DOPING AND ANTI-DOPING IN CYCLING

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For many years, cycling has been synonymous with doping in sports. Many scandals in the last decade have reinforced this image, which was shaped in the early days of the 20th century. In 1998, a team car was stopped at the start of the Tour de France with large supplies of performance enhancing substances, which triggered police investigations, arrests and convictions (the so-called 'Festina affair'). Many other scandals followed, exposing an engrained and extensive doping culture.

The aim of this article is to describe the development of doping and anti-doping in cycling and to highlight what other sports might learn from the cycling experience in terms of anti-doping management.

THE DARK YEARS

In the early 1990s, the commercial introduction of recombinant human erythropoietin (EPO) changed the face of endurance sport. This endogenous hormone regulates the amount of blood in the organism through a feedback mechanism in the kidney. The artificial form was initially developed to fight the anaemia associated with chronic kidney disease. The hormone stimulates the bone marrow to produce more red blood cells, thereby increasing the oxygen transport capacity of the blood and improving performance. Obviously, this mechanism is not only important for patients with anaemia, but might also be attractive to athletes. Many studies have unequivocally shown that maximal oxygen uptake (VO_2 max) is improved by ~6% after a typical EPO treatment cycle. Given that the difference in performance between first and 10th place at the pinnacle of elite sports is often below 1%, the impact of this substance on competitive results becomes clear. The substance was a 'game changer', its impact on performance in endurance events was very similar to the effect of anabolic steroids in strength-based sports. Greg LeMond, multiple Tour de France winner in the era before EPO became available, described the situation in 1991 with the following words: "I was the fittest I had ever been, my split times in spring training rides were the fastest of my career. But something was different in the 1991 Tour de France. There were riders from previous years who couldn't stay on my wheel who were now dropping me even on modest climbs". Given that EPO was recombinant, i.e. it was genetically engineered in cell cultures and thus identical to the endogenous human hormone, detection in conventional urine doping tests was not possible.

It can safely be assumed that in the 1990s, clean winners in elite endurance sport events such as cycling were the exception, as can be seen in the many scientific studies investigating blood values of athletes and

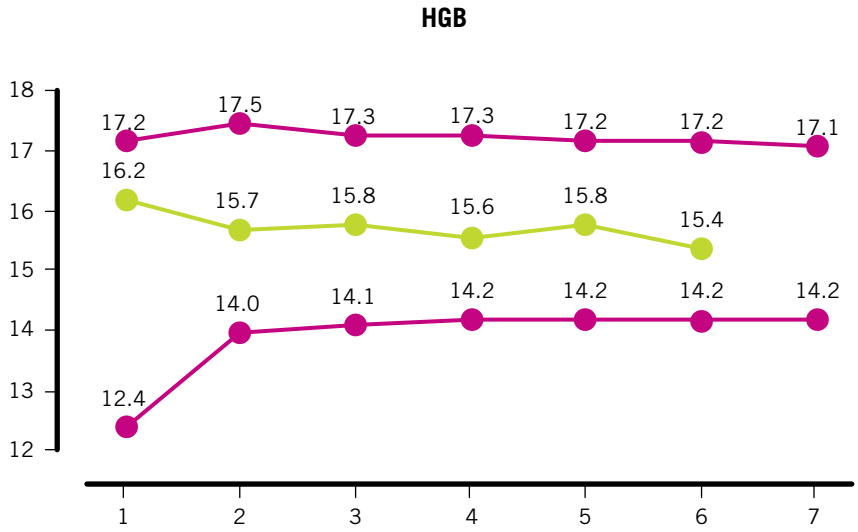

Figure 1: Graphical representation of a normal haematological profile of a male athlete (haemoglobin concentration (g/dl)). The horizontal axis represents the sample number, the vertical axis the level of haemoglobin. The green lines shows the measured values for each sample, the red lines represent the upper and lower individual limit as calculated by the statistical model at 99.5% specificity.

the development of performances in various sports[1].

Prevalence data on doping is not available from that time, but based on witness testimonies and admissions, it is very likely that the large majority of the professional cycling peloton used performance enhancing drugs. In retrospect, most athletes justified their behaviour with comments like "everybody was doing it" and "I had to do it to survive and to get a new contract to feed my family".

The consequence of the rampant drug abuse in cycling and the associated scandals was that TV stations and several media outlets withdrew from reporting on the sport, which caused the departure of many sponsors.

