tions in the H_2O molecule and OH^- ion. No indication of the H_3O^+ species is distinguishable in the spectra. Thus, the degree of dissociation of water cannot be determined from the Raman data. A lower bound on ion concentration can be estimated by assuming that mobile protons are the dominant charge carriers. By using a classical conductivity model and a mean free path of a molecular dimension, we estimate the proton concentration to be one proton for every ten original H_2O molecules at pressures above several tens of gigapascals. Thus, we estimate the degree of dissociation of water to be between 10 and 100% above 20 GPa and 1200 K.

At depths where the pressure exceeds 100 GPa and temperatures are several thousand degrees kelvin, molecules and ions are expected to dissociate and form dense, stiff monatomic or H–O–C–N species or both. This statement is based on observations of molecular dissociation at high shock pressures and temperatures. For example, N_2 starts to dissociate at only 30 GPa at 6000 K (*23*) but remains molecular to 130 GPa at 300 K (*24*), illustrating that high temperatures inside Uranus are expected to drive dissociation. Shock-compression curves for carbon (diamond) (*25*), nitrogen (*23*), and oxygen (*26*) and theoretical curves for monatomic simple-cubic N (*27*) and O (*28*) at 0 K are plotted as pressure versus volume in Fig. 3. The curves for the monatomic phases at 0 K are all steep; the shock-compression curves of liquid nitrogen and oxygen have comparable steep slopes above 60 GPa and 10,000 K. When dissociation is completed, intermolecular repulsion is replaced by stiffer interatomic repulsion. This transition is expected to proceed continuously along the planetary isentrope. In general, elements probably do not phase separate but form mixtures or react with each other to form compounds, which are nearly incompressible as in Fig. 3. Such materials might have high melting temperatures and condense out of the solution of the fluid "ice" mixture. Rock also has a stiff equation of state at high pressures. Thus, at pressures above 100 GPa planetary materials are probably close to their limiting compression, which contributes somewhat to the large volume of Uranus. That is, pressures above 100 GPa probably do not cause significant compression of the phases present because of their small compressibilities. Figure 3 suggests that all materials in the deep interior are dense, stiff materials having a high bulk modulus such as the diamond phase of carbon, which has been suggested to form inside Uranus (*29*).

