sists. I believe that this is a direct descendant of *Met. jacksoni*, and I distinguish it under the specific name *nyanzae* [*"Pronotochoerus" nyanzae*, Leakey, 1958 (*18*)], which has page priority over the rather more typical upper Bed II suid that Leakey called *Notochoerus compactus*. It is not clear where White and Harris place this material, but I suspect that it forms part of what they call *"Met. modestus,"* whereas I regard *modestus* as belonging to the genus *Phacochoerus* and to be a synonym of *P. antiquus*. *Phacochoerus modestus* (=*antiquus*) occurs at DK 1 at Olduvai and continues to Bed IV, along with *Met. nyanzae*. I am at a loss to decide what White and Harris mean by *Met. hopwoodi*, the type of which I consider to be a synonym of the advanced *M. andrewsi* (the *"meadowsi"* form).

White and Harris designate the very distinctive suid that I term *Stylochoerus compactus* as *Met. compactus*. This involves a taxonomic problem if the material termed *"Notochoerus" compactus* actually belongs within the genus *Metridiochoerus*, whether as a synonym of *Met. nyanzae* or of *"Met." modestus*. As I regard this peculiar suid as deserving separation at the generic level because of the unusual structure of its canines and the fact that they emerge at right angles to the axis of the skull and at an angle of about 45° to the palatal plane, the nomenclatorial problem does not arise in my taxonomic scheme.

Finally, in this group I place as a separate genus and species, confined to South Africa, the Makapansgat suid *Potamochoeroides shawi*. White and Harris apparently consider it a synonym of *Met. andrewsi* and regard it as representing a stage in this lineage corresponding to Omo Member C. It is true that there are some structural features of the molar dentition that resemble early stages of the line leading to *andrewsi*, and I believe that these resemblances demand descent from a common ancestor.

However, there are also major differences that cannot be overlooked when one considers the skull and dentition as a whole. At least three premolars are retained in the adult (sometimes also the upper first premolar), and they are normal teeth, much the same size as in *Sus scrofa* and with somewhat *Sus*-like morphology, although stouter and with the fourth premolars a little modified; in contrast, even fairly early *Metridiochoerus* specimens have only the third and fourth premolars, both of which are reduced. The muzzle in *Potamochoeroides* is shorter than in the bushpig, with little or no constriction of the mandible or palate in the region of the canines. The facial profile is steep. The parietal constriction is narrow and the occiput is also constricted, as in *Sus* and quite unlike the broad occiput characteristic in *Metridiochoerus*. The upper canines are short, stout, strongly curved teeth, with a broad ventral band of ribbed enamel, unlike the more or less phacochoerine canines of *Metridiochoerus*. It is thus very difficult to place the Makapansgat type in the same genus as *Metridiochoerus jacksoni* (or early *andrewsi*), let alone in the same species. Furthermore, this form is not confined to the Makapansgat locality, which could be contemporary with the early Shungura and thus provide a possible early stage. It is also found at Bolt's Farm and Gladysvale and may possibly occur at Taung. *Metridiochoerus andrewsi* (sensu stricto) occurs at Bolt's Farm, and so does *Phacochoerus modestus* (= *antiquus*), although they are from different patches of breccia and are not necessarily contemporary. It thus seems preferable to maintain *Potamochoeroides shawi* as a distinct form, confined to South Africa; unfortunately this placement precludes its use for comparisons of age, except in a very general way.

Despite the fact that my taxonomic interpretation differs in so many details from the views of White and Harris, I must emphasize that this has little or no impact on the correlations that they have derived, as the correlations are based on the occurrences of similar morphological entities and are little affected by the labels that are attached to those entities, except in a few rare instances. Theirs is the first definitive consideration of correlation problems within the Koobi Fora Formation, and their analysis is both timely and valuable. I await with interest the appearance of the detailed systematic revision to which they refer.

