hours. All bladders were allowed to acidify the lumen fluid to about the same degree. Mucosal samples for determination of the free dissolved CO_2 in the lumen fluid were drawn directly into the Van Slyke apparatus through the side arm. Manometric measurements were made at constant gas volume. Pressure P_1 was obtained after degassing the native sample, P_2 after degassing the acidified sample, and P_3 after degassing the alkalinized sample. Free CO_2 was determined from the difference $P_1 - P_3$ and HCO_3^- from $P_2 - P_1$. The sample volume was determined from the weight of displaced mercury. Lumen fluid *p*H was determined from a second anaerobic sample.

To test the analytical technique, portions of 13 final samples were paired with portions of 0.1*N* H_2SO_4 and equilibrated with the same gas. The concentrations of dissolved free CO_2 in the gas-equilibrated H_2SO_4 solution and mucosal fluid were determined as above and compared. The mean difference between them was 0.0054 ± 0.025 m*M*.

Dissolved CO_2 cannot be measured directly in the serosal fluid because the fluid contains buffers other than HCO_3^-. In each experiment serosal dissolved CO_2 was determined from total CO_2 and *p*H measurements (*pK* 6.19) and from measured CO_2 dissolved in 0.1*N* H_2SO_4 coequilibrated with the same gas. Whenever there was a discrepancy in these two values for the free dissolved CO_2 concentration, the value obtained in the coequilibrated acid was assumed to be correct. In 13 such paired measurements the mean difference between the concentrations of dissolved CO_2 determined in the acid and in the Ringer solution was 0.016 ± 0.014 m*M*. These control data on mucosal, serosal, and sulfuric acid solutions show that the analytical techniques are valid.

At the beginning of the incubation, the *p*H, dissolved CO_2, and HCO_3^- were determined in the mucosal and serosal fluid. At the end of the incubation period one to four sets of similar measurements were made, depending on the availability of the lumen fluid.

Table 1 shows the number of turtles housed at each of the three different temperatures together with the mean change in the CO_2 and HCO_3^- concentrations and *p*H of the lumen fluid during the incubation in vitro of the bladders from each group of turtles. In each case the *p*H of the lumen fluid fell by 0.6 and the luminal HCO_3^- was reduced by about 60 percent. While all incubations were at 26°C, the bladders from the 32°C turtles acidified the lumen fluid most rapidly. Since the initial free CO_2 of the lumen fluid approximated that of the serosal fluid by design, the temporal changes in luminal CO_2 reflect the final transmural difference in CO_2 in magnitude and direction. The critical data, the mean final transmural differences in free CO_2 (mucosal value minus serosal value), are given along with their standard errors and *P* values. It can be seen that the final luminal CO_2 concentration decreases as the bladder acidifies the lumen fluid more rapidly. The bladders from 32°C turtles caused the hydration of luminal CO_2 at a rate sufficient for the hydration to outrun the inward diffusion of metabolic CO_2 and drive the luminal CO_2 concentration below that of the serosal fluid. Therefore, the mechanism of acidification must be the transport of HCO_3^- ion from lumen to serosa. This is one example of a bicarbonate ion transport system capable of regulating the *p*H of a body fluid in the *p*H range 4 to 8. The temperatures for housing the turtles and incubating the bladders were chosen arbitrarily and may not be optimal values.

The temperature at which the turtles were housed was not taken into account in previous work on this problem. The data presented here show that workers housing turtles at different temperatures but doing otherwise identical experiments would be expected to get different results, and that the finding that the luminal P_{CO_2} is greater than the serosal P_{CO_2} should be interpreted as evidence for H^+ secretion.

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Frog Perspective on the Morphological Difference Between Humans and Chimpanzees

Abstract. *The body shapes of humans and chimpanzees were compared quantitatively by criteria chosen for their capacity to discriminate well among the body shapes of frogs. By these criteria, the difference in body shape between humans and chimpanzees was found to be greater than that between the most dissimilar pairs of frogs examined—that is, frogs classified in separate taxonomic suborders. Even though the morphological difference between the two primates is large by frog standards, the biochemical differences between the structural genes of these two species are small. The results of this study give quantitative support to the proposal that morphological evolution and biochemical evolution in structural genes can proceed at independent rates.*

Biochemistry and morphology give us contrasting views of the difference between humans and chimpanzees. Biochemical comparisons made with proteins and nucleic acids indicate that humans are remarkably similar to chimpanzees at the gene level (*1*). The structural genes of this pair of species are more similar than the structural genes of most pairs of species within a genus, regardless of whether the species compared are vertebrates or invertebrates (*1*). This biochemical picture, however, contrasts with that provided by morphologists who assign chimpanzees and humans not just to separate species but to separate taxonomic families (*2*). Thus, the morphological difference between these two species appears large, whereas the biochemical difference is small.

