Witness Statement
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I have been asked to provide an expert opinion as to whether the absence of a "failed" doping control test is proof that the athlete did not dope.

Drugs and Methods Abused in Cycling

The most effective means to increase performance is to increase the oxygen delivery to the muscle tissue and its conversion into energy. Binding of oxygen to hemoglobin (Hb) (which is exclusively present in the red blood cells (RBCs)) occurs in the lung and off-loading of oxygen occurs at the tissue. The maximal oxygen uptake ($\dot{V}_{O_2MAX}$) is the rate at which oxygen can be delivered to the tissue. Since Hb is carried exclusively in the RBC, an increase in Hb mass is reflected by an increase in the number (and volume) of RBCs. The Hb concentration is measured in g/L, while the RBCs are usually reported as the packed volume fraction of the blood occupied by RBCs. This fractional volume is called the hematocrit (Hct) and is reported in units of per cent (%).

Since elite level endurance athletes have high cardiac output volumes, total body hemoglobin (Hb) mass is the primary determinant of $\dot{V}_{O_2MAX}$. Total body Hb mass can be increased either by transfusing additional RBCs or by increasing natural RBC production by injecting erythropoietin (EPO). A transfusion can be done either with blood from another person (allogeneic or homologous) or with a rider's own blood that has been removed during training and then stored prior to reinfusion (autologous transfusion). Autologous transfusion is the preferred doping method since there is currently no direct method to detect it. EPO is normally produced by the kidney in response to a decrease in oxygen delivered to the kidney tissue. The EPO then causes maturation of precursor cells in the bone marrow to develop into RBCs. It takes about a week after the initiation of the maturation of the precursor cell before an increase in RBCs can be observed

Testosterone and other anabolic steroids result in construction of tissue and are used to increase the rate of recovery from hard work. In principle, this would allow the athlete to work harder during subsequent training sessions and to recover faster to enhance performance during a multiday event such as a stage race in cycling. Testosterone cannot be given orally, so it has been administered by injection, trans-dermally via a patch or cream, or sublingually (under the tongue). Testosterone is not sufficiently soluble in water to administer a concentrated dose, so peanut or olive oils are frequently used as a delivery fluid. Testosterone undecanoate is a chemical derivative (ester) of testosterone that is frequently used as the dosage form (e.g., Andriol). It is better absorbed into the blood.

Another class of drug that has been abused in cycling is glucocorticosteroids. This class of drugs is used for anti-inflammatory and immunosuppressive activity. It is also known to produce a sense of euphoria and may also work to relieve pain allowing the rider to ride longer and harder. One of the benefits for a professional cyclist may be that corticosteroids shift energy production from glycogen/glucose to fats and amino acids.

Doping in the Peloton

Unfortunately, the use of drugs in the peloton has been endemic since the 1920's. The use of stimulants like amphetamine to moderate the perception of fatigue has been succeeded by the use of corticosteroids to allow cyclists to ride longer and harder through the pain, anabolic steroids (e.g., testosterone) to allow rapid recovery between stages, and erythropoietin and its mimetics to increase the number of red blood cells (RBCs) and enhance power output. The systematic use of performance-enhancing drugs in the last 15 years has been well documented through the Festina Affair[1], the Freiburg Inquiry[2,3], and Operation Puerto[4,5].

It has not been lost on a number of commentators that the times of the peloton have continued to improve dramatically during this same period.[6] During the period 1981 through 1990, winners of the Tour averaged 37.369 km/h while in the 1970s the average was approximately 35 km/hr. From 1991 through 2005, the Tour winners averaged 39.661 km/h. Recent Tour winners have averaged about 41 km/h.[7] While performances alone do not constitute proof athletes doped, it is important to consider that the recent climbing power and speed of Tour de France champions day-after-day during the Tour de France cast doubt over the physiological credibility of such performances. Even when all external factors are optimized, combine the number of doping violations over recent times in the Tour, and serious plausibility questions are raised when relative power outputs of greater than 6 W/kg are sustained for longer than 30 min without the use of ergogenic aids.[8]

Power output is directly related to the number of RBCs in the body. Recombinant EPO (rEPO), which stimulates production of RBCs, was approved by the US Food and Drug Administration in 1987. It is estimated that rEPO can help a rider achieve a 10% to 20% increase in performance due to the increased energy, recovery and training capacity and endurance, and delayed fatigue, obtained through increased transport of oxygen to the rider's muscle cells, allowing for increased maximum aerobic output.[9] The use of rEPO causes an increase in reticulocytes (immature RBCs) which then mature into RBCs. Data available from the UCI's own blood tests shows that nearly 8% of the cyclists tested during 2000 and 2001 had extremely elevated

