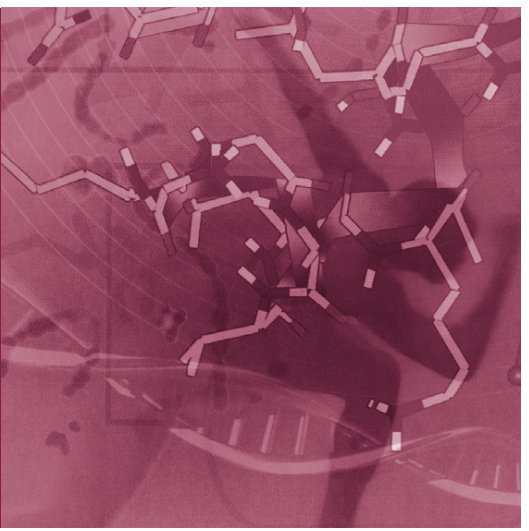
OFFICE OF TECHNOLOGY ASSESSMENT
AT THE GERMAN BUNDESTAG

Katrin Gerlinger
Thomas Petermann
Arnold Sauter

Gene doping

Scientific basis – gateways – monitoring

Final report



Technology Assessment Studies Series – 3

Gene doping

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The Office of Technology Assessment at the German Bundestag is an independent scientific institution created with the objective of advising the German Bundestag and its Committees on matters relating to research and technology.

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TAB's task is to design and implement technology assessment (TA) projects and to monitor and analyse important scientific and technological trends and the associated social developments (Monitoring, Future- and Innovation Reports, Policy-Benchmarking Reports).

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Report for the Committee on Education, Research and Technology Assessment

TAB
OFFICE OF TECHNOLOGY ASSESSMENT
AT THE GERMAN BUNDESTAG

Note

The orientation and content of this report cannot be taken as indicating the position of the German Bundestag or its Committees.

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THE COMMITTEE'S PREFACE

The promotion of recreational, competitive, and elite sport is an important social and political responsibility. Widespread abuse of performance-enhancing substances with intent to deceive, i.e. doping, seriously compromises comparisons of athletic performance and threatens competition by jeopardizing both equality of opportunity and the health of doping athletes. In addition, doping undermines the basic principles of fairness and playing by the rules – important elements that contribute to the social context of sport. For some time now, based on a growing body of knowledge from the field of human genome research, fears have been expressed that this threat will be further aggravated by novel methods of manipulation at the genetic level, an approach known as gene doping.

The potential explosiveness of the issue means that the legislature must address this problem at an early stage. In view of the paucity of currently available information, the Committee on Education, Research and Technology Assessment, at the suggestion of the Sports Committee, commissioned the Office for Technology Assessment of the German Bundestag (TAB) to carry out an investigation into gene doping. This report concludes that project.

The aim was to analyze the scientific and sociopolitical dimensions of gene doping by reviewing the status of doping-relevant findings from genome research with special attention to individual and social risks. This was accomplished by exploring detection and control possibilities, including the resulting need to refine relevant statutory instruments, and by discussing possible preventive strategies in the fields of information dissemination, education, and public debate.

This report provides what is probably the most comprehensive examination to date of foreseeable developments in the field of gene doping and its potential impact. It reveals that a broad range of new medical and pharmaceutical techniques and procedures – most still under development – could be misused to illegally enhance athletic performance. Possible points of entry include elite sport, the highly competitive bodybuilding scene, and in the long term anti-aging medicine as part of a general social trend towards manipulating performance in everyday life.

Besides the unpredictable risks to the health of users, this TAB report reveals the growing challenge of detecting potential gene doping methods and highlights the need for a comprehensive refinement of control and analysis methods. Other areas requiring action are the adaptation of statutory instruments and the development of educational measures targeted at specific groups.

This report provides the German Bundestag with valuable up-to-date information as a basis for parliamentary discussion of gene doping – a topic that is of relevance to sports, research, and social policymaking alike.

Berlin, April 30, 2008

The Committee on Education, Research and Technology Assessment

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CONTENTS

THE COMMITTEE'S PREFACE		5
SUMMARY		7
I.	INTRODUCTION	21
II.	GENE DOPING: SCIENTIFIC BASIS AND PERSPECTIVES OF USE	27
	1. Current situation: limits and targets	28
	1.1 Relevant knowldege about high-performance variants	28
	1.2 Gene regulation – target for gene doping	30
	1.3 Gene therapy: principle and approach	32
	1.4 Gene doping – in the narrow and broad senses	36
	2. Potential biological targets for gene doping	39
	2.1 Skeletal muscle	40
	2.2 Modulation of oxygen supply	48
	2.3 Modulation of energy supply	52
	2.4 Overview of Gene doping methods	54
	2.5 Development projects in the field of gene therapy	56
	3. Specific health risks?	60
	4. Perspectives of use	64
	4.1 Routes of access	64
	4.2 Access points and diffusion factors	67
III.	DETECTABILITY AND TEST DEVELOPMENT	69
	1. Detectability	70
	1.1 Direct methods of detection	70
	1.2 Indirect methods of detection	73
	2. Requirements of (gene) doping tests	77
IV.	GENE DOPING: PROHIBITION AND CONTROL PROCEDURES	81
	1. The World Anti-Doping Code: the international legal basis for sports organizations and public authorities	82

2. The NADA Code: the legal basis for sport in Germany 87
2.1 Statutes of association of sports organizations 88
2.2 Doping control procedures 91
2.3 Limits to the doping control process 101
2.4 Other approaches to doping control 106

3. (Gene) doping in the context of public law 107
3.1 International agreements 108
3.2 German law 109

V. DOPING BEHAVIOR IN ITS SOCIAL SETTING 115

1. Competitive sport 116
1.1 Attitudes and behavior 116
1.2 The athlete's milieu 126

2. Individual sport 134
2.1 Bodybuilding 134
2.2 Excursus: older athletes 138

VI. NEED FOR INFORMATION AND ACTION 141

BIBLIOGRAPHY 145

1. Commissioned expert reports 145

2. Other sources 145

APPENDIX 153

1. List of tables 153

2. List of figures 153

SUMMARY

In all likelihood a new form of doping will emerge in the coming years, posing new challenges in the fight against doping, namely the widespread use of a number of cutting-edge substances and procedures aimed specifically at modulating gene activity. These may be methods derived from gene and cell therapy or methods for manipulating gene expression based on the use of highly specific agents (collectively termed *gene doping* in the broad sense). By contrast, strategies aimed at inducing permanent changes in the genetic makeup of athletes (so far only theoretical in nature) are unlikely in the foreseeable future.

The following key questions form the keystones of the TAB report. What scientific findings might potential gene doping utilize? Where are the future points of entry in top-level and recreational sport? And how can bans and monitoring be applied in response these developments? To complement these thematic perspectives, gene doping will also be viewed in the context of social trends and structures. We will ask what behavioral patterns and attitudes play a role at the level of the individual athlete and how gene doping as a form of deviant behavior is influenced by various social contexts and actors.

This final report concludes the TAB Gene Doping Project. It was commissioned by the Select Committee for Education, Research, and Technology Assessment on the recommendation of the Sports Committee of the German Bundestag.

THE TERM GENE DOPING – IN THE NARROW AND BROAD SENSES

The term *gene doping* is often construed very narrowly, namely as the misuse of gene and cell therapy methods, by means of which genetic material in the form of DNA or RNA is inserted into a cell, an organ, or an organism. The TAB analysis is based on the broader perspective adopted by the World Anti-Doping Agency (WADA), which –in line with its Prohibited List – explicitly understands gene doping to also include the use of other methods aimed at modulating gene activity: »the nontherapeutic use of cells, genes, genetic elements, or the modulation of gene expression having the capacity to improve athletic performance«.

Only by adopting this broader interpretation is it possible to include as many relevant methods, procedures, and agents as possible in the impact assessment. The scientific basis for new methods of (gene) doping is formed by the ever-advancing techniques of molecular biology and growing knowledge of the molecular mechanisms of cell function. The social and political explosiveness of the topic arises from the fact that these advances will increase the possibilities for manipulating gene activity in specific and subtle ways that are likely to be in-

creasingly difficult to detect. Whether this process of manipulation occurs by transmission of actual genetic material, i.e. DNA or RNA, or by some other pharmacologic mechanism is not a reasonable exclusion criterion for the purposes of an impact analysis, especially in respect of future antidoping measures.

NO »GENETICALLY OPTIMIZED« ATHLETES IN THE FORESEEABLE FUTURE

According to a widely held notion, gene doping is aimed at »improving« the genetic makeup of athletes based on knowledge of which gene variants can bring about a particularly high level of performance, either by specifically manipulating the whole organism or by prenatal selection. However, a detailed analysis of genome research findings shows that molecular genetic knowledge of »high-performance gene variants« is still extremely limited, imprecise, and contradictory, with the result that »promising« techniques for inducing specific alterations in an individual's genetic constitution are h unlikely to be developed in the foreseeable future. Accordingly, the TAB project has uncovered no evidence that any strategies based on human selection or breeding for enhanced athletic ability are likely to become technically feasible within the foreseeable future. At present, therefore, notions about the possibility of gene doping in this narrow sense have no scientific basis.

THE AIM OF GENE DOPING: GENE REGULATION

The objective of gene doping is therefore to specifically influence (modify) the activities of the body's genes by activating them or by strengthening, weakening, or blocking their expression. The underlying biochemical and physiological processes are highly complex, both at the cellular level and at the level of overall regulation in the body (and therefore will only be outlined in this report). The network of regulatory mechanisms controlling attributes relevant to physiological performance presents a broad array of targets for pharmacological and molecular biological modulation – for new therapeutic treatment strategies as well as for doping purposes. The potential consequences of such interventions are extremely hard to predict. This continues to be seen in medical trials of treatments for patients (in the form of side effects or lack of drug efficacy). Where such methods and procedures are misused in healthy or highly trained individuals – who are also highly susceptible to interference despite their high level of physiological performance – the consequences are again likely to be highly unpredictable.

GENE THERAPY AND OTHER METHODS OF MODIFYING GENE ACTIVITY

Gene doping in the narrow sense misuses the techniques of gene and cell therapy for the purpose of enhancing physical performance. The term »gene therapy« is used to denote strategies in which genes or genetic elements are introduced into cells from outside to remedy inherited or acquired genetic disorders. Genes are introduced into the cells (a process known as *gene transfer*) by means of vectors (or *gene carriers*, usually specially modified viruses). Gene therapies already tested on humans have been directed mainly at cancers, monogenic inherited diseases, infectious diseases (especially HIV), and cardiovascular disorders. In contrast to what is commonly reported, the objective here is often not to effect a permanent change. Instead, the procedures are transient measures that may have to be repeated.

An assessment of the current results of gene therapy is important for evaluating its potential relevance to doping. Overall, gene therapy is not yet an established medical practice. It is essentially still at the experimental stage, and the evaluation of current therapeutic results is a matter of considerable controversy. Treatments are still frequently associated with serious side effects, including death. The vectors used are believed to be responsible for some of the side effects observed. The proportion of clinical experiments that forgo the use viral vectors, which are more efficient but also particularly risky, in favor of the use of so-called »naked« DNA has increased steadily in recent years. This is significant for potential gene doping, since nonviral DNA is probably much simpler and also less risky to use.

In addition to the methods that are unambiguously described as constituting gene therapy, there exist many other modern pharmacologic strategies that are intended to induce a specific modification of the body's gene activity in order to achieve a desired therapeutic outcome. The pharmacologic agents concerned include a broad range of, in some cases very complex, biomolecules such as proteins and RNA, but also some easily synthesized simple compounds.

PHYSIOLOGICAL APPROACHES AND MOLECULAR TARGETS – RESEARCH STRATEGIES AND DEVELOPMENT PROJECTS

The most likely methods by which gene doping might be attempted relate to three areas of physiology and their molecular regulation, namely formation of skeletal muscle, oxygen supply, and energy supply.

Among the research strategies and development projects identified in the TAB project and described in detail in the report which have already reached the stage of clinical testing, there is only one that pursues an explicit gene therapy approach. The other techniques at an advanced stage of development are all phar-

macological strategies for modifying gene activity. Success in the preclinical phase, i.e. in animal experiments, has been achieved with a large number of techniques that constitute gene doping both in the narrow sense (e.g. the well-known case of Repoxygen) and in the broad sense.

PHYSIOLOGICAL TARGETS FOR GENE DOPING STRATEGIES

- *Skeletal muscles:* Growth, structure, strength, endurance, regeneration (molecular targets: myostatin, HGH/IGF/MGF, Pax7, PPAR-delta)
- *Oxygen supply:* Hemoglobin concentration, blood vessel supply (molecular targets: EPO, HIF, VEGF)
- *Energy supply:* Fatty acid and glucose metabolism in the liver and muscles (molecular targets: FATPs, GLUTs, PTP-1B)

SPECIFIC HEALTH RISKS: AN EFFECTIVE OBSTACLE?

Common to all doping practice is the fact that the relevant techniques and agents were developed for the treatment of diseases and accordingly have not been studied in relation to their use for performance enhancement in healthy persons. Hence, the health risks associated with their misuse for doping purposes cannot be assessed. This is evidenced by the severe to catastrophic doping-induced ill effects on health, in some cases leading to death, that some athletes have suffered in the past.

From this point of view gene doping techniques could scarcely be riskier. At the same time, the principles that underlie the techniques used to bring about specific modifications of gene activity entail *specific risks* which, in the absence of empirical evidence, must be regarded merely as *scientifically plausible assumptions*. In this respect a distinction can be made between risks that arise as a result of insertion of genetic material into the organism (lack of tissue specificity of vectors leading to uncontrolled spread of the foreign gene in the organism; mutations and immune reactions) and risks that result from overexpression (i.e. excessive production in the body) of performance-relevant biomolecules (e.g. promotion of uncontrolled cell growth). Given the complexity of the mechanisms that regulate gene activity, it is highly likely that manipulation of these mechanisms can result in a broad variety of side effects and potentially in severe damage to health.

Nevertheless, experience gained with conventional doping practices casts considerable doubt on the notion that these imponderable health risks constitute an effective disincentive to the use of these methods, even if those that are scientifically unproven. Besides their availability, of course, the crucial factors governing the use and spread of gene doping techniques will probably be their presumed

achievable effect – i.e. a potential improvement in performance – and their detectability or lack thereof (see below).

ROUTES OF ACCESS

Therapeutic techniques and drugs that are either already licensed or at least at the clinical trial stage would appear to be the most likely initial candidates for misuse for doping purposes. In order to predict which gene doping strategies could become relevant within what period of time, it is essential to monitor progress in research and development, especially in pharmaceutical companies, on a continuous basis. Nevertheless, it must be assumed that by no means all projects that could be relevant in terms of gene doping become known to the public (at least in their early stages).

Along with misuse of licensed therapeutic agents or those in the process of being licensed, another, and potentially even more worrying, possibility is emerging – namely a form of »individual« gene doping in which all the testing procedures that form part of the drug regulatory process are circumvented. As in the case of the designer steroids that were explicitly manufactured by the Balco company for doping purposes, genetic-pharmaceutical gene doping agents could also be produced that are specifically tailored to individuals or a small group of athletes. In some cases, the time and expenditure involved would probably be no greater than for non-designer agents. Relatively simple methods include construction of virus-based gene vectors, production and administration of naked DNA, and the construction of gene vaccines to induce the production of antibodies. These are all routine tasks for molecular biologists, and many of the individual steps can be performed using standard procedures and apparatus and commercially available kits.

A common objection to gene doping is that the relevant methods are not validated and in particular that enhanced performance has not been demonstrated either in normal subjects or in highly trained athletes. Nevertheless, results obtained in preventive research oriented towards doping practice show that even when the effectiveness of a particular doping strategy has been repeatedly denied (as in the case of growth hormone), athletes will nevertheless continue to use it.

POINTS OF ENTRY: ELITE SPORT, BODYBUILDING, AND ANTI-AGING APPLICATIONS?

Overall we can assume that gene therapy-based methods (i.e. gene doping in the narrow sense) probably pose far greater obstacles to misuse than the many different techniques and pharmaceutical developments used for the specific manipulation of gene activity. Given the present state of advancement of a number of

projects being pursued by the biotechnology and pharmaceutical industries, it must be assumed that such methods can already be misused for doping purposes, since – as is apparent from experience gained with peptide hormones (EPO, growth hormone) – abusers can gain access to them in clinical studies.

In this respect it should be noted that misuse of myostatin inhibitors, for example, is far less likely to occur in competitive sport than in recreational sport, most notably in the world of bodybuilding, and these new drugs have long been discussed and sought after in internet forums that cater to bodybuilders.

In the longer term, a potentially far more significant route of access than illegal appropriation of gene-modulating substances and techniques from clinical trials (or the sort of »designer« gene doping referred to above) could arise at the fringes of the treatment of age-related disabilities, e.g. the treatment of excessive muscle loss with (by then) licensed drugs. This area of medicine borders on and blends imperceptibly into what has become known as »enhancement«, i.e. the nontherapeutic use of lifestyle drugs to improve everyday performance, an increasingly discussed topic that is of considerable social and political relevance.

DETECTABILITY AND TEST DEVELOPMENT

When strategies for preventing and combating doping are being devised, a key question is whether, and if so how, gene doping can be detected. Past experience suggests that reactive development of detection methods is quite inadequate as a means of combating doping effectively. The WADA responded to this problem some years ago by establishing an international program to promote research into methods of detecting gene doping.

Techniques of gene therapy or gene modulation are aimed either at inserting a gene or genetic element into specific somatic (body) cells and activating it, or else at activating or inhibiting an existing gene or genetic element. Where the inserted genetic or gene-regulating element is chemically different from the body's natural substances, direct detection should be both possible and qualitatively sufficient. However, due to the rapid pace of development in this field and the variety and complexity of gene modulation, most experts believe that techniques for direct detection are likely to become less important, since it would be far too expensive to test for all possible forms of genetic manipulation.

Though theoretically plausible, approaches based on vector detection (in gene therapy procedures) pose a number of problems, e.g. the difficulty of distinguishing them from naturally occurring viruses. Detection of nonviral vectors (naked DNA, siRNA) is likely to be far more difficult because of the short biological half-life of nucleic acids. At present it is entirely unclear whether and how detection might be possible in the case of gene doping techniques where cells are

removed from the body, genetically altered outside of the body, and then returned to the body (*ex vivo* techniques).

The vast majority of the 20 research projects currently being supported by the WADA are therefore aimed at identifying deviations from normal physiological conditions as indirect evidence of gene doping. This involves the determination of highly differentiated profiles of all sorts of molecules (DNA, RNA, proteins) in blood and tissue samples, so-called biomarkers or »molecular fingerprints«. The aim or strategy here is to develop an intelligent form of biomonitoring which provides unambiguous evidence of manipulated gene activity. This in itself might suffice as proof of tampering. This method might, however, also only allow an initial suspicion to be substantiated, requiring additional specific evidence in order to prove with reasonable analytic certainty that anti-doping regulations have been violated. The question as to whether the biomonitoring strategy will be successful in the long run cannot be answered at this time, since the relevant projects are in an early stage of development (for instance, the development of a specific practical test to determine overall myostatin activity is mentioned as an aim in just one project). There is, however, currently no alternative in sight.

TESTING AND SANCTIONS

Five years ago, as a precautionary measure, the WADA placed gene doping on the list of banned substances and methods (Prohibited List), which together with the World Anti-Doping Code (WADC) forms an important basis for measures employed by sports associations and national governments in their common fight against doping. All the defined violations of the WADC anti-doping regulations are applicable to gene doping. Self-administration, refusal to undergo testing, possession, trafficking, administration to others, and participation in various other activities are prohibited. Sports associations that have incorporated the WADC or NADA code for Germany into their statutes have thereby formally prohibited their members from engaging in gene doping. This is true of large sections of competitive sport, but not of individual sports activities such as those practiced at fitness clubs and the like.

The Prohibited List has also been incorporated into German law. The German Drug Law (*Arzneimittelgesetz*, AMG) forbids trafficking in substances on the Prohibited List, prescribing them, or administering them to others for doping purposes in sport (including any attempt at such actions). The same applies to substances required for use in the methods listed [including gene doping; § 6, no. 2, AMG]. However, there is no reference to § 4, no. 9, AMG which, defines gene transfer agents as medicinal products.