King and Wilson (*1*) inferred from this and other evidence that structural gene evolution and morphological evolution may proceed at independent rates. Some biologists, however, have been reluctant to agree with King and Wilson that there really is a contrast between the morphological and biochemical results of evaluating the difference between chimpanzee and human (*3*). Although these biologists are aware of the quantitative and objective nature of the biochemical comparisons, they are also aware that the chimpanzee-human morphological difference has never been compared quantitatively with the morphological differences existing among other species. This lack of confidence in the morphologists' judgment that the chimpanzee-human difference is as big as that among the families of other animals is illustrated by Merrell (*3*). He stated, in essence, that if a nonmammalian creature were to classify animals on the basis of morphol-

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ogy, the chimpanzee-human difference might seem very small. In particular, he suggested that the chimpanzee-human difference might be no larger than that between two sibling species of frog (*4*).

We have attempted to deal quantitatively and objectively with the problem of the magnitude of the morphological difference between chimpanzees and humans. To avoid any bias toward hominoids and against frogs, we chose a set of nine morphological traits that have been used to assess shape changes in frogs. These linear traits include measurements from all major parts of the body. Jameson and his co-workers showed that these traits, when analyzed multivariately, distinguish well between tree frogs belonging to separate populations within a species (*5*). In addition, many of these trait lengths are routinely used univariately by taxonomists who classify frogs (*6*). It is probable that almost any evolutionary change in body shape would be reflected in at least one of these measurements.

We have used the same nine traits to assess the magnitude of the morphological difference between humans and chimpanzees. If these two species are as similar as sibling species of frogs, we would expect them to differ in these traits to a lesser extent than do most pairs of species within a genus of frogs.

Summaries of the measurements we made on the skeletons of 16 adult humans and 12 adult chimpanzees appear in Table 1 (*7–9*). The mean length of each trait is expressed as a fraction of the combined length of all nine measurements. This fraction is referred to as the relative trait length. By this mathematical device, one can compare body proportions of creatures which differ in size. This method of standardization is used routinely by cytogeneticists to compare different karyotypes, the length of each chromosome being expressed as a fraction of the total length of all chromosomes in the karyotype. Morphologists use a similar device to compare measurements in lower vertebrates (*10*). Other methods of comparing body proportions were investigated (*11*), with results very similar to those we describe.

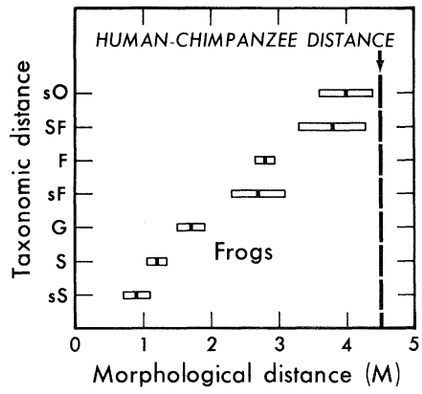

Fig. 1. Morphological distance, M, between humans and chimpanzees (dashed line) compared to the morphological distances between frog taxa. Horizontal bars indicate standard errors of the means for frogs. Frog taxa compared include: *sS*, subspecies of *Hyla regilla* (*16*); *S*, species of *Hyla*; *G*, the genera *Hyla, Phrynohyas*, and *Pternohyla* within the subfamily Hylinae and the genera *Phyllomedusa, Pachymedusa*, and *Agalychnis* within the subfamily Phyllomedusinae; *sF*, subfamilies Phyllomedusinae and Hylinae; *F*, families Bufonidae and Hylidae; *SF*, superfamilies Bufonoidea and Ranoidea, *sO*, suborders Xenoanura and Acosmanura. The number of frog specimens measured was 455; the species compared are given in (*17*). The *Hyla* data are from D. L. Jameson (personal communication).

