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A strategy to deter blood doping in sport

Blood doping is unacceptable on many levels. If practised naively it endangers the life of the athlete, and if medically supervised defies the Hippocratic Oath of the physician. Blood doping is an undeserved blemish on sport, its administrators and sponsors, and inevitably stains the reputation of innocent competitors. It is unconscionable from a moral standpoint, since the use of a banned substance or practice violates the rules of the sport and therefore makes redundant any subsequent sporting contest witnessed by the public. Finally, it can permit an athletic imposter to dethrone a worthy champion. Despite the biological complexity of blood, the goal of blood doping is relatively straightforward and singular – to increase circulating hemoglobin levels. This increases the oxygen concentration of arterial blood and therefore aerobic capacity. Although generally associated with endurance events, an enhanced oxygen carrying capacity can bestow a marked advantage in events lasting as little as 45 seconds, as well as recovery from intermittent efforts and general training drills. Therefore it is prudent to consider most sports (individual and team) at risk of blood doping.

Three accessible options for the athlete to boost circulating hemoglobin levels can be identified: 1) use of various pharmacologic products such as recombinant human erythropoietin to stimulate over-production of red cells in the bone marrow; 2) autologous or homologous blood transfusion; and 3) administration of hemoglobin-based oxygen carriers (HBOCs).

The implementation of testing methods for a single technique or class of blood doping merely allows cheats to move to another effective but undetectable approach, and it has been argued that this does not answer the needs of a *Fair competitor*.[1] The *Science and Industry Against Blood* doping (SIAB) project is a multinational collaboration between scientific researchers, pharmaceutical companies and hematologists, dedicated to conducting research to assist the implementation of effective strategies to address and deter the entire gamut of blood doping practices. The aim of this paper is to inform the scientific community of the issues faced by the group, and to publicize a novel approach to deter blood doping that may serve to stimulate further debate on this topic.

Introduction

In order to conceive an effective deterrent to blood doping, it is first necessary to identify the techniques prone to abuse, and when and how an athlete might use these methods. Then careful examination of the likely hematologic/physiologic consequences of these practices, together with a knowledge of the strengths and weaknesses of available detection strategies, may reveal congruencies that represent feasible opportunities to detect and thereby deter blood doping. A tenable solution must also be cognizant of the logistical difficulties associated with implementing test strategies. This article will apply this logic to known doping strategies, with an emphasis on the abuse of recombinant human erythropoietin that reflects the prevalence of its abuse in the sporting community.

Three classes of blood doping and their mode of abuse

Erythropoietic stimulants

The most widely abused erythropoietic stimulant (*EPS*) to date has been recombinant human erythropoietin (r-HuEPO). Immoral athletes use r-HuEPO to accelerate the rate of red cell production in the bone marrow. But r-HuEPO is an expensive drug, and to obtain maximum benefit an athlete would need to inject r-HuEPO every 2-3 days over a 3-4 week period. This would be accompanied by some form of exogenous iron administration (intravenous, intramuscular or oral) to ensure sufficient iron is available for haem synthesis. Because it takes several weeks before the full effect is realised, injections must commence around one month prior to a major competition or season. The r-HuEPO is rapidly removed from the bloodstream with a half-life of 4-12 hours, but a small amount is detectable unchanged in the urine for 24-96 hours after each injection. Once the red cell mass has been boosted,

the athlete can substantially reduce the dosage of r-HuEPO, since the erythropoietic rate need only match the basal rate of red cell destruction to maintain the circulating hemoglobin levels. During this *maintenance* phase it is difficult to discern the hematologic profile of a *maintenance* user from that of a non-user. One notable characteristic may be an elevated serum ferritin level associated with exogenous iron administration.

Instead of maintaining the elevated red cell mass, the athlete may cease using r-HuEPO if the goal was only to *peak* for a single competition. The body's homeostatic mechanisms will immediately seek to revert to the *normal* red cell mass. Because there is no active means of removing mature red cells, its goal is achieved by a shutdown of reticulocyte production. This is reflected in a dramatic reduction in both endogenous erythropoietin (EPO) production (and therefore serum EPO levels) and reticulocyte release (and therefore reticulocyte count). The *shutdown* will be maintained until the red cell mass is returned to normal, which will take several weeks (depending upon the nature and extent of the initial stimulation). During this time the athlete will experience a performance benefit commensurate with the excess red cell mass still present.

