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GRANTS AVAILABLE

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March 1       July 1       November 1

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“Chemistry of Anti-Doping: Deterring of Performance-Enhancing Drug Use by Athletes”

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This ACS Webinar was co-produced with the Partnership for Clean Competition

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Larry Bowers
President, LDBowers and former CSO, US Anti-Doping Agency

Jason Schaff
Forensic Chemist, US Government
Chemistry of Anti-Doping:

Deterring Performance-Enhancing Drug Use by Athletes

Larry D. Bowers, PhD

Why do athletes dope?

- It works!
- There are powerful incentives to dope
  - Lack of trust that others will not dope and thereby defraud the individual of their legitimate rewards
  - Concern that anti-doping programs do not catch cheaters
  - Concern that the sport organization is not committed to eliminating doping
  - Concern that some countries are not committed to eliminating doping
  - Huge personal and financial rewards
  - Immediate gratification versus delayed sanction (time discounting)
  - “Win at all costs” mentality
Doping is a rational choice

- Decision regarding doping behavior is made by evaluating the rewards versus risks

- Doping is
  - Instrumental
  - Communal
  - Requires expertise

Compliance and Sanction Threats

- Deterrence is based on threat assessment
  - **Certainty** of being detected and sanctioned
  - Severity of sanction
  - Timeliness (Celerity) of sanction

- Perceptions are more important in decision making than facts
  - Perceptual calibration
  - Perceptual deterrence
  - Perceptual (experiential) re-calibration
Is Random Drug Testing a Threat?

Assume that an individual uses a drug three times a month. The detection window for the drug is two days.

Assume that the drug testing program tests 5% of the eligible pool of athletes at random each month.

How long does it take to detect this drug user?

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Audience Challenge Question

ANSWER THE QUESTION ON BLUE SCREEN IN ONE MOMENT

How long does it take to detect this drug user?

- 4 months
- 9 months
- 4 years, 9 months
- 9 years, 4 months
- 19 years, 4 months
Does testing change behavior?


How can we influence perceptions?

- **Perceptual re-calibration** – ensure that experience with the system reinforces the certainty of being caught
  - *Research* to improve detection of doping agents
  - *Research* to identify new doping agents
  - Collection of information to guide testing strategies
  - "Non-analytical" cases

- **Ambiguity aversion** – uncertain situations increase certainty of detection
  - No-advance-notice out-of-competition sample collection
  - Alternative matrices (e.g., dried plasma spots) to cost-effectively increase testing numbers
Synthetic anabolic steroid detection

Steroid Metabolism (Phase I)

- Reduction or oxidation of hydroxyl/keto group
- Aromatization to form estrogens
- 16α/β-hydroxylation
- Reduction of double bond
- 4β-hydroxylation

Testosterone → Androsterone
Synthetic anabolic steroids can be detected in urine for how long after administration?

- Several days
- Several weeks
- Several months
- Several years
Detection of Urinary Steroids

**GC - MS and GC - MS/MS**
- SPE sample clean-up
- β-glucuronidase cleavage
- Extract free steroids with t-butylmethyl ether or pentane
- Derivatization with MSTFA/NH$_4$I/C$_2$H$_5$SH
- GC - MS SIM analysis

**HPLC - MS/MS**
- SPE sample clean-up
- Optional conjugate cleavage
- Extract free steroids
- LC – MS/MS analysis

### Pros & Cons of Derivatization

![Graphs showing relative abundance of steroids before and after derivatization](image)
Methandienone (Dianabol) → Epi-methandienone

~ 2-3 days


Long-lived Steroid Metabolites

- Tetrahydrogestrinone (THG)
- Tetrahydro-epi-methyltestosterone-3-sulfate
- 17-epi-stanozolol-N-glucuronide

Detection Window for Stanozolol Glucuronide Conjugates
Challenges with long-lived metabolite analysis

- Decreasing limits of detection and identification of long-lived metabolites allows detection of anabolic steroids for many months
- Re-analysis of samples from past Olympic Games results in more positive urine samples and medal re-distribution
- Detection of pg/mL metabolites in urine raises interpretive challenges
  - Residual metabolites versus new use
  - Inadvertent ingestion of contaminated meat or grain
  - “Off-label” medical treatment (e.g., clomiphene for male infertility)

Peptide and protein doping agent detection
**Audience Challenge Question**

ANSWER THE QUESTION ON BLUE SCREEN IN ONE MOMENT

Peptide hormones (less than 75 L-amino acids) can be detected in urine.

- True
- False

**Insulin-like Growth Factor 1**

Molecular mass: 7649 Daltons
Blood concentration: 30-400 ng/ml
LC-MS/MS Quantification of IGF-1

- Interlaboratory (n=5) study of IGF-1 bottom-up method
- Working group has developed serum reference material with a consensus concentration assigned for LC-MS/MS work
- Collaborating with the National Institute for Science and Technology (NIST) to develop an ISO traceable serum-based reference material

Urinary Analysis of GHRP2

(\{\text{D-Ala}\}-(\text{D-\beta-Nal})\text{-Ala-Trp-(D-Phe)-Lys-NH}_2 \quad \rightarrow \quad (\text{D-Ala})-(\text{D-\beta-Nal})\text{-Ala-NH}_2)

GHPRP 2
Summary and Conclusions

- Doping/cheating in sport is a reflection of society and its problems as a whole
- Anti-doping policies should be designed to deter the use of performance-enhancing drugs and involve complex interdisciplinary effort
- Perceptual deterrence model provides guidance for optimizing programs to achieve behavior change
- Research is an important factor in increasing the perceived certainty of detection, which is the primary factor in assessing risk
- Anti-doping testing requires a skilled laboratory staff with expertise in analytical science, biochemistry, clinical chemistry, exercise physiology, pharmacology, hematology, and endocrinology
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