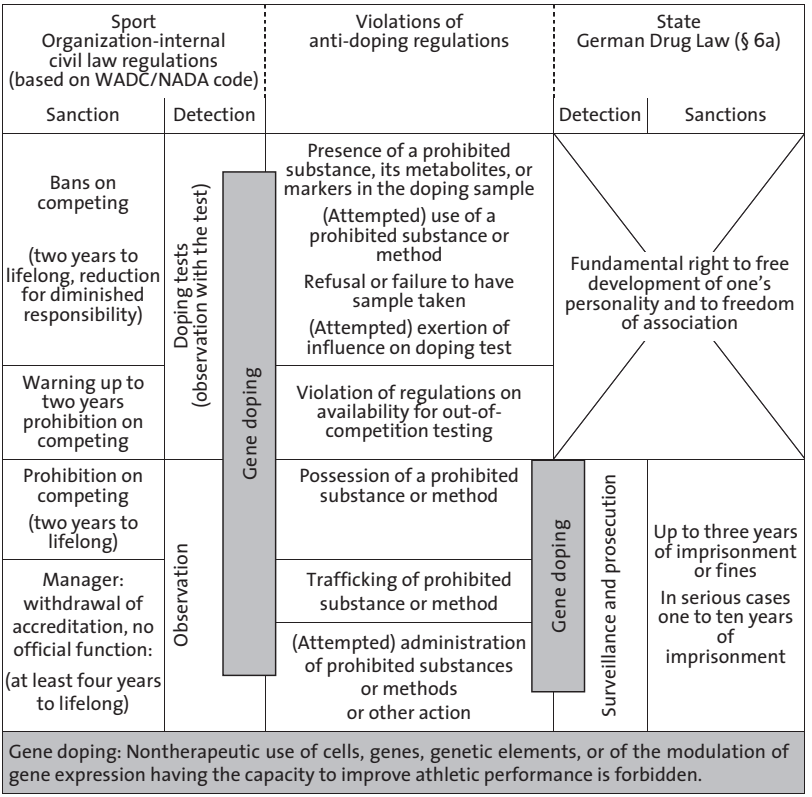
In the particular case of gene doping, the principal problem will lie not so much in prohibiting actions as in monitoring compliance with the prohibition and obtaining proof of violations that will stand up in a court of law (problem of enforcement). The main tool available to sports associations for monitoring compliance with these prohibitions is that of doping tests. The most reliable evidence that can be obtained by sports organizations is to be found in samples of body tissues and fluids on the basis of which a prohibited act can be demonstrated using detection methods that provide a sufficient degree of certainty. The state enjoys broader investigative authority. Since doping tests violate the individual rights of the athlete, the nature of the prohibited act must be formulated in a sufficiently precise manner (principle of clarity and definiteness). From the legal perspective it is doubtful whether the present definition of gene doping satisfies this requirement.

Detection of gene doping is likely to prove far more demanding than in the case of current doping practices. If gene doping is to be detected, the present system of in-competition and out-of-competition testing will need to be expanded. If it is necessary to take more blood samples or indeed tissue samples, the sampling requirements increase considerably. Since this bears on the personal rights of the athlete, the legality of the procedure must be well-founded as a matter of principle. This is probably possible only if a violation can be detected with sufficient certainty – i.e. if there is a test able to stand up in a court of law. All in all, as a result of gene doping the entire process of detecting gene doping will place even greater demands on sport jurisdiction than is the case with current doping practices.

The state has the capacity to assist organized sport in the pursuit of cases of gene doping. The setting up and training of special police units and specialized public prosecutor's offices for effective criminal prosecution of offenders, clearly defined contact routes and contact persons, and closer cooperation between prosecuting authorities and other relevant entities and individuals (science, sport, pharmaceutical manufacturers) are already important means for combating conventional doping and will be indispensable in the fight against gene doping.

Since these repressive measures in the fight against gene doping will be very expensive and are still beset by a number of unresolved legal issues, they are by themselves unlikely to act as an effective deterrent against gene doping and will need to be supplemented by strategies to prevent gene doping from occurring in the first place.

TABLE 1 DOPING VIOLATIONS AND THE REGIMEN OF SANCTIONS IN GERMANY



Source: WADA/NADA code, German Drug Law (*Arzneimittelgesetz)*, Prohibited List (*German Federal Law Gazette* 2007, Part II, No. 18)

SOCIAL ASPECTS OF DOPING

Doping is an act of an individual in a social context. Like other rule-breaking behavior, it is the outcome of individual developmental processes and conscious decisions. In view of the magnitude that doping has assumed in sport, however, it is not sufficient to point the finger at the deviant behavior of individual athletes. Rather, to gain a comprehensive understanding of doping activity it is important to consider its social contexts. These include, for instance, the global commercialization of competitive and top-level sport. Sport itself has become a business and for many athletes a professional career. This has been promoted by

the media and the expectations of a global audience, which also intensify the process of commodization of athletic performance. This makes winning »at any price« all the more important. The dominance of the performance imperative, together with the prospect of profits, gives rise to structures that are receptive to any means of improving performance.

In the system of sport, sports associations are the entities that seek to mediate between the demands for performance and success surrounding the athlete – politics, the media, sponsors, the public – on the one hand and the athlete him/herself on the other. They promote their athletes' willingness and capacity to perform, and they organize competitions to test performance. Their position and their influence on the overall course of events depend on the success of their athletes. Hence, like the athletes, they too are caught in a kind of »doping trap«. They must satisfy demands for clean, rule-abiding competitive sport by taking an active role in the fight against doping. But by testing and sanctioning, they tend to jeopardize their athletes' success. Much of what the sports associations do or fail to do with regard to doping can be better understood by considering their involvement in the »system logic« of competitive sport.

However, the diagnosis of structural involvement in doping activity is true not only of athletes, sports physicians, and organizations, but also of governmental entities. They promote sport because they are interested in success, but they also support structures for detecting and punishing doping and establish prohibitions and statutory offences in legal codes. Yet the success of anti-doping activities could mean a lack of success on the part of national athletes – possibly also because doping practices of foreign competitors are not countered with equal vigor.

Overall, doping must be understood as a product of specific social structures. By acting or failing to act, many actors have contributed to a system of organized irresponsibility. As a collectively engendered problem, the widespread practice of doping can only be solved through common action at multiple levels. Given the structures that have evolved over many years, optimism is out of place here. However, the considerable problems of credibility in competitive sport could certainly usher in effective curbing of doping practices. Gene doping could thus act as a warning sign, promote insights into the potential danger of doping for sport, and aid in the process of reorientation.

NEED FOR INFORMATION AND ACTION

Gene doping means entering a political sphere characterized by incomplete and uncertain knowledge coupled with an urgent need for action. The following actions could form the elements of a specific anti-gene-doping strategy.

SCREENING OF BIOMEDICAL AND PHARMACEUTICAL DEVELOPMENT PROJECTS FOCUSING ON THEIR RELEVANCE TO GENE DOPING

Gene doping misuses knowledge from basic and/or applied research in the life sciences that was intended to lead to new therapeutic strategies. Continuous predictive monitoring of biomedical and pharmaceutical development projects and of the potential demand side could provide strategically important information. This could become a kind of early warning system, providing guidance for those involved in the fight against doping and preventive doping research. A willingness on the part of the industry to cooperate in this area would be helpful.

INVESTIGATING DETECTABILITY, DEVELOPING TESTS, DESIGNING INTELLIGENT MONITORING SYSTEMS

There is a great need for research and development work in the detection of gene doping as a key element in the monitoring and sanctions system. A two-step approach currently appears to be the most promising. It covers intelligent monitoring and, where there are grounds for suspicion, specific tests for verification. This kind of monitoring requires both specialized (what parameters measured at what intervals provide evidence of doping-induced physiologic abnormalities?) and legal clarification with regard not only to sanctioning but also data protection and personal protection.

CONCEPTS AND ACTIVITIES FOR PUBLIC INFORMATION CAMPAIGNS SPECIFIC TO GENE DOPING

In parallel with the further development of testing and sanctioning structures, independent public information campaigns focusing on gene doping must be devised. For these to have a preventive effect, a broad concept is needed which covers the whole process of individual sports development during which mentalities and attitudes favorable to doping can gradually arise. Such an approach should take into consideration both the athlete's immediate milieu (trainers, managers, physicians) and the role of sponsors and the media.

ADAPTING FUNDING POLICIES

In the context of the public funding of sport, those receiving financial support are now required to adhere to the rules set down by the WADA and NADA. To this extent, gene doping is covered. Repayment of financial support in the event of violations, however, requires proof that will stand up in court. Here again detection proves to be the Achilles heel. Nevertheless, the demand for compliance with anti-doping rules should be upheld in any case and, indeed, applied even more stringently to gene doping. To this extent, the state could serve as a role model for private-sector sponsorship in its funding activities.

GERMAN DRUG LAW: CHECKING ITS APPLICABILITY AND FURTHER STATUTORY OFFENCES

The German *Gesetz zur Verbesserung der Bekämpfung des Dopings im Sport* (Law to Improve the Fight against Doping in Sport) has created better conditions for the prosecution of doping, particularly in the athlete's own milieu. However, the legislature must investigate whether and, if so, how these and other legal norms will be adapted to the dynamics of scientific and technical progress and doping practice. For example, gene doping could be more clearly defined as a prohibited act in order to satisfy the principle of clarity and definiteness. Given the recent extension of the definition of doping to include any substance intended for use in conjunction with prohibited methods, it should be possible to include substances relevant to gene doping. To satisfy the principle of clarity and definiteness, for instance, reference could be made in § 6a, nos. 2 and 2a AMG to § 4, no. 9a, AMG. In this way, the use of gene transfer agents for the purpose of gene doping could be prohibited. Furthermore, it should be considered whether the constituent element »*nicht geringe Menge*« (= more than a small amount) is even valid for gene doping or whether instead any medically unindicated use of gene transfer agents in humans should be made a punishable offence.

PARLIAMENTARY TECHNOLOGY IMPACT ASSESSMENT

The relevance of gene doping stems not only from its significance as a factor that will probably intensify the problem of doping in sport. Rather, it reflects a general social trend towards the use of pharmaceutical agents to manipulate physical and psychological performance. »Routine doping« or »enhancement« is a topical subject that will continue to be relevant to technology impact evaluation and the select committees of the German Bundestag in the future.

INTRODUCTION I.

BACKGROUND AND AIM OF THE TAB GENE DOPING PROJECT

Will gene doping be the next stage in the banned manipulation of performance in sport? This fear gained increasing immediacy as the Human Genome Project neared completion in the late 1990s. Although precise information on the scientific basis of such manipulation did not yet exist, the far-reaching aims and visions of human genome research and its potential application to gene diagnostics and therapy were projected – usually in vague terms – onto the competitive and even recreational sports arenas. Notions about human selection and human breeding were mooted. Often the term »gene doping« was and is used in the media as the superlative of »doping« in general.

Given a growing number of gene therapy studies, scientific committees and publications in recent years have also addressed the question as to whether, how, and when gene doping can or will pose a real threat to sport (Andersen et al. 2000; Schulz et al. 1998). In particular, some researchers investigating gene therapy methods for muscle diseases have drawn attention to the potential misuse of these techniques to boost performance in sport (Sweeney 2004). Given the long, uninterrupted tradition of doping, it appears plausible that, despite bans and threats of far-reaching sanctions, there is a strong tendency both in sport and in its illegal and fraudulent milieu to experiment with and use agents and techniques, including those that are highly risky and largely untested by medical science.

In 2001 – after gene doping had long been officially dismissed as an alarmist horror scenario – the Medical Commission of the International Olympic Committee (IOC) met for the first time to discuss the potential impact of gene therapy on sport. 2002 marked the first meeting of the World Anti-Doping Agency (WADA) on the subject of gene doping. In the same year the ethical problems, gene techniques, and manipulation of physical performance were the subject of two meetings of the United States President's Council on Bioethics, the results of which were included in the highly respected report »Beyond Therapy: Biotechnology and the Pursuit of Happiness« (The President's Council on Bioethics 2003). Shortly thereafter the IOC and WADA decided to prohibit gene doping. Since January 1, 2003 gene doping has been included as a prohibited method in the WADA's Anti-Doping Code. In Germany the Federal Institute of Sport Science, following up on the WADA's activities, held a »small conference« on gene doping in 2002 (BISp 2003).

Detailed investigations into and reports on gene doping remain patchy. In 2004 the Dutch Anti-Doping Agency published a brief report (NECEDO 2004); in 2005 the Rathenau Institute, the Dutch technology impact assessment body – published a study on the interfaces between (high-level) sport and gene technology in general (van Hilvoorde/Pasveer 2005). A bioethical discussion paper on »genetically modified athletes« was published by A. Miah in 2004. However, its reflections on the possible approval of (gene) doping (in the context of the question of the ethical acceptability of genetic modification in humans in general above and beyond its use in sport) is in stark opposition to the central principles underpinning the fight against doping (Miah 2004). More recent but condensed reports have come from WADA (WADA 2005) and the chair of the WADA Gene Doping Committee, T. Friedmann (Schneider/Friedmann 2006).

In view of the potential explosiveness of the subject coupled with the insufficient body of information available, the TAB, at the suggestion of the German Bundestag, was commissioned by the Committee for Education, Research, and Technology Impact Assessment to carry out a project on the subject of gene doping. Its aim was to investigate the scientific and sociopolitical dimensions of gene doping based on an analysis of the following main points:

- The status and perspectives of doping-relevant findings in genome research and relevant gene therapy techniques, taking into account individual and social risks;
- Methods for detecting gene doping and their implications for procedures and systems of doping control;
- The necessary further development of relevant (international) legal instruments;
- The necessary geopolitical conditions (education, prevention, prosecution, public debate, codes of conduct) and new internationally coordinated strategies.

PROCEDURE

The TAB carried out the project in two phases. Throughout the process, it engaged in intensive cooperation with a network of outside experts.

In the first phase of the project the relevant current status of genome and proteome research was characterized, an overview of the approaches of detection methods was given, and an attempt was undertaken to summarize the available empirical findings on the current doping situation. To this end three expert reports were commissioned:

- *Gene doping: Techniques, potential biological aims, and possibilities of detection* (Dr. Patrick Diel, Dr. Ulrike Friedel; German Sports University, Cologne)

- *Doping structures in sport with special consideration of the possibilities and limitations of doping detection* (Dr. Heiko Striegel; Bietigheim-Bissingen)
- *Status and perspectives of doping-relevant findings of genome research and relevant gene therapy techniques* (Dr. Bernd Wolfarth, Dr. Johannes Scherr, Anja Pertl; Munich Technical University/Klinikum rechts der Isar, Munich)

The aim of the second project phase was to carry out a review of the literature regarding the actors and structures of conventional doping and to predict the effects of gene doping on them. To this end several brief reports were commissioned, and their main theses were discussed at an expert workshop in September 2007.

- *Doping – a non-accidental dilemma: (traditional) responsibility of athletes in the (global) system world of sport* (Prof. Elk Franke; Berlin)
- *Nature and enhancement: The ethical evaluation of gene doping* (Dr. Michael Fuchs, Dr. Dirk Lanzerath, Prof. Dieter Sturma; Institute for Science and Ethics [IWE], Bonn)
- *Gene doping – potential suppliers and possible means of control* (Prof. Alexander S. Kekulé, Institut für Biologische Sicherheitsforschung GmbH, Halle)
- *The perpetrator-victim relationship in its ethical dimension and related limitations and possibilities of antidoping strategies* (Prof. Nikolaus Knoepffler in collaboration with Dr. Reyk Albrecht; Freising)
- *Legal aspects of gene doping in sport*
  (Prof. Jürgen Simon, Jürgen Robienski, Dr. Rainer Paslack; Lüneburg)
- *Doping in democratic social systems*
  (Andreas Singler, Prof. Gerhard Treutlein; Mainz/Heidelberg)

The aforementioned reports form a cornerstone of the present report. We wish to thank all the reviewing experts for their willing cooperation and several of them for commenting on the draft versions of individual sections. The authors of the TAB report are solely responsible for the selection and interpretation of the information presented in the reports. A special thanks goes out to our colleague Ulrike Goelsdorf for handling the illustrations and setting up the layout.

STRUCTURE OF THE REPORT

An important point of reference in the following report is formed by the relevant activities of the World Anti-Doping Agency (WADA). When the Prohibited List was adopted in 2003, gene doping was defined in terms analogous to the use of gene and cell-therapy strategies in medicine: »Gene or cell doping is defined as the non-therapeutic use of genes, genetic elements, and/or cells that have the capacity to enhance athletic performance.« However, the following year, in 2004, the WADA shifted its focus. Since then it has defined and prohibited doping in terms that include the modulation of gene expression without limiting the meth-

ods and techniques used: »The non-therapeutic use of cells, genes, genetic elements, *or of the modulation of gene expression, having the capacity to enhance athletic performance,* is prohibited.« (WADA 2008; italics added by the author).

In the Gene Doping Project the TAB adopted this expanded perspective of the WADA, which some experts criticize as being too vague. Why – despite the terminological vagueness – this is not only scientifically sound but necessary, especially with regard to future doping problems, is explained and justified in detail in Section II, »Scientific Basis and Perspectives of Use«.

The aim of that chapter is to present the scientific underpinnings and strategies of various forms of gene doping to derive plausible theses about the potential diffusion of gene doping in sport. First we give a brief overview of the levels of gene regulation and targets for manipulation in general (Section II.1), after which we present the principles, approaches, and current limitations of gene therapy in particular. We then summarize the findings presented in the reports by Wolfarth, Scherr und Pertl, which review and discuss the current status of genome research into »high-performance variants«, as it has been found that there is little in the way of concrete facts to report. The core of the chapter therefore presents – on the basis of the Diel and Friedel reports – a detailed but concise view of the most important potential biological targets of gene doping and the currently relevant research avenues and development projects (Section II.2). After presenting foreseeable health risks (Section II.3), we then discuss – with reference to the report by Kekulé – the plausibility of several scenarios of gene doping diffusion – routes of access, points of entry, and time horizons (Section II.4).

The chances of success in the fight against future gene doping depend largely on whether its use can be unambiguously detected. Section III is therefore devoted to the questions of detectability and test development, again on the basis of the Diel and Friedel reports. Again, the point of reference is formed by the activities of WADA, which has been strategically sponsoring research projects on the detection of gene doping since 2003. The questions those projects have raised about the foreseeable significance of indirect detection methods and of a biomonitoring or screening systems for athletes will be a crucial factor in determining if action needs to be taken.

Specific methods for detecting gene doping are an essential tool for monitoring compliance with regulations. Section IV looks at whether gene doping is already covered by existing legal norms, monitoring systems, and sanction structures and whether they are able to counter the potential future use of gene doping. The reports by Franke, von Simon, Robienski, Paslack, and Striegel serve as important sources of information. The chapter's central point of reference is the World Anti-Doping Code (WADC) with the Prohibited List, which has formed

the framework for action – increasingly based on a division of responsibilities – by sport organizations and politicians in many countries since 2003. Section IV.1 gives an overview of prohibited activities relevant to gene doping and their decision basis. Through a process of definition and adoption to the German legal landscape, the WADC and the Prohibition List are gradually being implemented in German law. Section IV.2 discusses the NADA Code as a basis for antidoping rules of German sport organizations that apply at the federation or club level. To counter increasingly subtle doping practices, the majority of sports organizations in Germany are broadening their doping monitoring and sanction systems in line with the NADA Code. Focusing on unanswered questions and foreseeable modifications and with the aim of ensuring compliance with the (gene) doping ban, an overview is given of the established doping monitoring methods and their limitations. Lawmakers must support the efforts of sport in the antidoping battle by ratifying international treaties (Section IV.3.1) and enacting national legislation (Section IV.3.2). We show how gene doping is already covered by the German Drug Law and other offenses and where regulation problems exist.

Despite bans and far-reaching sanctions, gene doping – like doping and other rule-breaking behavior before it – could gain a foothold across swathes of society. To understand and evaluate (gene) doping, the subject must be analyzed and discussed not only as a biological, chemical, and physiologic process but also as an individual action within social contexts. This is done in a cursory manner in Section V, which draws on the reports by Knoepffler, Albrecht, Singler and Treutlein, Fuchs, Lanzerath, and Sturma. Gene doping can be the result of individual developmental processes, in the course of which attitudes, mentalities, and behavioral patterns disposed toward doping are acquired.

Section V.1.1 explains this first in the context of high-level sport, addressing the specific role of medical managers, who are key players in determining whether a doping mentality develops and the practice of doping becomes entrenched among athletes. Section V.1.2 discusses other »peripheral players« who influence athletes. For example, it should be made clear to sport organizations and promoters that although athletes act and decide independently, they are influenced by their social milieu. Taking bodybuilding and sports pursued by older people as examples, Section V.2 examines the question of how doping behavior typically arises within individual sports. Both sections (V.1 and V.2) deal specifically with those factors that athletes are thought likely to consider when deciding for or against gene doping.

From an analysis and discussion of the scientific, legal, and social situation, it is possible to infer what information and action will be needed in the foreseeable future to address the subject of gene doping. This is summarized in the final part, Section VI.

GENE DOPING: SCIENTIFIC BASIS AND PERSPECTIVES OF USE II.

As explained in the introduction, this report is not restricted to the commonly encountered view of gene doping as the transfer of gene and cell therapy strategies in the narrow sense. Rather, it adopts the broadened perspective of the World Anti-Doping Code, which explicitly defines gene doping to include the modulation of gene activity by other methods as well, i.e. »the nontherapeutic use of cells, genes, genetic elements, or the modulation of gene expression having the capacity to improve athletic performance« (NADA 2006b).

In this report the term gene doping denotes gene doping in the broad sense as the targeted modification of gene activity. This includes the use of gene and cell-therapy strategies for the general purpose of enhancing physical performance, which is referred to as gene doping in the narrow sense, as well as other modern substances aimed specifically at influencing gene activity directly or indirectly insofar as they are based on an understanding of molecular processes and are potentially relevant to doping.

After giving a brief overview of genome research results, gene-regulation levels, and the principle and approach of gene therapy, Section II.1 explains why it is not just scientifically sound but necessary to adopt such a broadened perspective with regard to future doping problems. This is then justified in detail in Section II.2.

Section II.2 presents the three areas which according to a broad consensus are likely biological targets for gene doping: muscle formation, oxygen supply, and energy supply in the body. The basic molecular knowledge required for understanding the targets of molecular and gene-regulating manipulations is presented for each of these three fields based on the Diel/Friedel (2007) report.

Section II.3 examines the specific health risks of several gene doping methods. Section II.4 broadly discusses the perspectives of use and the plausibility of the broader use of gene doping, while giving due consideration to routes of access, time horizons, and points of entry.

CURRENT SITUATION: LIMITS AND TARGETS 1.

