# LETTERS

## Parallelisms

Two independent efforts to sequence the genomes of different strains of the tuberculosis bacterium could "take genome sequence comparison to an unprecedented level," according to an advisory panel of U.S. researchers. Complex "dynamic interactions of multiple deteriorating pacemakers" are said to precede the onset of menopause as women age. [Right, 5 July cover image taken from Gustav Klimt's *Three Ages of Woman* (1905).] The programmed cell death (PCD) exhibited by a certain bacterium and the occurrence of PCD in "divergent kingdoms of organisms" are discussed.


### Comparative Sequencing

We would like to respond to the letter by Julian E. Davies (30 Aug., p. 1155) expressing concern about the National Institutes of Health (NIH)-funded effort to sequence the genome of *Mycobacterium tuberculosis*. The NIH funding was a result of an investigator-initiated R01 application from The Institute for Genomic Research (TIGR) that scored exceptionally well in peer review this past February. The TIGR investigators became aware of a pending announcement by the Wellcome Trust of their intention to fund a similar effort at the Sanger Centre to sequence the H37Rv laboratory strain of *M. tuberculosis* (the same strain proposed in the TIGR application), and immediately notified the National Institute of Allergy and Infectious Diseases (NIAID). It was agreed to convene an External Advisory Panel (composed of the signatories of this letter), from a variety of *M. tuberculosis* research disciplines, to review the situation and to make a recommendation as to how and if to proceed. In early May we met to discuss alternatives to sequencing the H37Rv strain, including sequencing such genomes as *M. smegmatis*, virulent *M. bovis*, *M. bovis* bacille Calmette-Guérin (BCG), *M. avium*, *M. microti*, and a recent virulent clinical isolate of *M. tuberculosis*. Forceful arguments were made for and against sequencing each of these species. It was unanimously agreed that, while all the above organisms had their merits, the sequencing of a recent, drug-sensitive, genetically tractable, virulent, clinical isolate of *M. tuberculosis* would be of most value in light of the comparative data it would provide with the H37Rv laboratory strain. The panel decided that seed lots should be prepared from four recent clinical isolates—strains A, C, W, and Oshkosh—that these strains would be evaluated for their virulence in mice and transformability, and that sample sequencing would proceed from libraries prepared from each strain. This decision was subsequently reviewed and accepted by NIAID. This evaluation process is currently under way, and a final strain selection is pending these results. The decision to sequence a clinical isolate of *M. tuberculosis* in this particular initative should not be looked on as a lack of recognition of the importance of other organisms, including *M. smegmatis*, in pathogenesis and research.

Significant differences have been demonstrated between genomes of laboratory strains with long histories of passage and recent clinical isolates. H37Rv was first isolated in 1905 and has been passaged for many decades. Of greater importance is that H37Rv is of unknown virulence in humans. The selection of a clinical isolate that has been involved in a recent cluster of tuberculosis cases (that is, known to be transmissible and virulent in humans) ensures that the sequence of the genome of a fully virulent *M. tuberculosis* strain will be available in a timely fashion. Moreover, the availability of sequences from both genomes will provide the first opportunity for a complete comparison between two closely related organisms of the same bacterial species. The comparisons afforded by this opportunity provide the potential to recognize the genetic basis for successful human colonization, infectivity, and fully fledged transmission of a pathogen. These comparisons, along with the likely completion of the *M. leprae* genome, will take genome sequence comparison to an unprecedented level.

At a recent meeting at the World Health Organization in Geneva, there was unanimous enthusiasm from researchers in

the areas of detection, prevention, and therapy about the impact that the availability of these M. *tuberculosis* genome sequences would have on future research efforts to combat this ancient and reemerging killer.

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## The Advent of Menopause

The article "Menopause: The aging of multiple pacemakers" by Phyllis M. Wise *et al.* ("Patterns of Aging," 5 July, p. 67) addresses a cardinal component of the ageing process, menopause, a normal physiological process that has a profound impact on more than half of the population. One of the principal theses advanced by Wise *et al.* to explain the advent of menopause is a reduction in frequency of the hypothalamic signal generator that occasions the rhythmic release of GnRH, the neuropeptide that controls secretion of the gonadotropic hormones and thus governs ovarian function. The only direct evidence cited in support of this far-reaching hypothesis, however, is an abstract published in 1994 (*1*).

Although a hypothalamic deficit is clearly responsible for the cessation of ovarian function in the ageing rat, as documented by Wise *et al.*, as well as by others, the preponderance of the evidence, *in women*, is that the frequency of the GnRH pulse generator is not diminished in menopause (*2*). Rather, an increase in luteinizing hormone (LH) pulse frequency and amplitude seems to occur as menopause is approached (*3*), a finding consistent with the decline in inhibin levels and ovarian follicle depletion (*4*).

Wise *et al.* do not acknowledge the fundamental differences between primates and rodents (*5*) in the control of ovarian function and have extrapolated findings in rats to women in the elaboration of their theory.

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### References

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2. S. S. C. Yen *et al.*, *J. Clin. Endocrinol. Metab.* **34**, 671 (1972); B. Couzinet *et al.*, *Clin. Endocrinol.* **34**, 477 (1991).
3. N. E. Reame *et al.*, *J. Clin. Endocrinol. Metab.* **81**, 1512 (1996).
4. H. G. Burger *et al.*, *ibid.* **80**, 3537 (1995).
5. E. Knobil, in *Recent Progress in Hormone Research*, R. O. Greep, Ed. (Academic Press, New York, 1974), vol. 30, pp. 1–46.

*Response*: Knobil and Yen argue that changes in hypothalamic function are a consequence rather than a cause of the menopausal transition. One must examine mid-