REFERENCES AND NOTES

1. N. F. Ness *et al.*, *Science* **233**, 85 (1986).
2. W. B. Hubbard and J. M. MacFarlane, *J. Geophys. Res.* **85**, 225 (1980).
3. D. J. Stevenson, *Annu. Rev. Earth Planet. Sci.* **10**, 257 (1982).
4. M. D. Desch *et al.*, *Nature* **322**, 42 (1986).
5. R. L. Kirk and D. J. Stevenson, *Astrophys. J.* **316**, 836 (1987); D. J. Stevenson, *Bull. Am. Astron. Soc.* **19**, 851 (1987) and private communication.
6. W. B. Holzapfel, *J. Chem. Phys.* **50**, 4424 (1969).
7. T. V. Gudkova *et al.*, *Astron. Vestn.* (in Russian) **22**, 23 (1988).
8. J. M. Walsh and M. H. Rice, *J. Chem. Phys.* **26**, 815 (1957).
9. A. C. Mitchell and W. J. Nellis, *ibid.* **76**, 6273 (1982).
10. I. I. Sharipdzhanov *et al.*, *Combust. Explos. Shock Waves* (English translation) **19**, 668 (1984).
11. G. A. Lyzenga *et al.*, *J. Chem. Phys.* **76**, 6282 (1982).
12. H. G. David and S. D. Hamann, *Trans. Faraday Soc.* **55**, 72 (1959); S. D. Hamann and M. Linton, *ibid.* **65**, 2186 (1969).
13. N. C. Holmes *et al.*, *Phys. Rev. Lett.* **55**, 2433 (1985).
14. R. D. Dick, *J. Chem. Phys.* **74**, 4053 (1981).
15. W. J. Nellis *et al.*, *ibid.* **75**, 3055 (1981).
16. A. C. Mitchell *et al.*, in *High-Pressure Science and Technology*, B. Vodar and Ph. Marteau, Eds. (Pergamon, Oxford, 1980), vol. 2, pp. 1048–1050.
17. H. B. Radousky *et al.*, in *Shock Waves in Condensed Matter*, Y. M. Gupta, Ed. (Plenum, New York, 1986), pp. 467–472.
18. M. Ross, in *High Pressure in Research and Industry*, C.-M. Backman, T. Johannisson, L. Tegner, Eds. (Arkitektkopia, Uppsala, 1982), vol. 2, pp. 721–727.
19. D. C. Hamilton, thesis, University of California (1986) (available as Lawrence Livermore National Laboratory report UCRL-53768); D. C. Hamilton *et al.*, *J. Chem. Phys.* **88**, 5042 (1988). A high velocity impactor generates a shock wave by striking the front wall of a cavity containing a liquid specimen. Electrical conductivity is measured by inserting two thin metal foils into the specimen through the rear wall. The specimens are initially insulators. As the shock wave reaches the electrodes, the specimen becomes conductive and current flows. The change in the conductivity of the specimen is detected as a voltage deflection on fast-sweep oscilloscopes. Shock temperature is measured by allowing thermal radiation emitted by the shock front to exit the specimen holder through a window in the rear wall. The emitted light is reflected to a fast multichannel optical pyrometer. EOS data for synthetic Uranus are obtained by measuring the velocities of the impactor and of the resulting shock in the specimen and applying the Rankine-Hugoniot equations.
20. The upper limit of detection is $\gtrsim 100$ (ohm-cm)$^{-1}$. Conductivities larger than 20 (ohm-cm)$^{-1}$ were measured for shocked liquid O_2 [73 ± 10 (ohm-cm)$^{-1}$ at 43 GPa], liquid N_2 [47 ± 6 (ohm-cm)$^{-1}$ at 62 GPa], and liquid benzene [46 ± 9 (ohm-cm)$^{-1}$ at 50 GPa].
21. See, for example, D. J. Stevenson, *Rep. Prog. Phys.* **46**, 555 (1983).
22. F. H. Ree, *J. Chem. Phys.* **81**, 1251 (1984).
23. W. J. Nellis *et al.*, *Phys. Rev. Lett.* **53**, 1661 (1984); H. B. Radousky *et al.*, *ibid.* **57**, 2419 (1986); M. Ross, *J. Chem. Phys.* **86**, 7110 (1987).
24. R. Reichlin *et al.*, *Phys. Rev. Lett.* **55**, 1464 (1985).
25. M. N. Pavlovskii, *Sov. Phys. Solid State* **13**, 741 (1971).
26. W. J. Nellis and A. C. Mitchell, *J. Chem. Phys.* **73**, 6137 (1980).
27. A. K. McMahan and R. LeSar, *Phys. Rev. Lett.* **54**, 1929 (1985).
28. A. K. McMahan, private communication.
29. M. Ross, *Nature* **292**, 435 (1981).
30. We thank D. J. Stevenson and V. N. Zharkov for helpful discussions of their models. We thank A. K. McMahan for use of his unpublished 0 K isotherm for simple cubic O. One of us (M.N.) acknowledges support from the LLNL Branch of the University of California Institute of Geophysics and Planetary Physics and NASA grant NAGW-104. This work was performed under the auspices of the U.S. Department of Energy by the Lawrence Livermore National Laboratory under contract number W-7405-ENG-48, with partial support from the U.S. National Aeronautics and Space Administration under contract W-16, 180.

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Hand of *Paranthropus robustus* from Member 1, Swartkrans: Fossil Evidence for Tool Behavior

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New hand fossils from Swartkrans (dated at about 1.8 million years ago) indicate that the hand of *Paranthropus robustus* was adapted for precision grasping. Functional morphology suggests that *Paranthropus* could have used tools, possibly for plant procurement and processing. The new fossils further suggest that absence of tool behavior was not responsible for the demise of the "robust" lineage. Conversely, these new fossils indicate that the acquisition of tool behavior does not account for the emergence and success of early *Homo*.

