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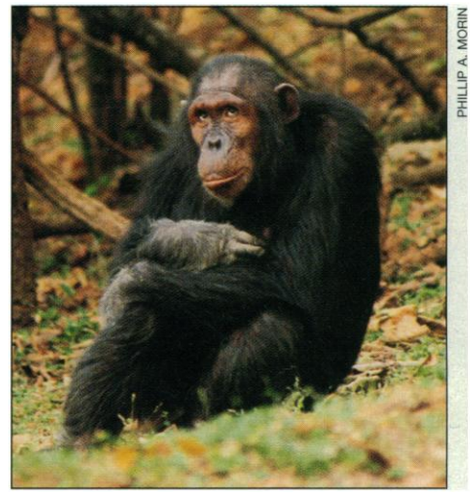
LETTERS

Chimpanzee Kinship

The article by Phillip A. Morin *et al.* "Kin selection, social structure, gene flow, and the evolution of chimpanzees" (26 Aug., p. 1193) exemplifies the valuable data that can be retrieved by use of the latest techniques of molecular genetics and the many creative uses to which such data can be put. Their use of genetic markers to test hypotheses about relatedness among chimpanzees of a population, and the sociobiological implications of its genetic structure, is innovative and exciting. However, we question some of their evolutionary and taxonomic conclusions. Morin *et al.* show that among "common" chimpanzees, a deep evolutionary divergence separates mitochondrial DNA (mtDNA) haplotypes carried by West African animals from those found in animals of Central and East African origin. They argue that this finding implies a *populational* separation of about 1.6 million years. They also suggest that, if this result is confirmed, the western chimpanzee merits elevation from a subspecies of *Pan troglodytes* to full species rank, as *P. verus*. The latter suggestion has already gained some acceptance (*1*).

However, using genetic distances to differentiate species from subspecies is problematic, if for no other reason than that no consistent standard can be found. Genera of mammals differ by a factor of more than 5 in the degree of genetic differentiation among their constituent species. Among all vertebrates, there is a 200-fold range in the degree of genetic differentiation among congeneric species (*2*). From a "frog's point of view" (*3*), the genetic distinctness of the western chimpanzee would appear trivial, while from a "bird's eye view," it would suggest separation at the family level (*4*).

Second, even if all the mtDNA haplotypes of chimpanzees from the extreme western end of their range are indeed very different from those found in other chimpanzees, this may be a result, not of ancient population isolation, but rather of the recent extinction, or nonsampling, of geographically (and perhaps genetically) intermediate populations. The distribution map included by Morin *et al.* in their figure 1 shows a gap of about 1700 kilometers between chimpanzee populations in western Côte d'Ivoire and those on the Nigeria-Cameroon border. This significantly overstates the geographical isolation of western


PHILLIP A. MORIN

Family ties. Pondering the problems of pongid relatedness.

chimpanzees today, let alone 50 or 500,000 years ago. Reports dating from 1930 to 1965 (*5*) suggest that chimpanzees survived into the middle decades of this century in much of southern Côte d'Ivoire, on the Ghana-Togo border, in western Nigeria, and in southern Benin. Recent surveys have confirmed the presence of chimpanzees in many areas of south-central and south-eastern Côte d'Ivoire (*6*) as well as in Ghana, western Nigeria, and the Niger delta (*7*). Thus, although West African chimpanzee populations are now undoubtedly highly fragmented and seriously threatened, their range within living memory appears to have been almost continuous from Senegal to Cameroon. This fact makes long-term genetic isolation of populations in the extreme west unlikely. Migration of female chimpanzees, and consequent interpopulational flow of mtDNA haplotypes, might have been impeded by the Dahomey Gap—a dry forest zone in southern Benin and southern Togo—or by major rivers, but this cannot be assumed (*8*). While we strongly agree that conservation efforts should take account of the genetic diversity of extant chimpanzee populations, we caution against drawing conclusions about their subspecific or specific status until a much broader sample has been surveyed. Relict West African populations such as those in eastern Côte d'Ivoire, Ghana, and western Nigeria merit the highest priority for both conservation efforts and phylogenetic analysis.