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References

1. T. D. White and J. M. Harris, *Science* **198**, 13 (1977).
2. H. B. S. Cooke, in *Proceedings of the 5th Congrès Néogène Méditerranéen, Lyon 1972* (Mémoire 78, Bureau de Recherches Géologiques et Minières, Paris, 1974), p. 99.
3. _____ and V. J. Maglio, in *Calibration of Hominoid Evolution*, W. W Bishop and A. J. Miller, Eds. (Scottish Academic Press, Edinburgh, 1972), p. 303.
4. H. B. S. Cooke, *Bull. Soc. Vertebr. Paleontol.* **90**, 2 (October 1970).
5. J. Leinders, *Bull. Mus. Natl. Hist. Nat. Sci. Terre Ser. 3* **46** (No. 341), 197 (1975).
6. L. K. Gabunia, *Dokl. Akad. Nauk SSSR* **102**, 6 (1955).
7. C. Arambourg, *C. R. Somm. Soc. Géol Fr.* **4**, 107 (1961).
8. P. Leonardi, *Rend. Accad. Naz. 40 Ser. 4* **4**, 75 (1952).
9. H. B. S. Cooke and R. F. Ewer, *Bull. Mus. Comp. Zool. Harv. Univ.* **143**, 149 (1972).
10. H. B. S. Cooke, *Kirtlandia*, in press.
11. _____ and S. C. Coryndon, *Fossil Vertebr. Af.* **2**, 109 (1970).
12. J. C. M. Shaw and H. B. S. Cooke, *Trans. R. Soc. S. Afr.* **28**, 293 (1941).
13. R. Broom, *Rec. Albany Mus. Grahamstown* **4**, 167 (1931).
14. E. C. N. Van Hoepen and H. E. Van Hoepen, *Paleontol. Navors. Nas. Mus. Bloemfontein* **2** (No. 4), 39 (1932).
15. H. B. S. Cooke, in *Earliest Man and Environments in the Lake Rudolf Basin*, Y. Coppens, F. C. Howell, G. Ll. Isaac, R. E. F. Leakey, Eds. (Univ. of Chicago Press, Chicago, 1976), p. 251.
16. W. C. McKerrow, in *The Species Concept in Palaeontology*, P. C. Sylvester-Bradley, Ed. (Systematics Society, London, 1956), p. 122.
17. T. Neville George, in *ibid.*, p. 123.
18. L. S. B. Leakey, *Br. Mus. (Nat. Hist.) Fossil Mamm. Afr.* **14** (1958).
19. _____, *J. East Afr. Uganda Nat. Hist. Soc. Natl. Mus.* **17**, 45 (1943).
20. H. B. S. Cooke, in *Evolution of African Mammals*, V. J. Maglio and H. B. S. Cooke, Eds. (Harvard Univ. Press, Cambridge, Mass., in press).

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Enkephalin-Like Material Elevated in Ventricular Cerebrospinal Fluid of Pain Patients After Analgetic Focal Stimulation

Abstract. *Enkephalin-like activity has been measured in the ventricular cerebrospinal fluid of patients with intractable pain. Electrical stimulation of periventricular brain sites resulted in significant decrease in persistent pain in these subjects. This analgesia, which was blocked by naloxone in 80 percent of the cases, was accompanied by a significant rise in ventricular enkephalin-like activity, as measured by two different methods. The results present evidence of in vivo release of enkephalin-like material in humans and suggest that stimulation analgesia may be partially due to this release.*

The enkephalins and endorphins (*1*) produce analgesia when administered in pharmacological doses to nonhuman mammals (*2*). The potential role of these endogenous opioids in regulation of pain perception has been suggested (*3*), and an endogenous pain inhibitory system with opioid and nonopioid components has been proposed (*4*). We now report that electrical stimulation of periventricular brain sites in humans suffering from intractable pain leads to relief, and is accompanied by a significant increase in enkephalin-like material

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Table 1. Changes in concentrations of enkephalin-like material (methionine-enkephalin equivalents, picomoles per milliliter) in ventricular cerebrospinal fluid on electrical stimulation in man. Percentages shown are percentages of baseline. N.C., not collected. For the statistical evaluation, the paired t-test, between stimulation and baseline values, was used.