THE GENUS *Paranthropus* GENERALLY has been assumed to consist of small-brained, large-toothed early hominids that subsisted on a vegetarian diet (*1*). Stone artifacts found with *Paranthropus* have been attributed to their contemporaries of the genus *Homo* (*2*). With a small brain and a vegetarian diet, it was thought that *Paranthropus* had neither the intellect nor the impetus to engage in tool behavior (*3*, *4*). Further, the lack of tool behavior was thought to have contributed to the eventual extinction of *Paranthropus* in the early middle Pleistocene. Most inferences about *Paranthropus* have come from studies of craniodental remains (*5*). Until now the only postcranial fossils referred to *Paranthropus* are seven bones from Swartkrans (*6*) and four from Kromdraai (*7*).

There are 22 hand bones among 37 new hominid postcranials from Swartkrans (*8*).

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These include one nearly complete pollical (=thumb) metacarpal, one complete pollical distal phalanx, three finger metacarpals, six proximal phalanges, eight middle phalanges, two distal phalanges, and a triquetral. Of the new hand fossils, eight are from Member 1. Member 1 (*9*), the earliest of five members, is dated at 1.8 million years (*10*). It has yielded remains of approximately 130 hominid individuals. The attribution of individual fossils to *Paranthropus* is complicated by the presence of a second hominid taxon (*Homo* cf. *erectus*) at Swartkrans. In Member 1, however, more than 95% of the craniodental remains are attributed to *Paranthropus*. This fact suggests that there is an overwhelming probability that any one specimen recovered from Member 1 samples *Paranthropus*. Equally important in this regard, morphological criteria can also be used to distinguish the two hominids at Swartkrans. For example, whereas SK 84 resembles a thumb metacarpal from East Africa that is clearly associated with a *Homo erectus* skeleton (WT 15000), both SK 84 and WT 15000 share a feature that is distinct to them (and presumably distinct to *Homo erectus*), and both differ from a new pollical metacarpal, SKX 5020. This suggests strongly that SKX 5020 ought to be assigned to *Paranthropus*. SKX 5016, a pollical distal phalanx, is consistent both metrically and morphologically with SKX 5020. SKX 5016 is incompatible in size with SK 84 (*11*).

These new fossils provide the first direct morphological evidence that bears on the question of whether or not *Paranthropus* had the capacity to make and use tools. When comparisons are made between *Paranthropus* and *Homo habilis* (from Bed I, Olduvai Gorge), the criteria used to infer the advent of a well-developed precision grip in *Homo habilis* (*12–14*) are present in *Paranthropus*. The hand evidence no longer supports the idea that early *Homo* is distinguished from *Paranthropus* by morphological adaptations to precision grasp (*15*) and tool behavior (*16*).

Numerous comparative and functional studies of living primates have identified morphological correlates of precision and power grasping (*13, 17–19*). These and other studies have documented the advent of human-like precision grasping in early hominids (*12, 13, 17–19*). The fossil record reveals that early hominids such as *Australopithecus afarensis*, dated at more than 3.0 million years old, did not possess a derived, human-like thumb or fingers (*20*). However, by approximately 1.8 million years ago (600,000 years after stone artifacts appear in the fossil record) hominid fossils show clear signs of a more human-like thumb and fingers.

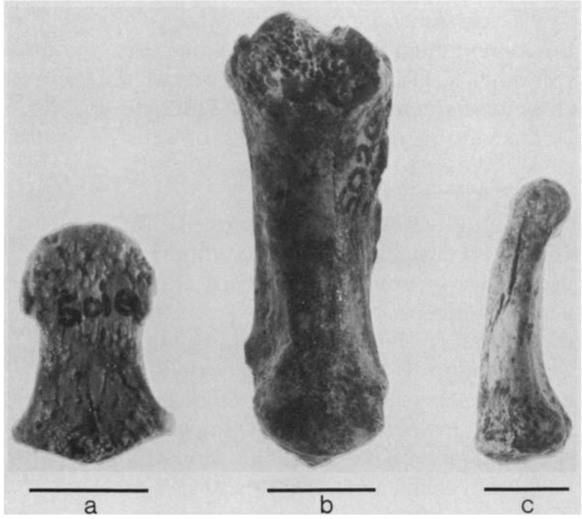

Fig. 1. (**a**) Volar surface of SKX 5016, pollical distal phalanx from Member 1. Note the broad apical tuft and large basal pit for insertion of an apparently well-developed, distinctly human-like flexor pollicis longus muscle. (**b**) SKX 5020; volar surface of first metacarpal from Member 1. This bone has a number of derived, human-like traits and is compatible in size with the SKX 5016 distal phalanx when the two are compared to an interspecific (African ape and human) regression of distal phalanx length on metacarpal length (*11*). (**c**) Manual proximal phalanx SKX 5018 from Member 1 (lateral view). SKX 5018 has a human-like curvature (included angle) while retaining a primitive (pongid-like) overall morphology (see Fig. 3). All scales, 1 cm.

