

## Correspondence

## Enophthalmos Is Not Present in Horner Syndrome

Robert Daroff

The case report by Nautiyal et al. [1] is an instructive reminder that the first episode of an acute painful Horner Syndrome should prompt imaging of the ipsilateral internal carotid artery, since carotid dissection (as well as other conditions, such as high-grade stenosis) needs to be ruled out. Unfortunately, the authors perpetuate the extremely common misconception that enophthalmos accompanies ptosis and miosis in human Horner Syndrome. It is only an illusion of enophthalmos caused by the ptosis. This is evident in the left eye of their patient in Figure 1 of the case report.

Actual measurement with exophthalmometry clearly demonstrates the lack of enophthalmos. As stated by Loewenfeld ([2], p. 1139), “Animals such as cats, rats, or dogs have enophthalmos on the side of the sympathetic lesion. But in man, the enophthalmos is only apparent. The small palpebral fissure makes the eye look sunken in on the affected side, but the position of the globe in the orbit remains virtually unchanged. This has been found by all workers who have measured the supposed enophthalmos objectively.” Loewenfeld cites four supportive references.

Thompson and Miller ([3], p. 964) provide four additional references that the enophthalmos “is apparent rather than real.” ■

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**Citation:** Daroff R (2005) Enophthalmos is not present in Horner Syndrome. *PLoS Med* 2(4): e120.

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**Competing Interests:** The author has declared that no competing interests exist.

**DOI:** 10.1371/journal.pmed.0020120

## Is American Bioethics Lost in the Woods?

Michael Cook

The debate between a libertarian bioethicist and a communitarian bioethicist [1] illustrates why American bioethics is becoming increasingly marginalised and irrelevant to the democratic society that it intends to serve.

Both participants in the debate, Arthur Caplan and Carl Elliott, explicitly reject the notion of “human nature” as a

foundation for bioethics. But without human nature, on what grounds can advances in biomedical knowledge be called good or bad, right or wrong, or even harmful or beneficial? Clearly Caplan and Elliott have to accept something as a touchstone of their bioethical discourse, or it will lapse into windy incoherence. Although they approach it from different angles, this benchmark is informed consent, with Elliott placing the stress on “informed” and Caplan on “consent”.

As a result, their lively disagreement over enhancement technology is just verbal sparring and not a battle of ideas. Caplan believes that the consumer-patient is sufficiently mature to weigh up the dangers; Elliott is more sceptical. Neither appears to think that it makes any sense to argue that technology should be suited to human nature. This belief seems to be widespread in the bioethics community. Ruth Macklin, a bioethicist at Albert Einstein College of Medicine, argued recently, for instance, that “human dignity” is an empty and meaningless concept [2].

However, academic discourse has failed to dislodge from the heads of the hoi polloi the conviction that the starting point of ethics is not consent but happiness. The man in the street, the ultimate consumer of bioethics, still believes in human nature. The notion that human dignity is meaningless would be regarded by nearly all Americans as not merely absurd but reprehensible.

What I find odd in the writings of many bioethicists is that they skirt around the question that the average person wants to ask: will this enhancement make me happy in a deeply satisfying and fulfilling way? He or she is much less interested in whether all the boxes on the informed consent form have been ticked properly.

Consequently, as the Caplan–Elliott bunfight demonstrates, bioethicists are now reduced to arguing that human enhancement is good if people want it—even if they want it mainly because powerful commercial interests have persuaded them to, even if it is weird and kinky, even if it won't make them happy. Elliott's fascinating book *Better than Well* [3] is evidence that exercising a right to enhancement still leaves many lives hollow and unhappy. Sooner or later people will ask why they hadn't been warned, and a lot of bioethicists will be looking for jobs. ■

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**Citation:** Cook M (2005) Is American bioethics lost in the woods? *PLoS Med* 2(4): e121.

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**Competing Interests:** The author has declared that no competing interests exist.

**DOI:** 10.1371/journal.pmed.0020121

## Developing an HIV Vaccine: The Role of Efficacy Studies in Nonhuman Primates

Klaus Überla

Given the scientific hurdles encountered in HIV/AIDS vaccine development, a global effort is needed, and the scientific strategic plan proposed by the Global HIV/AIDS Vaccine Enterprise [1] is a milestone. The plan also provides an important starting point for continued discussion.