Morin *et al.* conclude from their mtDNA tree that "*Pan paniscus* is seen to lie closer

to the *Pan-Homo* split as postulated by Zihlman and others" (9, p. 1199). This statement might be interpreted in several ways, but none of them seems to be supported by the tree. First, since all *Pan* haplotypes form a unified cluster, linked to the common human stem by a single line, no subcluster within the *Pan* grouping can be any closer *cladistically* to the common ancestor ("the split"). An alternative reading is that a special *patristic* relationship, with respect to mtDNA, links pygmy chimpanzees to the chimp-human ancestor; that is, that *P. paniscus* sequences are consistently closer to the reconstructed ancestral sequence. But no such conservatism is implied by the mtDNA data in (*1*), or any other data we know. Alternatively, Morin *et al.* could mean that their results support the actual thesis advanced by Zihlman *et al.* (9), namely, that of all members of the chimp-human-gorilla clade, pygmy chimpanzees most closely resemble the ancestral morphotype in some features of the skull, dentition, and postcranium. As far as we can see, mtDNA data are not relevant to such a speculation, and can neither refute nor support it.

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5. A Kortlandt, in *Food Acquisition and Processing in Primates*, D. J. Chivers, B. A. Wood, A. Bilsborough, Eds. (Plenum, New York, 1984), pp. 119–159; A. Kortlandt, open letter, 1 July 1991.
6. B. Hoppe-Dominik, *Primate Rep.* **31**, 45 (1991).
7. E. A. Agbelusi, *Nigerian Field* **59**, 73 (1994); L. Robinson, T. Struhsaker, J. Thornton, J. L. Werre, personal communications to J. F. Oates; J. F. Oates, unpublished observations.
8. Chimpanzees are known to occur in many dry forest areas [W. C. McGrew, P. J. Baldwin, C. E. G. Tutin, *J. Human Evol.* **10**, 227 (1981); J. Moore, in *Topics in Primatology, Human Origins*, T. Nishida, W. C. McGrew, P. Marler, M. Pickford, F. B. M. de Waal, Eds. (Tokyo Univ. Press, Tokyo, Japan), vol. 1, pp. 99–118]. The Niger has traditionally been assumed to separate *P. t. verus* from *P. t. troglodytes* [W. C. Osman Hill, in *The Chimpanzee, Anatomy, Behavior, and Diseases of Chimpanzees*, G. H. Bourne, Ed. (Karger, Basel, Switzerland, 1969), vol. 1, pp. 22–49]. Chimpanzees have been reported from the delta of the Niger, where channels are constantly changing, and we have been unable to find a careful comparison of chimpanzees from known locations immediately east and west of the river.
9. A. L. Zihlman, J. E. Cronin, D. L. Cramer, V. M. Sarich, *Nature* **275**, 744 (1978).

Response: Jolly *et al.* raise three points that are valid and well taken, but two were covered explicitly in our original article, and the third involves an ambiguous phrase, tangential to our thesis. They question "evolutionary and taxonomic conclusions" of our article, specifically discussing (i) the use of "genetic distances" to differentiate species from subspecies, (ii) the appropriateness of our sample for measuring the distance between western and central chimpanzee subspecies, and (iii) the wording of a sentence which describes the affinities of *Pan paniscus* on the phylogenetic tree.

In their first point, Jolly *et al.* use the term "genetic distance" in a historical sense to include a large amount of research on allozyme variation and speciation. Our work was on DNA sequences (rather than proteins) and specifically on two loci, for which we calculate genetic distances individually. Our "distances" are not directly

comparable to allozymic genetic distances, and we made that point in the article by comparing our data to those from other studies of the same loci only, and only those studies that reported the raw data so that we could use the same correction methods to calculate these distances. We further limited the comparison to other mammals only (our reference 35) because, as Jolly *et al.* correctly say, one cannot use all vertebrates as a standard. We carefully avoided any implication that genetic distance is a universal and simply interpretable metric. In a field where such data are still rare but accumulating quickly, it is up to informed readers to evaluate our data, which are placed within the literature, and to decide whether the data are significant, as stated in our article. Finally, we clearly stated that our data were (and still are) the only data available for this endangered species, and that more data (genetic and otherwise) are needed to confirm our result before further interpretation is justified.

The second point about geographic sampling overstates the problem. Sampling of more individuals in the western subspecies range is likely to increase our estimate of intrasubspecific variation, and may also *increase* the estimate of intersubspecific differentiation. Our data on the other two subspecies indicate that within a subspecies range the genetic variation is widely distributed, but that there is a clear differentiation between the subspecies. This pattern is also suggested in the western subspecies, where individuals separated by 900 kilometers are most similar genetically. The distance between our Ivory Coast samples and the putative "intermediates" in Nigeria would be at most 1400 kilometers. We have not "assumed" isolation of the subspecies, but have provided data in the form of genetic distinctiveness of all three subspecies, intrapopulational variation differences between western and central subspecies, and geographic patterns of that variation that indicate long-term *genetic* isolation of subspecies. We also stated in our article that more geographic sampling is necessary and especially in West Africa. There are almost no reliable recent or historical data on the animals in the critical area between our western and our central samples; we agree with Jolly *et al.* that filling in this gap should be a high priority. Pascal Gagneux, working in the laboratory of one of us (D.S.W.) has already extended the sampling 500 kilometers east of our reported sampling; sequences from two sites in extreme eastern Ivory Coast do not show any intermediacy.