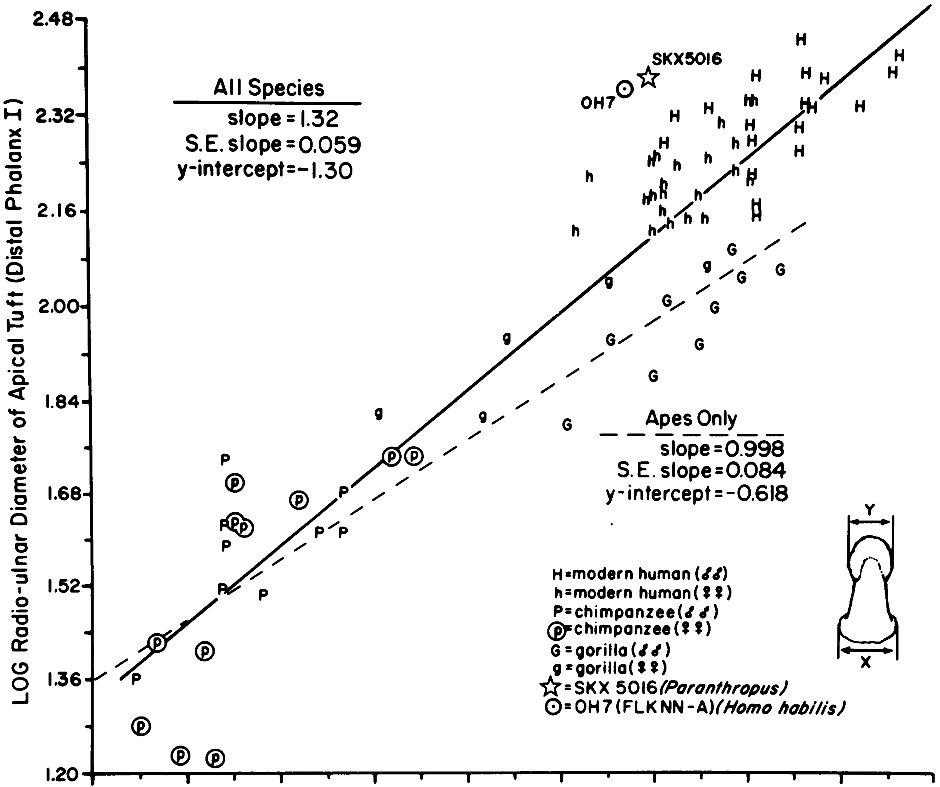

Fig. 2. Regression (least squares) of apex breadth on radio-ulnar breadth of the pollical distal phalanx. Humans display positive allometry of apical breadth (=expanded tuft) which reflects the broad, fleshy volar tip of the human thumb. Apes (dashed line) reveal an isometric relationship (slope, 0.998) of thumb tip to thumb base. Note the extreme breadth of the *Paranthropus* thumb which indicates an enhanced volar surface for precision grasping. OH7 from Bed I, Olduvai Gorge (roughly the same geologic age as Swartkrans Member 1), has a similar thumb morphology.