The Union Cycliste International (UCI) was initially overwhelmed by the situation and used denial as an approach to try to tackle the issue, obviously without much success, only causing more mistrust from clean athletes and the media.

From a scientific perspective, in the absence of a direct detection method for EPO, the UCI was looking for a solution to contain the rampant abuse of the substance. Given that the increase in red cell mass is usually visible in the blood through an increase in haemoglobin and haematocrit (the percentage of solid components – mainly red cells – in the blood), it was decided to introduce limits for haematocrit. Male athletes with haematocrits above 50% and women above 47% were not allowed to start a race 'for health reasons' and suspended for 14 days. Anecdotally, haematocrit values of 60% and haemoglobin concentrations of 20 g/dl have been reported in some athletes. Such values are similar to those observed after lengthy stays at altitudes above 6000 metres. The 'haematocrit cut off' method was not based on scientific facts, but voted by a show of hands in a meeting of team doctors ahead of the 1997 season at the Tirreno-Adriatico race. On the one hand, this approach limited the excessive abuse of EPO, but on the other hand, it also allowed for a large number of false negatives (athletes titrating their haematocrit up to the allowed limit). Unfortunately (and more importantly), it became apparent that there were also a number of false positives, as several athletes with naturally high haemoglobin were suspended (about 2.5% of the normal male population have a haematocrit above 50%). Furthermore, the haematocrit could easily be manipulated within a few minutes by using changes in body position, saline infusions or drinks to influence plasma volume.

In parallel, a test to detect EPO in conventional anti-doping urine tests was developed in 2000 and became operational in 2003. However, the detection window of the substance was very short (hours to days, depending on the dosage and type of administration), which limited the success rate of the test.

DEVELOPMENT OF THE ATHLETE BIOLOGICAL PASSPORT

The constant problem of doping in cycling warranted new approaches to anti-doping. In addition, developments in the pharmacological industry further highlighted the challenges to conventional anti-doping testing. Many different EPO variants were commercially available, which made a direct detection difficult, as tests have to be adapted for each variant.

Therefore, a paradigm shift in the fight against doping was warranted. Not the forbidden substance itself, but rather its effect on the organism should be detected. This 'indirect' detection method would have several advantages, as the doping effects would likely be similar for various products of the same class (for example different types of EPO), thus not requiring different tests. Also, these effects might still be visible in the biomarkers long after the forbidden substance itself had left the body.

To this end, in 2008 in co-operation with the World Anti-Doping Agency (WADA)[2], the longitudinal monitoring of biomarkers was introduced in cycling under the name of the Athlete Biological Passport (ABP). Given that blood doping through the abuse of EPO and related substances (erythropoiesis-stimulating agents) was the main issue in endurance sports, the first developments of the ABP focused on the indirect detection of this type of doping. As such, biomarkers related to the blood cell system were included in the protocol, namely haemoglobin concentration and the percentage of reticulocytes (young red blood cells). From these two markers, other measures such as the so-called 'OFF score' were calculated. The ABP profile is therefore a collection of tests conducted on an athlete over time.

The results of these tests are submitted to a software algorithm based on Bayesian statistics, which calculates the likelihood of each new result being normal for an athlete

(that is, within the individual reference range of each athlete), taking into account their previous results (Figure 1). If a result is found outside the individually calculated reference range, the profile is flagged and submitted anonymously to an independent expert, who must evaluate the likelihood of the constellation found in the profile in view of several hypotheses:

- The results are an extreme of physiological regulation.
- The result is caused by a pre-analytical or analytical problem.
- The result is caused by a pathology.
- The result is caused by doping.

If the expert concludes that the latter is highly likely, the profile is submitted to a further two experts, blinded to the results of the first review, who then also evaluate the profile. If all three experts agree independently that it is typical to find such a profile assuming doping, the athlete is asked for explanations of the observed abnormalities which are, again, evaluated by the experts in view of the data. If the explanations are dismissed, an anti-doping rule violation procedure is engaged against the athlete. The process of the ABP is illustrated in Figure 2 (adapted from Schumacher and d'Onofrio[3]).