Whilst EPO is the major humoral regulator of red cell production, there is a plethora of hormones that also influence the rate of erythropoeisis, and any one of these might be abused if a specific test method accelerates the likelihood of the use of other pharmacologic interventions. High demand and a lucrative market have led pharmaceutical companies to develop several permutations (α, β, ω) of recombinant human erythropoietin. The range of EPSs also include mimetic peptides that emulate the erythropoietic effect of EPO. One such product, *Aranesp*, has recently been approved for human use and is a more stable and potent stimulant than r-HuEPO.[2] Its manufacturer is cooperating with SIAB not only to provide technical advice on possible detection methods, but also to facilitate timely access to the product together with blood and urine samples required to validate detection methodologies.

It is also prudent to recognise that alternative approaches, such as gene-activated erythropoietin (currently in phase III clinical trials) or adeno-associated viral vectors able to deliver an EPO gene, could further expand the range of EPSs. Anti-doping strategies relying solely on direct detection of a specific molecule may be subverted if athletes begin using products for which no direct test has been validated.

Blood transfusions

In contrast to the 3-4 weeks required before an EPS will boost circulating hemoglobin by a physiologically significant amount, infusion of exogenously-derived hemoglobin will provide an immediate improvement in oxygen carrying capacity. Although there are serious health risks associated with transfusing blood obtained from a donor (homologous) or from self (autologous), these concerns have been largely ignored by immoral athletes seeking a performance advantage.

Because infused red cells that survive the first 24-hour period persist in the circulation for the lifespan of a normal red cell (up to 120 days), an athlete choosing to infuse homologous red cells could elect to administer the hemoglobin days or even weeks prior to arrival at the competition site, experiencing a performance benefit commensurate with the percentage of biologically-active infused red cells that remain in circulation at the time of competition. A partial agglutination reaction test performed on a blood sample, although not yet instigated by authorities, could serve as a powerful deterrent against the use of homologous blood transfusions.

However the situation is more complicated if the athlete chooses to harvest their own red cells (autologous) and store the cells until they are to be re-infused. Storage techniques for erythrocytes permit a shelf life of 35-42 days if stored at 4°C or up to 10 years if stored at -65°C in glycerol. If the athlete elects to store cells at 4°C, they must be harvested within 42 days of a major competition. This means that an athlete will experience a period of reduced aerobic capacity during the several weeks the bone marrow requires to replenish the harvested cells. From an exercise physiology perspective, this does not constitute an ideal preparation for a major competition. However the alternative of freezing erythrocytes at -65°C and thawing is time consuming and the cost of equipment, materials and skilled technologist's time considerable.

Although practical issues associated with blood transfusion makes this class of blood doping problematic (and this perhaps explains the anecdotal reports of athletes avoiding transfusions when r-HuEPO became available) there is substantial research into improving the viability and shelf life of stored erythrocytes which may eventually render this process more suitable to doping practices. It is also likely that athletes would overcome the technical difficulties associated with harvesting and storing hemoglobin (as they did prior to the appearance of r-HuEPO) if testing strategies for other approaches leave blood transfusion as the

only option for blood doping. For this reason a deterrent must also address transfusion as a possible avenue of blood doping.

Hemoglobin-based oxygen carriers

An alternative means of immediately increasing circulating hemoglobin levels is to infuse a hemoglobin-based oxygen carrier (HBOC). These products have been the focus of intense research and development in recent years to serve as a blood substitute that may ease the burden on blood donor supplies required in surgical settings and transfusion emergencies.