The new Swartkrans fossils are direct evidence by which to assess the manual dexterity of *Paranthropus robustus* and thus to judge the potential for tool behavior in the "robust" australopithecines. The thumb is the most diagnostic element of the human hand in that the thumb is relatively long in comparison to the fingers (*21*), the intrinsic thumb muscles (*22*) are well differentiated and a specifically human muscle, the flexor pollicis longus, is present. The flexor pollicis longus inserts on a large area on the anterobasal surface of the distal phalanx, and since no monkey or ape possesses a flexor pollicis

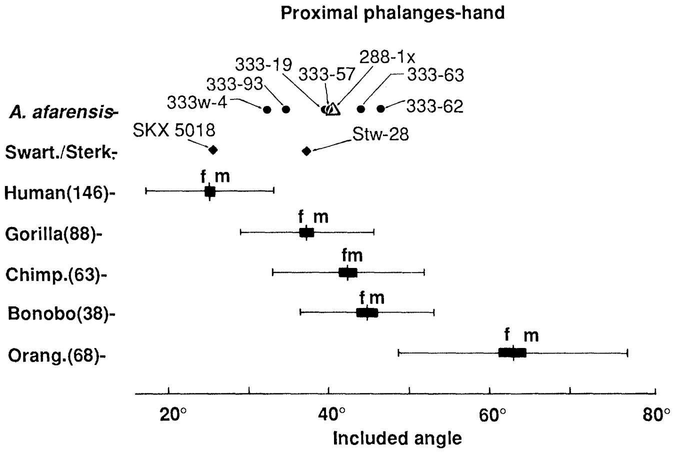

Fig. 3. Curvatures of manual proximal phalanges. Included angles are size-independent measures of longitudinal curvature. SKX 5018 is straight and essentially on the human mean whereas Stw-28, a presumptive gracile australopithecine from Member 4, Sterkfontein, and the geologically earlier *A. afarensis* phalanges fall within the African ape ranges. Vertical lines are group means, black bars are 95% confidence limits of the mean, and long bars are 95% limits of the population. *Australopithecus afarensis* from site AL 333 = ●; *A. afarensis* ("Lucy") = △. Male and female means = m and f.

longus muscle, its bony counterpart on the distal phalanx is lacking also in monkeys and apes. The thumb of *Paranthropus* did possess a flexor pollicis longus muscle as judged by the well-defined area of insertion proximally on the volar aspect of SKX 5016 (Fig. 1a).

Another distinctly human feature of SKX 5016 is the broad, expanded apical tuft on the distal end of the phalanx. A broad apical tuft is found on all five human manual rays but, among extant primates, it reaches its acme in the human thumb. These tufts have the effect of broadening the bony support for the well-innervated and well-vascularized, fleshy fingertip. Neither apes nor monkeys have enlarged fleshy pads on their fingertips and neither do these primates have expanded bony tufts on their distal phalanges. The relative development of the apical tuft on the human thumb is shown in Fig. 2. When breadth of the tuft is compared to the basal diameter of the distal phalanx, a dramatic size increase is seen in humans and especially *Paranthropus* and *Homo habilis* (Fig. 2). The interspecific regression, which is heavily weighted by the human sample, yields a positive slope (1.32). The African ape regression, with a slope of 0.998, reveals an isometric relation between tuft and phalangeal size in the apes. While apical tufting is pronounced in humans, it is even more so in *Paranthropus* (and *Homo habilis*). As judged by SKX 5016, the thumb of *Paranthropus* undoubtedly had a very pronounced fleshy tip.

The pollical metacarpal in humans is thick and has a very broad basal articular surface. SKX 5020, is a human-like, right first metacarpal with a thick shaft and a broad base. The saddle joint at the base of the thumb in Old World monkeys, apes, and humans allows concomitant flexion and axial rotation of the thumb so that its volar surface opposes those of the fingers. While Old World monkeys, apes, and humans all have a saddle joint at the base of the thumb, humans have an exceptionally broad basal joint. The increased surface area in the human thumb serves to reduce joint stress in the form of compressive forces that result from contraction of the powerful flexor pollicis longus and hypertrophic intrinsic thumb muscles. Joint compression forces in the carpometacarpal joint of humans average 12.0 kg during simple pinching; these forces reach 120 kg during strong grasping (*23*). Finally, the human thumb has a well-developed opponens pollicis muscle that serves to rotate the thumb into opposition with the fingers. An indication of the strong development of this muscle is seen at its insertion site on the metacarpal shaft at which point in humans a crest or other indication is normally found. SKX 5020 displays a human-like crest on its lateral margin (Fig. 1b).