Subject	Baseline	Change at intervals (min)			
		A 0 to 5	B 5 to 10	C 15 to 20	D 20 to 30
		Radio receptor assay			
Level 1	0.50 (100 %)	0.25 (50 %)	0.30 (60 %)	0.75 (150 %)	0.63 (126 %)
Level 2	0.55 (100 %)	N.C.	1.10 (200 %)	0.75 (136 %)	0.67 (122 %)
Level 3	1.63 (100 %)	0.40 (25 %)	1.55 (95 %)		2.00 (123 %)
Level 4	0.25 (100 %)	N.C.	0.50 (200 %)	0.50 (200 %)	0.60 (240 %)
Level 5	0.50 (100 %)	N.C.	0.35 (75 %)	0.66 (132 %)	0.50 (120 %)
$\bar{X}$ ± standard error	0.69 ± 0.2	0.33 ± 0.1	0.76 ± 0.2	0.67 ± 0.6*	0.9 ± 0.3†
% $\bar{X}$ ± standard error	100 ± 0	37.5 ± 12.5	126 ± 30.7	154 ± 15.6	146 ± 23.5
		Bioassay			
Level 6	Undetectable	N.C.	1.0	0.7	‡
Level 7	1.32 (100 %)	1.49 (113 %)	1.67 (127 %)	N.C.	2.98 (226 %)
Level 8	2.98 (100 %)	N.C.	2.72 (91 %)	2.65 (89 %)	4.21 (141 %)
$\bar{X}$ ± standard error§	2.15 ± 0.8		2.2 ± 0.5		3.60 ± 0.6‖
% $\bar{X}$ ± standard error§	100 ± 0		109 ± 18		183 ± 42.5

*t = 9.86, $P < .001$. †t = 3.57, $P < .02$. ‡Irreversible by naloxone. §For subjects 7 and 8. ‖t = 6.49, $P < .05$.

in the ventricular cerebrospinal fluid.

The subjects (seven males, one female, No. 5) are part of a series of 30 patients suffering from severe, intractable pain who underwent stereotaxic surgery for electrode implant in the periventricular gray region. This procedure is based on extensive animal work (*5*) and on a human study which determined the site that produced the most potent analgesia with minimal side effects (*6*). The surgical procedure and its overall clinical success have been described (*7*). The first stage of the surgery consisted of stereotaxically implanting an electrode at a site near the posterior aspect of the third ventricle medial to the nucleus parafascicularis, and in close proximity to the posterior commissure (*8*) (Schatelbrand and Bailey coordinates: Fp=10, Ht=0, Lat=2 to 5). During this stage, the patient was under local anesthesia and was able to report on the intensity of pain before and after stimulation. The site was chosen empirically, such that its stimulation produced the most potent relief with the least side effects. The electrode was then secured to the skull but remained externalized for further testing. The second stage was carried out several days later with the patient under general anesthesia. At that point, the electrode was internalized and connected to a Medtronics receiver implanted in the chest pectoralis region. A Medtronics transmitter was given to the patient to allow him to self-administer the current. Each patient was assisted in the selection of stimulation conditions (that is, duration, frequency, amplitude) that brought about maximal control of pain while minimizing the side effects.

In our study, the cerebrospinal fluid (CSF) samples were collected in stage 1 by an intraventricular catheter introduced into the third ventricle so that we could inject a Conray dye and visualize the commissure for the purposes of the stereotaxic implant. Four to five samples of ventricular fluid (approximately 4 ml each) were withdrawn. The first sample was obtained prior to any electrical stimulation and constituted the baseline control. All the other samples were collected at intervals of approximately 5 minutes after the onset of electrical stimulation. Some variability in the procedure was dictated by the patient's response and the necessity to adjust the stimulation amplitude or frequency: however, all patients exhibited significant analgesia to the stimulation during the procedure and for several months thereafter.

The CSF samples were frozen immediately after being collected. Prior to assay they were immersed in a boiling bath to halt the action of degradative enzymes and were then either lyophilized and shipped for the bioassay or they were immediately chromatographed and assayed. Two separate procedures were used to assay enkephalin-like activity. The first consisted of applying the samples to XAD-2, eluting in methanol, and measuring opiate-like activity in a bioassay of the vas deferens (*9*). The second procedure consisted of applying the samples to an anion exchange resin (AG1-X2), eluting in 0.2N acetic acid, and assaying portions of each sample in duplicate in a labeled receptor assay with [^{3}H]methionine-enkephalin and a radioimmunoassay (RIA) that specifically measured methionine-enkephalin. Both chromatographic techniques (XAD-2 and AG1-X2) optimize the recovery of enkephalin rather than larger peptides, particularly β-endorphin.

All patients reported significant or complete pain relief with periventricular stimulation. In these and other patients the procedure is adaptable for use for several months or years; the analgesia is partially reversible by naloxone in 80 percent of the patients tested; further a tolerance-like phenomenon could be observed with sustained use of the stimulation over several hours. However, it can be avoided by intermittent use of the stimulator.