Hemoglobin can be easily extracted from red blood cells, but breaks down in the body and also causes toxicity. HBOCs are obtained by chemical sterilization of hemoglobin extracted from a variety of sources (bovine, expired donor, recombinant human, and transgenic human hemoglobins). Biotechnological cross-linking, recombinant modifications and micro-encapsulation not only stabilize the hemoglobin molecule but provide a range of different blood substitutes with a variety of clinical benefits. The recent approval for human use of one product is accompanied by several other products at advanced stages of clinical trials. It is expected that investigators will be driven by the perceived market for alternatives to donor red cells to focus on second and third generation products.[3]

HBOCs are free of RBC blood group antigens and can be stored for a long time as a stable solution. Although this offers obvious advantages over obtaining hemoglobin via transfusion, the current generation of products are rapidly removed from circulation by the reticuloendothelial system resulting in a half-life of 12-24 hours (dependent on the pharmacokinetics of individual products). Therefore in order to experience the benefits of enhanced oxygen carrying capacity, an athlete would need to infuse the HBOC shortly before competition. The physiologically-significant benefits would only be experienced in the interim before the HBOC was cleared from the system.

It is pertinent to note that because HBOCs do not appear in the urine, it would not be possible to identify the abuse of this class of product definitively unless a blood sample was obtained, preferably within several hours (before or after competition) of administration.

Unless deterrents are put in place, it would appear inevitable that HBOCs are liable to be abused by immoral athletes. The pharmaceutical companies which develop these products for clinical use have been approached to participate in developing tests to deter illegitimate use of their products, and their cooperation is a cornerstone of SIAB's research efforts. These companies are unequivocally supportive of SIAB's goals and are negotiating how best to direct their assistance.

Strengths and limitations of detection strategies

Blood tests

Whilst the shortcomings of (as yet non-existent) deterrents for HBOC or blood transfusion abuse are self-evident, deterring the abuse of r-HuEPO and other EPSs is problematic on several fronts. Because of the inherent difficulty associated with detecting abuse of a naturally occurring hormone, and in the absence of a definitive test to identify r-HuEPO, initial efforts to deter r-HuEPO abuse by elite athletes focused on the end result of r-HuEPO abuse – an increased red cell mass as indicated by elevated hemoglobin (Hb) and/or hematocrit (Hct). The so-called *Hematocrit rule* results in the athlete being ruled ineligible to compete because of health concerns associated with elevated Hct/Hb.

The concept of an arbitrary limit as incorporated by the *Hematocrit rule* has since attracted criticism because a significant proportion of athletes (up to 5%) may exceed the threshold because of genetic factors and be unfairly banned from competition. It may also permit athletes to *titrate* their Hb/Hct to approach but not exceed the limits adopted by their sport, or to expand plasma volume and thus remain below allowable limits.

Several research groups have attempted to improve upon the *Hematocrit rule* by including additional hematologic parameters (for example percent reticulocytes, percent macrocytes, serum transferrin receptor, serum EPO) that are known to be perturbed during the accelerated erythropoeisis induced by r-HuEPO administration. The rationale is to reduce the likelihood of an individual with a single parameter out of range being removed from competition or being falsely accused of r-HuEPO abuse. Australian scientists extended this concept and validated an algorithm that combined five hematologic parameters sensitive to accelerated erythropoiesis,[4] and this test was eventually adopted by the International Olympic Committee (IOC) as part of the EPO test used at the Sydney 2000 Olympic Games.

However debate surrounding whether a blood test that is sensitive to accelerated erythropoiesis is ideally suited to deter r-HuEPO abuse has yet to be resolved. Altitude/training/genetic factors may

also be associated with a transient increase in erythropoiesis (albeit of a much smaller magnitude) which might lead to mistakenly accusing an athlete when no drug was taken. Or the magnitude of the disturbance caused by r-HuEPO (or other EPS) administration may be small compared with the range of values encountered in a normal population – and disturbances associated with *maintenance doses* may be virtually indistinguishable from normal. Such a test may fail to identify a sophisticated athlete who had deliberately titrated their dosage to minimize the hematologic disturbance. It seems that evidence of accelerated erythropoiesis will remain an extremely useful *screening* tool to identify potential drug abusers rather than serve as definitive proof of r-HuEPO abuse.