The finger bones (digits II through V) of *Paranthropus* also show signs of a well-developed precision grip and a lessened potential for power grasping. Evidence of a derived, human-like precision grip is suggested by the short, straight proximal phalanges of rays II through V. Whereas manual proximal phalanges II through V in earlier hominids such as *Australopithecus afarensis* (and *A. africanus*) possess ape-like curvatures and are relatively long (*24*), the proximal phalanges of *Paranthropus* lack primitive, ape-like curvatures (Fig. 3). SKX 5018, a complete proximal phalanx (Fig. 1c), has an included angle of 25.9°, essentially at the human mean of 24° and well outside of the 95% confidence limits of any ape mean. While this and other proximal phalanges from Swartkrans retain a somewhat primitive overall character (*25*), the reduced curvatures suggest a reduced emphasis on power grasping (compared to earlier hominids) and a diminished climbing ability.

Earlier assertions that *Paranthropus* was not a toolmaker or user (*26*) were not based on anatomical evidence. Earlier morphological and comparative evidence (*27*) consisted mainly of assumptions about the relation between brain volume (and intelligence) and cultural capacity. There were no fossils and, thus, there could be no discussion of relevant, diagnostic fossil evidence. The new Member 1 hand fossils indicate that the hand of *Paranthropus* was indeed "hominized." The human-like first metacarpal, the human-like first distal phalanx with its broad apical tuft and flexor pollicis longus insertion, and the short, straight fingers indicate that the robust australopithecines had much the same morphological potential for refined precision grasping and for tool behavior as do modern humans [and as did *Homo habilis* (*28*)].

Not only is the morphology of the hand of *Paranthropus* suggestive of tool behavior, but numerous bone and stone artifacts are also found in Member 1 and throughout Swartkrans (*29*). The bone artifacts are mostly shaft fragments that show signs of having been used for digging (*30*). The stone artifacts range in size from 13 g to 1257 g and have a primitive character (*31*). Given the widespread notion that *Paranthropus* lived on an essentially vegetarian diet consisting of hard food items (*32*), it might be that *Paranthropus* fashioned bone and stone implements and then used them for vegetable procurement and processing. If so, then perhaps *Paranthropus* invented or adapted tool behavior to vegetarian subsistence while the other early hominids applied their tools to a different dietary regime. In any case, the new evidence from Swartkrans demands a reassessment of traditional views of the robust australopithecines and long held notions that the advent of tool behavior and "culture" distinguished early *Homo* from other early hominids, that tools initiated the human career, and that, because of the lack of tool behavior (or the morphological potential for it), *Paranthropus* became extinct.

REFERENCES AND NOTES

1. J. T. Robinson, *Evolution* **8**, 324 (1954); J. T. Robinson (*3*); M. A. Wolpoff, *Am. J. Phys. Anthropol.* **39**, 375 (1973); E. L. Du Brul, *ibid.* **47**, 305 (1977); F. E. Grine, *S. Afr. J. Sci.* 77, 203 (1981).
2. J. T. Robinson, *Am. J. Phys. Anthropol.* **11**, 445 (1953); R. J. Mason, *S. Afr. Archeol. Bull.* **17**, 109 (1962); P. V. Tobias, *ibid.* **20**, 167 (1965).
3. J. T. Robinson, in *Evolution and Hominisation*, G. Kurth, Ed. (Fischer, Stuttgart, 1962), pp. 120–140.
4. ———, *S. Afr. Archaeol. Bull.* 17, 85 (1962).
5. R. Broom and J. T. Robinson, *Trans. Mus. Mem. 6* (1952); P. V. Tobias, *The Brain in Hominid Evolution* (Columbia Univ. Press, New York, 1971); Y. Rak, *The Australopithecine Face* (Academic Press, New York, 1983).

