1,720). All these patients were also homozygous for the particular alleles of the loci in between. This haplotype, extending from i82 through HLA-A, 6.7, HLA-F, and D6S105, was found in 76% of patients, in either one or two copies. More precisely, 48.8% of GH chromosomes carried this haplotype. This is comparable to the frequency (50.4%) of the haplotype described by Yaouanq et al. (1994) in their patients.

Furthermore, our analysis shows that two alleles of HLA-A3 may be distinguished by HLA-A RFLP analysis and by their association with particular alleles of i82, 6.7, and the microsatellite locus D6S265 (Worwood et al. 1994; Dorak et al., in press). The common allele, HLA-A*0301 has the haplotype "i82-A-6.7" = "2-A3-1" described by the French group and shows an absolute correlation with the 124-bp allele of D6S265 (allele 1). The rare allele HLA-A*0302 does not share the same associations, and this explains the findings in their normal chromosomes. Therefore, the haplotype described by Yaouanq et al. simply represents the common HLA-A3 subtype associated with GH.

These findings show the importance of HLA-A DNA

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.

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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.

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