Chimpanzees differ significantly from humans in the relative length of every trait. For each of the nine traits considered, a two-tailed t-test was done to calculate the probability that the human and chimpanzee samples could both have come from one normal distribution. The P values range from less than 10^{-9} to 1.8×10^{-2}. Thus, with frog criteria, one can distinguish readily between the body shapes of a chimpanzee and a human.

We next compared the magnitude of the morphological difference between the two hominoid species with that between various pairs of frog species. To estimate the overall degree of morphological difference (M) between two species (X and Y), we used the formula

$$M = \frac{1}{n} \sum_{i=1}^{n} \frac{(|\bar{x}_i - \bar{y}_i|)}{\bar{\sigma}_i}$$

where n is the number of traits, $\bar{x}_i$ and $\bar{y}_i$ are the mean values of the relative length of the ith trait, in species X and Y, respectively, and $\bar{\sigma}_i$ is the mean standard deviation (*12*) for the ith trait. Thus, M is the average number of standard deviations by which the two species differ per trait measured.

As shown in Fig. 1, M increases as we successively compare frogs that are further apart in the taxonomic classification. The most dissimilar frogs that we compared are those which taxonomists assign to different suborders. We found that frogs belonging to different suborders differ by a mean M value of 4.0 (standard error 0.4).

The chimpanzee-human comparison gives an M value of 4.5. This value falls above the mean found for frogs belonging to separate suborders. Thus, the results in Fig. 1 give no support to those who suspected that the chimpanzee-human difference would be very small if evaluated with criteria used to distinguish among frog taxa (*13*).

The observation that M is related approximately linearly to the taxonomic distance scale for frogs (Fig. 1) and mammals (*14*) is consistent with the intriguing possibility that M is a satisfactory measure of our intuitive concept of how different animals are at the organismal level.

In summary, we conducted a quantitative comparative study of body shapes, the results of which are consistent with the proposal that the morphological difference between chimpanzees and humans is large in relation to the structural gene differences between the two species. So long as this proposal was based in part on qualitative estimates of

Table 1. Quantitative comparison of the body shapes of humans and chimpanzees by means of frog criteria. The $\bar{x}$ and $\bar{y}$ values are the means of the standarized lengths (see text) of the traits measured. The σ_x and σ_y values are the standard deviations of the standardized lengths.

Frog trait*	Relative trait length				t value	Probability of identity (P)
	Humans		Chimpanzees			
	$\bar{x}$	σ_x	$\bar{y}$	σ_y		
(i) Shank length	.224	.005	.163	.004	33.5	$< 10^{-9}$
(ii) Head length	.067	.004	.102	.004	22.1	$< 10^{-9}$
(iii) Nostril-lip	.011	.002	.024	.002	16.4	$< 10^{-9}$
(iv) Forearm length	.158	.007	.190	.005	12.9	$< 10^{-9}$
(v) Vertebral length	.372	.011	.340	.010	7.6	4.3×10^{-8}
(vi) Eye-nostril	.014	.001	.017	.002	5.0	3.3×10^{-5}
(vii) Head width	.056	.003	.060	.003	3.4	2.4×10^{-3}
(viii) Eye-tympanum	.053	.003	.057	.005	2.5	1.8×10^{-2}
(ix) Toe length	.046	.002	.048	.002	2.5	1.8×10^{-2}

*The measurements used on frogs are described and illustrated in Jameson *et al.* (*5*). The corresponding traits in humans and chimpanzees were measured as follows: (i) maximum length of tibia; (ii) anterior edge of premaxillae to posterior-most projection of occipital condyles; (iii) center of the bottom edge of nostril opening to bottom edge of premaxillae, excluding teeth; (iv) maximum length of ulna; (v) ventral length of articulated vertebral column, from axis to end of sacrum; (vi) central posterior edge of lacrimal bone to anterior-most point of suture along midline of paired nasal bones; (vii) greatest width across maxillae; (viii) central posterior edge of lacrimal bone to nearest anterior point of external auditory meatus; (ix) maximum length of third metatarsal.

morphological difference, some biologists were understandably reluctant to accept them. The taxonomists' judgment has now been supported by a quantitative approach which seems to avoid a bias in favor of hominoids, confirming that morphological evolution and structural gene evolution can proceed at independent rates. Knowledge of this independence has generated new ideas about the mechanism of evolution. These ideas have been discussed in review articles (*15*).