6. R. Broom and J. T. Robinson, *Nature* **164**, 841 (1949); J. R. Napier, *Br. Mus. Nat. Hist. Fossil Mamm. Afr. 17* (1959); J. T. Robinson in (*16*); G. P. Rightmire, *Science* **176**, 159 (1972); C. K. Brain, E. S. Vrba, J. T. Robinson, *Ann. Trans. Mus.* **29**, 55 (1974).
7. R. Broom and G. W. H. Schepers, *Trans. Mus. Mem. 2* (1946). There are other hominid postcranials described by Broom from Kromdraai. The TM 1517 hand bones are, in fact, those of a cercopithecoid monkey (personal observation; M. H. Day and G. M. B. Thornton, *Anthropos.* **23**, 91 (1986).
8. R. L. Susman and C. K. Brain, in preparation.
9. Member 1 is the earliest of five distinct members at Swartkrans. Member 1 corresponds to the former "orange" or "pink" breccia of Broom and Robinson. There is a minimum of 125 *Paranthropus* individuals represented by craniodental remains in Member 1. *Homo cf. erectus* is represented by only five individuals.
10. E. S. Vrba, in *Pretirage, 1^er^ Congres International Paleontologie Humaine*, F. DeLumley and M. A. DeLumley, Eds. (Centre National de la Recherche Scientifique, Nice, 1982), pp. 707–752.
11. SKX 5016 compares favorably to the larger of the two metacarpals (SKX 5020) from Swartkrans. The slope of the line (logged) comparing length of chimpanzee and human thumb metacarpals and pollical distal phalanges is 1.34 (SE = 0.126 and *y*-intercept −1.996). The line predicts a distal phalanx with a length of 20.9 mm when *x* = the length of SKX 5020. The actual length of SKX 5016 is 19.8 mm. SK 84, a first metacarpal from Swartkrans described earlier by Napier in (*6*) and most likely that of *Homo erectus*, predicts a distal phalanx with a length of only 15.7 mm (well outside the 95% confidence limits of the interspecific regression line).
12. J. R. Napier, *Nature* **196**, 409 (1962).
13. *Sci. Am.* **205**, 2 (December 1962).
14. L. S. B. Leakey, P. V. Tobias, J. R. Napier, *Nature* **202**, 7 (1964).
15. These adaptations include expanded breadth of the distal (terminal) phalanges resulting in broad, fleshy fingertips; long thumb relative to the index and other fingers; a broad basal articular surface on the first metacarpal; well-developed and well-differentiated intrinsic and extrinsic thumb muscles; and relatively short and straight fingers.
16. J. T. Robinson, *Early Hominid Posture and Locomotion*, (Univ. of Chicago Press, Chicago, 1972).
17. J. R. Napier, *J. Bone Jt. Surg. 38B*, 902; *Symp. Zool. Soc. London No. 5* (1961); R. L. Susman, *Am. J. Phys. Anthropol.* **50**, 215 (1979); M. W. Marzke, *J. Hum. Evol.* **12**, 197 (1983).
18. M. W. Marzke and M. S. Shackley, *J. Hum. Evol.* **15**, 439 (1986).
19. R. L. Susman and N. Creel, *Am. J. Phys. Anthropol.* **51**, 311 (1979).
20. R. L. Susman and J. T. Stern, *ibid.* **50**, 565 (1979); M. E. Bush, *Am. J. Anthropol.* **52**, 210 (1980); M. E. Bush, C. O. Lovejoy, D. C. Johanson, Y. Coppens, *Am. J. Phys. Anthropol.* **57**, 651 (1982).
21. C. Midlo, *Am. J. Phys. Anthropol.* **19**, 337 (1934); J. R. Napier and P. H. Napier, *Handbook of the Living Primates* (Academic Press, London, 1967); J. R. Napier, *Hands* (Pantheon, New York, 1980).
22. The "intrinsic" thumb muscles are the adductor pollicis (oblique and transverse heads), the opponens pollicis, the abductor pollicis brevis, and the flexor pollicis brevis (superficial and deep heads). Occasionally in humans an additional muscle is found, the first volar interosseous muscle of Henle.
23. W. P. Cooney and E. Y. S. Chao, *J. Bone Jt. Surg.* **59A**, 27 (1977).
24. J. T. Stern and R. L. Susman, *Am. J. Phys. Anthropol.* **60**, 279 (1983); R. L. Susman, J. T. Stern, W. L. Jungers, *Folia Primatol.* **43**, 113 (1984).
25. R. L. Susman, in *Evolutionary History of the Robust Australopithecines*, F. E. Grine, Ed. (Plenum, New York, in press).
26. J. T. Robinson, in (*2*); J. T. Robinson, *S. Afr. J. Sci.* **57**, 3 (1961); R. J. Mason in (*2*).
27. P. V. Tobias in (*2*).
28. It is possible that *Paranthropus* and other early hominids evolved human-like hands for precision grasping of something other than stone or bone artifacts. Arguing against this proposition is the fact that while primates such as baboons and geladas are adept at handling small food objects, and free-ranging chimpanzees manipulate food objects and handle stones and sticks, no monkey or ape displays human-like thumbs or fingers as did early hominids such as *Paranthropus* and *Homo habilis*.
29. C. K. Brain, in *Pretirage ler Congres International Paleontologie Humaine*, H. DeLumley and M. A. DeLumley, Eds. (Centre National de la Recherche Scientifique, Nice, 1982), pp. 676–706.
30. ———, in *Ancestors: The Hard Evidence*, E. Delson, Ed. (Liss, New York, 1985), pp. 72–75.
31. M. D. Leakey, *Nature* **225**, 13 (1970).
32. F. E. Grine, *S. Afr. J. Sci.* 77, 203 (1981); F. E. Grine, *J. Hum. Evol.* **15**, 783 (1986).
33. I thank C. K. Brain for the opportunity to study the Swartkrans fossils and for his invaluable insights into the paleobiology and geology of the Swartkrans site. I also thank F. Grine for sharing his insights on Plio-Pleistocene hominids with me and for his comments on this manuscript. Supported by NSF grants BNS 83-112906 and BNS 85-19747. Funds were also provided by a BRSG from the School of Medicine, SUNY, Stony Brook.

