COMMENTS AND RESPONSES

Misleading Interpretations and Public Misinformation on Human Growth Hormone in Athletes

TO THE EDITOR: The article by Meinhardt and colleagues (1) is important and informative. This randomized, controlled trial evaluating the independent and synergistic effects of exogenous growth hormone and testosterone on selected physiologic and athletic performance measures is a valuable contribution to the scientific literature. It also provides critical evidence to the ongoing social and scientific debate surrounding sports doping.

The study shows significant increases in anaerobic work capacity, as measured by the Wingate cycle test, after 8 weeks of treatment with growth hormone, with and without concurrent testosterone administration. Although effect sizes were modest (0.22 to 0.38 for growth hormone alone and 0.61 for growth hormone and testosterone), these findings suggest a previously unreported physiologic effect that has potential implications for athletic performance. The authors correctly conclude, however, that the athletic significance of these findings is uncertain.

Unfortunately, oversights in the presentation of this important work have led to erroneous interpretations in the mainstream media that compromise its effect and carry dangerous ramifications, especially when viewed by an untrained audience.

The characterization of anaerobic work capacity as "sprint capacity" is inaccurate and misleading. Although equivocal support exists for cycle ergometry as a significant predictor of sprinting performance (2, 3), it is widely recognized that additional factors, including strength and power, are important determinants (4, 5). To suggest even semantically that Wingate test performance and sprint capacity are equivalent measures is wrong.

More egregiously, even while acknowledging such limitations, the authors go on to speculate in specific terms how their findings in recreational athletes translate to 100-meter running times and 50-meter swimming times in world-class competitors: "We do not know how an improvement in Wingate test performance translates to performance in the sporting field, but we speculate that the approximately 4% increase in sprint capacity that we observed could translate to an improvement of 0.4 second in a 10-second sprint over 100 meters or of 1.2 seconds in a 30-second swim over 50 meters." This claim is made without basis, evidence, or even a compelling explanation. Nonetheless, it forms the featured conclusion of numerous prominent media reports, including this from the *Los Angeles Times*: "Injections of human growth hormone can improve sprint capacity enough to turn the last-place finisher in the Olympic 100-meter dash into a gold-medal winner, according to a study released Monday" (6). Disturbingly, at least 1 study author seems to have expressly endorsed this interpretation: "Dr. Ken Ho, who led the study, said: 'This improvement could turn the last place finisher in the Olympic finals into a gold medal winner'" (7).

Such gross mischaracterization of the study findings is possible only because authors, reviewers, and editors did not screen this language from the article. Although some may view this media attention as a victory in the highly publicized battle against sports doping, it is scientifically inaccurate, unethical, and irresponsible. Ironically, it could also encourage the abuse of doping agents by exaggerating their efficacy.

As scientists, we have a responsibility to present facts and interpretations to colleagues and lay audiences alike in a manner that promotes truth and understanding. We are obliged to objectively express in context not only our findings, but also our limitations and biases. It is regrettable that our community has missed such a key opportunity to do so.

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Potential Conflicts of Interest: None disclosed.

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6. Roan S. Study shows growth hormone boosts sprint speed. Los Angeles Times. 3 May 2010. Accessed at http://articles.latimes.com/2010/may/03/science/la-sci-growth-hormone-20100504 on 27 July 2010.

7. Hutchison P. Human growth hormone 'makes worst athlete the best'. Daily Telegraph. 4 May 2010. Accessed at www.telegraph.co.uk/health/healthnews/7672390/Human-growth-hormone-makes-worst-athlete-the-best.html on 27 July 2010.

TO THE EDITOR: Meinhardt and colleagues (1) reported significant water retention and reduction of fat mass after administration of growth hormone, whereas endurance, strength, power, and muscle mass were not significantly altered. These findings are in line with previous studies (2, 3). Meinhardt and colleagues are the first to suggest an effect of growth hormone in a Wingate test procedure. Experts in exercise physiology are critically debating the athletic significance of the Wingate test (4), but Meinhardt and colleagues speculate in their article and in a video message addressed to the mass media that their findings could translate into an improvement of 0.4 second in a 10-second sprint over 100 meters. Given the study population, a more rational speculation could have been that a recreational athlete might be able to improve their time in the 100-meter dash by about half a second. Therefore, we should have a closer look at the precise scientific findings of this study and at their potential significance for the field of exercise physiology.