A commonly held view is that gene doping methods aim to »improve« the genetic makeup of athletes. It assumes that in recent decades human genome research has produced an extensive body of knowledge about gene variants that have a specific effect on performance. Using techniques of gene and/or stem-cell therapy, these »high-performance gene variants«, it is believed, may some day be transferred to individuals – whether in the embryonic stage, in childhood, or in adulthood – to replace less performance-enhancing variants. Other conceivable options arising from such a scenario are prenatal and preimplantation diagnostic tests where the »selected parameters« are genetic factors for specific physical and/or mental characteristics.

The TAB project uncovered no evidence whatsoever that such scenarios of human selection or breeding for athletic prowess will be technically feasible in the foreseeable future. Such gene doping scenarios are scientifically unfounded and misleading in that they divert attention from far more urgent and practicable developments demanding consideration and action.

As a preliminary comment to the results presented in this report, it should be stressed that a whole series of new pharmaceutical methods and techniques exist or are under development which could potentially be misused for illegally boosting performance and as such could be seen as and referred to as gene doping in the narrow or broad sense. Among these are several which would probably be no more complicated to use or more expensive than current doping methods but would be at least as difficult to detect (see Section III for a full discussion of this point).

Before the aspects of gene regulation and gene therapy relevant to the future practice of gene doping are explained below, we should justify why visions of human selection or breeding for athletic performance in the foreseeable future have no scientific basis.

RELEVANT KNOWLDEGE ABOUT HIGH-PERFORMANCE VARIANTS 1.1

Does a relevant body of molecular genetic knowledge exist about »high-performance variants« that could potentially be used to enhance athletic performance? A detailed examination of findings from the fields of genome analysis and genetic diagnostics gives the following picture regarding genes that could be used to redress individual »genetic disadvantages« through targeted gene manipulation (Wolfarth et al. 2007): Molecular genetic knowledge of »high-performance gene variants« (or performance-relevant polymorphisms) is still

extremely limited, imprecise, and contradictory, with the result that »promising« techniques for inducing specific alterations in an individual's genetic disposition are extremely unlikely to be developed in the foreseeable future. This consensus of the reviewing experts is summarized below. (The experts are [founding] members of an international research group which has been reviewing international research findings from molecular genetic studies on phenotypes relevant to physical performance and fitness since 2001) (Wolfarth et al. 2007, pp. 4 ff.).

Genome research has been examining the phenomenon of physical performance for the past 40 years or so. In the 1970s and 1980s the main research tool was the study of twins. However, in the past 15 years researchers have increasingly also been investigating individual genetic variants with the help modern molecular biological methods. As has happened in many other fields of medical science (e.g. research into the causes of prevalent diseases such as hypertension, diabetes, obesity, and coronary heart disease), the initial euphoria about the genetic basis of physical performance as a complex quality has since given way to a more sobering view. Although the number of publications in this research field has risen steeply in the past 20 years, a breakthrough in the form of robust data is still nowhere in sight. Even extensively studied physiologic subsystems that are relevant to performance (e.g. the hormonal renin-angiotensin system and adrenergic receptors) have so far yielded highly contradictory results regarding the effects of gene variants. As in other fields of medical science, large population studies have failed to identify or confirm any links between genetic variations and physical performance.[1]

It is expected that technical progress will bring about further changes in the research field of genome analysis and that the increasing efficiency of high-volume methods will open up ever new quantitative and qualitative dimensions of genome analysis. Whether these technical developments will simplify or resolve the problem of characterizing and explaining complex genetic traits remains unanswered. It is possible that, owing to their complexity, the genetic basis of many physiologic traits and parameters cannot be definitively explained – or at least not in such a way that they could be used for selection or as »blueprints« for athletes.

The question of whether it is possible to specifically manipulate the genome to enhance physical performance based on scientifically sound findings from polymorphism research must be answered with a categorical »no« at present. Nor is it possible to predict reliably whether and when such a potential could arise in the future. The discovery of just one truly performance-enhancing gene could change the situation suddenly, at least insofar as it could be used to select off-

1 To be fair it should be noted that in comparison to medically and therefore economically more relevant parameters, less research is devoted to questions regarding the non-pathogenic impairment of performance.

spring by means of preimplantation diagnostics (Kekulé 2007). Judging from genome research findings from the past 15 years, a »breakthrough« is highly unlikely, at least not within the next five to ten years.

GENE REGULATION – TARGET FOR GENE DOPING 1.2

The human body consists of around 100 trillion cells, each of which (with few exceptions, e.g. red blood cells) contains the complete genome (Diel/Friedel 2007, pp. 8 ff.). The genetic substance itself is DNA (deoxyribonucleic acid), which occurs in the cell nucleus in the form of 46 chromosomes (one set of 23 homologous chromosomes from each parent). Each chromosome is made up of a long strand of DNA, which is compressed by supercoiling so that it fits inside the tiny cell nucleus. The highly specific sequence of the four »building blocks« of DNA (adenosine, cytosine, guanine, and thymine), which is essentially identical within a given species, contains the biological information for many thousands of functional DNA segments or genes.

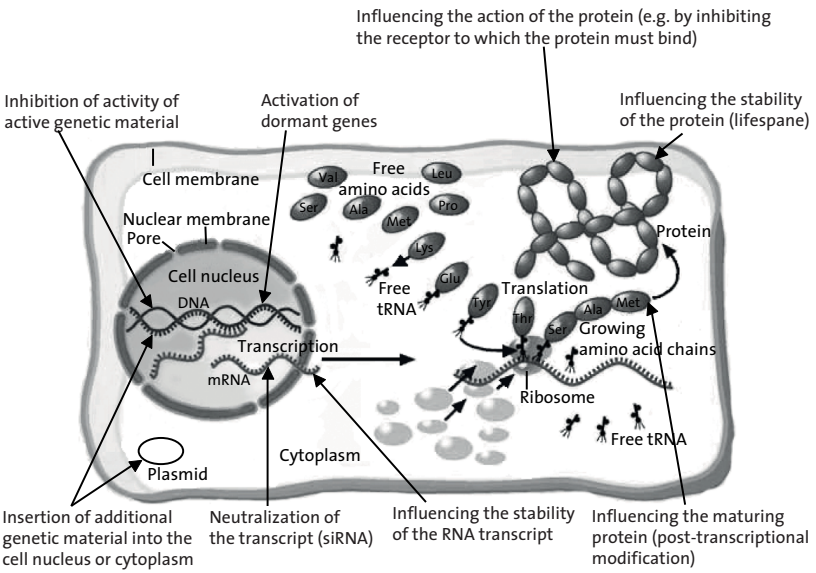
Classical or *coding* genes are active when they are expressed, i.e. when the information they contain is read, causing the cell to produce a functionally active protein (Fig. 1).[2] In the first step of this process the segment of the nuclear DNA that codes for the protein concerned is copied, not in the form of DNA, but in a slightly altered chemical form as RNA. The product of this process of *transcription* is known as messenger RNA (mRNA). In a complex process known as *translation*, mRNA serves as a template for the production of a highly specific protein. The primary structure of the protein is determined by the sequence of the gene that was read. However, in the course of the protein biosynthesis process, modifications may occur at various sites, depending on the physiologic state of the cell. This is one reason why proteins with very different effects can be traced back to individual genes and one of the reasons why the »gene« is such a fuzzy, hard-to-define concept.

The body's mechanisms for controlling and influencing this gene expression are collectively known as *gene regulation*. Gene regulation forms the basis of cellular differentiation and morphogenesis (organ and form development) and for the variety and adaptability of all organisms. For these highly complex processes to take place, the right gene must be expressed in the right cells, in the right amount, and at the right time (Diel/Friedel 2007). Although the relevant body of knowledge is enormous, it is also severely limited. New knowledge is continu-

2 »Classic« because in the early days of gene research it was thought that this is the main function of the DNA in human chromosomes (one gene, one protein model). It is now known that the bulk of DNA exerts its functions through other mechanisms. These mechanisms are often regulatory in nature but research into them is still very limited.

ously being gained from genome research and proteome research (research into the entire complement of proteins), with every finding throwing up new questions, so that the real complexity of these biological processes is now becoming clear.

FIG. 1 METHODS OF MODIFYING THE BODY'S GENE ACTIVITY



Source: P. Diel, using an illustration from Roche

Since each and every step in gene expression is subject to highly complex physiological regulatory mechanisms, there are many points at which pharmacologic or molecular biological modulation is potentially possible – either for therapeutic intervention or for doping purposes (Fig. 1).

Over moderate and long physiologic periods gene expression in the body is controlled, e.g. via chemical modification of DNA and altered spatial arrangement (condensation) of DNA segments. In particular, *methylation* (the attachment of methyl groups to specific parts of the DNA molecule) leads to gene silencing, as it prevents the genes from being read. Such inactivation can be very long-lasting and can even be inherited. Mechanisms that modify gene expression without altering the DNA sequence are subsumed under the term *epigenetics*. Methods to specifically influence methylation, for example, are still in the early stages of research (Callinan/Feinberg 2006).

Short-term physiologic gene regulation, by contrast, is achieved via the interaction of DNA with specific proteins known as transcription factors, which influence the production of messenger RNA (mRNA). A scientifically satisfactory description of the highly complex regulatory mechanisms of transcription and translation goes well beyond the scope of this report. Relevant facts are therefore given only in relation to the examples of developments pertinent to (gene) doping in Section II.2.

GENE THERAPY: PRINCIPLE AND APPROACH 1.3

When a gene fails to fulfill its normal function in a cell, tissue, or organ and this circumstance gives rise to a disease, a *genetic defect* is said to exist. A genetic defect can be inherited or can arise in the course of a person's life (so-called somatic mutations, which are implicated, for example, in cancer development). Such defects may be due to changes in individual DNA building blocks (base or point mutations) or to the rearrangement or loss of longer DNA segments. More generally, any disorder of gene regulation can be regarded as a genetic defect (Diel/Friedel 2007, p. 14).

Gene therapy is a term used to denote strategies that aim to eliminate genetic defects by inserting genes or genetic elements into tissue or cells for the purpose of obtaining therapeutic or preventive benefits associated with the expression and function of those genes (DFG 2006, p. 6).

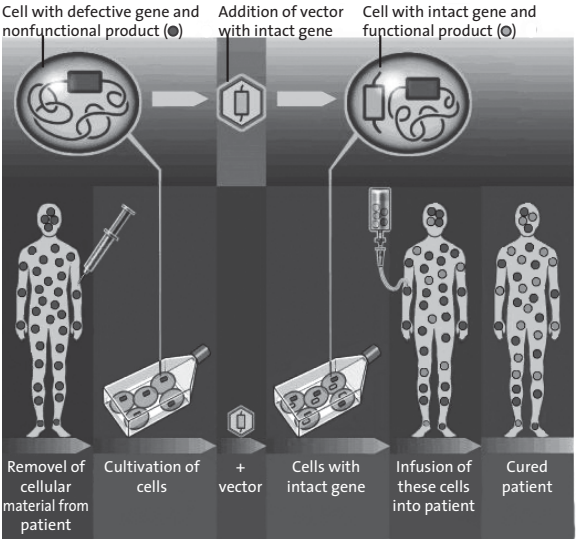
The process of introducing genes into cells is known as *gene transfer*. In most cases this is achieved with the help of a *vector* which carries the therapeutic genetic element (corrective gene, foreign gene, transgene) (Fig. 2). Gene therapy is intended to enable the body to, as it were, produce its own medicine (Diel/Friedel 2007, p. 15). Notwithstanding commonly held notions to the contrary, in many cases the change thus induced is impermanent, being a transitory modification that might have to be repeated.

In principle it a therapeutic gene could be inserted either into *somatic cells* (normal body cells) or into *germ cells* (reproductive cells, i.e. ovum or sperm cells). In Germany only somatic gene therapy is allowed. There is a broad international consensus that germ-line therapy is scientifically and ethically unacceptable at present, due to the incalculable risk of transmission and diffusion of the transferred gene in the human population.

Depending on the gene-transfer method used, somatic gene therapy is divided into *in vivo* and *ex vivo* techniques (Fig. 2). In *ex vivo* therapy, cells are removed from the body. The corrective gene is then inserted into those cells in a laboratory, after which the cells are put back into the body. Ideally, the cells migrate to their site of action, where they multiply, differentiate, and start producing the missing protein.

However, only a few types of somatic cells can be cultivated outside the body (e.g. blood cells), and few of these can be successfully reintroduced into the body.

FIG. 2 PRINCIPLE OF *EX VIVO* GENE THERAPY



Source: Bibliographisches Institut & F.A. Brockhaus

In *in vivo* therapy, the therapeutic gene is inserted directly into cells inside the body. This gene-transfer approach would be desirable for reasons of efficiency, but it is beset by a number of practical problems. The vectors injected into the blood are rapidly diluted. En route through the body they encounter many cell types that are unaffected by the disorder concerned. In these circumstances stringent requirements for vectorial specificity, effectiveness, and safety and for therapeutic efficacy must be met – requirements that the today's usual vectors cannot satisfy (see below).

A general distinction can be made between the following methods of gene therapy (Kekulé 2007, pp. 9 ff.):

- *Gene correction:* A strategy to correct mutation, gene correction is still purely theoretical.
- *Gene replacement:* It would be more realistic to replace a gene as a whole. To do so the original gene must be removed from the genome and the replacement gene inserted (at the same or another site). This too has so far worked

only in a few animal experiments and is therefore a long way from being used for medical purposes in humans.

- *Gene addition*: A new gene is inserted into the cell without removing the original (defective or suboptimal) gene. In this way the total amount of gene product is increased or, in the case of a regulative gene, the new gene takes over function of the original (assuming that it is not affected by the presence of the original gene). The additional gene does not necessarily have to be integrated into the genome (i.e. into a chromosome). The extrachromosomal insertion of a gene into a plasmid, which can move around freely within the cell or cell nucleus, is also conceivable. By inactivating the plasmid it is theoretically possible to reverse the gene addition more easily.
- *Gene inactivation*: This can be achieved in several ways – by destroying the gene itself (i.e. the corresponding DNA sequence on the chromosome), by modifying the regulator sequence, or by inactivating mRNA (e.g. by blocking it with complementary *antisense RNA* or by modifying its base sequence to accelerate its breakdown). RNA blockade methods in particular could be used reversibly.
- *Gene activation*: It is also theoretically possible to activate genes by modifying the regulator sequences or mRNA (e.g. by modifying its base sequence to slow its breakdown).

In principle, these methods could be combined. For example, one could insert a foreign gene (gene addition) and then control its expression with the help of anti-mRNA.

To date, successful attempts at gene therapy in human beings have been limited to techniques based on gene *addition* (so far only undirected, i.e. by random chromosomal or extrachromosomal integration) and gene *inactivation* (see Section II.3.1 for details).

The »therapeutic« or »corrective« gene itself must be:

- therapeutically effective
- easily regulated (control of the time and intensity of its expression), and
- safe (without adverse effects).

Theoretically many diseases could be treated with gene therapy. The gene therapies that have been tested in humans to date have been directed mostly at cancers, monogenic hereditary diseases, infectious diseases (especially HIV infection), and cardiovascular disorders, with over 60% of studies focusing on cancers (Diel/Friedel 2007, p. 17). However, the assessment of gene therapy results achieved to date remains a matter of great contention.

VECTORS

The success and risk of gene therapy depend largely on vectors used to transport the corrective gene into the cells. The vector must (Diel/Friedel 2007, pp. 16 ff.)

- be able to penetrate into specific cells (tissue specificity and efficiency of cell entry),
- ensure sufficiently strong, lasting gene expression (expression rate and persistence), and
- have as few side effects as possible (safety).

The type of vector used not only determines the efficiency of the gene transfer but also influences the intensity and duration of gene expression and may contribute to regulatory functions. In the case of undirected gene transfer without a vector, the probability of a therapeutic gene being successfully integrated is between 1:1000 and 1:100,000. In a targeted transfer using a vector, success rates are much higher, and the case of hemopoietic cells, success rates of 1:2 can be achieved (Diel/Friedel 2007, p. 16).

So far mostly *viral* vectors have been used in gene therapy (see box). Viral vectors are viruses that are unable to replicate. They have been genetically modified so that they are harmless and so that they are able to transport normal DNA into cell nuclei. Recently a growing use of *nonviral* vectors has been observed (Diel/Friedel 2007, p. 17). There is no such thing as *the* ideal vector; each must be adapted specifically to the nature of the genetic defect being treated (form of administration, tissue specificity, expression characteristics, etc.). The challenge of gene therapy lies in designing the best vector for treating the disease concerned (Diel/Friedel 2007, p. 44).

VECTORS FOR GENE THERAPY (FROM DIEL/FRIEDEL 2007, PP. 49 FF.)

Retroviruses and lentviruses: The genetic information of these viruses (which include HIV) is inserted into the chromosomes of the recipient cells and is passed on when the cells divide. In principle this allows the efficient production of gene therapy proteins but can also cause severe side effects (including cancer) due to integration in nuclear DNA.

Adenoviruses: The DNA of these viruses (which include the common cold viruses) remain outside the chromosomes rather than being integrated within them. This limits the possible duration of action but also prevents the aforementioned adverse effects of integration. However, severe immune reactions remain a problem.

Adeno-associated viruses: These particularly small, harmless viruses usually integrate at a specific site within nuclear DNA without severe consequences and with a very high expression rate of the transferred genes. Their major disadvantage is their limited capacity to transport genes.

Naked DNA: The integration of naked DNA in somatic cells (without the biological insertion mechanisms of viruses) is greatly limited but can be enhanced by *lipofection* (coupling to suitable molecules) or *electroporation* (use of electrical pulses). The greatly limited intracellular efficacy of naked DNA is offset by the major advantages of simple production and few adverse effects.

ADVERSE EFFECTS

Gene therapy, elegant as it may seem in theory, has proved extraordinarily difficult and risky in reality (Diel/Friedel 2007, p. 24). The causes of the (in some cases very serious) complications observed, e.g. severe immune reactions, leukemia-like symptoms, and even death, lie at the cellular and subcellular levels (see Section II.3.2 for details).

A comparatively mild complication is the *functional loss of the cells treated by gene therapy*. In the simplest case this could be due to dilution of the corrective gene: Once a therapeutic gene has been inserted into the target cells, for example by an adenovirus, it remains outside the nuclear (chromosomal) DNA. When the target cell divides, the corrective gene is passed on to only one of the daughter cells. Thus its concentration in the tissue decreases steadily, as does its therapeutic effect (Diel/Friedel 2007, p. 24).

The long-term efficacy of gene therapy is also determined by the stability and life span of the target cells. If the life of the host cells is only a few months, gene therapy must be repeated at regular intervals. This increases the risk of immune reactions and – if inserting vector systems are used – the likelihood that foreign DNA will be integrated at an unsuitable site in the genome, thus causing severe untoward effects, e.g. the promotion of cancer (Section II.3.2). The latter can also be caused by the corrective genes themselves, in particular by cytokines (tissue hormones), which play an important role in cancer therapy but are also candidates for doping misuse.

GENE DOPING – IN THE NARROW AND BROAD SENSES 1.4

Certainly not all the experts have adopted the concept of gene doping inherent in the broadened WADA definition (»the nontherapeutic use of cells, genes, genetic elements, or the modulation of gene expression having the capacity to improve athletic performance«). Kekulé (2007, pp. 6 ff.), for example, points out that both in the vernacular of the major cultural languages and in scientific parlance gene doping is understood as the use of gene and cell-therapy methods for the purpose of doping. He emphasizes that in its official publications even the WADA uses the term »gene doping« to refer exclusively to gene and cell-therapy

methods. For this reason, the broader formulation derived from the WADA's Prohibited List should not be construed as being the WADA definition. Owing to the special characteristics of genetic methods, gene doping in the narrow sense must be defined and analyzed separately in terms of its effects on performance enhancement and health and its detectability. Kekulé is therefore against subsuming conventional methods for the (indirect) modulation of gene activity under the term gene doping (Kekulé 2007, p. 6). On the other hand, he points out that conventional hormones, for example, would otherwise fall under the term gene doping, since they indirectly influence gene activity. According to Kekulé (2007), modern nongenetic molecular biological methods harbor their own perils of misuse for doping purposes which are even more acute in the short term than those associated with gene doping (in the narrow sense). Precisely because of this danger, he believes, novel nongenetic doping methods should be distinguished from gene doping and investigated separately. Diel/Friedel (2007, pp. 6 ff.) also confirm that a strict understanding of gene doping implies the transfer of genetic material, but they stress that in many cases it is very difficult and therefore unhelpful to draw a sharp distinction between gene doping and »conventional« methods.

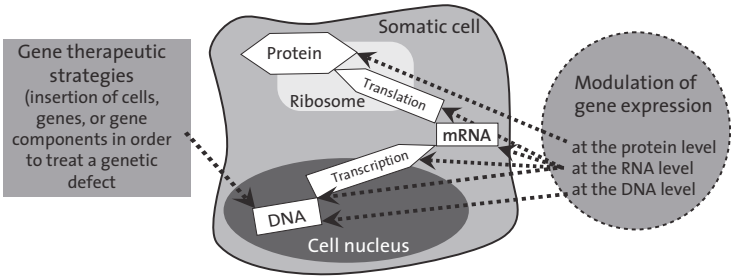
These terminological imprecisions are not easily resolved. It is undisputed that the shared scientific basis of new and foreseeable doping possibilities lies in our burgeoning knowledge about the molecular mechanisms of cellular function and the increasingly sophisticated molecular biological techniques and possibilities facilitated by the targeted, subtle manipulation of gene activity, which, moreover, will presumably become increasing difficult to detect (Diel/Friedel 2007, p. 7). In many senses whether a manipulation process involves the transfer of genetic material in the strict sense, i.e. DNA or RNA, or is otherwise accomplished pharmacologically is not a sensible exclusion criterion in the fields of impact assessment and prevention research.