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Insulin-Resistant Diabetes Due to a Point Mutation That Prevents Insulin Proreceptor Processing

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A point mutation in the human insulin receptor gene in a patient with type A insulin resistance alters the amino acid sequence within the tetrabasic processing site of the proreceptor molecule from Arg-Lys-Arg-Arg to Arg-Lys-Arg-Ser. Epstein-Barr virus–transformed lymphocytes from this patient synthesize an insulin receptor precursor that is normally glycosylated and inserted into the plasma membrane but is not cleaved to mature α and β subunits. Insulin binding to these cells is severely reduced but can be increased about fivefold by gentle treatment with trypsin, accompanied by the appearance of normal α subunits. These results indicate that proteolysis of the proreceptor is necessary for its normal full insulin-binding sensitivity and signal-transducing activity and that a cellular protease that is more stringent in its specificity than trypsin is required to process the receptor precursor.

The insulin receptor is a heterotetrameric integral membrane protein composed of two α and two β subunits. The α subunit contains the insulin binding site and is disulfide-bonded to the NH_2-terminal portion of the β subunit. The receptor is anchored in the plasma membrane through a single membrane-spanning region in the β subunit (*1, 2*). The α and β subunits are generated by proteolytic processing of a single chain proreceptor. Cleavage of the proreceptor normally occurs during the intracellular migration of the newly synthesized protein from the rough endoplasmic reticulum to the plasma membrane, presumably in the Golgi apparatus or an early post-Golgi vesicular stage (*3*).

The subject described here was a 23-year-old Japanese woman who was the product of a consanguineous marriage. Diabetes was first diagnosed at age six; she exhibited many of the clinical features associated with the type A syndrome of severe insulin resistance (*4*), including insulin-resistant (nonketotic) diabetes mellitus with markedly elevated serum insulin values (rising from a fasting level of 242 to 1421 μU/ml at 2 hours after glucose administration), acanthosis nigricans, hirsutism, and virilization. Her older sister was similarly affected. In addition, they exhibited some features not normally considered part of this syndrome, including mental retardation, short stature, and dental dysplasia. The latter two features have also been reported in an unrelated subject with Rabson-Mendenhall syndrome who expressed an altered insulin receptor (*5*).

Studies with Epstein-Barr virus (EBV)–transformed lymphocytes of this individual revealed the following abnormalities: (i) markedly reduced binding of ^{125}I-labeled insulin in both intact cells and lectin-purified membrane preparations, (ii) the virtual absence of normal mature α and β subunits, (iii) increased amounts of immunoprecipitable material corresponding in size to the 210-kD uncleaved form of the fully glycosy-

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