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4. Another reason for doubt about the large morphological differences among mammals came from Schopf *et al.* who argued that humans have a bias toward detecting morphological differences among more complex creatures, like mammals [T. J. M. Schopf, D. M. Raup, S. J. Gould, D. S. Simberloff, *Paleobiology* **1**, 63 (1975)]. Although we are not convinced that frogs are simpler morphologically than mammals, we admit that the possibility exists, So, the Schopf *et al.* argument could apply to the case where one is comparing morphological evolution in frogs and mammals. We have overcome this problem by using homologous traits for the comparison of morphological evolution in the two groups.
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6. Although frog taxonomists do not restrict their attention to comparison of body shape, we feel that the major part of what a taxonomist perceives when first confronting a potential new species is the degree to which it differs in body shape from known species.
7. Although morphological studies in frogs are commonly made on pickled specimens, it is unusual for museums to preserve whole carcasses of mammals. Likewise, it is difficult to make measurements on live chimpanzees. We therefore decided to make measurements on osteological features that underlie the traits which frog workers measured. Thus, instead of measuring shank length, we measured tibia length. In most cases, the decision as to which osteological feature to measure was straightforward. However, in the case of head width, it is apparent that in frogs this refers to the maximum distance across the maxillae, whereas in humans the maximum width refers to the cranial width, or distance across the zygomatic arches. As our goal was to deal with homologous traits, our decision was to measure maximum width across the maxillae in humans and chimpanzees. We suspect that our decision to use osteological measurements on hominoids but soft-part measurements on frogs is probably biased in favor of detecting differences among frogs. It is known that, whereas one can easily distinguish between human races on the basis of morphology of soft parts, it is more difficult to do so with skeletons.
8. Unexpectedly, our study was hampered by the scarcity of complete human skeletons in American anthropological and medical collections. Despite extensive searching we did not succeed in finding a single such specimen in anthropology departments at universities or museums in California, Massachusetts, or New York. One department has a large collection of human skeletons, but none of the many skeletons examined was complete enough for this study. In many cases, skeletons at medical schools could not be used because there was doubt about their homogeneity—that is, it was likely that the bones in one skeleton were not all from the same individual. Of the 16 usable skeletons eventually located in medical schools, no information was available about sex, age, or exact place of origin.
9. The adult chimpanzees that we measured are fairly similar to humans in combined length of the nine traits; the average combined lengths are 166.68 cm for humans and 150.67 cm for chimpanzees.
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12. The weighted standard deviation is defined as