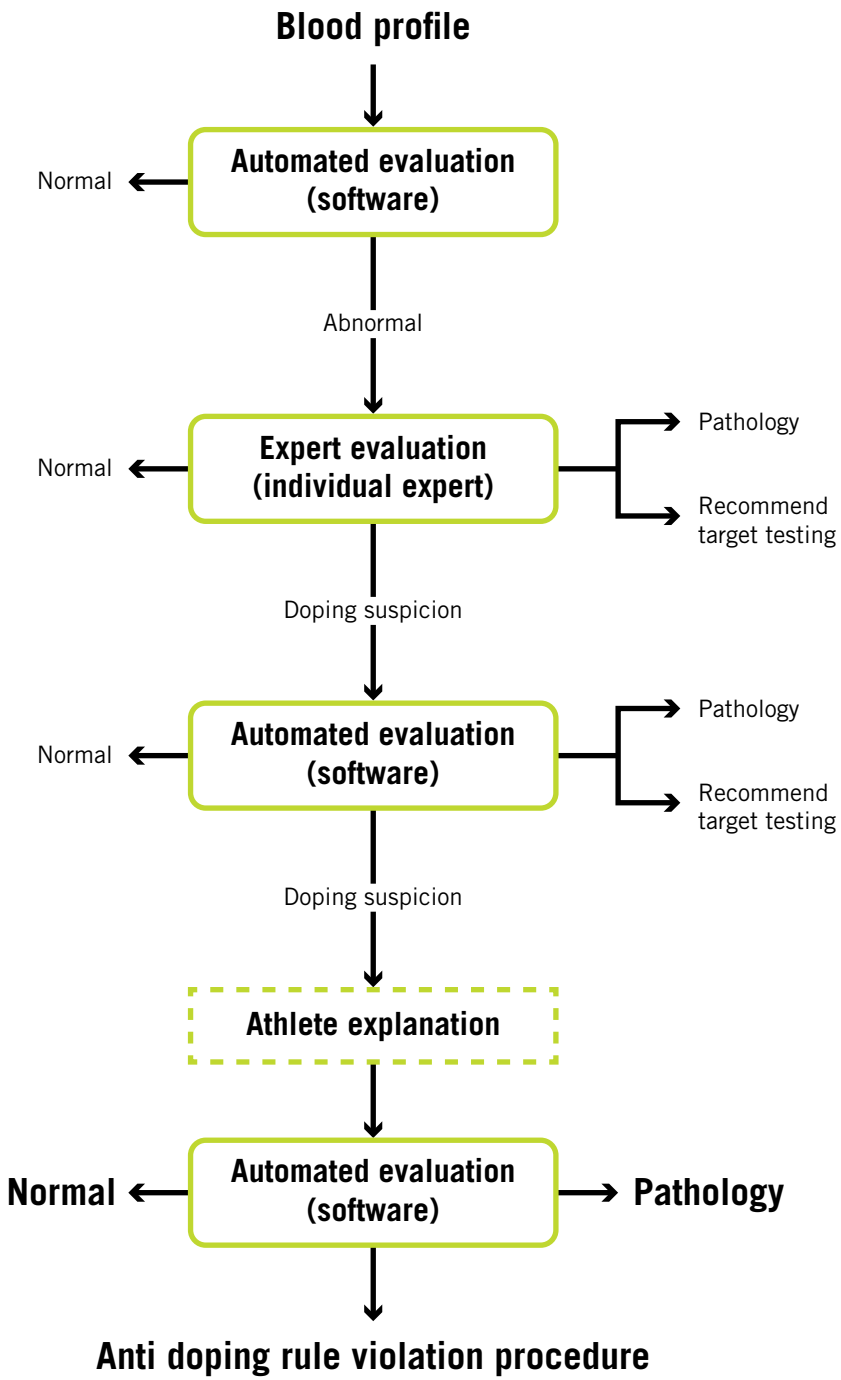

Figure 2: Process of the Athlete Biological Passport (modified from Schumacher, 2014[3])

EFFECT OF THE ATHLETE BIOLOGICAL PASSPORT

In 2010, the first athletes were convicted based only on their blood profile and the decisions were confirmed by the Court of Arbitration for Sports, after having been challenged in the first instance. This was a major step forward, as after the scientific validation of the ABP (through the publication of its procedures in numerous articles to the scientific community), the legal 'validation' was still pending. These first cases were the proof that the novel concept was a new option in the fight against doping.

