in Syria. The problem with naming these as the sites of first domestication is that charred seeds of wild *T. m. boeticum* have been abundantly found, but no spikelets remain there. It has been hypothesized that wild einkorn was gathered at a distance, threshed at the camp collection site to reduce the volume, and transported (*5*). Where it was taken is not known. We have reported that *T. m. boeoticum* from Karacadağ is the progenitor of the cultivated einkorn and that the excavated sites cited in our report (which are near those mountains) reveal a transition from wild to cultivated genotypes. These were the observations on which the title of our report was based.

Manfred Heun
Department of Biotechnological Sciences, Agricultural University of Norway, Post Office Box 5040, N - 1432 As, Norway
Basilio Borghi
Istituto Sperimentale, per la Cerealicoltura, I - 20079 Sant'Angelo Lodigiano Milano, Italy
F. Salamini
Max-Planck-Institut für Züchtungsforschung, Carl-von-Linné-Weg, D-50829 Köln, Germany

References and Notes

1. M. Nesbitt and D. Samuel, in *Hulled Wheats*, S. Padulosi, K. Hammer, J. Heller, Eds. (International Plant Genetic Resources Institute, Rome, 1996), pp. 41–100.
2. The data available are Abu Hureyra, Prepottery Neolithic, 7700–5000 B.C., cultivated einkorn; Cafer Höyük, PPNB, 7600–6200 B.C., wild and cultivated; Cayönü PPN, 7500–6700 B.C., cultivated; Nevali Cori, PPNB, 7200 B.C., cultivated; and Jericho, PPNB, 7200–6800 B.C., cultivated. Other cited sites are more recent, including Tell Aswad (II), PPN, 6900–6600, B.C., cultivated. For Jericho, PPNA, 7400 B.C.; Tell Aswad (I), PPN, 7800–7300 B.C.; and Netiv Hagdud, PPNA, 8000–7400 B.C., no einkorn data are available.
3. D. Zohary and M. Hopf, *Domestication of Plants in the Old World* (Clarendon, Oxford, 1993).
4. G. Hillman, in *The Origins and Spread of Agriculture and Pastoralism in Eurasia*, D. R. Harris, Ed. (University College London Press, London, 1996), pp. 159–203.
5. W. Van Zeist and W. A. Casparie, *Acta Botan. Neerl.* **17**, 44 (1968); G. C. Hillman, in A. T. M. Moore, *Proc. Prehistoric Soc.* **41**, 70 (1975); W. Van Zeist and J. A. H. Bakker-Heeres, *Palaeohistoria* **26**, 171 (1984).

■

Aging and Endocrinology

In their article "The endocrinology of aging" (17 Oct., p. 419), Steven W. J. Lamberts *et al.* describe many aspects of aging that are benefited by dehydroepiandrosterone (DHEA) or testosterone replacement. Not mentioned is the decline in melatonin production, correlated with increasing age-related disfunction, that can be partially ameliorated with melatonin therapy (*1*). Neither was there discussion of multiple hormone supplementation, synergistic effects, or other studies of the simultaneous replacement of DHEA and melatonin (*1*, *2*).

In young mice with murine-acquired immune deficiency disease that results in B cell leukemia or in old mice with immunosenescence, replacing melatonin and DHEA had a synergistic effect: cytokine and immune regulation were normalized, and increased oxidation and loss of vitamin E were prevented (*3*). In older humans, we have found no toxicity resulting from supplementing melatonin and DHEA for 1 year. Also, treatment with melatonin, DHEA, and vitamin E together led to the regression of esophageal dysplasia in older people.

Lamberts *et al.* correctly note that many, perhaps millions, of Americans (and their doctors) are esentially testing the hypothesis that supplementing DHEA, melatonin, or testosterone will slow aging. Our studies suggest that long-term human trials should test the effectiveness and toxicity of not only single, but multiple, hormone replace-

ment. DHEA supplementation delayed death in very old C57BL/6 female mice; 78% were surviving after 10 weeks of DHEA consumption, while only 37% of old, untreated mice still lived. Although the National Institute on Aging warns (*4*), correctly, of the potential risks of such actions because of the absence of data from any long-term human trials, it is not aggressively requesting or supporting such research. In the absence of scientific, longitudinal studies, we at least ought to investigate what the public is already doing.