Jolly *et al.*'s third point concerns our sentence "*Pan paniscus* is seen to lie closer to the *Pan-Homo* split as postulated by Zihlman and others" (on anatomical grounds). The issue here is that our choice of words created an ambiguity. Our sentence correctly describes what one sees when one looks at our figure. Jolly *et al.* correctly note that it could mean other things. Their description of a cladistic interpretation of our genetic data (including the putative ancestral sequence) is correct, but not what we meant to imply. Despite evidence reported since our publication that apes are morphologically conserved (reference 1 in Jolly *et al.*'s letter), we did not mean to imply that there has been sequence conservation in any one clade. Our study involved chimpanzees (*P. troglodytes*), not bonobos (*P. paniscus*), but because we included two bonobo sequences as outgroups, we merely commented on their placement on the tree.

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The Theory of DNA Bending

A. D. Mirzabekov and A. Rich (*1*) conjectured in 1979 that charge neutralization of phosphate groups along one side of a DNA segment could cause the DNA to bend toward the neutralized side. Ten years later, this reasonable idea was finally analyzed with the tools of polyelectrolyte and elasticity theory (*2*), and it was concluded that even low degrees of unilateral phosphate neutralization would be sufficient to bend DNA to a structurally significant extent. The conjecture and supporting theory were recently confirmed experimentally by Juliane K. Strauss and L. James Maher III in their Research Article "DNA bending by asymmetric phosphate neutralization" (16 Dec., p. 1829), which was also discussed in an accompanying Perspective by D. M. Crothers (p. 1819). The experimental data are reported to be in general agreement with the predictions of the theory. Strauss and Maher note, however, that one of the quantitative predictions of the theory is not observed. The theory predicts that the radius of curvature of the bend depends on the length of the DNA segment. The observation is that the radius is the same over the length range studied.

The discrepancy is only apparent. The DNA molecules synthesized by Strauss and Maher possess discrete "patches" six base pairs long, completely neutralized on one side. DNA molecules of different lengths contain more patches, but the bending is localized to each patch. The radius of curvature is the radius characterizing the bent six–base pair neutral patch, regardless of the overall length of the DNA within which the patches are embedded.

The theoretical equations are applicable to the DNA segment that is unilaterally neutralized. In this case they are applicable to the six–base pair patch completely neutralized along one side. I have set the length parameter L in the theory equal to the length of six base pairs of DNA. I have also set the fractional extent of unilateral charge neutralization α equal to unity. In univalent buffer the theoretical formula then predicts that the bending angle is about 9°. The value of the bending angle in tris buffer measured by Strauss and Maher is about 21°. The list of reasons not to expect better than factor of 2 agreement between theory and experiment is long. Perhaps the most obvious is the almost complete lack of molecular-structural detail in the theoretical model.

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Biotech Patents and "Usefulness"

The article by Richard Stone "Rules would drop need for clinical data" (News, 6 Jan., p. 23) could leave the reader with a misleading impression about guidelines proposed by the U.S. Patent and Trademark Office (PTO) with respect to the standard to which patent applicants are held in substantiating the "usefulness" of an invention. Far from being a "significant concession" to the demands of the biotechnology industry, the PTO guidelines provide a road map to help patent examiners to apply what has been long-settled law in this area.

The clinical data which PTO examiners have sought from inventors were not merely "unrealistic," but also were not required by law. Case law established over many years mandates that the PTO must accept an inventor's assertion of a utility for an invention unless a reasonable, scientific basis exists to doubt that assertion.

In the course of analyzing patent applications in the biotechnology area, many examiners stood this principle on its head by presuming therapeutic inventions to be "incredible" unless proven otherwise; this, despite the fact that the category of "incredible" inventions had been reserved for perpetual motion machines, engines that run on tapwater, and the like. Applicants then were subjected to what many felt were unreasonable demands for evidence, including human clinical data, to prove that the invention was useful in a practical sense.

According to the proposed guidelines, by contrast, examiners of biotechnology applications are to consider the utility of a claimed invention in conformance with established U.S. patent law practice. The guidelines (*1*) state, for example, that examiners should consider whether a patent applicant "has asserted that the *claimed* invention is useful for any particular purpose and that assertion would be consid-