$$\sqrt{(N_x\sigma_x^2 + N_y\sigma_y^2)/(N_x + N_y - 2)}$$

where N_x and N_y are the number of specimens measured in species X and Y, respectively. This corrects the average standard deviation for differing sample sizes in the species measured.
13. Although our approach ignores problems of allometry [S. J. Gould, *Biol. Rev.* **41**, 587 (1966)], we point out that M is used here only as a measure of difference in body shape, regardless of the causes underlying this difference.
14. L. M. Cherry and A. C. Wilson, unpublished work.
15. A. C. Wilson, S. S. Carlson, T. J. White, *Ann. Rev. Biochem.* **46**, 573 (1977); A. C. Wilson, T. J. White, S. S. Carlson, L. M. Cherry, in *Molecular Human Cytogenetics*, R. S. Sparkes, D. E. Comings, C. F. Fox, Eds. (Academic Press, New York, 1977), pp. 375–393.
16. This classification is questioned by some herpetologists, who feel that the *Hyla regilla* subspecies would be more appropriately classified as populations [S. M. Case, P. G. Haneline, M. F. Smith, *Syst. Zool.* **24**, 281 (1975)].
17. The frogs compared were (see Fig. 1): Subspecies (sS) within a species (see *16*): *Hyla regilla palouse* vs. *H. r. cascadae, H. r. palouse* vs. *H. r. regilla; H. r. palouse* vs. *H. r. pacifica; H. r. cascadae* vs. *H. r. regilla; H. r. cascadae* vs. *H. r. pacifica; H. r. regilla* vs. *H. r. pacifica*. Species (S) within a genus: *Hyla eximia* vs. *H. crucifer; H. eximia* vs. *H. femoralis; H. eximia* vs. *H. squirella; H. eximia* vs. *H. chrysoscelis; H. crucifer* vs. *H. femoralis; H. crucifer* vs. *H. squirella; H. crucifer* vs. *H. chrysoscelis; H. femoralis* vs. *H. squirella; H. femoralis* vs. *H. chrysoscelis; H. squirella* vs. *H. chrysoscelis*. Genera (G) within a subfamily: *Hyla eximia* vs. *Phrynohyas venulosa; H. eximia* vs. *Pternohyla fodiens; Phrynohyas venulosa* vs. *Pternohyla fodiens; Phyllomedusa tarsius* vs. *Pachymedusa dachnicolor; Phyllomedusa tarsius* vs. *Agalychnis annae; Pachymedusa dachnicolor* vs. *A. annae*. Subfamilies (sF) within a family: *Phyllomedusa tarsius* vs. *Hyla eximia, Pachymedusa dachnicolor* vs. *Phrynohyas venulosa, Agalychnis annae* vs. *Pternohyla fodiens*. Families (F) within a superfamily—*Bufo americanus* vs. *Phyllomedusa tarsius, B. americanus* vs. *Hyla eximia*. Superfamilies (SF) within a suborder—*Bufo americanus* vs. *Rana pipiens, Hyla eximia* vs. *R. pipiens*. Suborders (sO) within an order—*Xenopus laevis* vs. *Bufo americanus, X. laevis* vs. *Hyla eximia, X. laevis* vs. *Rana pipiens*. (Because the eye-tympanum measurement cannot be made in *Xenopus*, the subordinal comparisons are based on eight trait lengths, instead of nine. The data have been restandardized accordingly.)
18. We thank D. L. Jameson for supplying the raw measurements for the species of *Hyla*; S. Anderson, P. Goldstein, H. Shapiro, P. Ward, D. Gunner, R. G. Zweifel, R. C. Stebbins, and the Office of Learning Resources (University of California San Diego School of Medicine) for access to specimens used in this study; and J. L. Patton, M.-C. King, D. B. Wake, S. M. Beverley, T. J. White, T. M. Hursh, S. Kortlucke, V. M. Sarich, J. Peto, J. Kunkel, and S. Carr for discussions. Supported by research grants from NSF and NIH, and by funding administered under the genetics joint doctoral program, San Diego State University, San Diego, and the University of California, Berkeley.
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Oral Cocaine: Plasma Concentrations and Central Effects

Abstract. *Cocaine (2.0 milligrams per kilogram) given by the oral route is at least as effective as the same dose given intranasally. Cocaine is not detected in the plasma until 30 minutes after oral administration, but peak plasma concentrations are similar after both routes. The subjective "highs" in man are greater after oral than after intranasal administration.*

We have measured and compared both plasma concentrations and subjective effects of cocaine following oral and intranasal administration. To our knowledge, concentrations of cocaine in plasma after oral administration have not been reported. Andean Indians have chewed coca leaves religiously since ancient times with a reputed beneficial effect on endurance and hunger. It has been estimated that 3 to 4 million people in Peru and Bolivia now chew coca leaves (*1*). Despite this wide usage, it is commonly assumed in the United States that cocaine is inactive when given orally (*2*). Textbooks of pharmacology (*3*) state that cocaine is hydrolyzed in the gastrointestinal tract and rendered ineffective. A result of this belief has been a marked disinterest by modern street and laboratory researchers in the effects of oral cocaine. Nevertheless, accidental deaths from overdosage of ingested cocaine have been reported (*4*).

Cocaine is still used in otolaryngology and anesthesiology because of its effectiveness as a local anesthetic and vasoconstrictor. In animals, it is known to block the reuptake of endogenous amines in the sympathetic nervous system and to potentiate the effects of exogenous amines (*3*). Socially, cocaine is considered to be a major drug of abuse that has dramatically increased in popularity. It produces an intense euphoria shortly after intranasal application and

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