The anti-doping community soon realised that longitudinal monitoring had other effects, in addition of the direct conviction of athletes for abnormal profiles. It allows for identification of suspicious variations in the blood profile, even if a full case cannot be brought forward. Such variations are usually followed up with targeted, conventional anti-doping tests, which very often return positive results. The number of positive, conventional EPO tests since the introduction of the ABP has increased by 400%, suggesting that conventional anti-doping tests are being used more efficiently, based on the information obtained from the passport data.

Furthermore, distinct changes in the blood picture of the athlete population have been identified. Zorzoli and Rossi[4] studied the results of the official blood tests conducted over a period of 10 years in cyclists. In this analysis, several patterns are visible. Whereas before the introduction of the EPO urine test in 2002, a large number of tests with high reticulocytes were noted, suggesting an ongoing stimulation of the bone marrow (possibly through the ongoing abuse of EPO, which, at the time, could not be detected by the doping system in place), this pattern shifted to an unnaturally high number of very low reticulocytes after the introduction of the urine test (2002 to 2008). Athletes had changed their behaviour to discontinue EPO use before likely tests (mostly conducted at races) to avoid detection, which then causes a suppression of the endogenous red cell production to

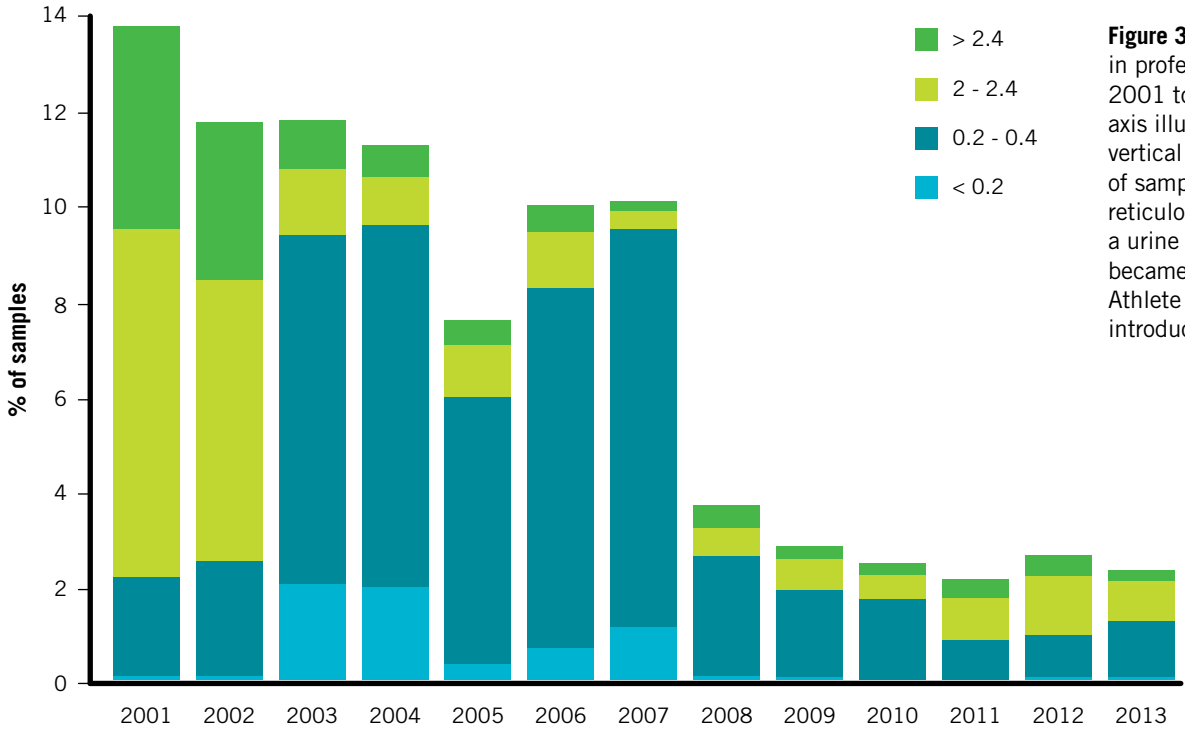

Figure 3: Reticulocyte values in professional cyclists from 2001 to 2013. The horizontal axis illustrates the years, the vertical axis the percentage of samples within a specific reticulocyte range. In 2003, a urine test for EPO detection became available, in 2008, the Athlete Biological Passport was introduced.

compensate for the artificially increased red cell mass. Interestingly, since the introduction of the ABP in 2008, both high and low reticulocyte patterns have virtually disappeared (Figure 3, adapted from Zorzoli and Rossi[4]). This highlights that the ABP has had a considerable deterrent effect and caused a massive change in behaviour, to a point where the blood picture of the professional peloton is now similar to the one found in the normal population.