Since only a limited number of HIV/AIDS vaccines can be tested for efficacy in phase-III studies, evidence-based criteria for selection of candidate HIV/AIDS vaccines for these trials have to be defined. If an immune correlate of protection were available, small-scale immunogenicity studies in humans would provide required parameters. However, the specific immune responses needed for a successful HIV/AIDS vaccine remain unknown. The Global HIV/AIDS Vaccine Enterprise prioritizes research on vaccines eliciting neutralizing antibodies and T cell responses [1]. Standardization of laboratory assays measuring these parameters is proposed to allow comparison of different vaccines.

The main reasons to assume that T cell responses and neutralizing antibodies are important for HIV/AIDS vaccine efficacy are the following: (i) T cell responses and neutralizing antibodies are known to have a role in preventing infection or disease by other viruses, (ii) there is an inverse correlation of T cell responses with viral load in patients with HIV, (iii) depletion of CD8<sup>+</sup> T cells in nonhuman primate models of AIDS increases viral load, and (iv) passive immunization can provide protection in some of the nonhuman primate models [2]. However, extensive studies during the last 15 years using various T cell assays have failed to provide an accepted immune correlate of protection in nonhuman primates. Although more sophisticated assays and larger groups of animals might reveal such a correlate, protection could also be mediated by a mechanism not yet defined and therefore not monitored.

While the Vaccine Enterprise proposes to search for correlates of immune protection in nonhuman primate models of AIDS, efficacy studies in these models are not mentioned [1]. The limitations of these models have been extensively discussed [3], and there is no proof that these models predict efficacy in humans. However, if one accepts that nonhuman primate models are valid for determination of immune correlates of protection, it seems reasonable to also assume that a more effective vaccine approach in an appropriate nonhuman primate model would also be more effective in humans. Thus, by comparing efficacies of different vaccines in these models, it should be possible to select the most promising vaccine approaches for clinical evaluation. In the past, the nonhuman primate models have been little informative with respect to relative vaccine efficacy: the results from different laboratories were difficult to compare because of differences in, among other things, the monkey species, the inoculation route and dose, the pathogenicity of the challenge virus, the homology between vaccine and challenge virus, and the read-out assays used. This problem was recognized almost ten years ago already, but no agreement has yet been reached on which models most closely resemble HIV transmission and infection in humans. Different aspects of vaccine research require different animal models. In addition, worldwide use of one or two selected models would lead to a shortage in the monkey species needed for these models. Therefore, it is unlikely that an agreement can be reached at all. Rather

than going through great and costly efforts to standardize the animal models and laboratory assays, a standardized “state of the art” vaccine approach could be included as a control group in each study. The immunogenicity and efficacy of all novel vaccine candidates could then be determined relative to the immunogenicity and efficacy of the vaccine standard.

A number of issues would need to be discussed with respect to a generally acceptable vaccine standard. Ideally, results from a human efficacy study with the standardized vaccine approach should be available in near future. The standardized vaccine approach should be based on one of the most promising vaccines available at present. Due to the diversity of immunodeficiency viruses used in various nonhuman primate models of AIDS, the vaccine standard cannot be a single vaccine, but must be a standardized vaccine approach. For example, the vaccine approach could be defined by subcutaneous immunization of monkeys with a defined dose of a defined viral vector expressing codon-optimized *gag* and *env* genes at 24 and eight weeks before challenge. The degree of homology of the encoded Gag and Env proteins of the standard vaccine and the challenge virus should be the same as the homology between the antigens of the novel vaccine to be tested and those of the challenge virus. Thus, depending on the novel vaccines to be tested, different vaccine standards of the standardized vaccine approach are needed.

Including defined vaccine standards in future efficacy studies in nonhuman primate models would greatly facilitate preclinical evaluation of novel vaccine candidates and provide evidence-based criteria for their selection for clinical studies. Once an agreement on a standard vaccine approach has been reached, the approach could be implemented quickly, since efficacy studies in nonhuman primates are well established. Given the urgent need for an HIV/AIDS vaccine, we cannot afford to ignore the only animal models that might well predict efficacy in humans. Exploitation of the potential of carefully controlled comparative efficacy studies in nonhuman primates should be considered by the Global HIV/AIDS Vaccine Enterprise. It remains to be discussed whether inclusion of a vaccine standard in clinical studies might also solve some of the standardization problems encountered. ■

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**Citation:** Überla K (2005) Developing an HIV vaccine: The role of efficacy studies in nonhuman primates. *PLoS Med* 2(4): e119.

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**Competing Interests:** I am actively engaged in HIV/AIDS vaccine development and receive research grants from the European Community, the German Research Foundation, and the Wilhelm-Sander Foundation.

**DOI:** 10.1371/journal.pmed.0020119