The origin of the frameshift mutations in the *hMSH3* and *hMSH6* genes is not clear. They may be the result of a previous defect in mismatch repair because they occur at hotspots for slippage-generated mutations[8]. If this hypothesis is correct, it would imply that the MMP unfolds in consecutive steps. Rare homozygous mutations in a DNA mismatch-repair gene (such as *hMSH2* or *hMLH1*) may lead to mutations in other mismatch-repair genes as they contain targets for the mutagenic action of the first mutator mutations[1]. Because these slippage-induced mutations are much less frequent in other genes containing $(A)_8$ and $(G)_8$ tracks, the frameshift mutations in these secondary mutator genes appear to be under a positive selective pressure during tumorigenesis. These mutations may contribute to the genomic instability of the tumour cells. This enhanced (or broader) genomic instability may accelerate even more the accumulation of mutations in cancer genes during tumour progression.

This progressive model of mutator mutations helps to explain the redundancy in DNA mismatch repair and its causal relationship with cancer of the MMP, and the temporal relationships and hierarchies among different mutator genes[2,6]. This model may also help account for the phenotypic properties of tumour cells of the MMP[1–3,13] and for the rarity of occurrence of tumours in homozygous knockout mice for mismatch-repair genes[15].

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Direct dating of Florisbad hominid

SIR — In 1932, hominid remains were found at the Florisbad spring, near Bloemfontein, South Africa[1]. The partial cranium which shows damage by hyena chewing was part of a natural accumulation of mostly carnivore prey remains, which were trapped in vertical spring vents. The spring and associated white-sand bodies intruded horizontal sand and clay layers when the spring was active in a specific locality. When the spring migrated to another area, these vents were sealed by the horizontal deposits, resulting in a succession of ancient spring vents at various depths (and age). The horizontal deposits are interbedded with dark organic clay horizons (peats). "Peat II" represents an old land surface on which Middle Stone Age artefacts and bones occur[2].

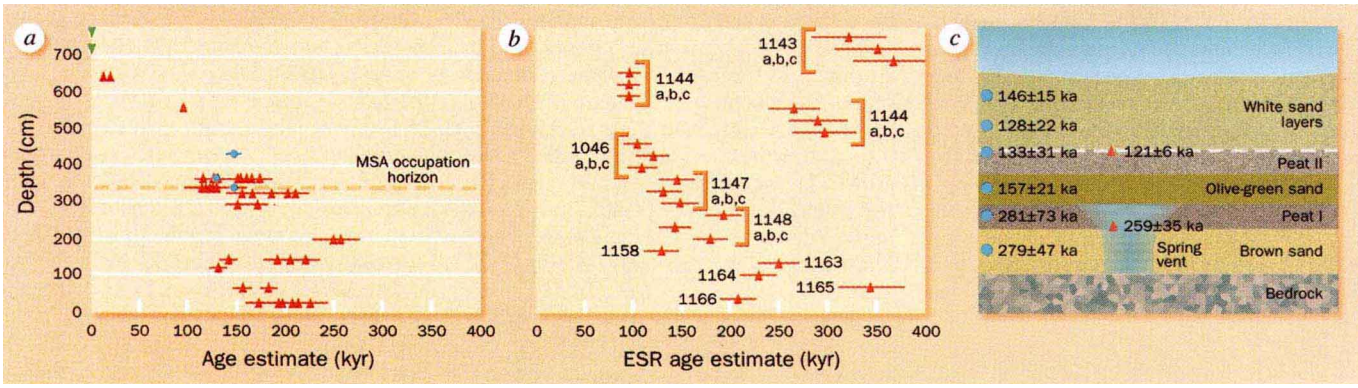
The hominid remains consist of much of the frontal bone and right side of the face, together with parts of the parietals, maxillae and the right M^3 tooth. Based on the last reconstruction in 1983 (ref. 3), the Florisbad fossil is most reasonably classified with other late archaic specimens such as Ngaloba, Eliye Springs, Omo 2 and Singa from East Africa and Jebel Irhoud 1 and 2 from North Africa. Most of these fossils have age estimates in the range of 100,000 to 200,000 years old[4].

