

'clustered positively charged groups'. Antibodies bound to the heparan sulphate-binding domain can change the charge of this peptide or can inhibit it by steric hindrance thus interfering with the heparan sulphate binding.

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COLE ET AL. REPLY—Heparin was used as a structural analogue of heparan sulphate in our work because of the similarity in structure between the two molecules. Previous studies involving laminin or fibronectin used heparin-agarose to demonstrate that these molecules possessed domains for interaction with heparin^{1,2}. However, it is now well documented that the actual cell ligand that interacts with these molecules is heparan sulphate-proteoglycan. Thus, heparin was used as an analogue of heparan sulphate. In our studies³ both heparin and heparan sulphate, which are structurally related, inhibit cell-cell adhesion and therefore heparin would not serve as an adequate control. Chondroitin sulphate was used as a control to demonstrate that a specificity existed for the glycosaminoglycan-binding domain. We have also shown that dermatan sulphate or hyaluronic acid do not inhibit heparin binding to N-CAM (unpublished observations). If nonspecific binding was occurring to a cluster of basic amino acids, it would be assumed that chondroitin sulphate (or other glycosaminoglycans) would also bind nonspecifically. Additionally, other glycosaminoglycans (chondroitin sulphate and hyaluronic acid) also interact with fibronectin, and these interactions occur at domains distinct from the heparin-binding region¹. It is thus apparent that these glycosaminoglycans are interacting specifically with these adhesive molecules, and that chondroitin sulphate is an appropriate control.

With regard to Lubec's comment about the type of sulphation on chondroitin sulphate and heparin/heparan sulphate, he states that chondroitin sulphate is *O*-sulphated and heparin/heparan sulphate is *N*-sulphated. He therefore concludes that chondroitin sulphate is not an appropriate control because the *O*-sulphation may contribute to a different charge distribution than observed with heparin/heparan sulphate. It should be noted that heparin is also *O*-sulphated, and in fact a 3-*O*-sulphate group on a

pentasaccharide fragment derived from heparin is required for the ability of heparin to inhibit the proliferation of vascular smooth muscle cells⁴. Our laboratory has used fractionated heparin molecules to obtain similar results, as heparin molecules that inhibit smooth muscle cell proliferation also bind to N-CAM (manuscript in preparation). Therefore, because both chondroitin sulphate and heparin contain *O*-sulphate groups, but only heparin binds to N-CAM, it appears that the heparin-binding domain of N-CAM exhibits glycosaminoglycan specificity.

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Evolutionary relationships of human populations

WAINSCOAT ET AL.¹ state that the phylogenetic tree of human races based on blood groups has its primary division between the mongoloid and the caucasoid-negroid groups, in contrast to the one they derived from nuclear DNA polymorphisms. This is a misreading of their quoted source, a paper by Professor L. L. Cavalli-Sforza and me² in which we constructed a tree for 15 populations from just 5 blood-group systems. Apart from the fact that this tree was computed 23 years ago and should thus be remembered (if at all) for the originality of the method rather than the definitiveness of the result, we wrote "It should be noted that the origin of the tree, which we have set near the centre of the system, is arbitrary, but the splits and the computed segment lengths would be unchanged whatever the origin".

The reason for this is that we used our 'method of minimum evolution'³ (now often called the 'principle of parsimony', although that phrase properly belongs to the classical geometrical notion that figures are to be constructed with ruler and compass only⁴) which does not allow an origin to be inferred as it does not explicitly allow for a time dimension. Indeed, on another occasion on which we presented the same tree⁵ we used a different arbitrary origin.

In fact our published tree² shows that the longest segment by far is between the African group (Ethiopian, Bantu and Ghanaian) and the rest, a feature amply confirmed by the associated analysis into two and three principal components. To

paraphrase the summary of Wainscoat *et al.*¹, "genetic distance analysis based on these blood-group polymorphisms indicates a major division of human populations into an African and a Eurasian group".

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WAINSCOAT ET AL. REPLY—We accept Dr Edwards's interpretation of the classic paper¹ by himself and Professor Cavalli-Sforza in that, although their phylogenetic tree (their Fig. 5) does have the first split between the mongoloid and caucasoid-negroid groups, this division is arbitrary. However, much more data both on blood groups and protein in loci have been obtained over the past 20 years and this has recently been comprehensively analysed by Nei and Roychoudhury². Interestingly, there is still a discrepancy between the evolutionary analyses based on blood groups and protein loci as stated in our paper³. Thus, the total blood group data now available are inconsistent with Dr Edwards's suggested paraphrase of our summary.

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