Opiate-like activity obtained from eight patients under the various conditions is shown in Table 1. The baseline activity (0.59 ± 0.2 pmole/ml, expressed in methionine-enkephalin equivalents) appears somewhat lower than the mean value in lumbar CSF in a group of normal male control subjects assayed in the same manner (mean = 3.4 ± 1.1 pmole/ml). At the end of 20 minutes, most patients exhibited a significant rise in opiate-like activity as compared to their own baseline (paired t-test at 15 to 20 minutes, t = 9.86 and $P < .001$; at 20 to 30 minutes, t = 3.57 and $P < .02$). A number of subjects exhibited a transient decrease in the early period after stimulation followed by the rise.

Both procedures, bioassay and binding assays, led to similar conclusions; thus the effect was probably not due to an artifact of the assay system. Furthermore, our use of the receptor assay and the RIA have yielded a correlation coefficient of .9, suggesting that the material measured by the opiate receptor procedure is very similar to methionine-enkephalin (*10*).

The demonstration of an increase in enkephalin-like activity upon electrical stimulation appears to be the first demonstration of in vivo release of an endorphin, and it supports the view that stimulation-produced analgesia in humans may be, in part, due to activation of an endogenous pain modulation system with opioid components since it is partially blocked by naloxone (*7*, *11*) and is accompanied by apparent release of opioids into the CSF. Further, it is consistent with animal findings (*12*) showing changes in concentrations of brain opioids upon electrical stimulation. Finally, the findings that baseline levels in these patients are lower than normal supports the finding (*13*) that concentrations of endogenous opioids in the CSF in patients with persistent pain may be depressed.

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References and Notes

1. J. Hughes, T. W. Smith, H. W. Kosterlitz, *Nature (London)* **258**, 577 (1975); C. H. Li and D. Chung, *Proc. Natl. Acad. Sci. U.S.A.* **73**, 1145 (1976); R. Guillemin, N. Ling, R. Burgus, *C. R. Acad. Sci. Ser. D* **282**, 783 (1976).
2. J. D. Belluzzi, N. Grant, V. Garsky, D. Sarantakis, C. D. Wise, L. Stein, *Nature (London)* **260**, 625 (1976); H. H. Büscher, R. C. Hill, D. Romer, F. Cardinaux, A. Closse, D. Hauser, J. Pless, *ibid.* **261**, 423 (1976); L. Graf. J. I. Szekely, A. Z. Ronai, Z. Dunai-Kovacs, S. Bajusz, *ibid.* **263**, 240 (1976); E. Wei and H. Loh, in *Opiates and Endogenous Opioid Peptides*, H. W. Kosterlitz, Ed. (North-Holland, Amsterdam, 1976), pp. 303–310.
3. T. Hökfelt, R. Elde, O. Johansson, L. Terenius, L. Stein, *Neurosci. Lett.* **5**, 25 (1977).
4. H. Akil, J. Madden, R. Patrick, J. D. Barchas, in *Opiates and Endogenous Opioid Peptides*, H. W. Kosterlitz, Ed. (North-Holland, Amsterdam, 1976), pp. 63–70; H. Akil and J. D. Barchas, in preparati → D. J. Mayer and D. D. Price, *Pain* **2**, 379 (1976).
5. D. J. Mayer, T. L. Wolfle, H. Akil, B. Carder, J. C. Liebeskind, *Science* **174**, 1351 (1971); J. C. Liebeskind, D. J. Mayer, H. Akil, *Adv. Neurol.* **4**, 261 (1974).
6. D. E. Richardson and H. Akil, *J. Neurosurg.* **47**, 178 (1977).
7. ———, *ibid.*, p. 184.
8. G. Schatelbrand and P. Bailey, *Introduction to Stereotaxis with an Atlas of the Human Brain* (Grune & Stratton, New York, 1959).
9. T. W. Smith *et al.*, in *Opiates and Endogenous Opioid Peptides*, H. W. Kosterlitz, Ed. (North-Holland, Amsterdam, 1976), pp. 57–62.
10. H. Akil, S. Sullivan, S. J. Watson, J. D. Barchas, *Life Sci.*, in press. While this material cochromatographs with enkephalins in many systems and interacts with opiate receptors in the binding assay and bioassay, its quantities are too low to permit a positive identification as enkephalin. We have, therefore, chosen the term "enkephalin-like" throughout. We suggest that this opioid is similar to the fraction II opioid material identified in CSF by A. Whalstrom, L. Johansson, L. Terenius [in *Opiates and Endogenous Opioid Peptides*, H. W. Kosterlitz, Ed. (North-Holland, Amsterdam, 1976), pp. 49–56].
11. Y. Hosobuchi, J. E. Adams, R. Linchitz, *Science* **197**, 183 (1977).
12. H. Akil, S. J. Watson, J. D. Barchas, *Soc. Neurosci.* **2**, 563 (1976).
13. L. Terenius and A. Wahlstrom, *Life Sci.* **16**, 1759 (1975).
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Central Nervous System Dysfunction Due to Lead Exposure