The following detailed presentation of potential molecular target structures for gene doping and the related relevant therapeutic and pharmaceutical developments (Section II.2) confirms the need for a broad perspective. As will be made clear, most gene therapy techniques aim to modulate gene activity through enhancement, activation or blockade. In principle, it can therefore be said that the modulation of gene activity is the aim or purpose, while gene and cell therapy as well as other pharmacologic techniques are the means or methods.

For the purposes of this report »gene doping« will be understood in the broad sense to denote both gene and cell therapy methods and modern »conventional« substances used for the direct and indirect modulation of gene activity where the latter are based specifically on knowledge of molecular processes and have a potential for doping. The misuse of gene and cell therapy strategies in itself is not considered gene doping in the narrow sense.

Strictly speaking, some of the new manipulation methods presented below fall outside the broad definition of gene doping because, for example, they only influence the effect of a protein (as a gene product) but not genetic activity or gene expression (e.g. blockade of a hormone or receptor with specific antibodies). Because these are not covered by the gene doping prohibition of WADA, it would be sensible to broaden or redefine the term in the future (Section IV.1).

FIG. 3 POSSIBLE FOUNDATIONS FOR GENE DOPING: GENE THERAPY AND MODULATION OF GENE EXPRESSION



Own illustration

POTENTIAL BIOLOGICAL TARGETS FOR GENE DOPING 2.

In recent years debate and speculation have been ripe at international symposia and conferences as well as among the public regarding which biological targets might be relevant to gene doping. In principle, all molecular factors that promote or inhibit human performance come into question. The consensus among all the experts consulted in the TAB project and in the scientific literature is that the most likely targets for gene doping lie in three physiologic areas and their molecular regulation: the formation of skeletal muscle, oxygen supply, and energy supply (specific references to the modulation of pain sensitivity by gene doping, as is sometimes mooted, could not be found.

PHYSIOLOGICAL TARGETS FOR GENE DOPING STRATEGIES

- *Oxygen supply:* Hemoglobin concentration, blood vessel supply (molecular targets: EPO, HIF, VEGF)
- *Skeletal muscles:* Growth, structure, strength, endurance, regeneration (molecular targets: myostatin, HGH/IGF/MGF, Pax7, PPAR-delta)
- *Energy supply:* Fatty acid and glucose metabolism in the liver and muscles (molecular targets: FATPs, GLUTs, PTP-1B)

The following discussion of these areas and potential molecular targets for gene doping is based on the Diel/Friedel report (2007, pp. 58 ff.) but does not cite the report in detail. At the same time the status of relevant therapeutic developments is reviewed. When dealing with scientific technical developments in the early stage, as is the case with (potential) gene doping methods, it is useful to identify the phase of research and development that has been reached, because this determines the time horizons for possible utilization. In the case of medical and pharmacologic developments, it is helpful to use a classification system corresponding to the phases of clinical testing and drug development (see box). A noteworthy difference, however, is that because of the assumed unpredictability of complications (Section II.3.2), only patients with life-threatening disease and no alternative treatment options are entered in clinical phase I gene therapy trials.

PHASES OF CLINICAL TESTING AND DRUG DEVELOPMENT

Preclinical research: Search for drug candidates, including testing in animal models and experiments.

Phase I: Tested for the first time in (up to 50) healthy volunteers to investigate tolerance and initial adverse effects and to determine the minimum and maximum doses; duration: several weeks.

Phase II: First proof of concept in a limited number of patients (50 to 200) having the disease concerned; investigation of various doses; duration: several months.

Phase III: Randomized and preferably double-blind studies in 100 to 10,000 patients; investigation of efficacy compared to established drugs and/or placebo, risk-benefit analysis; duration: up to 2½ years; aim/completion: drug licensing.

Phase IV: Postmarketing surveillance, i.e. long-term observation and recording of adverse effects of the treatment in several tens of thousands of patients; possibly also identification of new indications.

Source: Kollek et al. 2004, p. 93; www.wikipedia.org

SKELETAL MUSCLE 2.1

Skeletal muscle is one of the most highly developed and largest organs in the human body. In common with bones and nerves, skeletal muscle in essential for physical activity and forms the basis of locomotion in humans and other animals. Its development at the molecular, cellular, and organ level has been extensively researched (Wassarman 2002). Skeletal muscle is characterized by its plasticity, i.e. its ability to respond to external stimuli (such as physical work or athletic exertion) by adapting in shape and performance over time.

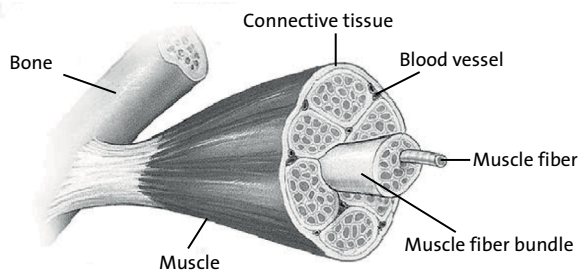
SKELETAL MUSCLE DEVELOPMENT AND COMPOSITION – MOLECULAR BASIS

Knowledge of the molecular mechanisms regulating skeletal muscle is being applied to the development of therapeutic methods, e.g. for degenerative muscle diseases. The same information is also being used to identify targets for pharmacologic and genetic manipulation aimed at enhancing performance.

Embryonic *myogenesis* (muscle development) proceeds from muscle precursor cells, which form skeletal muscle after undergoing differentiation and fusion. In the process, muscle-specific genes are expressed to produce the muscle-specific proteins *actin* and *myosin*, which make up the *contractile units* (dynamic molecular structures that are responsible for muscle contraction and strength) (Jones et al. 2004). The skeletal muscle continues to mature into adolescence but retains its ability to adapt to outside stimuli even after the growth process has ceased.

Whereas most muscle cells fuse to form multinucleated muscle fibers (which in turn are arranged in bundles to form of individual muscle groups; Fig. 4), around 5% to 10% remain in the form individual cells with a potential to divide and differentiate. These cells, known as satellite cells, act as stem cells for the formation of skeletal muscle.

FIG. 4 STRUCTURE OF SKELETAL MUSCLE CONSISTING OF INDIVIDUAL BUNDLES COMPOSED, IN TURN, OF INDIVIDUAL MUSCLE FIBERS



Source: http://en.wikipedia.org/wiki/Muscle_fascicle

Research into molecular, embryonic developmental processes has identified two main types of specific transcription factors: muscle regulatory factors (MRFs) and myocyte enhancer factor 2 (MEF2). These are key sites of myogenesis regulation, influencing the development of all skeletal muscle. In addition, there are other transcription factors, e.g. for the development of special muscle groups,

skeletal muscle regeneration, and the development and maintenance of satellite cells (e.g. Pax7; see below).

Besides muscle-specific factors, higher-level growth factors also have an important influence on the reproduction and differentiation of satellite cells, especially during regeneration of skeletal muscle. These include insulin-like growth factors I and II (IGF-I and IGF-II), hepatocyte growth factor (HGF), fibroblast growth factors (FGFs), and interleukin 6 and leukemia inhibitory factor (LIF). The particularly relevant factor *myostatin,* a member of the TGF-ß family (transforming growth factors), inhibits, for example, the muscle regulation factor MyoD.

MOLECULAR REGULATION OF MUSCLE-FIBER COMPOSITION

Human skeletal muscle consists mainly of red type 1 (slow-twitch) fibers and white types Iia and Iix (fast-twitch) fibers. The latter are distinguished by their metabolic and regulatory properties. The distribution of these muscle-fiber types has a major influence on an individual's performance. Locomotor muscles have a larger share of fast (and fast tiring) fibers; supportive muscle, by contrast, has significantly more slow fibers (for greater endurance). In most people muscle composition is rather uniform, differing within an individual by only about 20%. However, through intensive training – probably genetically »enhanced« in most cases – much greater deviations from the norm can be achieved with extreme distributions of 90:10 or 10:90 in some muscles. The sprinter Carl Lewis, for example, had an over 90% proportion of fast-twitch fibers in his leg muscles. The different roles played by heredity and training remain unclear (Section II.1.1). Recently, however, it has been found that muscle-fiber composition can be specifically influenced by pharmacologic and genetic manipulation (e.g. via PPAR-delta).

POTENTIAL TARGETS FOR MUSCLE GENE DOPING

MYOSTATIN

Myostatin, a (negative) growth factor (i.e. actually a growth inhibitor), is one of the most commonly mentioned potential targets for a range of quite different molecular doping manipulations. Blockade of its action can lead to an increase in skeletal muscle mass. Myostatin is an extracellular chemical messenger. It is formed in the body by skeletal muscle cells and – as the product of a complex signal chain – is secreted when the physiologically desired length of a muscle has been reached in response to its physical developmental state or external stimuli, e.g. physical training (Ma et al. 2003).

Mutations or variants of the gene that codes for myostatin have been described in some people, including some athletes, although no specific correlation with

performance has been established. In some cattle breeds, by contrast, the effects of naturally occurring mutations of the myostatin gene are quite obvious. For over 200 years so-called double-muscled lines such as the Belgian Blue, Piedmontese, and Asturiana de los Valles have been bred which have 20% to 30% more muscle mass than normal cattle. This effect was created experimentally in the late 1990s by deactivating the myostatin gene in what are known as *knock-out mice*. This involves a permanent change in the genome that is also passed on to offspring. According to a broad international consensus, such manipulation of the germ line in humans would be absolutely prohibited, as it could have biologically and medically unpredictable risks and its use would be ethically unacceptable.

Muscle mass gain as a consequence of myostatin blockade is due to *hypertrophy* (increase in muscle fiber thickness) as well as *hyperplasia* (increase in the number of fibers) (Huet et al. 2001; Lee/McPherron 2001; McPherron et al. 1997). Targeted inhibition of the myostatin signal pathway could be utilized for breeding transgenic animals for agriculture and has been experimentally achieved in chickens and sheep with corresponding effects on body structure.

Apart from inhibition of the myostatin gene itself (e.g. by means of inhibitory RNA), the myostatin signal pathway can be blocked at the next level by inhibiting the synthesis of the myostatin protein or preventing its *maturation* (or processing; Section II.1.2) into a functional form. This maturation process depends on, among other things, metalloproteases (enzymes that are able to specifically cut or shorten proteins), whose inhibition also appears to suppress tumor growth. Metalloprotease inhibitors have been developed mainly with the latter indication in mind, and clinical trials in humans are under preparation (Coussens et al. 2002).

FOUR POSSIBLE LEVELS OF MYOSTATIN BLOCKADE

(Prohibited as a germ-line manipulation: permanent, inheritable inactivation of the gene in nuclear DNA [knock-out]).

1. Gene doping in the narrow sense: Inhibition of gene reading or myostatin production by means of inhibitory RNA.
2. Gene doping in the broad sense: Prevention of *maturation* of the myostatin protein (by means of enzyme blockade).

Same effect, but no gene doping:

3. Blockade of the myostatin receptor, e.g. by competitive proteins.
4. Blockade of myostatin itself by specific antibodies.

A third level is blockade of the myostatin receptor on target cells, so that although myostatin is produced, the signal to end muscle growth is no longer re-

layed to the muscle cells. Such a blockade can be achieved, for example, with the help of competitive proteins or specific blocking antibodies, which can be produced in the laboratory for almost any protein. Both methods have been successfully tried in mice (Bogdanovich et al. 2002; Lee/McPherron 2001), and corresponding drugs for use in humans are being developed and prepared for clinical testing (see box on ACE-031).

ACE-031 – A MYOSTATIN-INHIBITING PROTEIN (ACELERON PHARMA, USA)

ACE-031 is a protein which, according to Aceleron Pharma (www.acceleronpharma.com/content/products/ace-03x.jsp), blocks the type IIB activin receptor IIB (ActRIIB), thus inhibiting the action of myostatin. ACE-031 is the first of various myostatin inhibitors to be clinically tested by the company. All the others are still in the preclinical research stage. The specified clinical indications are sarcopenia, dystrophy, and other diseases associated with loss of muscle mass.

The fourth level would then involve the specific inhibition of myostatin itself, which probably has the greatest importance for potential doping misuse. Here too antibodies (see box on Stamulumab), which have been shown to lead to a dramatic gain in muscle mass in wild-type mice (Whittemore et al. 2003), could be used.

STAMULUMAB (MYO-029) – A BLOCKING ANTIBODY AGAINST THE GROWTH FACTOR MYOSTATIN (WYETH, USA)

According to Wyeth, the aim of the company's development work is to treat muscular degenerative diseases, e.g. Duchenne muscular dystrophy. The website of Metamorphix, which holds the rights for the growth factor (Myostatin™), states that Wyeth has also set its sights on conditions such as cachexia (pathological weight loss), ALS (amyotrophic lateral sclerosis), sarcopenia, and metabolic diseases such as type 2 diabetes (www.metamorphix-inc.com/MMIcorpoverviewpres.pdf). The myostatin-blocking antibody MYO-029 (proprietary name Stamulumab) has been undergoing phase I and II clinical testing since the spring of 2005 (www. wyeth.com/research_hcp/ pipeline_hcp). The initial results of these studies were announced for the spring of 2007 but were not yet available as of January 2008.

In the last two methods mentioned, it is not the production of myostatin that is inhibited but its action. These methods therefore do not constitute gene doping *per se*. The examples were included purposely to highlight the fact that even the broad definition of gene doping as the modulation of gene expression has its

limitations and that it will be necessary to keep an eye on all these developments in the interest of fighting doping efficiently (Section IV.1).

GROWTH HORMONE AND IGF-1

Growth hormone is often called *somatotropin* (somatotropic hormone, STH) or HGH (human growth hormone). It is one of the peptide hormones that has long been misused for doping purposes and is included in the list of prohibited substances (Section II.1.2.2). It is produced in and secreted by the pituitary mainly during growth phases, with a peak occurring during puberty. When height growth ceases, the production of the hormone falls sharply but continues to be stimulated by energy-consuming processes (physical activity, mental stress, hunger).

If the production of growth hormone or the response of cells to growth hormone is impaired, the result is short status; that of excess production gigantism or enlargement of some parts or organs of the body. The chief target organs in which growth hormone exerts anabolic (building) effects are the bones, skeletal muscle, and liver. Growth hormone increases amino acid uptake and utilization, raises blood glucose levels, and reduces fat. It is therefore praised by some as an anti-aging wonder drug, despite the fact that there is no reliable scientific basis for such an effect.

The »conventional« misuse of growth hormone in sport is already the subject of intensive reporting and speculation. Growth hormone is produced by recombinant techniques by a large number of pharmaceutical companies. Although the manufacturers claim that they take rigorous steps to prevent illegal sale of the drug, numerous anonymous pharmaceutical vendors are hawking somatotropin products on the internet. It is therefore assumed that appreciable amounts of growth hormone will find their way to athletes.

The production of growth hormone in skeletal muscle itself has been achieved via gene transfer in a number of experiments on mice. Effective expression of the transferred gene has been accomplished with the help of both viruses and plasmids (Peroni et al. 2005), which brought about functional improvements of skeletal muscle (strength increase) and systemic effects (e.g. a reduction of the body's fat index). Human gene therapy with growth hormone is usually discussed in the context of therapies for muscular dystrophies. WADA expects that growth hormone could be one of the first candidates for gene doping strategies (WADA 2005).

On the subject of growth hormone, the effects of the somatomedins IGF-1 and IGF-2 (insulin-like growth factors) must also be considered. These are produced in the liver and, as secondary hormones mediate (along with a number of other substances) the differentiated effects of growth hormone on specific organs and

cells, e.g. most of the growth-promoting effects observed in skeletal muscle. In addition to its direct anabolic effect on skeletal muscle, e.g. in the form of increased protein synthesis, IGF-1 also promotes the proliferation and differentiation of muscle stem cells (satellite cells). However, the cell-proliferation-promoting effect of IGF-1 is associated with health risks, particularly with regard to cancer development (Baserga 1999). Elevated serum IGF-1 levels have been found in prostate cancer, colorectal carcinoma, and lung cancer (Grimberg/Cohen 2000).

As in the case of growth hormone, a number of research groups have succeeded in producing therapeutic effects through gene transfer and the expression of IGF-1 in the skeletal muscle of animal models (mice), e.g. improved regeneration capacity after injury and a slowing of disease progression in muscular dystrophy models (Schakman et al. 2005; Schertzer/Lynch 2006; Takahashi et al. 2003). Reports in recent years of a variant of IGF-1 specific to skeletal muscle, MGF (mechano growth factor) have attracted attention (also in the internet forums of the bodybuilding scene: if you enter »MGF« into Google, these are the first hits). The functional significance of MGF is still highly controversial, but the substance appears to play an important role in skeletal muscle regeneration following injuries (Goldspink/Yang 2004).

TRANSCRIPTION FACTORS OF THE PAX TYPE

An interesting molecular target – though one that his hitherto received little attention in connection with doping – is transcription factor Pax7, a specific marker for resting and activated satellite cells (Seale et al. 2004), whose function, however, has yet to be definitively elucidated. The interplay between Pax proteins and MRF genes (muscle regulation factors) probably determines the self-renewal of satellite cells (Olguin/Olwin 2004). Progressive loss of satellite cells and a severe defect in muscle regeneration have been observed in *Pax7 knockout mice* (i.e. mice in which the Pax7 gene has been blocked) (Ustanina 2005; Seale et al. 2004).

High hopes have been pinned on satellite cells as therapeutic stem cells, e.g. for the treatment of muscular diseases such as Duchenne muscular dystrophy. In this context Pax7 could be a prime target for the manipulation of satellite cells (Relaix et al. 2005; Seale/Rudnicki 2000; Seale et al. 2004). Pax7 is also discussed in connection with the possible treatment of age-related muscle loss, in which a decline in the satellite cell population appears to play a key role (Chargé/Rudnicki 2004; Chi/Epstein 2002; Relaix 2006).

PPAR-DELTA

Several years ago molecular mechanisms were described, by means of which the fiber composition of muscles can apparently be altered (Wang et al. 2004). In

transgenic mice the overproduction of *PPAR-delta* (peroxisome proliferator-activated receptor delta) results in the conversion of fast to slow muscle fibers. This protein controls an entire series of genes involved in energy metabolism in muscle and increases the fat burning rate. The use of *PPAR-delta agonists* (substances that bind to the receptor and activate it) is therefore being discussed in connection with the treatment of metabolic syndrome (a condition marked by the interdependent factors of obesity, diabetes, dyslipidemia, and hypertension). In genetically modified mice it transformed fast fibers (type II) into slow fibers (type I), which obtain their energy supply to a far greater extent from the burning of fat. The endurance of muscle is largely determined by its ability to metabolize fat. In fact, the genetically modified mice were able to run twice as long on a treadmill as their untreated counterparts. At the same time the mice were protected from the usual adverse consequences of a high-fat diet: they neither gained significant weight nor developed insulin resistance or type 2 diabetes. These animals, dubbed »marathon mice«, have since gained media fame.

Investigations in humans also appear to have confirmed a relationship between PPAR-delta and endurance (Kramer et al. 2006). Professional cyclists have a significantly greater proportion of type I muscle and PPAR-delta receptors than untrained individuals – and they, in turn, a greater proportion than paraplegics. This change is accompanied by growing insulin sensitivity (i.e. more glucose transported to the now better-performing muscle). However, as far as the magnitude of the training effect is concerned, marked differences – possibly genetic in nature – have been observed between individuals. Overall, these findings indicate that it could be possible to influence endurance by way of genetic manipulations at the level of skeletal muscle. Medical pharmaceutical strategies to modulate the activity of PPAR delta could therefore be potentially misused for doping purposes, irrespective of whether the techniques used are genetic or pharmacologic in nature.

PPAR-DELTA DRUG DISCOVERY PROGRAM (GALPAGOS NV/HILLCREST THERAPEUTICS, USA)

In a communiqué to the market issued in late 2006, the two US companies Galpagos NV and Hillcrest Therapeutics announced a joint drug discovery program for PPAR-delta agonists (www.bionity.com/news/e/61454/). Paramount BioSciences, a subsidiary of Hillcrest Therapeutics, will be responsible for clinical testing and commercialization. The strategies that will ultimately be pursued are left open. The communiqué states that drug candidates have already been identified.

MODULATION OF OXYGEN SUPPLY 2.2

In addition to modifying muscle-fiber composition and the supply of energy to muscles, the supply of oxygen to muscles is an important factor, particularly for endurance. The main parameters governing the availability of oxygen to muscle tissue are:

- Gas exchange in the lungs (the efficiency of oxygen uptake)
- The performance of the heart as a pump
- The oxygen transport function of the blood
- The degree of capillarization (i.e. the network of fine blood vessels) in the target tissue (muscle), which determines oxygen-exchange capacity.

These parameters can be differentially modified by various training methods but also by pharmacologic and possibly genetic intervention. Gas exchange in the lungs and cardiac performance have hitherto been amenable to pharmacologic manipulation only to a limited extent (e.g. modification of pulmonary capacity by amphetamines). By contrast, the oxygen-transport capacity of the blood can readily be modified by pharmacologic means.

The (relative) concentration of oxygen-transporting red blood cells (erythrocytes) and thus the oxygen transport protein it contains (hemoglobin, measured by the hematocrit concentration) can be improved only to a limited degree by normal physical training. This makes physiologic sense, because an increase in the hematocrit concentration – especially during hard, prolonged exercise – would greatly reduce cardiac output due to greater viscosity (thickness) of the blood. This would slow blood flow, thus impairing other vital functions of the blood (nutrient transport, heat regulation). Differences in oxygen-transport-related physical performance between athletes and nonathletes or between children and adults are due mainly to the blood volume and hence the total amount of hemoglobin in the body.