Urine tests

It appears that the French test able to identify isoforms of r-HuEPO in the urine[5] has already been associated with a significant deterrent effect. It is expected that further refinement and widespread adoption of a urine-based test that directly identifies r-HuEPO will continue to be a powerful deterrent. However the expense and time required to conduct the assay, combined with the exhaustive validation procedures required for a test that differentiates between naturally and recombinant-derived molecules, has so far limited the application of this assay. Nor is the expertise required to conduct the assay always readily available.

However the major drawback of the urine-based test, which is seemingly inevitable and directly attributable to the pharmacodynamic characteristics of r-HuEPO, is the disappearance of measurable levels of r-HuEPO from the urine soon after injections cease. Urine tests are useful during, but not after, r-HuEPO use. Therefore if testing is announced, or occurs at major events, it is likely that athletes will escape sanction by ceasing r-HuEPO injections several days prior to testing. Because of the short half-life of r-HuEPO, all traces of the drug would have left the system when the urine sample is collected, despite the athlete retaining the physiologic benefits associated with an elevated red cell mass.

Logistical difficulties

Since the Sydney 2000 Olympics, sporting federations have been criticized in some quarters for their reluctance to instigate blood tests based on this model. However critics may not be fully cognizant of the pragmatic considerations and implementation issues faced by federations wishing to implement such blood tests. Perhaps the single greatest challenge facing officials is the uniqueness of the blood matrix.

Unlike urine, blood is not suitable for freezing and therefore cannot be transported long distances. A blood sample must be drawn in a location that is within close proximity to a testing site. Because federations cannot dictate where an athlete may live and train, out-of-competition blood testing is therefore limited by the proximity of the athlete's training venue to an accredited testing laboratory. Furthermore the test adopted by the IOC, although scientifically excellent, includes parameters that can only be measured using sophisticated analyzers, and the cost and logistics of having access to a properly calibrated analyzer must be taken into account. Unfortunately a quality control system to ensure that results are comparable when analyzed in separate locations is both essential and a convoluted process to instigate. SIAB is consulting with a multinational analytical instrument manufacturer with the twin objectives of minimizing analytical error in critical analytes, and harnessing their accrued expertise to develop calibration protocols that minimize inter-laboratory variation between instruments.

A global strategy to deter blood doping

A strategy that effectively deters the abuse of all known blood doping methods is necessarily multifaceted and extensive. The following proposal is a consensus of opinion distilled from the intellectual expertise within SIAB, and is intended to seed further debate on this complicated topic.

Out-of-competition testing

The essential characteristic of any antidoping strategy is the ability to sanction an athlete based upon identification of a banned substance. Because EPS abuse will occur in the weeks preceding an event, the athlete must be subject to random, unannounced testing during the weeks they are likely to boost their red cell production. Because of the difficulties associated with storage/transport of blood samples from remote locations, it seems this must be in the form of a urine-based test capable of directly identifying known EPSs. A crucial aspect of SIAB's work is to facilitate timely access to the drugs and biological samples required by our analytical chemists, to ensure they have ample opportunity to develop and validate direct detection methodologies.

The efficacy of this deterrent will then be determined first by the ability to predict correctly at what stage of the year an immoral athlete is using

the EPS, second by the development of a sanctionable test that directly identifies whichever EPS was used, and finally having knowledge of the whereabouts and then access required to the athlete during these periods.

From a pragmatic standpoint it can be argued that a sophisticated athlete, faced with the possibility of a sanctionable test for r-HuEPO (or any EPS), will seek to evade antidoping officials during the weeks they are injecting the drug. However to take physiologic advantage of their doping they must eventually arrive at the competition site and be prone to whatever testing procedures the authorities wish to implement. It is at this juncture that antidoping authorities have access not only to the athlete but also to whatever sample collection and analysis strategies they elect to use. This seems a logical point on which to focus antidoping efforts.

Mobile blood testing laboratory and post-race blood collection

Although the existing paradigm is to use blood and urine tests concurrently to identify r-HuEPO abuse – albeit using blood as a *screen* in some situations – this is not necessarily optimal. This not only limits its application in out-of-competition situations, but also dictates that the test can only be conducted at events that have ready access to sophisticated hematology analyzers.

