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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2. G. G. Simpson, *Principles of Animal Taxonomy* (Columbia Univ. Press, New York, 1961); G. G. Simpson, in *Classification and Human Evolution*, S. L. Washburn, Ed. (Aldine, Chicago, 1963), p. 1; L. Van Valen [*Am. J. Phys. Anthropol.* **30**, 295 (1969)] has suggested that humans and chimpanzees be placed in separate superfamilies.
3. D. J. Merrell, *Science* **189**, 838 (1975).
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.
5. D. L. Jameson, J. P. Mackey, R. C. Richmond, *Proc. Calif. Acad. Sci.* **33**, 551 (1966); D. L. Jameson and R. C. Richmond, *Evolution* **25**, 497 (1971).
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.
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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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has gained an almost mythic position in the drug pantheon. Recent studies have defined the euphorigenic and cardiovascular effects of both intranasal and intravenous cocaine (*5*). Because the widespread custom of chewing coca leaves belied the current opinion that cocaine is not effective orally, we investigated the comparative efficacy of oral and intranasal cocaine.

The subjects (ages 25, 25, 31, and 32 years) were healthy males who had used cocaine previously for recreational purposes. They were informed about the study and agreed to participate (*6*). In an initial set of experiments, a 10 percent solution of cocaine hydrochloride (2.0 mg per kilogram of body weight) was applied topically to the nasal mucosa. The total dose ranged from 115 to 246 mg (*7*). In subsequent experiments, the subjects swallowed the same dosage (that is, 2.0 mg per kilogram of body weight) of crystalline cocaine hydrochloride in a gelatin capsule (*8*). The cocaine was administered a minimum of 4 hours after a light breakfast. In all experiments, we obtained 10-ml samples of blood before the cocaine was administered, and samples were again taken 15, 30, 60, 120, and 240 minutes afterward. Samples were also obtained 20, 40, 50, 70, 80, 90, 180, 300, and 360 minutes after oral administration. Blood samples were collected in heparinized glass syringes, and 250 μl of a saturated solution of sodium fluoride was added immediately to prevent the in vitro hydrolysis of cocaine (*9*). The plasma was then separated, and the concentration of cocaine was measured by previously reported gas-liquid chromatographic methods in which a nitrogen-sensitive detector that specifically distinguished cocaine from its metabolites was used (*10*). Before the drug was administered and again at regular intervals after administration the subjects were asked to rate themselves on a 6-point "high" scale. The subjects also completed the morphine and amphetamine significant scales of the Addiction Research Center Inventory (ARCI) before drug administration and again ½ and 2 hours after cocaine was given (*11*).

Cocaine was not detected in the plasma until 30 minutes after oral administration, and it then increased rapidly for the next 30 minutes. Peak plasma concentrations (range 104 to 424 ng/ml) occurred at 50 to 90 minutes and then decreased gradually over the next 4.5 to 5 hours (Table 1). After intranasal application, cocaine was detected in the plasma by 15 minutes, reached peak concentrations (range 61 to 408 ng/ml) at 60 to 120 minutes, and then decreased gradually over the next 2 to 3 hours (Table 2). The difference in mean peak plasma concentrations for the two routes of administration was not significant. However, in three of four subjects the peak plasma concentrations were higher after oral cocaine than after intranasal cocaine at the same dosage.

Prior to cocaine administration, all subjects rated themselves as having no subjective drug effects. After oral administration, measurable effects on the "high" scale occurred within 15 to 75 minutes and peaked at 45 to 90 minutes. Peak effects lasted as long as 60 minutes and then declined over the next 4 hours (Table 1). After intranasal application measurable effects on the "high" scale were noted within 15 to 30 minutes, peaked from 15 to 60 minutes, lasted as long as 60 minutes, and then decreased over the next 2 to 3 hours (Table 2). Peak "highs" after oral administration were significantly greater than those reported after intranasal application (Student's t-test = 4.3; $P < .05$). The total number of positive responses on the morphine and amphetamine significant scales of the ARCI were identical after both the oral and intranasal routes of administration (*12*). However, all four subjects responded positively to the descriptors, "I have a floating feeling" and "My head feels light," after oral administration but not after intranasal application.

Table 1. Time course of cocaine concentrations in the plasma and self-reports of "highs" after oral administration. The values are expressed as means ± standard errors. The numbers in parentheses indicate the number of subjects.