Unlike normal training, high-altitude training leads to a marked increase in erythrocyte concentration. This adaptation process is controlled mainly by the hormone *erythropoietin*, which is therefore an obvious target for pharmacologic and genetic manipulation of the blood's oxygen-transport capacity.

The actual supply of oxygen to muscle cells depends largely on the vascularization of the muscle, i.e. the density of the fine blood vessels, the capillaries, which transport oxygen to and metabolic breakdown products from the tissue. When muscles are working, selective vascular dilation results in a redistribution of the blood, so that during exercise around 80% of total blood flow goes to the muscles, compared to around 20% at rest. Local blood flow thus increases by a factor of 15 to 20. Training can improve both blood flow and capillary density (by up to 45%).

Some time ago factors were identified at the molecular level that influence the capillarization of tissues, e.g. VEGF (vascular endothelial growth factor). The inhibition or activation of such factors has long been the subject of medical research as a strategy for fighting cancer but has also opened up avenues for the pharmacologic or genetic manipulation of performance.

ERYTHROPOIETIN

Erythropoietin (EPO) is a glycoprotein hormone that is synthesized primarily in the kidneys. It plays a key role in hemopoiesis (the formation of blood cells) as a growth factor which promotes the formation of erythrocytes (red blood cells). As a therapeutic agent, recombinant erythropoietin is used mainly for the treatment of anemia in dialysis patients, in whom blood formation is impaired due to the underlying kidney disease. In addition, EPO is currently one of the best-known doping agents, especially in endurance sports (Donati 2007).

However, the physiologic function of erythropoietin is not limited to erythrocyte formation. Erythropoietin receptors occur in a range of cell types, notably in brain cells but also in heart muscle cells. It has been shown to influence cell division processes, vascularization, and *apoptosis* (programmed cell death).

After the human EPO gene was isolated in 1983, it was successfully produced by recombinant techniques in *Escherichia coli* cells in 1984 and in mammalian cells in 1985. EPO was one of the first genetically engineered drugs produced on a large scale, and since its market launch by the Amgen company in 1989 it has been far and away the biggest selling biopharmaceutical (i.e. recombinant drug).

Today EPO is produced by a number of pharmaceutical companies and is sold in slightly modified forms for various indications. The enormous success of the first EPO products (unlike other recombinant growth factors) gave rise to numerous strategies to enhance the activity of the EPO molecule, facilitate its administration, or improve its tolerance. Among the latest developments in this field are EPO analogs, also known as mimetics, gene-therapeutic strategies for improving EPO availability *in vivo,* and combination products with neuroprotective substances for use in the treatment of neurodegenerative diseases (Ehrenreich et al. 2004). Two development projects are especially relevant to gene doping: Repoxygen™ and *FG-2216* (see box).

REPOXYGEN™– PRODUCTION OF ERYTHROPOIETIN BY GENE THERAPY METHODS (OXFORD BIOMEDICA, UK)

Repoxygen™ is the proprietary name of a gene therapy method for the controlled intracorporeal production of erythropoietin (EPO). Repoxygen surfaced in the media in connection with investigations against the light athletics trainer Springstein, who mentioned the substance in the context of doping in

emails. Repoxygen was developed by Oxford BioMedica for the treatment of anemia (www.oxfordbio medica.co.uk/news/2002-ob-05.htm). It is a viral gene-delivery vector containing the human EPO gene. The gene is activated by a hypoxia (oxygen deficiency) control element, so that erythropoietin is formed only in the presence of reduced oxygen concentrations. It is administered intramuscularly and contains adenoviral vectors for transporting the EPO gene into muscle cells. Despite media reports, Oxford BioMedica says that Repoxygen has only been tested in preclinical studies, i.e. in animal experiments. Its efficacy (or inefficacy) in humans is therefore unknown. According to the company, development of the product has been suspended until further notice while a commercial partner is sought. Nevertheless, the system appears to be technically mature and therefore could theoretically be misused for doping purposes.

FG-2216 AND FG-4592 – INHIBITION OF THE ENZYME PROLYLHYDROXYLASE FOR STABILIZING HYPOXIA-INDUCED FACTORS (HIF) (FIBROGEN, USA)

The drug candidates that go by the names FG-2216 and FG-4592 are thought to influence the stability of a transcription factor, thereby increasing EPO synthesis. A special property of 2216 and FG-4592 is that they are orally administered, chemically synthesized, low-molecular-weight compounds (and not, like the other examples, complex recombinant protein molecules that have to be injected). The two substances inhibit the function of the enzyme prolylhydroxylase, which is responsible for breaking down hypoxia-induced factor (HIF). As a result of HIF stabilization, the EPO gene is overexpressed. FG-4592 is intended for use in the treatment of ACD (anemia of chronic disease) syndrome. In April 2006 the Japanese pharmaceutical company Astellas acquired the commercial rights for FG-4592 and FG-2216 outside the USA (www.astellas.com/global/about/news/2006/060428_eg.html). In May 2007 a death was reported in a phase II clinical trial (www.astellas.com/global/about/news/2007/pdf/070507_eg.pdf), the cause of which remains unknown. As a result, the clinical trials were suspended (in Poland, Finland, and Germany, among other countries).

ANGIOGENESIS AND VEGF

The term *angiogenesis* denotes the growth of small blood vessels and capillaries. It is distinguished from the new formation of blood vessels, known as vasculogenesis. VEGF (*vascular endothelial growth factor*) is an important growth factor in the control of angiogenesis. Its chief function is to activate the cell types responsible for the formation of vessel walls (endothelial cells, pericytes, smooth muscle cells). Angiogenesis is of considerable biological and medical importance. For

example, solid tumors depend on a growing capillary network to supply them with oxygen and nutrients. Many pharmaceutical companies are therefore developing angiogenesis *inhibitors* for the treatment of cancer. So far around 60 angiogenesis inhibitors with various mechanisms of action have been tested in clinical studies (including antibodies to VEGF, VEGF receptor tyrosine kinase inhibitors, direct inhibitors of endothelial cell activation, and substances that attack newly formed blood vessels).

Conversely, the *stimulation* of angiogenesis could be a therapeutic strategy, namely for the treatment of ischemia – the deficient supply of oxygen to a tissue or organ due to poor blood flow. If protracted, it can lead to cell *necrosis* (death) (e.g. as occurs in a heart attack). Ischemia is usually caused by blood vessel changes in the form of a constriction or occlusion. A number of research groups are working on stimulating the capillarization of tissues by transferring a gene for VEGF or other potentially effective growth factors (endostatin, T-cadherin and HIF_ialpha), and they have already chalked up successes in animal models (Arsic et al 2004; Barandon et al. 2004; Idris et al. 2004). An ongoing development project is focusing on the use of naked DNA (see box).

GENASIS – INDUCTION OF THE EXPRESSION OF VEGF-2 IN CARDIAC MUSCLE USING NAKED DNA (CORAUTUS GENETICS INC., USA)

In this form of gene therapy the gene for VEGF-2 is inserted directly into cardiac muscle – not by means of a viral vector (Section II.1.3) but in the form of a naked DNA plasmid. The object is to stimulate blood-vessel formation, e.g. in order to repair damage in patients with coronary heart disease (angina). Following successful animal experiments (Kawamoto et al. 2004), Corautus Genetics ran a clinical phase II trial from August 2004 to August 2006 which went by the name of *GENASIS* (genetic angiogenic stimulation investigational study). However, no therapeutic effect was achieved compared to the placebo controls. Nevertheless, the company announced that it wishes to conduct further preclinical tests of VEGF-2 for other indications (diabetic neuropathy, critical ischemia of the legs; www.medicalnewstoday.com/articles/53786.php). With regard to the potential of this specific approach for gene doping purposes, although it may seem irrelevant, the gene-transfer technique was at least used without dramatic adverse effects, which presumably also applies to skeletal muscle. Even in an early announcement Corautus Genetics pointed out that the execution of this (*in vivo*) gene transfer study, the biggest in the world, was in itself a noteworthy success and important outcome of the clinical trial (www.prnewswire.com/cgi-bin/stories.pl?ACCT= 104&STORY=/www/story/03-30-2005/0003291252&EDATE=).

MODULATION OF ENERGY SUPPLY 2.3

The metabolism of glucose (sugar) and fatty acids in skeletal muscle is the primary mechanism by which energy is supplied for physical activity. Thus, it also a factor determining the endurance capacity of athletes. Molecular mechanisms that control the efficiency by which muscle cells are supplied with fuel and the quality of its metabolism are not only potential targets for genetic and pharmacologic manipulations aimed at improving performance. Given their importance for the treatment of widespread diseases such as obesity and diabetes, they are also a major focus of medical and commercial pharmaceutical research. Among the bewildering number of research and development projects in this field, there are probably many that could potentially be misused for gene doping purposes.

FATTY ACID TRANSPORTERS

All mammals have systems for transporting high-energy substrates through cell membranes. The uptake of fatty acids in cells is regulated by (a family of closely related) fatty acid transport proteins in the cell membrane (e.g. FATP1, CD36) (Hamilton/Kamp 1999; Stahl 2004). Gene transfer experiments with naked DNA in animals have shown that the expression of fatty acid transporters in skeletal muscle induces an increase in fatty acid uptake in muscle (Clarke et al. 2004) – theoretically a strategy that could be used for gene doping purposes.

GLUCOSE TRANSPORTERS

Transport proteins for glucose can, depending on the cell type, stimulate the flow of glucose into cells (e.g. in muscle) or out of cells (e.g. from the liver as the central metabolic organ). Like fatty acid transport proteins, glucose transporters (GLUTs) also make up a family of six closely related proteins, the products of different genes being designated GLUT1-5 and GLUT7 (Kayano et al. 1990). GLUTs exhibit tissue-specific distribution and transport glucose (and other sugar molecules) with varying degrees of efficiency (Gould/Holman 1993). GLUT4, for example, is the predominant insulin-sensitive glucose transporter in fat and muscle tissue in rats and humans (Friedman et al. 1991; Rodnick et al. 1992).

In the past decade numerous research groups have shown in transgenic mice that glucose utilization can be enhanced by overexpression of the gene for GLUT4, either specifically in skeletal muscle (Tsao et al. 1996) or in all tissues in which GLUT4 is normally expressed (skeletal muscle, cardiac and fat tissue) (Deems et al. 1994; Ren et al. 1995; Treadway et al. 1994). Strategies to increase GLUT4 expression in skeletal muscle or to modulate the efficiency of GLUT4 have therefore been proposed for the treatment of type 2 diabetes. In principle, proteins involved in the regulation of GLUT4 are targets for the development of

pharmacologic and genetic molecular techniques to modulate glucose uptake in skeletal muscle.

Another target for manipulating glucose availability is the insulin receptor (see box for example).

PROTEIN-TYROSINE-PHOSPHATASE 1B SIRNA (SIRNA THERAPEUTICS, INC., USA)

The enzyme protein-tyrosine phosphatase 1B (PTP-1B) plays a role in the development of insulin resistance and type 2 diabetes by reducing the sensitivity of the insulin receptor. Accordingly, inhibition of this enzyme should be associated with increased insulin sensitivity and the transport of glucose into muscle cells. The company Sirna Therapeutics, which specializes in the development of siRNA strategies (si for *small interfering*) (Section II.1.3), has produced an siRNA molecule to block the mRNA coding for PTP-1B which reduced the expression of PTP-1B in the liver by up to 67% (www.sirna.com/wt/page/metabolic_disease). Because the availability of glucose is a crucial factor for the performance of skeletal muscle, this technique could also be used for doping. It is not known if clinical trials with these siRNA molecules are planned.

PPAR

The importance of peroxisome proliferator-activated receptors (PPAR), transcription factors that regulate a whole series of genes involved in energy metabolism, have already been mentioned in the chapter on *muscle gene doping*. You will recall that PPAR-delta influences the composition of muscle cell fibers (Section II.2.1). The manipulation of other subtypes (three are known at present: PPAR-alpha, beta/delta, and gamma, which are expressed to varying degrees in different organs; Gervois et al. 2007), has potential significance for doping insofar as these substances promote the supply of glucose to muscle. Thiazolidindiones (also known as glitazones), compounds used as oral antidiabetic drugs, bind with high affinity to PPAR-gamma (Levetan 2007). Although the mechanism of action has not yet been elucidated, it is believed that through mediation of the PPAR effect either a factor is expressed that reduces insulin resistance, or conversely that the expression of a factor is reduced, resulting in insulin resistance (Ishizuka et al. 2007).

OVERVIEW OF GENE DOPING METHODS 2.4

The following tables again summarize the examples of research avenues and development projects relevant to gene doping that were identified in the framework of the TAB project. It is clear that of the techniques currently undergoing *clinical testing*, there is or was just one (induction of the expression of VEGF-2 in cardiac muscle using naked DNA) that explicitly constitutes a gene therapy technique. The other methods developed are pharmacologic strategies to modify gene activity or to target protein activity. A number of potential gene doping methods in the broad sense are in the preclinical (i.e. animal experiment) stage (e.g. the well-known substance Repoxygen).

TABLE 2 GENE DOPING TECHNIQUES: *MODULATION OF ENERGY SUPPLY*

Molecular target	Intended therapeutic use (diseases)	Potential performance enhancement	Method/technique (*R&D stage*)
Increased uptake rate of fatty acids in muscle			
Fatty acid transport proteins (FATP1, CD36)	Obesity	Increased endurance due to improved lipid utilization	Overexpression of fatty acid transport proteins by means of »naked« DNA (animal experiment)
Increased glucose release rate in the liver, increased uptake rate in muscle			
Glucose transport proteins (GLUTs) Insulin receptor	Diabetes	Enhanced performance due to improved glucose utilization	Overexpression of GLUTs by means of gene addition (animal experiment) Inhibition of the enzyme PTP-1B by means of siRNA, resulting in activation of the insulin receptor (animal experiment)

Own compilation on the basis of Diel/Friedel 2007

TABLE 3 GENE DOPING TECHNIQUES: *STRUCTURE/PROPERTIES OF SKELETAL MUSCLE*

Molecular target	Intended therapeutic use (diseases)	Potential performance enhancement	Method/technique (*R&D stage*)
Muscle growth (increased mass)			
Myostatin (growth-limiting factor)	Hereditary and age-related muscular atrophy Possibly type 2 diabetes	Obvious potential for use particularly in strength-intensive sports; natural mutations known to occur in humans and, e.g., cattle	Inhibition of myostatin by: a) blockade of the myostatin gene (*animal experiment)* b) inhibition of myostatin synthesis by metalloproteinases (*animal experiment*) c) Blockade of the myostatin receptor (*clinical study*) d) Inhibition of myostatin itself by antibodies (*clinical study)*
Muscle metabolism and regeneration			
HGH (human growth hormone) in combination with IGF or MGF (muscle-specific variant)	Growth disorders, muscular atrophy	Increased strength and mass Lipid breakdown (anti-aging!)	Increased HGH and IGF production in muscle by gene addition (*animal experiment*)
Transcription factor Pax7 (influences muscle regulation factors)	(Regeneration after) injuries	Better regeneration	Pax7 blockade causes defect in muscle regeneration; (*animal experiment*)
Muscle composition: increased proportion of type I fibers (slow contraction, lipid combustion)			
Receptor protein PPAR-delta (induces transformation of muscle fibers)	Metabolic syndrome	Increased endurance, e.g. due to improved lipid utilization (»marathon mouse«)	Overexpression of PPAR-delta by gene addition (*animal experiment*) Activation of PPAR-delta agonists (*drug screening*)

Own compilation on the basis of Diel/Friedel 2007

TABLE 4 GENE DOPING TECHNIQUES: *MODULATION OF OXYGEN SUPPLY*

Molecular target	Intended therapeutic use (diseases)	Potential performance enhancement	Method/technique (*R&D stage*)
Increased number of red blood cells			
Erythropoietin (EPO)	Blood diseases, especially anemia in dialysis patients	Increased oxygen transport function of blood (known and established as a result of EPO use in endurance sports)	Increased production of EPO in muscle as a result of gene addition (*Repoxygen; animal experiments*) Stabilization of transcription factor HIF by means of small molecules leading to overexpression of EPO (*clinical study stopped because of possible side effect*)
Increased number of blood vessels in tissues (angiogenesis)			
Vascular endothelial growth factor (VEGF)	Ischemia (lack of blood supply) or destruction of blood vessels resulting from heart disease Cancer (angiogenesis *inhibitors* can be used to retard cancer growth)	Increased oxygen exchange capacity in tissues	Induction of expression of VEGF-2 in heart muscle by means of naked DNA (*clinical study showed no effect in phase II for primary indication; other indications planned.*)

Own compilation on the basis of Diel/Friedel 2007

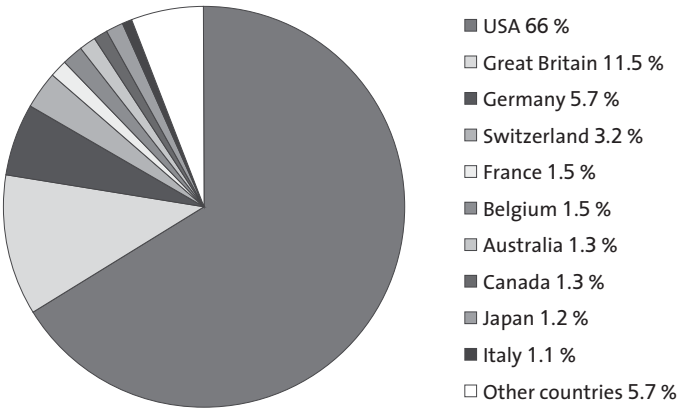
To provide further information on potentially relevant scientific developments, Section II.2.5 looks at underlying trends in the field of gene therapy that could become relevant to gene doping.

DEVELOPMENT PROJECTS IN THE FIELD OF GENE THERAPY 2.5

The list of gene therapy targets is growing but is not overwhelming. An overview of developments in this field can be found on the websites of the *Journal of Gene Medicine* (www.wiley.co.uk/genetherapy/clinical/), which are briefly summarized below (from Diel/Friedel 2007, pp. 98 ff.). According to the source, in the period between 1989 and mid-2007 1,309 clinical studies were conducted

worldwide in the field of gene therapy (Fig. 5)[3], 882 (67.4%) of them in the USA and 358 (27.3%) in Europe, with Germany leading in Europe (5.7%) (DFG 2006). Two thirds of the gene therapy studies focused on the treatment of cancer (Fig. 6). However, a trend reversal appears to be taking place. Since 2006, clinical studies have also been conducted for non-life-threatening conditions that only impair quality of life (e.g. erectile dysfunction; Melman et al. 2006).

FIG. 5 CLINICAL GENE THERAPY STUDIES BY COUNTRY (1989–2007)

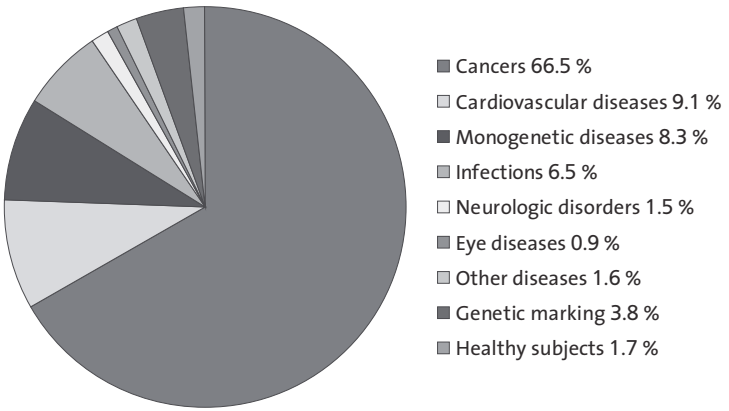


Source: www.abedia.com/wiley/countries.php

Approximately two thirds were clinical phase I trials in which the gene therapies were tested only in (a small number of) severely ill patients as a last resort (cf introduction to Section II.2). Not until clinical phase III is the actual efficacy of a new agent demonstrated in comparison to established drugs and/or placebo. This stage accounts for just 3.4% of gene therapy studies (43 studies), although there is a rising trend. A license application for a gene therapy drug for the treatment of an aggressive type of brain tumor was submitted to the European Medicines Evaluation Agency in 2005, while in China the first gene therapy agent (Gendicine™) for the treatment of specific types of malignant head and neck tumors was approved by the country's health authority as early as 2003.

3 It is surprising that China is not listed, because it is supposed to be contending with the USA for the leading role in this field (http://marketplace.publicradio.org/shows/2006/10/12/ PM200610125.html).

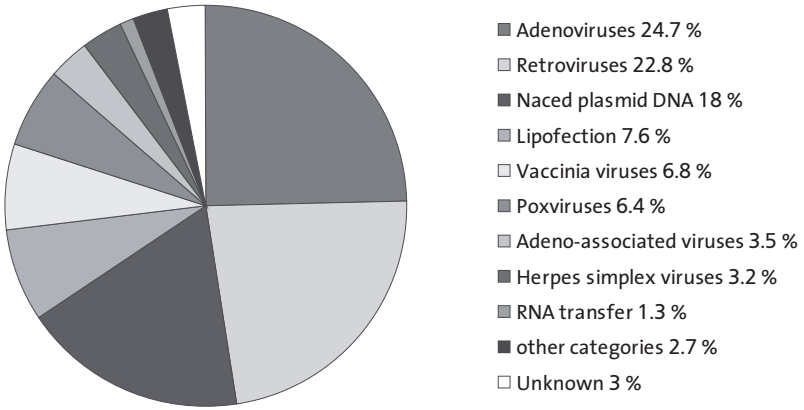
FIG. 6 INDICATIONS OF CLINICAL GENE THERAPY STUDIES (1989–2007)



Source: www.abedia.com/wiley/indications.php

With regard to the gene therapy methods employed, protocols using naked DNA have increased steadily in recent years and now account for 18% (Fig. 7). This situation is highly relevant to gene doping, as nonviral DNA is much easier and probably also less risky to use than viral vectors.