However one tenable solution that addresses these concerns is to create a mobile testing facility equipped with a hematology analyzer able to process the blood sample without delay, as well as freezing capacity to store the urine sample for later analysis. Rather than equipping a multitude of laboratories with expensive hematology analyzers that may sit dormant except for occasions when an event is in close proximity to the laboratory, purchasing a single analyzer and mounting it within a mobile testing facility seems to be a cost-effective alternative. The mobile laboratory could relocate to a remote competition site – in a similar manner to the way media utilize mobile television broadcasting stations to cover sporting events.

Provision of a mobile blood testing facility would also allow authorities to instigate a critical aspect of our proposed strategy to deter the gamut of blood doping practices – making place-getters subject to blood testing immediately after competition. As has been demonstrated at major events such as the Sydney 2000 Olympic Games and the 2001 IAAF World Championships, blood collection at the competition site is both feasible and ideally suited to the unique biological characteristics of the blood matrix. It is also the only practical way to detect athletes who have used *acute* interventions such as HBOCs or blood transfusion to obtain an illegal performance advantage.

Locating a blood testing facility at the competition site has many potential benefits. Because blood samples can typically be assayed and reported within minutes, samples could be analyzed on the morning of a race, or immediately post-race from podium finishers, and results conveyed to officials. Athletes who failed a test could be ruled ineligible to compete or receive a medal, avoiding the scandal associated with stripping an award already bestowed on an athlete. If each international sporting federation had a dedicated mobile blood testing facility, this would greatly simplify quality control issues since all samples from athletes in that sport would be analyzed using a single instrument. It would also facilitate the vital element of unannounced testing, as federations would be under no obligation to publicize when and where they would locate the mobile laboratory to conduct testing.

Although clearly capable of following a competition season to a variety of destinations, the laboratory could maximize the return on investment by collecting out-of-competition samples from athletes who elect to train in remote locations, and may be an attractive option for individual sporting federations seeking to implement comprehensive blood testing programs.

Indirect evidence of blood doping

But there are persuasive arguments – financial and physiologic – for deterrent strategies related to blood doping to increase their reliance on indirect evidence. Financially, the expense associated with having a validated test for every pharmaceutical product capable of stimulating red cell production is substantial and demands a heavy allocation of resources. Physiologically, as the sophistication of medical technology expands its horizons and strives to mimic natural biological processes more closely, it is to be expected that pharmacologic intervention will become more and more difficult – and expensive – to detect.

Demanding that pharmaceutical companies *label* their difficult-to-detect products with a biological *tag* is unrealistic, since such an approach requires companies to regress back to the initial stages of clinical trials and waste the intellectual and financial input invested in a drug's development. Instead, seeking corporate approval and intellectual input from company scientists to develop and

validate detection strategies in advance of the product being (surreptitiously) available to athletes is both realistic and has been favorably received by pharmaceutical companies approached by SIAB.

Unlike the abuse of stimulants, narcotics or anabolic agents which alter physiologic parameters that are difficult to objectively quantify or monitor, the goal of blood doping is to increase a single, easily measurable, and relatively stable hematologic parameter – circulating hemoglobin. This sole focus may ultimately prove to be blood doping's Achilles heel.

Rather than seeking to identify the EPS or blood doping method used to increase circulating hemoglobin, an alternative that can be developed alongside direct detection techniques, and ideally lessen the reliance on this approach, is to monitor the blood profile of the athlete over time. A profile that deviates substantially from expected may lead to follow-up testing or medical examination. This would deter cheats from using any illegal practice that disturbs their hematologic profile – whether the administration of novel r-HuEPO variants or any one of the myriad of hormones involved in the hematopoietic cascade.

The *International Cycling Union* (UCI) has already instigated a similar concept – its athletes are required to undergo regular medical examination and provide a blood sample and are ineligible to compete and subject to medical examination if their hematologic profile does not fall within normal ranges. However the sensitivity of their stance is limited because the reference ranges they use are derived from population statistics. This inevitably provides a large margin of tolerance, and allows unscrupulous athletes an opportunity to elevate critical parameters – such as circulating hemoglobin – to remain just below threshold levels.