Time (minutes)	Cocaine in plasma (ng/ml)	"High" rating
0	0.0 (4)	0.0 (4)
15	0.0 (4)	0.6 ± 0.3 (4)
20	0.0 (3)	
30	54.2 ± 24.2 (4)	0.8 ± 0.4 (4)
40	147.2 ± 59.7 (4)	
45		2.8 ± 0.8 (4)
50	197.6 ± 75.4 (4)	
60	209.8 ± 57.9 (4)	2.9 ± 0.8 (4)
70	168.3 ± 40.5 (3)	
75		3.2 ± 0.2 (4)
80	152.0 ± 31.0 (3)	
90	120.6 ± 12.1 (3)	2.9 ± 0.4 (4)
105		2.5 ± 0.6 (4)
120	99.2 ± 15.6 (4)	2.0 ± 0.6 (4)
180	44.7 ± 8.1 (4)	0.9 ± 0.4 (4)
240	21.0 ± 4.5 (4)	0.2 ± 0.2 (4)
300	10.8 ± 3.7 (4)	0.0 (4)
360	6.2 ± 2.7 (4)	0.0 (4)

Table 2. Time course of cocaine concentrations in the plasma and self-reports of "highs" after intranasal application. The values are expressed as means ± standard errors. The numbers in parentheses indicate the number of subjects.

Time (minutes)	Cocaine in plasma (ng/ml)	"High" rating
0	0.0 (4)	0.0 (4)
15	36.2 ± 9.4 (4)	1.1 ± 0.6 (4)
30	93.0 ± 40.7 (4)	2.0 ± 0.4 (4)
60	160.6 ± 73.8 (4)	1.9 ± 0.6 (4)
120	95.0 ± 15.6 (4)	0.8 ± 0.2 (4)
240	35.6 ± 10.8 (4)	0.0 (4)

Despite the common belief that cocaine is not effective when given orally, there is evidence to the contrary. Chewing coca leaves has been a part of the culture of South American natives for more than a millennium. It can reasonably be presumed that any benefit derived from this practice is from the cocaine contained in the leaves. Whether cocaine is primarily absorbed from the oropharynx or more distally in the stomach or small intestine has never been clear (*13*). Freud in 1884 (*14*) described euphoria, decreased fatigue, and alterations in his pulse and respiration after oral administration of cocaine. Among other suggested uses for cocaine Freud advocated it as a treatment for digestive disorders of the stomach. Post *et al.* (*15*) gave cocaine orally (dose range 30 to 200 mg) to five depressed patients; they found no therapeutic effect but did note a reduction in total sleep and rapid eye movement (REM) sleep. There was also a rebound in REM sleep after the cocaine was discontinued. To our knowledge, Woods *et al.* (*16*) were the only investigators to measure plasma concentrations of cocaine after oral administration in animals. They administered cocaine orally to dogs (15 mg per kilogram of body weight) and found peak plasma concentrations of 1000 ng/ml approximately 2 hours after the drug was given. Our dosage was much less and our peak values were all less than the minimum they were able to detect.

Our findings indicate that cocaine is well absorbed from the gastrointestinal tract. Measurable absorption does not reliably occur until 30 minutes after oral administration. The reason for this delay is not clear. The gelatin capsules, which we used to eliminate the possibility of absorption from the oropharynx, may not have dissolved immediately (*8*). A more likely explanation is that cocaine ($pK_a = 8.6$) is ionized in the acid medium of the stomach and is not well absorbed until it reaches the alkaline environment of the small intestine. Andean Indians may be empirically exploiting

the same principle when they chew coca leaves with alkaline material to enhance its subjective effects (*1*). Once absorption begins from the gastrointestinal tract it is rapid, and peak plasma concentrations are reached 20 to 60 minutes later.

There was no significant difference in the peak plasma concentrations between the two routes of administration. Once the peak concentrations occurred for both routes, the levels of cocaine decreased in a log-linear fashion with the apparent half-life in plasma being 0.9 hour after the oral route and 1.3 hours after the intranasal route. The difference in the half-lives for the two routes was not significant (*17*).

Maximum subjective effects on the "high" scale occurred earlier (15 to 60 minutes) after intranasal application than after oral administration (45 to 90 minutes). This is probably a reflection of the delay in absorption of cocaine from the gastrointestinal tract. Three of the four subjects experienced more intense "highs" after oral administration. Peak "highs" after both routes were maintained for as long as 60 minutes, which is in contrast to the reports of street users. These reports indicate peak psychological "highs" within 3 to 5 minutes and almost no effect 15 minutes after intranasal application.

This confirmation of old knowledge raises a number of issues. First one might suspect that a certain amount of the activity of intranasal cocaine may be due to the actions of material passed through the nasopharynx and swallowed. Second, the mystique of cocaine abuse with its golden spoons, rolled banknotes, and inhalation rituals should be somewhat dampened since the drug appears to be as effective if taken orally. Finally, one might conclude that it is scientifically imprudent to ignore reports which have been consistent for 2000 years.

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6. The selection of subjects and the consent procedures for this study were approved by the Human Investigations Committee of Yale University and by the National Institute on Drug Abuse.
7. The cocaine was supplied through the courtesy of R. Willette of the National Institute on Drug Abuse.
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