The authors clearly state that this is an analysis of secondary outcome data. Therefore, it is not surprising that "training quantity" as an important factor influencing performance outcome measurements is not

well-distributed between the different groups, as shown in Table 1. This raises the question of whether the study should be called "a randomized trial." The study uses the term "$\dot{V}o_2$max." In fact, the Methods section reads as if only an "estimated $\dot{V}o_2$max" had been determined by using a population-derived nomogram for a relationship between heart rate and power output, a method that is irrelevant for the determination of growth hormone–induced intraindividual differences in $\dot{V}o_2$max. Concerning the "significant" improvement in the Wingate value as 1 of 4 other secondary outcome variables for physical performance, the authors corrected for multiple comparisons across the different groups by a not-very-conservative Holm correction, although they did not correct for the number of different secondary outcome variables. We speculate that *Annals* would not have published this study if it was related to a clinically relevant outcome measure. The study is just about an 0.4-second improvement in the 100-meter dash, which does not hurt any patient. However, it just may harm athletes, who are not within the scope of the journal.

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Potential Conflicts of Interest: None disclosed.

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IN RESPONSE: Mr. Sorensen and Dr. Tobias and colleagues voice concerns about the interpretation and media communication of our findings, focusing on a sentence in the Discussion section of our article. The issue centers on what an improvement in Wingate performance means.

Wingate test performance depends on all available forms of muscle energy supply and is primarily a measure of power and anaerobic capacity (1). In the context of the broad performance categories assessed in our study, it is the form of testing that is most closely aligned to sprint events (rather than endurance running, weightlifting, or high jump). We did not state that the Wingate test and sprint capacity are "equivalent measures," as Mr. Sorensen says. Although strength and power are determinants of sprint capacity (2), we found no evidence that either was enhanced by growth hormone, leading us to postulate that the anaerobic energy required to drive contractile muscle function may be increased by growth hormone. Indeed, several studies (3, 4) have shown a positive relationship between Wingate anaerobic capacity and sprint performance.

Having stated that "we do not know how an improvement in Wingate test performance translates to performance in the sporting field," our speculation of what this might mean in a sprint event is based on mechanistic and conceptual extrapolation. To cast this as an unsubstantiated claim is to misread a considered deduction that has passed the most stringent standards of expert review.

Dr. Tobias and colleagues also raised concerns about training bias, analysis, and performance methodology. In suggesting that the unequal distribution in training quantity may have influenced the finding that growth hormone improved Wingate performance, they infer that such a bias, if present, is of sufficient magnitude to overcome the rigors of stringent randomization in a double-blind, placebo-controlled design. This contention is plausible only if there is evidence that the level of training influences the measures of performance change with growth hormone administration, and on Wingate performance only, which there is not. Dr. Tobias and colleagues criticize the use of the Holm method for multiple-group comparison but do not offer an alternative. We used several statistical methods, including Tukey and Bonferroni corrections, all of which gave similar findings, but we settled on the Holm method during review discussions with one of *Annals'* statisticians. Estimated $\dot{V}o_2$max from a population-derived nomogram is a validated, time-honored method. Direct measurement improves accuracy, and its use may have tightened the variance but would not have changed the outcome that $\dot{V}o_2$max was not affected by growth hormone, a finding that matches previous studies assessing the performance effects of growth hormone in athletes (5).

We agree that challenges remain in bridging the gulf between scientific findings and media communication. Selected and simplified information in a compressed media platform can be distorted, and so can the reaction to one specific sentence.

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Potential Conflicts of Interest: None disclosed.