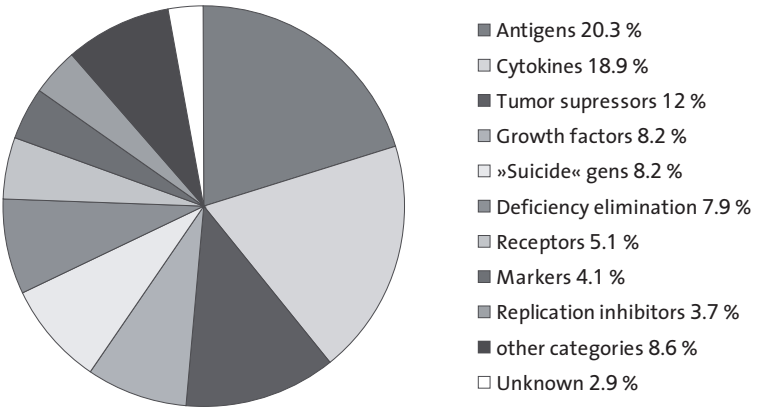
FIG. 7 CLINICAL GENE THERAPY VECTORS USED (1989–2007)



Source: www.abedia.com/wiley/vectors.php

The molecular targets of the clinical trials vary considerably. As shown in Figure 8, a large portion of the gene therapy strategies focused on tissue hormones (cytokines and growth factors). This too is relevant to gene doping, because these molecules already represent one of the foremost misused drug groups in current »conventional« doping practice.

FIG. 8 GENES TRANSFERRED TO CLINICAL GENE THERAPY TECHNIQUES (1989–2007)



Source: www.abedia.com/wiley/genes.php

CONTROVERSIAL EVALUATION OF THE SUCCESS OF GENE THERAPY

Assessments of the results of gene therapy methods are anything but unanimous, and the expert reports consulted in the TAB project were no exception. Diel/Friedel (2007, p. 17) emphasize that technical implementation remains problematic, but they do see some success with gene therapy, especially in the treatment of congenital immunodeficiency diseases (such as SCID and septic granulomatosis). In addition, there is early evidence that gene therapy is effective in a type of leukemia, in skin cancer, and in the blood-clotting disorder hemophilia B.

Kekulé (2007, p. 13), on the other hand, views some of the aforementioned examples (especially SCID and septic granulomatosis) much more negatively. He concludes that that there has so far been no success with gene therapy (in the narrow sense) that could be applied to gene doping.

Diel/Friedel (2007, p. 27) (in agreement with the assessment of the Senate Committee on Basic Issues of Gene Research; DFG 2006) also believe that ongoing trials are unlikely to produce drugs suitable for routine use in the foreseeable

future, especially since most of the studies are investigating preliminary methods for the treatment of very rare diseases, and that mature gene therapy techniques are still many years in the future. Nevertheless, they expect licenses to be granted for gene therapy agents in Germany within the next ten years – a period that is often cited in the international debate. The methods most likely to be approved are those that do not involve the integration of extraneous genetic material in the patient's DNA. The DFG Senate Committee on Basic Issues of Gene Research sees no fundamental difference between such noninsertional, transient active systems and other pharmaceutical agents and predicts their future use in non-life-threatening conditions as well (DFG 2006, p. 9). In the present context this indicates the early availability and ready accessibility of potential gene doping methods (in the narrow sense) in the field of easy-to-use vectors (naked DNA, plasmids).

SPECIFIC HEALTH RISKS? 3.

In all doping approaches the methods and agents used were developed for the treatment of diseases and therefore have not been tested for use in enhancing performance in healthy individuals. Knowledge about the health risks of drugs and other therapeutic methods is gained by observing patients treated with the smallest effective dose possible. Misuse for doping purposes, by contrast, always involves an entirely different physiologic situation (use by highly trained athletes) and purpose (maximum effect with minimum likelihood of detection). For this reason the health risks arising from misuse for doping purposes cannot be reliably assessed on the basis of clinical drug trials. This view is confirmed by serious and disabling health damage that some athletes have suffered in the past, sometimes with a fatal outcome.

From this perspective gene doping methods could hardly be riskier. Nevertheless, from the principle underlying methods for the targeted modification of gene activity it is possible to identify some *specific risks*. However, without an empirical basis, these remain merely *scientifically plausible assumptions*. In this context a distinction can be drawn between risks arising from the insertion of genetic material and risks arising from excessive expression (e.g. production in the body) of performance-relevant biomolecules. The following discussion briefly summarizes the relevant findings from Diel/Friedel (2007, pp. 110 ff.).

RISKS ARISING FROM THE INSERTION OF GENETIC MATERIAL

It is true of every new pharmacologic substance – including gene therapy in its current state of development – that initially very little is known or can be known about long-term outcomes.

NONTRANSFERABILITY OF RESULTS FROM ANIMAL MODELS TO HUMANS

Most of the »successes« of gene therapy have been achieved in mouse, dog, and monkey models (in preclinical studies; cf. introduction to Section II.2). It is not always possible to transfer these results to humans. A dramatic example is provided by the trial of TGN1412, an immunomodulating humanized monoclonal antibody, in 2006. In phase I of clinical testing all six healthy volunteers developed multiple organ failure, and at least two of them suffered permanent damage (Mitchell 2007). Because of the assumed unpredictability of the side effects, at present only patients with life-threatening conditions who have no alternative treatment options receive gene therapy in phase I clinical trials. In the case of unapproved gene therapy methods the usual doping practice of self-experimentation is tantamount to a fatal risk.

LACK OF TISSUE SPECIFICITY OF THE VECTORS

With many of the relevant vector systems, tissue-specific gene transfer is not possible (Section II.1.3). The unintentional transfer of genes into germ-line cells would be particularly dramatic, as the transgene could also be passed on to the recipient's offspring – with incalculable consequences. Viral vectors tend to be more specific for target cells than nonviral vectors. However, there are major differences among viral vectors, ranging from high specificity (e.g. herpes viruses for nerve cells) to no specificity at all (adeno-associated viruses).

UNCONTROLLED SPREAD OF THE FOREIGN GENE IN THE BODY

Even if tissue-specific gene transfer is accomplished, the foreign gene could subsequently spread uncontrollably through the organ system concerned or even the entire body. Some experts see this as one of the major problems of gene therapy (A. Amalfitano; www.msu.edu/~folandwa/kathryn_thesis.doc). If, for example, a gene transferred to skeletal muscle were to enter all the muscle cells in the body, it would also be expressed in cardiac muscle and in smooth intestinal muscle, resulting in severe disorders in those systems (e.g. hypertrophy of the heart). In the case of growth factor genes, their uncontrolled dissemination would probably affect cell growth in the entire body – a process closely associated with the development of cancer.

AUTOIMMUNE REACTIONS

The function of the immune system is to recognize and eliminate foreign molecules in the body. The immune system often also recognizes transferred genes and their products as foreign and attacks the cells that contain them. When it is exposed to invaders again, the immune system recognizes them immediately and launches a rapid, efficient response. This »memory« function of the immune system poses a problem for the repetition of gene therapy – a circumstance that

could be of major relevance to gene doping, which after all would probably have to be repeated several times. For example, in macaque monkeys that received gene therapy, the immune system first attacked the slightly modified transgene and later the body's natural erythropoietin, leading to multiple organ failure and death (Chenuaud et al. 2004).

INSERTIONAL MUTAGENESIS

With the insertional vector systems usually employed, it is impossible to control the precise site in the genome where the foreign DNA is inserted. If the foreign DNA were integrated into another gene, for example a key enzyme of cellular metabolism, this would have serious consequences. If the vector were integrated into a regulatory DNA element, it could upset a finely tuned balance, and if the regulatory element is a tumor suppressor gene, the result could be uncontrolled cell growth.

SIDE EFFECTS OF THE VECTOR: INDUCTION OF IMMUNE REACTIONS

When nonviral vectors are used (e.g. the direct injection of plasmid DNA into muscle tissue; McMahon et al. 1988; Wang et al. 2005) it is mainly local inflammatory reactions that are observed.

By contrast, viral vectors usually trigger systemic reactions that can be severe or even life-threatening. These reactions may be due to residual intrinsic toxicity of the »defused« virus, but in principle there is also a risk of the viral vectors cross-replicating with other viruses in the body, thus re-acquiring their original pathogenicity, i.e. their ability to cause illness.

CONSEQUENCES OF THE SUPRAPHYSIOLOGIC EXPRESSION OF PERFORMANCE-RELEVANT BIOMOLECULES

A distinction must be made between the health risks arising from a change in the concentration of the factor being modulated and the risks generally associated with the manipulation of regulatory mechanisms. The risks posed by the supraphysiologic expression of performance-relevant biomolecules are not unique to gene doping but apply in general to any genetic or pharmacologic manipulation. The following can be differentiated:

- Side effects that arise solely from the nonphysiologically high expression of the factor (A), and
- Side effects that arise from the factor in supraphysiologic concentrations no longer having tissue-specific but rather systemic activity (B).

A classical example of (A) are the risks resulting from the supraphysiologic administration (via recombinant EPO) or the (still hypothetical) amplification of

the expression (by gene transfer) of erythropoietin: both lead to the desired increase in hematocrit concentration as well as an undesirable increase in the risk of thrombosis.

An example of (B) is the effect of anabolic steroids (AS) on cardiac muscle and spermatogenesis. AS are used for doping due to their boosting effect on skeletal muscle. This requires high doses at which the activity of the AS is no longer limited to skeletal muscle but also affects cardiac muscle, which also enlarges and becomes susceptible to disease. In addition, AS have an inhibitory effect on the release of follicle-stimulating hormone (FH), which in turn stimulates testosterone production in the testicles. The result is a testosterone deficiency that can lead to temporary infertility.

Homeostasis (state of equilibrium) in tissue is generally determined by a balance between *proliferation* (cell growth) and *apoptosis* (cell death). Any disturbance of this balance is thought to be a key precondition for the development of tumors and thus cancer. Growth hormones in particular interfere with these processes. Supraphysiologic concentrations can, at least in the long term, promote cancerous changes in cells or stimulate pre-existing tumors. A carcinogenic effect has been demonstrated, for example, for the doping candidates HGH, IGF-1, MGF, EPO, VEGF, Pax7, and PPAR-delta (Section II.2).

RISKS ARISING FROM THE MANIPULATION OF GENE ACTIVITY

In view of the complexity of the intracellular regulation of gene activity (Section II.1.2), it is understandable why manipulation of these mechanisms can lead to a variety of side effects – and potentially cause serious damage to health.

The substance FG-2216 (see box in Section II.2.2), for example, ultimately promotes EPO production because it prevents the breakdown of an essential transcription factor (HIF). It is assumed that this is not the only effect and that:

- the stability of other transcription factors is also affected;
- HIF also affects other genes, possibly in multiple tissues and organs.

The next level, *translation*, i.e. the translation of the *genetic blueprint* (RNA) to produce a specific protein, could be disrupted, especially by siRNA methods (see box in Section II.2.3) if they not only block the RNA target molecule in a highly specific way but also block molecules with a similar structure. Relevant examples are known (Jackson et al. 2003; Sledz et al. 2003).

The *maturation* of (precursor) proteins is often achieved when enzymes remove or cut off parts of the molecule or append additional side groups or side chains to form a functional hormone. These enzymes are usually not absolutely specific in their action, i.e. they are able to process several different proteins. Manipulat-

ing such enzymes, e.g. to inhibit myostatin (Section II.2.1), could be employed but would almost inevitably also have unintended consequences.

PERSPECTIVES OF USE 4.

Based on experience with current conventional doping practices, several assumptions can be formulated as to whether, how, and to what extent gene doping (in the narrow sense and in the broad senses of specifically modulating gene regulation) will be practiced in the future (Diel/Friedel 2007, p. 97). The crucial factors determining the use and dissemination of such methods are likely to be – apart from their general availability – their presumed achievable effect, i.e. their potential enhancement of performance, and their detectability or lack thereof (Section III). The assessment of potential health risks is of somewhat subsidiary importance.

ROUTES OF ACCESS 4.1

Approved methods and agents used in therapy and those in clinical trials are probably the most likely candidates for doping. Presumably, experience gained in the 1990s with recombinant proteins (e.g. growth hormone and erythropoietin) can be directly transferred. In order to assess which gene doping strategies might be relevant in what time window, it is important to keep an eye on current research and development trends, especially at pharmaceutical companies. This approach to preventive doping research could play a key role as a scientific basis for the development of future anti- (gene) doping measures. The molecular targets described and the related genetic pharmacologic developments (Section II.2) reveal the variety of therapeutic strategies that could be exploited for doping purposes. In addition, it is assumed that by no means all projects relevant to gene doping become known to the public (at least not in their early stages).

INDIVIDUAL GENE DOPING – EVEN WITHOUT PROOF OF CONCEPT?

Beside the misuse of approved (or pending) gene-modulating compounds produced to scientific standards and in compliance with safety regulations and the potential use of scientifically based gene therapy methods in the future, Diel/Friedel (2007, p. 97) have identified another potentially even more worrying possibility: a kind of *individual gene doping* (in the narrow sense) that circumvents all the review mechanisms of drug regulatory procedures. As in the Balco affair, in which a small company developed and synthesized designer steroids explicitly for doping purposes, including the anabolic hormone tetrahydrogestrinone (THG), pharmaceutical gene doping agents could also be produced that

are specifically tailored to individuals or a small group of athletes. These drugs were never approved as medications and therefore were never tested for side effects. The existence of THG was not known to the doping control laboratories, let alone to the public at large.

According to Diel/Friedel (2007), an analogous situation is also conceivable for gene doping in the narrow sense. The time and expenditure involved (e.g. for constructing expression vectors) would probably be no greater than in the aforementioned example involving the chemical synthesis of a low-molecular-weight steroid compound. The unpredictability of adverse effects, including death, would not be a qualitatively new situation, as evidenced by plentiful cases in the history of doping.

Relatively simple conceivable scenarios in which gene doping is used would be, for example (Diel/Friedel 2007, p. 108):

- The construction of viral-based gene carriers
- The transfection of naked DNA, e.g. in the form of plasmids
- The synthesis and administration of siRNA
- The production of gene vaccines to stimulate the production of antibodies (e.g. to block receptors).

The production of the vectors required for such individual gene doping (in the narrow sense) or the synthesis of siRNA can be easily accomplished by any competent molecular biologist. Appropriate kits are available from many biotechnology companies. The production of such vectors and molecules is already routine practice in normal research establishments. Thus, expression vectors for the transfection of cells as well as for experiments on mice and rats are being produced and used on a large scale in thousands of laboratories around the world. It is theoretically conceivable to construct or modify a vector for individual gene doping within a few days. As in the case of designer steroids, small laboratories could offer their services to individuals for a fee. Many small companies are already offering expertise in aspects of gene therapy (e.g. transfection or the construction of vectors). Taking an example, Diel/Friedel (2007, pp. 127 ff.) estimate the likely costs at 10,000 to 15,000 euros – a figure which shows that the amounts involved could be well within those already being paid for doping.

Whether such an expression vector is administered to an experimental animal or a human may make a significant difference from an ethical point of view, but technically the differences are small (Diel/Friedel 2007, p. 108). An expression vector that works in a mouse could in principle also work in humans, though with incalculable risks and irresponsible risk-taking on the part of the subjects (Section II.3.3). The implementation of individual gene doping according to the above scenario would in no way be subject to logic or to the same timescale as the serious development of gene therapy methods for medical use in humans. In

particular, if we can apply experience with current doping practices – and there is no plausible reason why we cannot – potential side effects, which form the main obstacle (and also the main cost driver) in the development of gene therapies, would play an entirely different (i.e. a wholly subsidiary) role.[4]

A common objection to such scenarios of (individual in the sense described) gene doping in the narrow sense is that the required methods are not validated and specifically that potential performance enhancements have not been demonstrated in healthy subjects, let alone in highly trained athletes. This objection is worthy of consideration. From the point of view of research into the prevention of doping, however, past experience shows us that medical experts have repeatedly refuted the efficacy of certain doping strategies (e.g. in the case of growth hormone), yet athletes availed themselves of those methods for doping purposes anyway (Diel/Friedel 2007, p. 125).

As for the future of doping, including all forms of potential gene doping in the narrow and broad senses, the following will in all probability continue to apply: Athletes who are potential doping candidates and their milieu will not wait until a therapeutic strategy has proven effective in clinical trials. Instead, taking enormous risks, they will first proceed on a trial-and-error basis – presumably with the dramatic consequences sometimes seen in the past (e.g. numerous deaths linked to the use of EPO among cyclists in the early 1990s).

Kekulé (2007, pp. 14 ff.), by contrast, believes it unlikely that the scenario of individual gene doping (in the narrow sense) painted by Diel and Friedel will come to pass in the next decade. In view of the marginal success of reputable gene therapy to date – despite enormous efforts – he thinks illegal doping laboratories are very unlikely to achieve better results. The commercially available kits that Diel/Friedel (2007) regard as sufficient for developing a new individual gene doping method are, he says, unsuitable for the purpose. In particular, so far no suitable genes have been identified for the predicted purpose of individual gene doping. The likelihood that such a gene will be found by an illegal laboratory and not by far better equipped research facilities, he claims, is extremely small. Kekulé (2007) therefore predicts that for the next ten years gene doping methods will arise solely from misuse of the results of reputable research.

4 The basic willingness to experiment with highly risky potential gene doping practices is regularly expressed openenly in internet forums for the bodybuilder scene, and scientists who have published papers on gene transfer in skeletal muscle of animals frequently report that soon after publishing they received offers from healthy individuals to act as test subjects (Diel/Friedel 2007, S. 109).

ACCESS POINTS AND DIFFUSION FACTORS 4.2

The question of when genetic doping strategies can be used for the first time is one that has occupied doping researchers as well as international sports associations and organizations for at least the past ten years, and there is still no clear answer. A basic distinction should be drawn between the use of gene therapy-based methods to modulate gene expression by introducing genetic material (gene doping in the narrow sense) and methods for manipulating gene activity (gene doping in the broad sense). Overall, gene therapy-based methods must overcome much higher misuse barriers, even if, as a whole, the aforementioned scenarios of potential individual gene doping appears plausible (Section II.4.1).

Much more likely is the misuse of the wide variety of methods and pharmaceutical developments for the targeted manipulation of gene activity as a further development of conventional doping with the help of new findings and methods of molecular biology. Here – given the current state of development of various projects in the biotechnology and pharmaceutical industries – it must be assumed that such methods can already be employed for doping purposes, because misusers can find access points in clinical trials, as experience in the field of peptide hormones (EPO, growth hormone) has shown. Diel/Friedel (2007, p. 124) therefore see an acute danger in, for example, methods for manipulating the myostatin signal transduction pathway (Section II.2.1) and for modifying the oxygen-binding capacity of the blood (Section II.2.2). As yet, there are no detection methods for any of these manipulations (Section III).

Based on past experience, elite sport is without doubt a possible point of entry, presumably including the highly commercial areas that are already at the focus of doping control structures (Section IV.2.2) and in which pressure to use undetectable methods is especially great. Here, given the availability of gene doping methods, the key factors determining their spread will be their detectability and risk of discovery (Section V.1).

A second point of entry could be highly ambitious or extreme bodybuilding (Section V.2). Although this sport normally has fewer financial rewards, there is a strong fixation on supernatural physical results and a high motivation for unconditional goal achievement. It is plausible that availability and supposed effect will play a major role. In internet forums of the bodybuilder scene, for example, myostatin inhibitors have long been discussed and requested (Diel/Friedel 2007, p. 104). At the same time, for years a growing number of companies that make dietary supplements have been advertising and successfully selling products specifically pitched as myostatin inhibitors (e.g. by names such as Myostat, Myozap, Myoblast) (Diel/Friedel 2007, pp. 76 ff.). The active components of all these products is an extract from the marine alga *Cystoseira canariensis*. A substance in it (CSP-3, a sulfated polysaccharide) is claimed to inactivate myostatin

protein, a feat that has never been scientifically demonstrated (it has only been shown to bind to circulating myostatin; Ramazanov et al. 2003). The example illustrates how keen interest is in new doping substances even without scientific proof of efficacy. Clinically tested myostatin inhibitors would certainly be even more attractive.

In the long term, however, a significant diffusion pathway could emerge in the field of anti-aging medicine, namely if licensed drugs, e.g. for the treatment of excessive muscle loss, become everyday drugs. Then the main factors determining the rate and extent of their spread will probably be the costs and the health risks involved.

This socially and politically highly pertinent development is being increasingly discussed under terms like »lifestyle drugs«, »routine doping«, and »enhancement«, and will doubtlessly become even more important in the future. Trends to date relate mainly to the field of psychopharmaceuticals, raising prospects of mental performance enhancement and emotional control (TAB 2007 u. Hennen et al. 2008). This alone is relevant to physical performance. However, applications that can be specifically exploited for doping in sport are probably those that are at the fringes of treatment for age-related impairments, e.g. treatment for excessive muscle loss. Because muscle degeneration often sets in as early as middle age, and the question of when it becomes so pronounced that it is regarded as pathological (and then termed *sarcopenia*) cannot be unambiguously answered, the number of potential consumers is enormous, as is the potential volume of sales. In view of the required development investment of several hundreds of million euros, pharmaceutical and biotechnology companies have an interest in marketing their new products as widely as possible. At least since the release of Viagra there has also been an unmistakable trend in Europe towards drug marketing based on claims of potential performance enhancement.