Previous dating attempts produced infinite radiocarbon results for the human occupation layer and a uranium-series estimate of >100,000 years for "Peat I" (ref. 3). Our first ESR (electron spin resonance) study followed conventional procedures[5], which involves grinding of large portions of tooth enamel (200–400 mg). We collected one set of tooth samples *in situ* from the third test pit which spans the whole sedimentary sequence at Florisbad, and a second set from the original spring collection[1,2]. We carried out optically stimulated luminescence (OSL) dating[6] on quartz separates from sediment samples and measured the gamma dose rate *in situ*. We used a large sediment sample from a hippopotamus mandible for the calculation of the gamma dose rate of the spring collection samples. We checked OSL bulk samples for radioactive disequilibrium using high resolution gamma spectrometry.

The samples from the third test pit, which were usually small tooth fragments, show considerable spread of ESR results within layers (*a* in the figure), indicating re-working of material by spring action. The age spread is smallest for the Middle Stone Age human occupation horizon (121,000±6,000 years) where the taphonomy clearly indicates a short-term event, and re-working can be excluded. The samples of the spring collection (*b* in the figure) yielded age estimates from about 100,000 to 300,000 years old. Because the precise locations of the specimens were not recorded, the age scatter can be explained by the continuous spring activity.

To tighten the age of the Florisbad hominid, we directly analysed the associated hominid tooth. It is the only dental sample clearly associated with the other hominid remains, and its stratigraphical position has been recorded[1]. A newly developed ESR technique allows the measurement of dental fragments without any further destruction[7]. We separated and analysed two fragments (10.5 and 25 mg), subsequently re-inserting them into the original specimen. For age calculation, we used saturation water contents, a cosmic dose rate for a depth of 5±1 m and the average concentration of radioactive elements of white sand layers. All other teeth of the spring collection had low uranium concentrations (enamel: 3–101 p.p.b. (parts per billion); dentine: 10–268 p.p.b.), so we assumed the human tooth to be within these limits. Considering all uncertainties, we obtained a result of 259,000±35,000 years old (weighted mean).

The ESR and OSL results (*c* in the fig-



a, Age estimates for the third test pit (the results of the occupation horizon are projected into the sequence) (ages are in thousand years) *b*, Tentative ESR age estimates of the spring collection samples. *c*, Schematic diagram of the lower part of the sediment sequence at Florisbad with a reconstruction of the spring vent yielding the hominid fossils (not to scale). The spring mount dissected the basal sand and Peat I and was covered by the olive green sand. The ESR results yield an age of 259,000±35,000 years for the human tooth and an age of 121,000±6,000 years for the younger human occupation horizon on top of Peat II. Although having larger errors (because of saturation problems), the OSL age estimates confirm the large age span between the beginning of sedimentation to the deposition of the occupation horizon. Green triangles, radiocarbon; red triangles, EU-ESR; blue circles, OSL.

ure) support an age for the occupation horizon corresponding to the last interglacial (125,000 years ago). The hominid is clearly older, perhaps coinciding with the previous interglacial. Our results confirm the view that Peat I and Peat II were separated by an entire landscape cycle and that the hominid remains may relate to an earlier Middle Stone Age industry[8].

The relatively old age of the hominid fits well with its combination of archaic and modern characteristics, considering that anatomically modern humans are known from several southern African sites from the last interglacial[4]. We are confident that this new method of direct ESR analysis will allow age estimates for further enigmatic hominid fossils such as those from Broken Hill, Skhul and Tabun.

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Denial of disabilities in anosognosia

SIR — A certain proportion of right-hemisphere stroke patients who have left-sided hemiplegia will vehemently deny their paralysis, even though they may be mentally quite lucid in other respects ("denial" or anosognosia[1–4]). We studied three such patients and found, surprisingly, that two of them also refused to acknowledge the paralysis of a fourth patient (or a "stooge") who was in a wheelchair next to them. Thus, in at least some instances, a patient's denial may generalize to include the disabilities of other people's body movements.