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review: the effects of growth hormone on athletic performance. Ann Intern Med. 2008;148:747-58. [PMID: 18347346]

Vessels of Mercy

TO THE EDITOR: I read with interest the article by Amundson and colleagues (1). I recently returned from volunteering as an internist, in the position of crew physician, on the largest nongovernmental hospital ship in the world: the *MV Africa Mercy*, which is currently in service in West Africa (www.mercyships.org). Although the *USNS COMFORT* and the *Africa Mercy* are 2 tertiary care hospital ships with different models (one catastrophic, military-funded and the other elective, charity-funded), they face strikingly similar challenges.

The *Africa Mercy* also faces specific challenges regarding the large influx of patients on "opening day," the difficulties of infection control in an open-bay ward design, screening for tuberculosis and other infectious diseases, transportation of patients to and from the ship, high nurse-to-patient ratios, having a single intensive care unit for all age groups, and the difficulties of placing patients back into the local and resource-limited health care environment.

Additional challenges unique to Mercy Ships include a dependence on donations, both monetary and equipment, from many philanthropic organizations and private donors. Supply shortages, although rare thanks to dedicated sponsors, can greatly impair our ability to provide life-changing surgeries and to tackle the previously mentioned problems. The elective and charity nature of care provided requires that ongoing geopolitical negotiations with target nations be successful. Having a multinational crew adds flavor to the already diverse language mix involved in daily patient care, although the language barrier was effortlessly overcome, possibly because of the unmatched and resolute dedication of the volunteers to the Mercy Ship credo, "Bringing hope and healing to the forgotten poor." The high turnover of volunteer staff presents challenges to the "institutional memory" of running a Mercy Ship hospital.

These big hospital ships, regardless of their affiliations, are testimonies to the human spirit's endeavor to relieve suffering in the face of diverse calamities, from war, acts of nature, and inexplicable affliction from fellow human beings. Their successful operation requires huge support structures not typical to a land-based hospital system. They are indeed the "long arm of medicine," aiding those in need of comfort and mercy through advanced technologies and unselfish giving without discrimination.

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Potential Conflicts of Interest: None disclosed.

Reference

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Clinical Observation

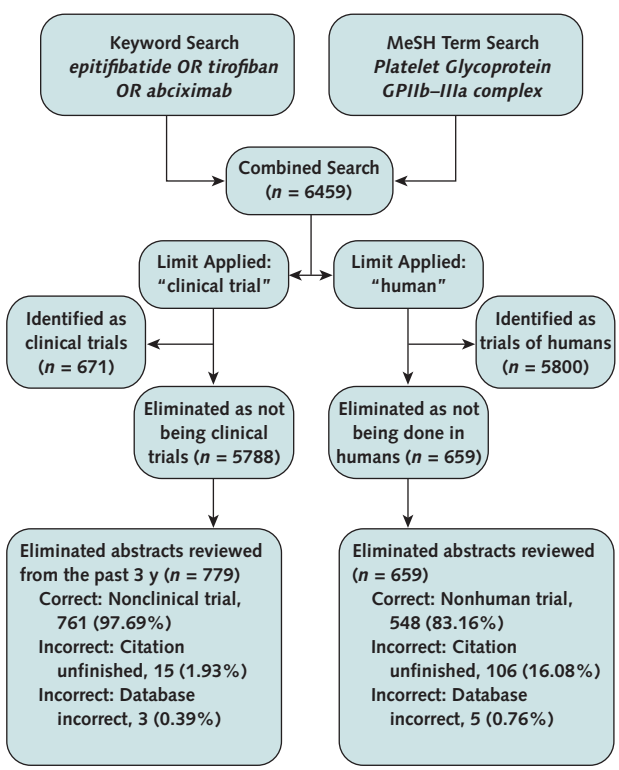
Limitations of the MEDLINE Database in Constructing Meta-analyses

Background: Meta-analyses are important for aggregating trial results to identify conclusions that cannot be made through separate examination. A thorough literature search is of utmost importance in constructing a meta-analysis. The PubMed interface from the National Library of Medicine is a cornerstone of many meta-analysis searches, and the largest component of PubMed is the MEDLINE database. Each article in this database has a unique entry with information about the study's participants and design. However, database entries are available for public search before the entry is finished, leaving a lag time during which data about the study design and participants may not yet be recorded in the database.