Ronald Ross Watson
Immunosenescence Laboratory,
Arizona Prevention Center,
University of Arizona School of Medicine,
1501 North Campbell Avenue,
Tucson, AZ 81724, USA
E-mail: rwatson@u.arizona.edu

References

1. A. Call, H. R. Matz, R. R. Watson, *Exp. Opin. Invest. Drugs* **5**, 1647 (1996).
2. R. R. Watsson, S. Chung, A. Huls, M. Araghiniknam, *Drugs Aging* **9**, 225 (1996).
3. R. R. Watson, B. Liang, P. Inserra, Z. Zhang, M. Araghiniknam, *J. Am. Coll. Nutr.* **16**, 494 (1997); S. K. Araghiniknam *et al.*, *Proc. Soc. Exp. Med. Biol.* **216**, 386 (1997).
4. *Pills, Patches, and Shots: Can Hormones Prevent Aging?* (National Institute on Aging, Bethesda, MD, 1997).

In their excellent article, Lamberts *et al.* note that testosterone is among the circulating hormones with concentrations that decrease as men age. Maintaining the testosterone concentration of a younger age could have beneficial anabolic effects and affect social and psychological behavior (*1*). However, testosterone replacement therapy in elderly men is limited in use, Lambert *et al.* note, because of its unpredictable effects on the prostate.

Testosterone is strongly and inversely related to percentage of body fat (*2*), suggesting that age-related decrease in testosterone may be the result of the weight gain that commonly accompanies aging in our society. If this idea is correct, testosterone levels might be sustained in elderly men through diet and exercise.

I examined testosterone and weight changes in 1880 male U.S. Air Force veterans who participated in four examination cycles (in 1982, 1985, 1987, and 1992) as subjects in the Air Force Health Study, which was intended to evaluate health effects of exposure to Agent Orange during the Vietnam War (3). In 1992, the mean age of these men was 53.8 years (SD = 7.6 years). Testosterone was assayed in duplicate from morning blood samples after an overnight fast. For each cycle, a constant was added to all testosterone values in order to remove cycle-to-cycle variation in measurements that are unrelated to age. Percentage of body fat was calculated from height and weight measurements.

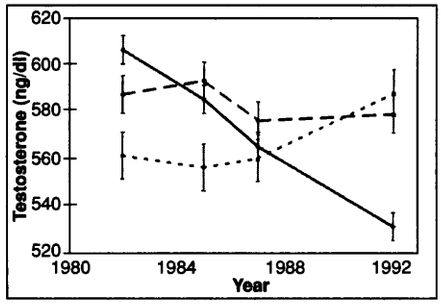

Fig. 1. Changes in serum testosterone of Air Force veterans over 10 years. Men who lost body fat (n = 383) (- -); gained 0 to 10% body fat (n = 589) (— —); or gained more than 10% body fat (n = 908) (—). Data (mean and standard error) are shown by year of cycle. Testosterone measured in nanograms per deciliter (ng/dl).

For men with more than a 10% increase in fat (which was the largest group), testosterone declined across the decade, as expected (Fig. 1). For men with slight increases in fat, testosterone remained essentially level from 1982 to 1992. For men who lost fat over the decade, testosterone actually increased. These groups differed significantly in testosterone at the first cycle,

which suggests a predisposition toward subsequent gain or loss.

One cannot tell from these results if maintaining body fat at a constant level would prevent a decline in testosterone, but they do suggest that possibility.

Allan Mazur
Maxwell School of Public Affairs, Syracuse University, Syracuse, NY 13244, USA
E-mail: amazur@syr.edu

References

1. A. Mazur and A. Booth, *Behav. Brain Sci.*, in press.
2. D. Freedman, T. O'Brien, W. Flanders, F. DeStefano, J. Barboriak, *Arterioscler. Thromb.* **11**, 307 (1991).
3. W. Wolfe *et al.*, *J. Am. Med. Assoc.* **264**, 1824 (1990).; G. Hendriksen, J. Michalek, J. Swaby, A. Rahe, *Epidemiology* **7**, 352 (1996).

Response: Watson describes the successful use of the simultaneous replacement of DHEA and melatonin in elderly and sick mice. One should realize how dangerous and uninformative studies with mice and rats are, with regard to their meaning and interpretation for human aging research. In mice and rats, DHEA is hardly, or not at all, produced by the adrenal cortex, while melatonin plays an important role in their physiology. In humans, DHEA is an important product of adrenal cortical steroidogenesis, while a physiological role of melatonin has not yet been demonstrated. The message of our article was that one should not extrapolate too much from animal experiments. As Watson states, long-term controlled clinical trials of elderly individuals seem the only way to approach the unsolved question of whether hormone replacement therapy is efficacious and safe.