All three patients (L.H., F.D. and L.R.; ages 77, 77 and 78) were right-handed women with a left hemiplegia. Computed tomography scans confirmed the presence of a subacute right middle cerebral artery and right cerebellar artery infarct in F.D.; a right middle cerebral artery and left cerebellar artery infarct in L.H.; and a right frontoparietal infarct in L.R. At the time of testing, L.R. and F.A. were completely lucid mentally (for example, able to orient in time and place; subtract serial twos; digit span; and so on), fluent in conversation, and of average intelligence. L.H. was also fluent in conversation but her digit span was four. Each patient was asked the following sequence of questions repeatedly: can you walk; can you use both hands; can you use your right hand; can you use your left hand; are both hands equally strong? They were deemed anosognosic only if they answered all questions in the affirmative[4].

Would an anosognosic patient deny another patients' paralysis? Before each experiment, we first verified the patient was mentally alert and was still in denial as revealed by affirmative answers to the sequence of questions cited above. We then conducted an abbreviated neurological examination on a left-hemiplegic patient in the adjacent wheelchair. (In one case we had to use a student "stooge" pretending to have left hemiplegia.) The wheelchair was in the non-neglected (right) side of the anosognosia patient and was rotated so that the stooge always sat face-to-face with the patient. The patient was then asked carefully to watch the stooge in the wheelchair. From this position, our patient could clearly observe that the stooge's right hand was functioning well but that his left hand was not responding to the examiner's commands.

Immediately after demonstrating the paralysis of the stooges' left hand, each patient was asked "Is that patient moving his arm properly or is he paralysed?" This was done three times in a row and interspersed with brief, irrelevant, distracting questions such as "What do you think of the O. J. trial?" The same experiment was then repeated the following day (L.H. & F.D.) or a week later (L.R.). On all six trials, both L. H. and F. D. responded without hesitation that the other patient was "OK" and that "he is moving his arm up and down". L.R. seemed very surprised by the question, answering "of course he is paralysed; he is not moving his arm", even though she vehemently denied her own paralysis. It is noteworthy, also, that even when L.R. watched her failure to move her arm in a mirror she continued to insist that she was not paralysed.

Finally, we verified that the patients had no problem with other aspects of their body image, for example, they could name their own as well as other people's body parts (no autotopagnosia) and they could perform skilled movements (for example, touching their nose; waving goodbye; pretending to stir sugar in a cup of tea) with their right hands in response to commands (no apraxia). Nor did they have left parietal or frontal lesions of the kind that might be expected to produce such disturbances. The failures cannot therefore be attributed to simple body-part confusion or to general confusion about limb movements.

We conclude that at least some anosognosic patients will refuse to acknowledge the paralysis of another patient[4]. The observation raises the interesting question of whether the patient needs to believe that the other individual is also a patient. Or, is it the case that some of these patients are unable to access their own body schemata and that such access is necessary even for making judgments about the movements of another human being? Additional experiments are needed to resolve these questions. Certain cells in the monkey frontal lobes[5] respond not only to their own hand performing certain actions but also to the visual image of another monkey's hand performing the same action: would these cells provide the neural substrate for the delusions experienced by these patients?

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Biological activity of interleukin-16

SIR — Bazan and Schall[1] implied that the predicted existence of an interleukin-16 (IL-16) precursor protein was evidence that the cloned complementary DNA[2] does not represent the originally described native biological activity[3]. But these implications are not supported by our published experimental evidence.

IL-16, formerly known as lymphocyte chemoattractant factor, was identified as a secreted T-cell product that induces motility and interleukin-2-receptor expression in CD4+ T cells; functions that are selectively inhibited by Fab of the OKT4 antibody[4]. IL-16 appears in culture supernatants as a relative molecular mass (M_r) ~56,000 biologically active non-covalently linked tetramer, but migrates in monomeric form