Hematologic passport

An alternative may be to compare an athlete's current values with their historical levels obtained from previous blood collections. The *Italian Cycling Federation* decided from November 2000 that all first-year juniors had to undergo an hematocrit test to provide a benchmark to help show up abnormalities in the future. Because hematologic parameters are quite stable over time in healthy adults, unusually large disparities between an athlete's historic values contained in their *Hematologic Passport* and values obtained from a recent blood test may alert officials to potential cases of blood doping or a medical condition requiring closer examination.

A major component of the work undertaken by SIAB is to validate the concept of a *Hematologic Passport*. It is essential to quantify the expected biological variation of critical hematologic parameters. Although some work has been undertaken on healthy subjects, scientific rigor demands that biological variation is established in the elite athletic population. The extent to which sporting federations, sporting institutions and SIAB can cooperate to achieve this goal is being explored.

The benefits of adopting a *Hematologic Passport* concept are far-reaching. Athletes could use the Passport as a tool to demonstrate objectively – via their constant and normal longitudinal blood profile – that they had not used blood doping practices. A longitudinal record of hematologic profiles is an invaluable tool to assist physicians in diagnosis of pathology. This has genuine benefits for all competitors who provide regular blood samples for analysis. Protection of the athletes' health and well-being is a principal reason for antidoping strategies, and aligning the emphasis of antidoping strategies towards providing a genuine health service has substantial merit.

Exclusion based on medical evidence

It is perhaps fortuitous then that an emphasis on health monitoring also provides an opportunity to harness a powerful deterrent to existing (as well as conceivable but not yet realised) blood doping practices. Iron overload and depressed erythropoiesis have been shown to accompany cessation of r-HuEPO and blood transfusion, and both are medically justifiable reasons for the athlete to be excluded from competition until the underlying cause has been identified. Further, it is logical to expect that a side-effect from any doping practice that enhances circulating hemoglobin levels (HBOCs, transfusion, r-HuEPO or any hormone within the erythropoietic cascade) would be a transitory period of depressed erythropoiesis whilst the body regained its previous homeostatic set point. Expanding exclusion criteria to include both of these pathologic situations – which can be readily identified through simple hematologic analyses – would serve as a strong deterrent to experiment with novel drugs, since exclusion from competition would negate any advantage obtained from prior drug abuse.

This concept is supported by scientific data already collected for the EPO2000 project.[4] Research demonstrated that the so-called *OFF-model* (*OFF r-HuEPO administration*) is capable of delineating athletes who ceased r-HuEPO from placebo subjects

for several weeks after injections stopped. Blood profiling data collected from in excess of 1000 athletes around the world failed to find any subject with a natural hematologic profile similar to the depressed erythropoietic state encountered in subjects who had ceased r-HuEPO injections (*unpublished observations*).

Once this abnormal hematologic profile has been detected by antidoping authorities, it becomes a matter of policy and sports law as to what consequences the athlete faces.

How would this work in practice?

Were each of the separate facets of this proposal implemented, it would place dishonest athletes in an impossible quandary, regardless of which blood doping strategy they had used to surreptitiously obtain a podium finish.

If they had elected to *run the gauntlet* and continued to use an EPS up until the time of competition or had infused a HBOC immediately before competition, they would risk sanction if the drug was detected directly (either in urine for an EPS or in a blood sample for HBOC).

If instead they sought to evade detection by stopping EPS administration several days prior to competition, or had infused hemoglobin via a transfusion, they would risk exclusion from competition if the increase in circulating hemoglobin was beyond the margins of accepted biological variation compared with their *Hematologic Passport* values, or if the mandatory iron administration associated with r-HuEPO abuse had elevated their ferritin values beyond safe limits.

But perhaps the most potent weapon to deter blood doping is recognition that an inevitable consequence of an athlete boosting circulating hemoglobin levels is the unmistakable depression of red cell production that follows when the stimulant is removed. Our understanding of the hematopoietic process suggests that, regardless of which stimulant was used, when usage ceased there would be an extended period of elevated Hb/Hct in combination with depressed erythropoiesis until the set point was regained. Excluding athletes from competition until the underlying cause for this pathologic situation had been identified would make it extremely difficult for an athlete to successfully compete whilst retaining any physiologic advantage from prior drug abuse.