Objective: To assess the accuracy of MEDLINE's "human" and "clinical trial" search limits, which are used by authors to focus literature searches on relevant articles.

Methods: We searched PubMed for articles on glycoprotein 2b/3a inhibitors published from inception to February 2010 and found 6459 studies (**Figure**). Applying the "human" limit eliminated 659 studies, and separately applying the "clinical trial" limit eliminated 5788 studies. We hand-searched the abstracts of publications eliminated by these search limits to assess their accuracy. We also examined publications we believed were incorrectly eliminated to determine the cause of elimination.

Figure. **Search strategy and results.**



MeSH = Medical Subject Heading.

Results: Of the 659 publications eliminated by the "human" search limit, 548 (83.2%) were correctly identified as being studies on nonhuman participants, and the other 111 were studies in humans. Of these 111 studies, 106 (16.1%) were eliminated because the MEDLINE entry was unfinished and 5 studies (0.8%) had database entries that were finished but incorrect. Because we could not review all 5788 studies eliminated by the "clinical trial" limit, we confined our review to the 779 studies from the past 3 years. Of these, 761 studies (97.7%) were correctly eliminated, 15 studies (1.9%) had unfinished entries, and 3 studies (0.4%) had entries that were finished but incorrect.

Discussion: Others have described methodological inaccuracies in meta-analyses (1) and limitations of MEDLINE database terms (2). Our analysis revealed that MEDLINE database search limits can inadvertently eliminate an important number of articles. Instructions on the PubMed Web site warn that the "human" and "clinical trial" search limits will eliminate articles with unfinished database entries. Because recently published articles are more likely to have unfinished entries, using these search limits without addressing this problem could introduce systematic bias to a literature review by selectively eliminating more recent publications. One solution is to search with the term "NOT medline [sb]," which will isolate all unfinished PubMed entries so that they can be hand-searched. This solution, however, will not identify entries that are finished but incorrect, and we found that the overall accuracy of the database for these search limits is high but not perfect, with an error rate of approximately 0.5%. Our observations apply only to the MEDLINE database, and the limitations we have illustrated will be minimized by using multiple databases. We reported the rare errors we detected to National Library of Medicine staff, who promptly corrected them.

Conclusion: MEDLINE is a comprehensive database of medical literature, but researchers must be aware of its limitations to conduct optimum searches.

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Potential Conflicts of Interest: None disclosed.

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Corrections

Correction: Weight and Metabolic Outcomes After 2 Years on a Low-Carbohydrate Versus Low-Fat Diet

The Grant Support section of Foster and colleagues' recent article (1) was incorrect. It should read as follows:

Grant Support: By the National Institutes of Health (NIH) (grant R01 AT1103) to Temple University; NIH grant UL1RR024134 to University of Pennsylvania; NIH grant UL1 RR000051 to University of Colorado; and NIH grant UL1 RR024992 and DK 56341 to Washington University.

The online version has been corrected.

Reference

1. Foster GD, Wyatt HR, Hill JO, Makris AP, Rosenbaum DL, Brill C, et al. Weight and metabolic outcomes after 2 years on a low-carbohydrate versus low-fat diet. A randomized trial Ann Intern Med. 2010;153:147-157.

Correction: Candidate Performance Measures for Screening for, Assessing, and Treating Unhealthy Substance Use in Hospitals

The first sentence of the penultimate paragraph of the Perspective by Saitz (1) should read as follows: "Patients with addictions who are in hospitals and seek help have great difficulty receiving addiction-specialty treatment."

The online version has been corrected.

Reference

1. Saitz R. Candidate performance measures for screening for, assessing, and treating unhealthy substance use in hospitals: advocacy or evidence-based practice? Ann Intern Med. 2010;153:40-3.