Mazur describes an interesting observation in a large group of elderly U.S. Air Force veterans. Those men demonstrating a clear decrease in total testosterone showed a considerable increase in body fat. Mazur suggests that this age-related decrease in testosterone may be the result of weight gain, and that testosterone levels might be sustained in elderly men through diet and exercise.

It should be mentioned, however, that it has not been demonstrated to my knowledge whether and how the well-known changes in body composition during aging (loss of muscle mass and increase in body fat, for example) are related to changes in testosterone bioactivity only. In parallel, decreases in levels of growth hormone insulin-like growth factor I and in DHEA also occur. I also know of no evidence that dieting and exercise might prevent the age-related decrease in testosterone. For the time being, the interesting observations by Mazur suggest that healthy, elderly males demonstrate a variable change in total testosterone levels (decrease, unchanged, and slight increase), which is accompanied by changes in body fat (increase, unchanged, and slight decrease, respectively).

Steven W. J. Lamberts
Department of Medicine, Erasmus University, 3000 DR Rotterdam, The Netherlands

■

Immediate Release of Crystallographic Data: A Proposal

There has been an incredibly rapid increase in the rate of determination of three-dimensional (3D) structures of biomacromolecules, as reflected by the deposition of a new structure in the Protein Data Bank (PDB) at the Brookhaven National Laboratory (*1*), on average, every 5 hours. Unfortunately, in parallel, an increasing proportion of depositors take advantage of the PDB's policy of allowing structures to be kept "on hold" for up to a year after coordinate deposition. Despite a recent drop in the number of structures put"on hold," nearly half the entries deposited are not released immediately. The policy of the PDB is based on rules drawn up by the International Union of Crystallography (IUCr) in the late 1980s for papers published in IUCr journals. These rules (*2*) also provide the basis for the policies of most other scientific journals and of a number of government funding agencies, such as the National Institutes of Health, for work undertaken with grant support.

It is time to consider whether this policy is still appropriate. When it was debated and accepted by the community 10 years ago, the time needed to solve a macromolecular structure was often measured in years and was rarely less than 1 year. The time needed for detailed analysis of such structures was also fairly long. The 1-year hold on coordinates was therefore instituted to allow the authors to reap the fruit of their tremendous investment of time and effort. Because of recent advances in protein expression and purification, crystallization procedures, x-ray instrumentation, and computer software, the time needed to solve a structure is often shorter than the allowed hold period. In light of such developments, it is difficult to justify withholding coordinates for any period once the paper has been published.

Biomolecular structure analysis has succeeded in bringing 3D structures to the forefront of molecular biological research. This success has expanded both the interest in and utility of the information being deposited in the PDB. The molecular modeling community has grown and evolved considerably, due to the expansion of this source of experimental data. The value of the data rests in their availability to the broader community. Methods are continuously being developed to analyze new structures and their relationships to the collection of existing structures. New uses for these data, such as statistical potentials for folding and threading calculations, and interface recognition tools, are evolving rapidly. No single research group can fully exhaust this wealth of information. The value of the resource grows proportionally to the timeliness of the data and to the number of scientists who have access to them. Three-dimensional structural information is also a crucial link elucidating the role of a translated region of a DNA sequence of unknown function.

The time has come to change the rules of deposition so as to ensure that the coordinates are released concomitantly with publication of the paper (or papers) describing the structure. We are convinced that without access to the coordinates, the structures cannot be used for comparison with other proteins, for theoretical analysis or, more and more important, for drug design.

We propose that coordinates deposited at the PDB should be marked as either "for immediate release" or "to be released upon publication." We also recommend that the maximum hold for primary data (that is, x-ray structure factors, and nuclear magnetic resonance proton-proton distance and dihedral angle restraints) be reduced from 4 years to 1 year. The PDB is already working on a "layered approach" to deposition so that it will be possible to release entries as submitted, after the authors have checked for outliers and errors through the PDB's WEB-based AutoDep procedure, on the same day that they are deposited (with the permission of authors), or when the article related to the structure is published, if the authors request "release on publication date" rather than "hold for a year." It is clear that such a change in policy will require cooperation of both the granting agencies and the scientific journals, as well as the overwhelming support of the scientists doing the research. It should be stressed that even the current policy is not uniformly enforced. These changes would bring macromolecular crystallography into line with the requirements of other fields, such as gene sequencing, which have never allowed extended hold periods. We hope that this proposed change in the deposition policy will be publicly debated and ultimately accepted.

Alexander Wlodawer
Macromolecular Structure Laboratory, Frederick Cancer Research, and Development Center, National Cancer Institute, Frederick, MD 21702, USA
E-mail:wlodawer@ncifcrf.gov