Once effective products of this kind are on the market – here we can draw an analogy to EPO and HGH – they will be used for doping purposes on a grand scale, even if they are only available on prescription. Their spread among athletes, especially in recreational sport, will depend mainly on cost. In principle most of the drugs mentioned in Section II.2 will be no more expensive than the currently available recombinant growth factors. In the case of low-molecular-weight compounds, for example HIF stabilizers (Section II.2.2), the costs may even be lower.

A key issue in the fight against and prevention of doping is whether and how gene doping can be detected. Past experience would suggest that a reactive development of detection methods is extremely unlikely to act as an effective deterrent against doping. This calls for the development of new doping control strategies which will entail not only the consistent predictive monitoring of relevant scientific developments but probably also whole new forms of athlete monitoring. This then is the subject of the following section.

DETECTABILITY AND TEST DEVELOPMENT III.

In the public discussion about the peculiarities and new dimensions of gene doping, the foreseeable difficulties of detection (as a precondition for the imposition of sanctions that will stand up in a court of law; cf. Section IV) are identified again and again as a major problem – not surprisingly, given that the presently available methods and techniques of detection are generally assumed to be inapplicable. There can be little doubt that by themselves, individual sports organizations and anti-doping institutions will not be up to the task of developing valid detection and testing methods for the multitude of potential gene doping methods referred to in the preceding section.

In 2002 WADA set up a »gene doping panel« to deal specifically with the subject of gene doping. The task of this panel is to continuously monitor the findings of relevant research in the fields of gene therapy and gene modulation in terms of their potential for abuse. The fact that WADA included gene doping in its 2003 Prohibited List shows that even at that time it considered gene doping to be potentially important, though it did not name any specific methods of gene doping or provide any information on the availability or use of such methods.

Since 2003 WADA has specifically financed projects aimed at detecting gene doping. Among other things, this can help scientists who are conducting research into gene therapy or gene modulation techniques that have a potential for abuse to take account of this potential for abuse and to develop methods of detection in parallel with their research.[5] The forward-looking approach of such projects constitutes an enormous advance over the situation that prevailed during the development of recombinant peptide hormones[6] and is described in more detail in Section III.1.2.

Nevertheless, detection is no more than a first step and is far from being a reliable test yielding results that constitute legally valid evidence of abuse of a substance or technique for doping purposes. The Chair of WADA's gene doping panel describes the present situation with regard to gene doping and its detection as follows: »The technology is still in its infancy. We are encouraged by the fact that proof can be found that foreign genes have been introduced into a person's body. However, the problem is not just that of developing a test; rather, such a

5 For example, G. Goldspink (UK) is presently conducting research into gene therapy methods of maintaining muscle mass in pathologic conditions and at the same time working on methods of detecting possible abuse (www.wada-ama.org/en/dynamic.ch2?pageCategory.id=347).

6 The performance-enhancing potential of recombinant erythropoietin was known even before the drug was licensed for use, yet only rarely mentioned by doping analysts and scarcely discussed in public during the first few years in which the drug was used.

test also has to be validated to the extent that its results can be presented to a tribunal or court of law and can be shown to be the only plausible explanation for a particular finding. That is very difficult to do and will require a lot more work.« (Friedmann, quoted in Diel/Friedel 2007, p. 140)

The following two sections deal with the fundamental scientific challenges posed by, and the concrete research strategies used to detect, gene doping (Section IV.1) and the criteria for tests that will stand up in a court of law (Section IV.2).

DETECTABILITY 1.

In order for doping manipulations to be successfully demonstrated, three basic conditions must be satisfied (Diel/Friedel 2007, p. 131):

- Information on methods and drugs that may have been used for doping purposes must be available.
- Effective detection methods that are practicable, reliable, and valid must be available.
- A doping control system that applies not only to competitions but also to training and that ideally is adapted to available methods of detection must be in place.

At present, no concrete gene doping methods or substances can be named; rather, only gene doping »candidates« (EPO, VEGF-2, myostatin, etc.) are known (Section II.2). Accordingly, no specific detection methods exist as yet. The following discussion therefore provides only a general summary of basic detection strategies and draws attention to known problems. In some cases reference is made to results obtained using existing doping detection methods, however it must always be borne in mind that future methods of manipulation may be far more complex and refined than those that have been used to date (Section II). The available data do not permit a more detailed exposition than that given here.

Independently of the type of doping, a distinction can be made between direct and indirect methods of detection.

DIRECT METHODS OF DETECTION 1.1

A direct method of detection demonstrates the presence of a prohibited substance or its degradation products (metabolites) or specific markers. In the case of exogenous substances (or substances that differ to a sufficient extent from endogenous substances) (e.g. synthetic anabolic steroids or recombinant protein

hormones with definite and easily detectable structural changes), *qualitative* detection is sufficient in principle. In the case of endogenous substances or substances that are identical to endogenous substances (e.g. human hormones), on the other hand, *quantitative* determination is required in order to demonstrate the presence of nonphysiological concentrations of the substance. More commonly, however, the most that can be obtained is indirect evidence of a nonphysiological deviation from the normal state indicative of an (intended) effect of the administered substance (e.g. an abnormal hematocrit or hemoglobin level in the case of blood doping with EPO). Almost all currently licensed doping tests are based on direct evidence, even though many peptide hormones, for example, have extremely short biological half-lives (of the order of a few days), whereas their effects persist for much longer (Diel/Friedel 2007, p. 130). For this reason alone, in-competition testing is inadequate and must be supplemented by out-of-competition testing (Section IV.2.3).

In gene therapy and gene modulation, attempts are made either to introduce a gene or a gene component into certain cells of the body and there to activate it, or else to activate or inhibit an existing gene or gene component. Where the introduced genetic or gene-regulating element is chemically different from endogenous substances, direct demonstration of it is both possible and qualitatively sufficient. Where this is not the case, quantitative indirect demonstration of a nonphysiological state is required. In relation to gene doping in the narrow sense (as compared to conventional doping techniques), demonstration of gene vectors likewise constitutes only indirect evidence and is subject to the same problems.

DIRECT DEMONSTRATION OF GENETIC ELEMENTS

Given the extremely high sensitivity – and, moreover, the relative technical simplicity – of techniques of DNA and RNA detection as compared to techniques of protein detection, doping by means of genetic elements, i.e. gene doping in the narrow sense, might be expected to be easily detectable. However, many gene doping techniques have characteristics that make detection difficult.

A precondition for direct demonstration of a gene or gene component is that the structure (i.e. in most cases concretely the DNA or RNA sequence) of the introduced material be known. Where a coding gene, e.g. one that codes for a performance-enhancing hormone, is introduced into the cells of a recipient for doping purposes by means of gene transfer, the sequence is necessarily known, since otherwise the gene could not have been synthesized and introduced into the recipient's cells.

The presence of a transferred DNA sequence that was identical with the corresponding DNA sequence of the recipient's genome would be impossible to demonstrate. At least under present circumstances, however, this situation is unlikely to arise for at least two reasons:

Firstly, the DNA sequences that are transferred are mostly sequences from which certain segments (»introns«) that are not required for translation of the genetic information into proteins (Section II.1.2) have been omitted. Techniques for detecting gene doping such as are being developed at University Hospital Tübingen by P. Simon's working group with the support of WADA are based upon demonstration of this difference, e.g. the difference between a possibly transferred EPO gene and the corresponding endogenous gene (see box in Section III.1.2).

Secondly, promoters and other flanking sequences are generally transferred along with the coding region in order to permit integration of the coding region into the recipient's nuclear DNA and bring about intensive protein production. These sequences too are mostly known, though in many cases not in relation to a particular gene. Rather, many such sequences are commercially available »standard elements« the detection of which provides evidence only of some form of genetic manipulation (and thus may constitute indirect evidence in support of an initial suspicion).

There are two purely hypothetical circumstances in which the actual coding sequence might not be known. The first of these would arise with use of a gene whose performance-enhancing effect had not been described in the scientific literature. This is extremely unlikely firstly because of the cost of demonstrating an effect on performance, and secondly because this would be a rare scientific finding (Section II.1.1).

The second hypothetical circumstance is deliberate synthesis of (possibly even more effective) DNA variants of known performance-influencing gene sequences exclusively for doping purposes without publication in a scientific journal or the like. This is unlikely because such altered molecules would generally retain such structural similarity with the corresponding unaltered molecule that existing methods of detection (based either on base pairings or on antibodies) would detect them along with the unaltered molecule. Were they not to do so, the situation would be similar to that which occurred in the BALCO scandal, in which steroids that had been synthesized specifically for doping purposes and whose existence (or use) was completely unknown to doping analysts were used (Diel/Friedel 2007, p. 129).

According to many experts, however, the major obstacle to demonstrating the presence of introduced genetic elements lies less in the difficulty of demonstrating structural peculiarities of molecules as in a lack of *accessibility* or *detectability*. If they are to exert an action, introduced genetic elements almost always have to be inserted into body cells and in some cases even into cell nuclei – and ideally, only into those of certain organs. They pass into the urine at most only in the form of nonspecific degradation products, while their concentration in the

blood also tends to be very low, e.g. because naked DNA is very rapidly broken down. The temporal window available for their detection is thus likely to be far shorter even than that for the detection of peptide hormones – while the alternative of obtaining tissue samples raises a completely different set of (procedural and legal) questions than does the obtaining of urine or blood samples (Section IV.2.3).

DIRECT DEMONSTRATION OF GENE-REGULATING SUBSTANCES

In some cases the chances of being able to directly demonstrate a modulation of gene expression are certainly better if the method or substance concerned is known. For example, administration of a blocking antibody is relatively easy to demonstrate using immunological methods. In principle, this is true also of compounds of low molecular weight (e.g. the HIF stabilizer FG-2216; Section II.2.2) (Diel/Friedel 2007, p. 131 ff.).

Based on the dynamics of the development of gene doping as described in Section II.2 and on the diversity and complexity of the field of gene modulation, however, it must be assumed that techniques of direct demonstration will generally become less important for screening purposes, since it would be far too expensive to test for all possible manipulations. Given, for example, that expression of the growth factor myostatin can be influenced at at least four different levels (transcription, translation, post-translational modification, and intracellular signal transduction; Section II.2.1) by correspondingly different substances, it is far more expedient to demonstrate a nonphysiological change in effect (in this case a fall in myostatin concentration) and only if there are concrete grounds for suspicion to attempt to identify the specific type of manipulation practiced (this is the objective of two projects supported by WADA; see box in Section III.1.2).

This approach is also supported by the pace of development to date. Whereas in the early 1980s the number of methods and substance classes to be considered was still manageable, in the 1990s the number increased greatly due to the abuse of recombinant growth factors. Even painstakingly developed detection methods (such as the test for ingestion of erythropoietin) lost much of their conclusiveness within a few years because of the development of new variants of substances or procedures. For example, it is believed that the drug Dynepo cannot be detected by means of the presently used test for EPO (Diel/Friedel 2007, p. 131 ff.).

INDIRECT METHODS OF DETECTION 1.2

For the reasons stated above, most of the projects presently being supported by WADA are intended to provide indirect evidence of gene doping – by detecting either the gene vectors used or deviations from the normal physiological state of

the organism (Diel/Friedel 2007, p. 132). Whereas up to now very basic, easily determined parameters such as the concentration of red blood cells or of certain steroid hormones have served this purpose, in the future highly differentiated profiles of the most varied molecules, i.e. biomarkers, will need to be determined in blood and tissue samples taken from athletes if evidence of the wide variety of possible manipulations is to be obtained.

DETECTION OF THE TRANSPORT VECTOR

As explained in Section II.1.3, there are many different ways in which a gene or a gene component can be inserted into a cell or cell nucleus. Like detection of the genetic element itself, detection of the vector requires knowledge of its structure (i.e. in this case also, a typical DNA sequence).

So far, attempts at gene therapy have mostly used viral vectors, i.e. viruses a part of whose genetic information has been replaced by therapeutic genes. In principle, these viral vectors can be detected in the same way as normal viruses, i.e. on the basis of the presence of specific antibodies that the immune system produces as a reaction to viral infection and that persist in the immune system for a long time (»immunological memory«, »acquired immunity«). Attenuated human viruses are most commonly used as vectors. However, since organisms are regularly infected with a variety of viruses, the existence of immunological cross reactions will in some cases make it difficult to use the presence of antibodies against viral vectors as specific evidence of gene doping (Diel/Friedel 2007, p. 132).

Moreover, as compared to a »normal«, illness-inducing, infection, viral vectors introduced for the purpose of gene therapy are used in small amounts precisely so that they will not induce an immune reaction. Also, whenever possible they are administered locally, i.e. only to a single organ or tissue (e.g. skeletal muscle), so that they will not induce a systemic reaction in the form of an immune response.

Though detection of viral vectors remains conceivable, detection of nonviral vectors (naked DNA, siRNA) is many times more difficult because of the short biological half-life of nucleic acids. Though these techniques are to a large extent still at an early stage of development, they are becoming increasingly important. Free nucleic acids, especially exogenous nucleic acids, are very rapidly destroyed by the immune system (Diel/Friedel 2007, p. 132).

In the case of techniques in which cells are taken from the body, genetically altered outside of the body (ex vivo), and then returned to the body, it is at present entirely unclear whether, and if so how, evidence of such manipulation can be obtained.

A perusal of the twenty WADA-supported projects on detection of gene doping shows that only one of these is aimed at directly detecting vectors (development of a test for naked plasmid DNA after intramuscular injection; no. 18 in the box in the following section).

DETERMINATION OF NONPHYSIOLOGICALLY ALTERED PARAMETERS

The importance of this approach for future detection of gene doping in both the narrow and the broad sense, and specifically for the development of screening tests for doping, is clear from a consideration of the projects that have been supported by WADA to date (see box). Apart from the project on plasmid detection referred to above, only two of these projects (no. 11 and no. 13) deal with the possibility of detecting transferred genetic elements or concrete genes for IGF or other »candidates«, whereas all the others are aimed at determining whether molecular patterns in the body show characteristic changes after manipulation. In these approaches the entire repertoire of modern biomolecular analysis (DNA and protein arrays, imaging techniques, mass spectrometric methods, high-resolution gel electrophoresis, etc.) is used in order to establish molecular fingerprints (i.e. highly differentiated and highly specific analytical results for DNA, RNA, and protein composition) that occur as a reaction to administration of exogenous substances in order to alter gene activity rather than as a physiological reaction to ingestion of permitted substances and/or use of training methods.

Almost all the research projects of this type that have been undertaken to date are focused on individual »pathways« of manipulation (e.g. manipulation of the synthesis of EPO, growth hormone, or myostatin) and belong in the field of basic research (Diel/Friedel 2007, p. 139). They aim to determine whether »molecular fingerprints« that constitute evidence of manipulation can really be specifically described and reproduced under realistic conditions. Many projects also aim to detect genetic manipulation without thereby providing a specific explanation of a performance-enhancing effect.

WADA-SUPPORTED RESEARCH PROJECTS ON GENE DOPING (STATUS: JANUARY 2008)

1. Goldspink et al. (UK/I): *Manipulation of muscle mass via the growth hormone/insulin-like growth factor axis* (completed)
2. Gmeiner et al. (A): *Application of microarray technology for the detection of changes in gene expression after doping with recombinant human growth hormone* (completed)
3. Friedman/Smith (USA): *Microarray detection methods for GH and IGF-1*
4. Segura et al. (E): *IMAGENE: Non-invasive molecular imaging of gene expression useful for doping control: Pilot study in animals after erythropoietin gene transfer* (completed)

5. Roberts et al. (UK): *The application of cellular chemistry and proteomic approaches to the detection of gene doping*
6. Rupert/McKenzie (CDN): *Development of a prototype blood-based test for exogenous erythropoietin activity based on transcriptional profiling*
7. Ho et al. (A/AUS): *Detection of growth hormone doping by gene expression profiling of peripheral blood cells in humans*
8. Imagawa/Yamamotot (J): *Detection of Hypoxia Inducible Gene Manipulation*
9. Diel et al. (D, Sporthochschule Köln): *High sensitive detection of genetically and pharmacological manipulations of the myostatin signal transduction pathway by multiplex immuno PCR fingerprint analysis*
10. Thevis et al. (D, Sporthochschule Köln): *Analysis of growth hormone isoform profiles in human plasma using proteomics strategies*
11. Giacca et al. (I): *Molecular signatures of IGF-1 gene doping after AAV-mediated gene transfer*
12. Segura et al. (E): *IMAGENE: Non-invasive molecular imaging of gene expression useful for doping control: Extension study in animals after erythropoietin gene transfer* (continuation of no. 1)
13. Simon et al. (D, Universitätsklinik Tübingen): *Sensitivity and specificity of a gene doping test detecting transgenic DNA on a single molecule level in peripheral blood probes*
14. Jorgensen/Kopchick (DK): *Proteomic analysis of serum exposed to GH: a future assay for detection of GH doping*
15. Khurana/Bogdanovich (USA): *Development of tests for detecting myostatin-based doping to enhance athletic performance*
16. Gmeiner et al. (A): *Application of microarray technology for the detection of changes in gene expression after doping with recombinant HGH – part 2* (continuation of no. 4)
17. Schönfelder et al. (D, TU München): *Comparative gene expression profiling in human buccal epithelium and leukocytes after the abuse of beta-2-agonists and anabolic steroids*
18. Snyder/Moullier (USA/F): *A pilot study to develop a reliable blood test for the detection of gene doping after intramuscular injection of naked plasmid DNA*
19. Berg et al. (N): *Genetic regulation of epitestosterone glucuronidation. Consequences for evaluation of urinary T/E ratio*
20. Bhasker (USA): *Pilot project for a WADA bioinformatics core facility*

Source: www.wada-ama.org/en/dynamic.ch2?pageCategory.id=347

Only one of the projects listed above (a standardized test for total myostatin activity; no. 15) names the concrete development of a usable test as one of its objectives. Two of the projects (on HGH/IGF and EPO respectively) have now been completed. In neither case will the results lead to the development of a doping test within the foreseeable future (Diel/Friedel 2007, p. 139 ff.).

In a kind of metastudy or cross-sectional evaluation of the individual projects, one of the projects (no. 20) addresses the question of which of the enormous number of measurement parameters that can be derived from the individual molecular fingerprints of the various potential manipulation techniques could prove

to be especially informative and suitable for use in future routine doping tests. An important question about test practice is touched upon in projects no. 9 and no. 17, among others: Given the legal and ethical difficulty of obtaining biological samples, the question is addressed of whether analysis of easily accessible blood cells and oral mucosal cells (for myostatin expression and for RNA pattern after administration of anabolic agents, respectively) is sufficiently reliable for test purposes. Behind this lies the question of whether other types of tissue sample may be required in the future.

The answer to this question, and to the fundamental question of whether this whole approach will eventually prove successful, is not yet known. From the analytical perspective, however, no alternative is apparent at present.

REQUIREMENTS OF (GENE) DOPING TESTS 2.

Only if the existence of a prohibited substance or method can be demonstrated in principle can a test method for it be developed. The result of such a test is generally the only basis on which doping activity can be established. As this evidence must be able to stand up in a court of law (Section IV.2.1), the standard of proof in all cases is greater than a mere balance of probability but less than proof beyond a reasonable doubt (WADA 2004a, p. 13). According to WADA (2004c, p. 19), the criteria for acceptance as a positive test result must be scientifically well founded. Analytical methods for the detection of substances are therefore based on WADA-accredited, validated methods. The annex to the WADA International Standard for Laboratories (WADA 2004c, p. 57) refers to a series of technical documents, however the documents that describe the validated methods are not freely available. It has not proved possible in the context of the present report to specify the concrete requirements that apply to the quality parameters of tests. Nevertheless, it can be assumed that the following basic quality criteria of medical tests must also be satisfied by doping tests:

- *Validity:* This provides general information about the applicability of a statement. In the present context it means that detection of a certain substance must unambiguously prove that a certain method, and no other, has been used.
- *Reliability:* This is a measure of formal accuracy of measurement and indicates the extent to which a test is free from random errors.
- *Sensitivity*: This is a measure of the sensitivity of a test (true-positive rate, i.e. the proportion of doped people who are correctly identified as such).
- *Specificity*: This is a measure of the correctness of a test (true-negative rate, i.e. the proportion of doped people who are correctly identified as such).

Though the quality criteria that apply to doping tests have yet to be published, they are certainly taken into account in the accreditation procedure. Compliance with quality criteria, which poses a major challenge even with »conventional« doping methods,[7] is crucially important for obtaining proof. Carelessness in this regard could compromise the value of the evidence obtained, since other sequences of events (i.e. other than doping) could then no longer be excluded with a satisfactory degree of certainty. One consequence of this would be an increased number of legal disputes aimed at establishing the validity of test results.

»INTELLIGENT« BIOMONITORING AS A BASIS FOR DETECTING GENE DOPING

Detection strategies employed to date are aimed at providing evidence of the presence of a prohibited substance or method that will stand up in a court of law. For this purpose the evidence must be direct. If the presence of such a substance or its metabolites or markers has been directly demonstrated, the purpose for which it was used – physiological performance enhancement – is immaterial. Even with conventional doping agents and methods, such detection strategies are becoming increasingly difficult and expensive.[8] A possible alternative would be a graduated approach in which standardized analytical measurements of parameters that are relevant to physiological performance would be performed at specified intervals and followed by specific tests only if any of the standard tests yielded abnormal results.