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[1] http://autobus.cyclingnews.com/results/2000/oct00/oct25news.shtml

[2] http://autobus.cyclingnews.com/news.php?id=features/2009/freiburg_report_may09

[3] http://www.cyclingnews.com/news/freiburg-doctor-pays-fine-to-settle-doping-related-charges

[4] http://web.archive.org/web/20070509113145/http://news.yahoo.com/s/ap/20070507/ap_on_sp_ot/cyc_basso_doping

[5] http://autobus.cyclingnews.com/news.php?id=news/2007/apr07/apr04news

[6] El Helou N, Berthelot G, Thibault V, Tafflet M, Nassif H, Campion F, Hermine O, Toussaint JF. Tour de France, Giro, Vuelta, and classic European races show a unique progression of road cycling speed in the last 20 years. *J Sports Sci.* 2010;28:789-96.

[7] Perneger TV. Speed trends of major cycling races: does slower mean cleaner? *Int J Sports Med.* 2010;31:261-4. Epub 2010 Feb 10.

[8] Vogt S, Schumacher YO, Roecker K, Dickhuth HH, Schoberer U, Schmid A, Heinrich L. Power output during the Tour de France. *Int J Sports Med.* 2007;28:756-61. Epub 2007 May 11.

[9] Sawka MN, Joyner MJ, Miles DS, Robertson RJ, Spriet LL, Young AJ. American College of Sports Medicine position stand. The use of blood doping as an ergogenic aid. *Med Sci Sports Exerc.* 1996;18:i-viii

reticulocytes, consistent with rEPO use.[10] In 2001, a test for rEPO was implemented resulting in the first adverse analytical findings for rEPO in cycling.[11] In the early years of EPO testing, the criteria used to report an adverse analytical finding were set conservatively at a high level (80% basic band area percentage). The current criteria would allow a sample in the 20-80% basic band area percentage to be reported as an adverse analytical finding if it met other criteria laid out in the EPO Technical Document. In response to the implementation of a test for EPO, cyclists changed their doping behavior.

A second method to increase the number of RBCs in the body is through transfusion.[12] The use of either allogeneic or autologous transfusion of RBCs is rapidly followed by the suppression of natural RBC production as reflected by an abnormally low number of reticulocytes. Again, UCI's own data shows that during the period 2002-2007, between 6% and 9% of cyclists had an abnormally low percentage of reticulocytes – again consistent with blood transfusion doping.[12] In 2004, a test for allogeneic blood transfusion was implemented, and a doping violation based on the test was successfully prosecuted by USADA.[13] There is no test for autologous transfusion, so it not possible to detect its use. The use of rEPO to increase the number of one's own RBCs for harvest and later re-infusion was pioneered for elective surgery. This would be consistent with the reports of cyclists' stored blood in the Freiburg Inquiry and Operation Puerto.

In 2008, the UCI implemented the Athlete Biological Passport (ABP), a system which monitors a cyclists' hematological parameters, such as hematocrit, hemoglobin concentration, OFF-score[14], and ABPS[15], over time. A predictive model is used to calculate a range for each parameter that would be consistent with prior test results. If the latest result is not consistent with previous results, the latest result is subject to investigation. The UCI data show that the cyclists' results in 2008-2009 are much more normal that in the previous seven years. Unfortunately, cyclist blogs from the same period suggest that intravenous micro-doses of rEPO are being used to generate enough reticulocytes to mask their doping with transfusions. Thus, while it is theoretically possible to detect autologous blood transfusions using the ABP, it would require a sophisticated and well-timed collection process to do so.

Drug test statistics

It is Important to understand that not every sample that is collected from an athlete is tested for all of the Prohibited Substances and Methods. For example, UCI has not analyzed every urine sample it has collected for EPO. Whole blood samples collected for the Athlete Biological Passport would not be tested for growth hormone. And UCI's "health check" blood samples,

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[10] M. Zorzoli, F. Rossi. Implementation of the biological passport: The experience of the International Cycling Union. *Drug Test. Analysis* 2010, 2, 542.
[11] CAS 2001/A/343 UCI v/ Hamburger
[12] Eichner RE. Blood Doping – Infusions, Erythropoietin and Artificial Blood. *Sports Med* 2007 37: 389-91.
[13] CAS 2005/A/884 Hamilton v/USADA
[14] Sharpe K., Ashenden M.J., Schumacher Y.O. A third generation approach to detect erythropoietin abuse in athletes. *Haematologica.* 2006; 91(3): 356-63.
[15] Sottas, P. E., Robinson, N., Saugy, M. The athlete's biological passport and indirect markers of blood doping. *Handb Exp Pharmacol.* 2010; 305-26.

collected to ensure that all riders hematocrits were below 50%, were not tested for any prohibited substances or methods.