Before signing a new rider, many professional teams now also request the ABP data from potential candidates and submit the data to an internal review before offering professional contracts. This has led to several riders being unable to secure new contracts despite good race results in the recent past.

ADMINISTRATIVE MEASURES

The major scandals in cycling also caused a major reorganisation of the anti-doping system in the sport. For this purpose, the UCI has created an independent foundation (the Cycling Anti-Doping Foundation, CADF) to manage its anti-doping programme.

The CADF is financed by contributions from the professional teams, race organisers and federations and is governed by a board independent from the UCI. CADF fulfills its duty through contractual agreements with the UCI. With this approach, the UCI was one of the first federations to make its anti-doping efforts independent from the sporting organisation.

From an operational side, cycling has also introduced team bans. Teams in which two riders are found guilty of an anti-doping rule violation within a period of 6 months are suspended for 14 days. Most teams have obviously passed on this pressure to their athletes by including stringent anti-doping clauses in the professional contracts, including liability and damages if an athlete is found positive. This rule has successfully been applied several times in the past, where teams have missed major races of the season, thereby significantly impacting their professional image.

The situation today

As mentioned, the prevalence of blood doping in cycling has certainly massively decreased in the last decade due to the introduction of the ABP. However, from forbidden substances, the focus has shifted to 'grey zone products', which are not prohibited by the international regulations, but which still might provide a performance benefit at the cost of significant, detrimental side effects. Such substances include tramadol (a pain killer) or glucocorticoids. Steps are currently being taken by various stakeholders in the sport to address these

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issues and requests have been made to introduce several of these substances on the WADA list of prohibited substances and methods.

New approaches

Although the journey of cycling through the abyss of (anti-) doping has improved the anti-doping system and reduced the impact of performance enhancing substances and methods to a minimum compared to the past, it is important to further develop methods in the fight against doping. For this purpose, several new approaches are currently being discussed and implemented. Building on the indirect approach through the ABP and the fact that many doping scandals have gained momentum via whistleblowers and other, non-analytical information after having been triggered by positive tests (e.g. the Armstrong Affair or IAAF scandal), intelligence information on the trafficking of doping products and connections between suspicious athletes are currently being explored as part of a forensic approach to anti-doping. This approach, very similar to traditional strategies in the fight against crime where different pieces of evidence are assembled to build a case, is being progressively implemented in cycling, with legal issues being the main hurdle.

Power profile

From a scientific perspective, efforts are being made to further investigate the effects of doping on the organism. It is clear that the result of a 'successful' doping scheme will be an unnatural increase in performance. As performance can easily be measured or estimated in cycling, several scientists have suggested the implementation of a performance monitoring system similar to the ABP, where performance over time of each athlete in the form of a 'performance profile'[5] is measured and unnatural increases in performance are scrutinised further with appropriate anti-doping tools. Climbing times over defined ascents during major races have been used to model power output, which has proven to be relatively accurate in creating these profiles. Such models have been validated against direct power measurements from athletes during the same race.

SUMMARY AND OUTLOOK

In recent decades, cycling has tackled a massive doping problem within the sport, inherent from a century-old doping culture based on a longstanding tradition of performance enhancement. Through various measures on a scientific, organisational and administrative level, the sport has embraced the problem and has thereby been able to significantly decrease the prevalence of doping in the professional peloton and, more importantly, to provide a playing field in which clean athletes can win major competitions.

To make this situation sustainable, efforts are now being made to implement 'anti-doping' behaviours in young athletes through various educational campaigns at all levels. At the same time, the anti-doping procedures through conventional testing, the ABP and – lately – the gathering of intelligence and other forms of evidence, are constantly being refined.

Given the looming scandals in many other sports, the path of cycling in the fight against doping, with all its positive and negative aspects and experiences, might serve as an example of what many sports may have to come to terms with in the future. Unfortunately, there are few signs that these lessons have been learned.

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