Abstract. *Central nervous system dysfunction was investigated in workers at a secondary lead smelter by means of performance tests. Correlations between test scores and zinc protoporphyrin levels, a biological indicator of lead toxicity, are statistically significant. This correlation should prove to be useful in current efforts to evaluate effects of lead exposure.*

Long-term lead poisoning has been shown to cause neurologic injury (*1*, *2*), to reduce nerve conduction velocity in adults (*3*), and to lead to mental retardation (*4–7*) and hyperactivity (*8*) in children. The question of what, if any, level of lead exposure is acceptable without risking central nervous system (CNS) dysfunction has remained unanswered, in part because of a paucity of quantitative data relating CNS effects to the magnitude of lead absorption. The study reported here provides such data.

With recent advances in understanding the biochemical effects of lead on various enzyme systems, particularly those involved in heme synthesis, the zinc protoporphyrin (ZPP) level in blood has emerged as a useful biological indicator of long-term lead effects (*9*, *10*). We report here correlations between scores for several performance tests for the evaluation of brain dysfunction and the concentrations of ZPP and lead in the blood of lead-exposed workers. Correlations between performance test scores and ZPP levels were found that were highly significant within the test population.

The data were obtained in the course of a clinical field survey of 90 workers at a secondary lead smelter in California (*11*). Each worker's occupational history was recorded, and he was given a thorough medical examination, as well as hematological, biochemical, and other clinical laboratory tests (*12*). The neurobehavioral tests used in this study included the block design (BD) (*13*), digit symbol (DS) (*13*), and embedded figures (EF) tests (*14*) and the Santa Ana dexterity test for the dominant hand (DH) and for both hands (BH) (*15*). In the BD test the subject is presented with a set of cubes whose faces are half red and half white, the halves being separated by a diagonal. The subject is asked to arrange the cubes within a time limit in a way which duplicates a pattern shown to him. In the DS test the subject is given a list in which symbols are associated with the digits from 1 to 9 and is asked to enter the symbols into the blank spaces next to a list of random digits. In the EF test the subject is shown four sets of ten superimposed outline drawings of common objects and is required to identify as many as possible. The Santa Ana dexterity test uses a metal plate with an array of square holes. Each hole holds a square peg, and the subject is required to lift, rotate through 180°, and replace as many pegs as possible within 30 seconds. This test is performed first with the dominant hand and then with both hands.

Table 1. Performance test scores, corrected for age, correlated with blood lead and zinc protoporphyrin (ZPP) levels.

Test	Lead		ZPP		Slope† (%)
	*r**	*P*	*r**	*P*	
BD	.207	<.03	.294	<.003	16
DS	.061	N.S.‡	.244	<.02	7
EF	.216	<.03	.296	<.003	5
DH	.007	N.S.	.005	N.S.	N.S.
BH	.003	N.S.	.007	N.S.	N.S.

*Multiple correlation coefficient of the fit with Eq. 2. †Percentage drop in scores for the first 100 μg of ZPP per deciliter. ‡N.S., not significant.

Blood lead levels were measured by atomic absorption spectrophotometry. The ZPP concentration in blood was measured by a hematofluorometer (Aviv Associates, Lakewood, N.J.). This instrument provides an accurate value for the concentration of ZPP from a small drop of blood obtained by finger puncture (*16–18*).

Before attempting to compare ZPP and blood lead as indicators of biologically active lead, it is useful to review briefly the origin of ZPP during erythropoiesis. Lead ions interfere with the ferrochelatase system, which catalyzes the

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