Considerations for an effective drug testing program

The ability to detect an abused performance-enhancing drug is dependent on a number of factors:

1. The timing of the sample collection process

   The time at which a sample of urine or blood is collected relative to when a particular drug is taken is one of the most important factors in whether a drug or its metabolites or markers can be detected. As drugs with shorter detection windows have been developed for treatment of disease, the necessity of no-notice out-of-competition testing has become even more important. The detection window for micro-doses of EPO can be very narrow. Bernhard Kohl admitted that he used erythropoietin (rEPO) after 11 PM because he had determined that the rEPO would be undetectable by 6 AM the next morning when a sample could next be legally obtained in Austria.

2. The integrity of the sample collection process

   The integrity of the collection process is also critical to detection of a drug in either urine or blood. For example, the 1990 Dubin Commission reported that athletes discarded their own urine, catheterized themselves, and performed a retrograde injection of drug-free urine into their bladder in order to produce a "clean" sample.[16] The WADA International Standard for Testing states that the objective of the notification process "is to ensure that … there are no opportunities to manipulate the Sample to be provided … "[17] Further, no advance notice testing is defined as "a *Doping Control* which takes place with no advance notice to the *Athlete* and where the *Athlete* is continuously chaperoned from the moment of notification through *Sample* provision."

   UCI post-competition test notification has been done through the team who was responsible for ensuring that the athlete was available within a required time window. WADA had an independent observer (IO) team monitor testing at the 2003 and 2010 Tour de France. In the 2003 report, the IOC stated "if there are riders who know for sure that they will not be tested twenty minutes before the finish line or even before they started (time-trial stages) and have the opportunity to perform some kind of physical manipulation before they reach the doping control station, the system cannot guarantee sporting equality."[18] In 2008, chaperones were introduced for post-competition testing at the Tour de France.

   With respect to pre-competition testing, the WADA 2010 IO report states "It was clear to the IO team that it was well known to the teams that the arrival of the UCI team could be

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[16] *Dubin CL. Commission of Inquiry in the Use of Drugs and Banned Practices Intended to Increase Athletic Performance. Canadian Government Publishing Center, Ottawa, CA, 1990.* pp 142-4

[17] The World Anti-Doping Code, International Standard for Testing, January, 2009.. p 16.

[18] World Anti-Doping Agency Independent Observer Report, Tour de France 2003 (Published 28 October 2010). http://www.wada-ama.org/rtecontent/document/tdf_io_report.pdf Retrieved September 7, 2012.

observed by checking the hotel car park. On two occasions, the IO Team could see two persons watching the parking from their room windows half-hidden behind the curtain as well as a team member seated in front of the hotel who immediately used his cell phone when he saw the UCI Team." [19] An unattended period of time when the athlete knows he is going to be tested allows the use of masking methods such as urine substitution or saline infusion into the blood (see below).

3. Masking

   As mentioned above, the integrity of the collection process is critical in order for any test to succeed. Urine substitution was mentioned in the Dubin report as one potential masking tactic. Procedures such as urine substitution require unattended time between the time that the athlete finds out that a doping control is going to be performed and the provision of the sample in order to prepare the masking materials. There are a variety of masking agents (S.5 and M.2 of the Prohibited List) that can either be ingested or added to the urine sample in order to hide or destroy substances that would otherwise result in an AAF. Proteases (proteins that hydrolyze other proteins) have been used to destroy EPO that was excreted in the urine. Many of the established masking procedures require careful direct observation of the urine stream in order to detect the masking attempt.

   The ability to have un-monitored time after notification can also be used to mask use of blood doping methods. Blood consists of two parts – the straw-colored plasma (mostly water) and several types of cellular components. The blood is a dynamic matrix with water capable of moving back and forth between the circulatory system (4-5 L) and the extracellular spaces in the body (about 15 L). A temporary change in the volume of the plasma can be achieved by infusing saline solution. Similarly an infusion of albumin solution would not only add the volume of the infusion, but because the albumin in the circulatory space "pulls" water from the extracellular space, which results in an artificial decrease in the hematocrit. Since these are the values that are used in the hematological ABP, the result is that a high hematocrit can be made to look lower and thus "beat" the test.