This *OFF-model* profile has been demonstrated to accompany blood transfusion,[6] and has been shown to persist for several weeks after r-HuEPO injections cease.[4] Faced with the formidable array of possible methods to boost circulating hemoglobin, it would seem that a cost-effective utilization of scarce resources is to focus on deterring blood doping by detecting the hematologic signature of abuse rather than the product itself.

Summary

To level the playing field significantly, it has been suggested that a deterrent should produce no or very few false negatives, no false positives, address all accessible alternative ways of doping, and have minimal risks to the *Fair Competitor*.[1] Such an approach to deter blood doping is feasible, and entails the following:

- creation of a *Hematologic Passport* that contains historical blood profiles in order to obtain a license to compete;
- implementation of mobile blood testing facilities;
- collection of blood and urine samples post-race from medal winners;
- sanctioning if banned products are directly identified in the blood or urine (either out-of-competition or at the time of competition);
- exclusion based on health grounds for those competitors whose blood profile at the time of competition demonstrates depressed erythropoiesis, iron overload and/or hematologic parameters that deviate substantially from historical values.

Challenges associated with reaching this goal can be clearly defined, but are substantial. Success will require the concerted effort of all stakeholders. International federations and antidoping authorities must be cognizant of novel deterrents and seek to draft legislation to complement these approaches. However, we must remain mindful that in our zealous desire to rid sport of doping, we do not forsake the interests of those for whom we undertake these efforts – the athletes. It is vital that athletes are consulted during, and provide informed consent to, the implementation of antidoping measures. Although comprehensive testing is required in order to enjoy a more level playing field, a successful antidoping strategy must ultimately protect the athletes' health and also respect their privacy.

Michael Ashenden, PhD,
PO BOX 250, Gumeracha, SA 5233 Australia.
Phone: international +61.409797226.
Fax: international +61.409797557.
E-mail: siab@compuserve.com

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Further concerns about the medical risks of blood doping

This journal and its editor strongly oppose the spreading phenomenon of blood doping in sport.[1-3] Some time ago we wrote: «*As hematologists, over the next years we could face problems related to blood doping with increasing frequency: atypical cases of iron overload, erythrocytosis of unknown origin, unexplained anemias, atypical thomboembolic complications, and so on*».[1]

Recent observations emphasize the medical risks of blood doping, in particular those related to the abuse of recombinant human erythropoietin (rHuEpo). Casadevall *et al.*[4] have recently identified 22 cases of pure red-cell aplasia in patients with chronic renal failure who were receiving rHuEpo. These individuals develop anti-erythropoietin antibodies that neutralize both rHuEpo and endogenous erythropoietin, thus producing severe PRCA. These patients become totally transfusion-dependent and apparently do not respond to erythropoietin molecules other than that used before development of PRCA.[4] Additional cases have been independently reported.[5]

It must be clearly said that this risk is very low in renal patients (less than 1:10,000), and probably even lower in patients with anemia of malignancy receiving chemotherapy, so that this adverse event should be borne in mind by clinicians but should not prevent the vast majority of patients from benefiting from a treatment that can improve quality of life and prolong survival.

Doping with erythropoietin is a totally different issue. Athletes are healthy individuals who do not need any treatment. They abuse rHuEpo or related drugs to win games unfairly and earn money illicitly. Any medical risk related to drug abuse is unacceptable by definition: to realize this, simply consider to the drama of a (theoretical) young vigorous man who abuses rHuEpo to increase his red cell mass and athletic performance, develops PRCA and becomes transfusion-dependent for the rest of his life. According to current rumors, endurance athletes have started abusing darbepoetin alpha (Aranesp): since this molecule differs markedly from endogenous erythropoietin, the risk of developing cross-reacting antibodies on long-term abuse cannot be excluded *a priori*.[6]

Finally, we totally agree with the conclusion of Casadevall *et al*.[4] that the severity of rHuEpo-induced PRCA argues also against the use of this drug for unlicensed indications.

Mario Cazzola, M.D.
Department of Hematology,
University of Pavia Medical School,
27100 Pavia, Italy

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