4. The route of drug administration
   The manner in which the drug is administered (oral, transdermal, subcutaneous, intravenous, etc.) also has an impact on the detection window for a drug or its metabolites or its markers. For example, the injection of a "bubble" of fluid containing the drug just under the skin (subcutaneous) allows the drug to be relatively slowly absorbed into the circulation. As a result, the drug can be detected for a longer period of time than an administration directly into a vein (intravenous). As a contemporary example, rEPO is an approved therapeutic agent that is administered to patients subcutaneously so that it has its effects over days. This is an advantage to an ill patient because they do not need to take the drug as frequently.

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[19] Report of the Independent Observers, Tour de France 2010 (Published 28 October 2010). http://www.wada-ama.org/en/Media-Center/Archives/Articles/Tour-de-France-Independent-Observer-Report-Now-Published/ Retrieved September 7, 2012. p 22.

In contrast, some individuals within the cycling community have advocated the strategy of administering rEPO intravenously specifically to decrease the window of opportunity for detection and thus decrease the probability of being caught.[20] Similarly, testosterone administered sublingually (e.g., under the tongue) or through a patch applied for a few hours during the evening would be difficult to detect the next day.

5. The amount (dose) of the drug taken

   The amount or dose of the drug taken also affects the ability of a test to detect the drug or its metabolites or markers. Given an analytical testing procedure that can detect a specific amount of drug or metabolite or marker, a larger amount of drug can be detected for a longer period of time than a smaller amount of drug.

   The amount of drug taken is related to the desired effect of the drug. For example, if the purpose of rEPO is to stimulate formation of new RBCs, then a dose on the order of 300 U/kg/day (21000 U/d for a 70 kg man) three times per week would be efficacious. One might use this strategy to increase the mass of RBCs prior to harvesting them for storage and infusion at a later date (autologous transfusion). This would not be done during a period of competitions, but rather during recreation or limited training periods.

   With the advent of the WADA ABP, EPO has also been used as a masking agent. If an autologous or allogeneic (infusion of blood from another individual from the same species) transfusion of blood was administered to increase the RBC mass, the normal physiological response would be to suppress the formation of reticulocytes (immature RBCs). This would trigger an adverse analytical finding in the ABP. Small doses of rEPO (300 IU/day) could be taken to "force" the production of some reticulocytes in the presence of suppression. The production of some reticulocytes would thus mask the use of a transfusion. The use of "micro-dosing" has been well documented on a number of cycling and other blogs.

   Another potential approach to masking a transfusion is to artificially stimulate the production of EPO through the use of a hypoxic tent. By increasing the EPO production, reticulocyte counts can be increased to the point that the transfusion cannot be unequivocally detected.

   In the case of naturally-produced hormones like testosterone, administration of low doses would be difficult to discriminate from natural production.

When all of the above factors are considered, it is not possible to equate a "negative test" with the absence of doping at the current time,. It would be relatively easy to avoid detection for doping if the anti-doping program is not as rigorous as it should be. Even with a well-executed collection and testing system, however, it is possible to use some products in specific routes of administration that would be very difficult to detect. In addition, there are some prohibited substances and methods for which there is no effective test (e.g., autologous blood transfusion and until very recently GH). The unfortunate result of this situation is, as illustrated by

[20] My opinion is based on interviews with athletes who have admitted doping with EPO and on surveillance of web sites.

contemporary examples such as Marion Jones, David Millar, and many others, athletes who have claimed never to have failed a drug test have later admitted their use of performance-enhancing drugs. As Bernhard Kohl stated "200 Dopingkontrollen . Lediglich 1 Mal überführt!! - 100 Mal hätte ich positiv sein müssen."

I swear or affirm that the foregoing statements are true to the best of my knowledge, information and belief.

Dated this 8th day of October, 2012.

Larry D. Bowers, PhD

STATE OF COLORADO)
) ss.
COUNTY OF EL PASO)

Subscribed and sworn to before me by Larry D. Bowers, PhD on this 8th day of October, 2012.

Witness my hand and official seal.

My commission expires: 8-20-16

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MY COMMISSION EXPIRES AUG. 20, 2016