Regular determination of easily measured parameters to detect doping practices is already being discussed and in a few instances even tried. A number of sports organizations, especially in the field of cycling, have discussed the possibility of establishing individual blood profiles. The International Cycling Union (*Union Cycliste Internationale*, UCI) says that it is working with WADA and the French Ministry of Health, Youth Affairs, and Sport to develop a »biological passport« that is to be tested in 2008. Similarly, Germany's National Anti-Doping Agency (*Nationale Anti Doping Agentur*, NADA) has announced that as from 2008 elite athletes from doping-affected sports will be tested several times a year via urine and blood samples (NADA 2007b). In the most favorable case these doping tests can directly demonstrate the presence of a prohibited substance, however even if they do not, monitoring of this kind can reveal a variety of doping-specific abnormalities. Where there are grounds for suspicion, more specific tests can be performed.

7 Though it is generally assumed that athletes use growth hormone illegally to enhance their performance and the structure of this hormone is known, no recognised test for detecting it is available as yet.

8 In Germany the cost of a doping test is already between 350 and 1500 euros, depending on what substances are being tested for.

At present this »monitoring approach« appears to have potential as a basis or preliminary stage for future detection of gene doping by analytically complex regular determination of athletes' molecular fingerprints as envisaged by WADA research projects (Section III.1.2). Unambiguous evidence of manipulation of gene activity obtained in this way would by itself constitute proof of gene doping. For legal reasons, however, it would probably be necessary to demonstrate the specific doping method used in each individual case.

As this type of monitoring could also provide athletes with a means of countering the growing phenomenon of »general suspicion«, most athletes are not likely to object to it in principle. The TAB project was unable to identify any existing »best-practice« examples of, or scientifically validated techniques for, monitoring of this kind (neither the parameters to be measured nor the frequency of measurement have been established on a scientific basis). In the development of a monitoring technique a number of factual, legal, and organizational considerations have to be taken into account, including responsibilities, financing, technical implementation, administration of results, and data protection. In these respects many common features are likely to be found between presently practiced forms of doping and gene doping.

GENE DOPING: PROHIBITION AND CONTROL PROCEDURES IV.

The struggle against doping has for many years been an area of activity not only of sports organizations, but also of political decision makers. Early national initiatives against doping were followed by international attempts to coordinate and unify the actions that were being taken. WADA was established as an independent entity in 1999 with the explicit objectives of harmonizing, coordinating, and advancing the international fight against doping, promoting the development of measures to prevent doping, and thereby protecting athletes' fundamental right to participate in doping-free sport worldwide. It arose from the anti-doping commission of the IOC and is funded by international sports organizations and individual countries. In 2002 WADA formed a »gene doping panel« to deal specifically with this subject. In 2003, in view of the rapid advances that were being made in terms of new medical therapies, gene doping was included in WADA's list of prohibited substances and methods (Prohibited List). This brought gene doping within the ambit of WADA's core document, the World Anti-Doping Code (WADC), which provides the basis for a coordinated fight against doping by sports organizations and public authorities at both international and national levels.

When the WADC and specific standards are incorporated into German law, care must be taken to ensure that the individual's right to self-determination is upheld (Article 2, Paragraph 1, *Grundgesetz*) (German Basic Law, GG). This means that no action may be taken to prevent individuals from jeopardizing their own health. Moreover, freedom of association must be preserved (Article 9, Paragraph 1, GG) and the right of sport to regulate itself and manage its own affairs must be respected unless a criminal offense has been committed. The question of criminal offenses related to doping has long been a matter of controversy and formed the impetus for the introduction of the *Gesetz zur Verbesserung der Bekämpfung des Dopings im Sport* (Law to Improve the Fight against Doping in Sport), which came into force in November 2007. This apportioned responsibilities in relation to doping between sport and the state.

The present section deals in particular with the question of to what extent existing legal norms, testing structures, and sanctions are adequate for dealing with gene doping at present and will prove adequate for doing so in the future. In Section IV.1 the WADC is introduced as the basic set of rules governing doping. Section IV.2 describes the implementation of the WADC in the form of the NADA code governing sports organizations in Germany and the application of the WADC in doping control procedures. Section IV.3 deals with existing legal norms that are applicable to gene doping. The following discussion of legal and

procedural foundations concentrates on aspects that are relevant to gene doping. Where necessary for a better overall understanding, some of these framework conditions are discussed in more detail.

1. THE WORLD ANTI-DOPING CODE: THE INTERNATIONAL LEGAL BASIS FOR SPORTS ORGANIZATIONS AND PUBLIC AUTHORITIES

As it is included in WADA's Prohibited List, gene doping is in principle covered by the World Anti-Doping Code (WADC) (WADA 2004a), which was drawn up and adopted in 2003 and came into force in 2004. A revised version is planned for 2008. More comprehensively and in more detail than does any other set of regulations in sport, the WADC defines the prohibition of doping, violations of this prohibition, and the principles and procedures of testing and sanctions. It points the way to an internationally harmonized set of minimum standards for combating doping. No sets of rules on gene doping that are not based on the WADC and the Prohibited List appear to exist. The WADC with its definitions and resulting set of rules thus forms the primary reference point for the following discussion.

The WADC defines prohibited doping actions, governs the monitoring of observance, and provides a framework for the imposition of sanctions. The enumerative definition of doping in the form of a list of rule violations is preceded by a value judgment of doping that serves as the basis for the prohibition.

DOPING AS BEING CONTRARY TO THE SPIRIT OF SPORT

In the introduction to the WADC the purpose of the Code is stated to be »to protect the Athletes' fundamental right to participate in doping-free sport and thus promote health, fairness and equality for Athletes worldwide« (WADA 2004a, p. 6 ff.). The fundamental rationale for the WADC is said to be to preserve what is intrinsically valuable about sport (referred to as »the spirit of sport«); this value is the essence of the Olympic ideal and accords with WADA's understanding of fairness and honesty in sport. The spirit of sport is defined as »the celebration of the human spirit, body, and mind« and is said to be characterized by the following values:

- »Ethics, fair play, and honesty
- Health
- Excellence in performance
- Character and education
- Fun and joy

- Teamwork
- Dedication and commitment
- Respect for rules and laws
- Respect for self and other participants
- Courage
- Community and solidarity

Doping is fundamentally contrary to the spirit of sport.« (WADA 2004a, p. 7 ff.)

In relation to this link between values, the spirit of sport, and violation of the spirit of sport in the form of doping, Franke (2007, p. 7) makes the following critical comment: »It is unclear whether this additive list of 'sporting values' is arbitrary, in need of further additions, or complete, whether the values are interrelated, whether they form a hierarchy, in what way violating them (e.g. 'fun and joy', 'courage', or 'education') inevitably leads to doping, in what way the individual values or groups of values can be 'linked' to individual actions, intended actions, or consequences of actions in competitive sport, and finally, in what way observance of them in a competitively orientated sports industry that receives media attention can be a realistic basis on which to make moral judgments. Even without a detailed critical analysis in terms of sports ethics, it is clear that attempts, including that of the WADA Code as it now stands, to establish a basis for value judgments have no action-determining consequences and cannot legitimize such a code.«

It may well be true that a mere »list of values« of this kind has few »action-determining consequences« and seems far removed from reality. Precisely in view of the competitive nature of the sports industry, however, the establishment of such a list at least has the virtue of insisting that rules should be made, and violation of rules condemned, on the basis of value judgments. In this way it at least answers – in however rudimentary a fashion – the question of the purpose of prohibiting doping in the sense that prohibited actions are not merely listed, but also related to ethical principles. Even if this relationship is not established by argument, the point is made that the rules of competition are more than just (external) behavior-influencing precepts and prohibitions; rather, they also presuppose and call for (internal) attitudes (such as fairness and solidarity).

DOPING AS A VIOLATION OF RULES

After establishing the ethical rationale for prohibiting doping, the WADC goes on in its Articles 1 and 2 to define doping in very precise terms as a violation of rules. Prohibited actions and violations of these prohibitions, together with prohibited substances and methods, are gathered together in lists (enumerative defi-

nition of doping).[9] Doping – and thus also gene doping as a prohibited method – is defined as the existence of one or more of the listed violations of anti-doping rules (Table 5).

All prohibited substances and methods are explicitly listed in a Prohibited List that is published separately by WADA as often as is necessary (but at least once yearly) (WADA 2008). The primary requirement for inclusion in the Prohibited List is the finding by the Medical Committee of WADA that any two of the following three criteria are met:

- »Medical or other scientific evidence, pharmacological effect, or experience that the substance or method has the potential to enhance or enhances sport performance;
- Medical or other scientific evidence, pharmacological effect, or experience that the use of the substance or method represents an actual or potential health risk to the athlete; or
- WADA's determination that the use of the substance or method violates the spirit of sport described in the Introduction to the Code.« (WADA 2004a, p. 16 ff.)

None of the three criteria (performance enhancement, health risk, violation of the spirit of sport) is sufficient by itself, since, for example, all training measures also have a potential for performance enhancement and health risks can also be associated with other products. On the other hand, a requirement that all three criteria be met would be inappropriate, since evidence of a health risk, in particular, is sometimes difficult or impossible to obtain (WADA 2004a, p. 17).

The decisions made by WADA on the basis of the three criteria are sometimes disputed, but according to the WADC are not negotiable.[10] The medical or scientific evidence on which the decisions are supposedly based are not published. This process of decision-making by the Medical Committee of WADA can therefore not be regarded as transparent or described in sufficient detail as to be traceable.

9 As compared with an imprecise definition of the nature of doping, this »enumerative« definition of doping has the advantage of (legal) precision, however its normative weakness must be borne in mind. Its (hidden) message is that no moral convictions are required in sport. Rather, all that is required is adherence to legally established rules and prohibitions. Moreover, nonprohibited actions and substances – even when they serve the same purpose of performance enhancement – are at least not illegal (Bette/Schimank 2006b, p. 171).

10 Decisions by WADA to prohibit substances and methods are final and cannot be challenged on the basis that the method concerned does not have the potential to enhance performance or does not represent a health risk or violate the spirit of sport (WADA 2004a, p. 17).

TABLE 5 ANTI-DOPING RULE VIOLATIONS AS PER THE WADC

No.	Violation	Evidence	
		Athlete	Athlete support personnel
1	The presence of a prohibited substance or its metabolites or markers in specimens of an athlete's bodily tissues or fluids	DT	
2	Use or attempted use of a prohibited substance or a prohibited method	DT, O(DT)	
3	Refusing, or failing without compelling justification, to submit to sample collection after notification as authorized in applicable anti-doping rules or otherwise evading sample collection	O(DT)	
4	Violation of applicable requirements regarding athlete availability for out-of-competition testing, including missed tests and failure to provide whereabouts information	O(DT)	
5	Tampering, or attempting to tamper, with any part of doping control	O(DT)	O(DT)
6	Possession of prohibited substances and methods	O	O
7	Trafficking in any prohibited substance or prohibited method	O	O
8	Administration or attempted administration of a prohibited substance or prohibited method to any athlete, or assisting, encouraging, aiding, abetting, covering up or any other type of complicity involving an anti-doping rule violation or any attempted violation	O	O

DT Doping test
O(DT) Observation made in connection with doping tests
O Observation, admission, or other evidence admissible in civil law

Source: WADA 2004a, p. 10 ff.

It is immaterial whether use of prohibited methods such as gene doping (Table 5, violation no. 2) enhances performance or not. For an anti-doping rule violation to be committed, it is sufficient that the prohibited method was used or that an attempt was made to use it (WADA 2004a, p. 12).

Table 6 summarizes the substance classes and methods that were classified as doping in 2007 and are wholly or partly prohibited until revision of the Prohibited List.

TABLE 6 SUMMARY OF FORBIDDEN SUBSTANCE CLASSES AND METHODS OF THE WADA PROHIBITED LIST

Substances (classes)		Methods	
S1	Anabolic agents	M1	Enhancement of oxygen transfer
S2	Hormones and related substances	M2	Chemical and physical manipulation
S3	Beta-2 agonists	M3	*Gene doping*
S4	Substances with anti-estrogenic activity		*The non-therapeutic use of cells, genes, genetic elements, or of the modulation of gene expression, having the capacity to enhance athletic performance, is forbidden.*
S5	Diuretics and other masking agents		
Substances (classes) prohibited in-competition		**Substances (classes), prohibited in particular sports**	
S6	Stimulants	P1	Alcohol
S7	Narcotics	P2	Beta-blockers
S8	Cannabinoids		
S9	Glucocorticosteroids		

Source: WADA 2008

The wholly or partly prohibited *substances* within each substance class (Table 6, substance classes S1 to S9) are individually named and distinguishable from one another. The presence of any of these named substances or their metabolites or markers in specimens of an athlete's bodily tissues or fluids is defined as doping. In order to keep up with pharmacologic developments, the entire list of prohibited substances is continuously extended and to an increasing extent no longer specified in unambiguous terms. This is achieved, for example, by means of the formulation »and other substances with a similar chemical structure or similar biological effect(s)« (WADA 2008). In this way a larger number of similar substances are included in the list, however the degree of precision of the list is reduced.[11]

To date, the detailed descriptions of prohibited *methods* included in the list have been less precise and do not constitute a positive list anywhere near as unambiguous as the list of prohibited substances. This is especially true of the description of gene doping. This problem of imprecision could be addressed by introducing subgroups of category M3 (gene doping) of the Prohibited List (Table 6).

11 The possibility therefore cannot be excluded that legal clarification of whether a substance is similar may be required at a later time.

Along with techniques that are classified as gene doping in either the narrow or the broad sense, Section II refers to other relevant lines of research based on modern molecular biological techniques (e.g. hormone or receptor blockade by means of specific antibodies) that can likewise be used to enhance physical performance. In the short term, the risk that such techniques could be abused for doping purposes is even greater than that with actual gene doping in the narrow or the broad sense. Any extension of the substance classes and/or methods in the Prohibited List must also cover these possibilities for abuse.

The basic descriptions of prohibited doping actions are followed by descriptions of control procedures. These are specified to some extent by means of the following separate standards:

- International Standard for Doping Control (ISDC) and International Standard for Testing (IST) (WADA 2004b)
- WADC International Standard for Laboratories (describes the requirements for accreditation as a recognized analytical laboratory) (WADA 2004c)
- International Standard for Therapeutic Use Exemptions (TUE) (WADA 2004d)

Adoption and observance of the WADC is basically voluntary for all organizations. When the WADC was first promulgated, the reactions of international, national, and national organizations ranged from cooperativeness through assertions of independence to rivalry. Despite this, WADA is now becoming increasingly accepted both in the world of sport and at the political level as an independent anti-doping organization. By the end of 2007 more than 570 sports organizations worldwide had adopted the WADC. At the same time the Copenhagen Declaration, which implements the WADC at the political level, had been signed by 191 governments (and ratified by 120 countries).

2. THE NADA CODE: THE LEGAL BASIS FOR SPORT IN GERMANY

In 2003 Germany's National Anti-Doping Agency (NADA), an independent foundation in civil law, took over responsibility for the fight against doping from the joint Anti-Doping Commission (*Anti-Doping-Kommission*, ADK) of the German Sports Confederation (*Deutscher Sportbund*, DSB) and Germany's National Olympic Committee (*Nationales Olympisches Komitee*, NOK), the precursor of the German Olympic Sports Confederation (*Deutscher Olympischer Sportbund*, DOSB). Though organizationally independent, NADA recognizes the umbrella role played by WADA and adapts the latter's regulations to German circumstances. The form of the WADC that applies to Germany is the

NADA Code (the set of anti-doping rules that applies to German sport; NADA 2006b, p. 7), which was drawn up by NADA in conjunction with the DSB and the NOK. It adopts both the WADA list of doping violations (Table 5)[12] and the WADA Prohibited List (Table 6) in its entirety. As a result, the NADA Code likewise defines gene doping as a prohibited method and specifies anti-doping rule violations.

The freedom of association referred to above allows sports organizations to determine their internal organizational structure within the framework of civil law and to monitor compliance therewith. They are therefore at liberty to incorporate or not to incorporate the NADA Code into their internal organizational statutes. The Federal Government nevertheless makes its support of sport conditional upon incorporation of the NADA Code into valid statutes of association. In 2007 the Federal Ministry of the Interior established a »Special Doping Testing« (*Sonderprüfung Doping*) project group for all grant recipients (31 umbrella organizations, 20 Olympic support centers, and four federal performance centers) and came to the conclusion that in most cases legal incorporation of the NADA Code into sports organizations' statutes of association was still causing the organizations major problems (BMI 2007b, p. 15).[13] Measures were therefore agreed to help rectify remaining deficiencies as promptly as possible.

The situation of sports organizations that are not supported by the Federal Government is even less clear. In principle, even fitness studios could act in accordance with the rules of the NADA Code, however no examples of this could be found.

STATUTES OF ASSOCIATION OF SPORTS ORGANIZATIONS 2.1

Sports organizations that observe the NADA Code have defined doping, and thus also gene doping, as behavior that is contrary to rules and consequently forbidden. The corresponding catalog of prohibitions must be incorporated into the organization's statutes and rules of association and/or employment contracts, is applicable only within the organization concerned, and within the or-

12 The NADA Code also prohibits participation or attempted participation in competition during a ban imposed by an international or national sports association (NADA 2006b, p. 11).

13 In a report commissioned by NADA, six federal umbrella associations of sports organizations were checked for incorporation of the NADA Code into their statutes: »A provisional finding is that only two associations have adequately incorporated the NADA Code into their statutes of association; the reporting experts consider that in the case of three associations an intention to incorporate the NADA Code is apparent but the actual incorporation shows deficiencies; and according to the findings of the legal expert report, in the case of one association incorporattion of the NADA Code is inadequate.« (BMI 2007b, p. 16)

ganization applies primarily to athletes but also to persons in the milieu of athletes.

(GENE) DOPING – RULE-VIOLATING BEHAVIOR BY AN ATHLETE

As the doping violations specified in Table 5, along with the associated doping controls, impinge upon the individual rights of the athlete, they must be individually specified (Haas 2002, p. 20, from Simon et al. 2007, p. 18). It is not sufficient to prohibit doping in general. The description of doping behavior associated with the *substances* included in the Prohibited List (Table 6, substance classes S1 to S9) should satisfy this requirement. Gene doping was included in the Prohibited List as a precaution in the absence of concrete evidence of its use. As even among experts there is no consensus as to which techniques and methods belong in the category of gene doping (Section II.1), Simon et al. (2007, p. 18) question whether the term »gene doping« can be regarded as sufficiently precise. In the future gene doping will need to be more precisely defined in order to satisfy the principle of clarity and definiteness. However, this will not be possible until concrete substances and methods of abuse emerge (Section II.3).

The principle of »no punishment without guilt« applies also to doping practices in sport. This means that the existence of *objective* and *subjective elements* of a rule violation must be demonstrated (Simon et al. 2007, p. 25).

OBJECTIVE ELEMENTS OF RULE VIOLATION

The sports organization bears the burden of proof that a prohibited substance, its metabolite, or marker is present in the body of the athlete, that a prohibited method has been used, or that some other violation of doping rules has been committed. Any form of evidence permitted by the code of civil procedure, including an admission, is admissible (NADA 2006b, p. 12). In most instances proof is established on the basis of doping tests for which, according to the International Standard for Testing (IST) (WADA 2004b), the required standard of proof is a sufficient degree of certainty (Section IV.2.2).

Essentially the same procedure is likely to apply to the demonstration of gene doping. Where proof is to be obtained by means of a doping test and a doping sample therefore needs to be collected, the right of an association or federation to determine its internal organizational structure must generally be weighed against the individual rights of the athlete. When these two interests are weighed against each other, the proportionateness of an examination must be considered (Simon et al. 2007, p. 19 ff.).

As a noninvasive intervention, collection of *urine samples* for the purpose of doping control is considered in sports law to satisfy the principle of proportion-

ateness. A control procedure is standardized and fairly well established (Section IV.2.3). However, it seems unlikely that gene doping could be detected by means of urine samples (Section III.1). As an invasive intervention, collection of *blood samples* is regarded as a substantial infringement of individual rights and according to most legal opinion in Germany satisfies the principle of proportionateness only when urine samples are not sufficient for detection. In addition, the athlete must have freely consented or contractually obliged himself/herself to have blood samples taken. Specific procedures are described in the NADA Code (NADA 2006b, p. 59 ff.), but not in the International Standard for Testing (WADA 2004b) or the International Standard for Laboratories (WADA 2004c). As with urine samples, however, at present it seems rather unlikely that gene doping could be detected on the basis of individual blood samples (Section III.1).

Should it turn out that gene doping can be detected only by means of *tissue samples*, a largely new legal field will arise, since collection of tissue samples is regarded as an even more invasive intervention than collection of blood samples. The legality of collecting tissue samples would have to be assessed on the basis of the same principles, i.e. a legitimate purpose, suitability, need, and proportionateness would all have to be present. In addition, the accredited persons who were to collect the samples would have to possess the necessary technical qualifications and equipment. The site of sample collection would be subject to entirely different requirements. Existing regional variations in terms of observance of standards would tend to become more pronounced, and control of the controllers would become more important (Section IV.2.3).

Along with the permissibility of sample collection (e.g. blood and tissue samples), the permissibility of novel specific diagnostic tests for the detection of gene doping will need to be considered at the appropriate time. Procedures and analytical techniques would be permissible if they provided proof that could stand up in court (Simon et al. 2007, p. 23).

SUBJECTIVE ELEMENTS OF RULE VIOLATION

Each identified violation must give rise to a sanctions procedure in which subjective guilt influences the severity of the sanction. Responsibility for this is borne either by the organizer of the competition or by the national association, which in this case refers the matter to an internal disciplinary organ or a court of arbitration (NADA 2006b, p. 31).

Where, on the basis of a doping test, a sports organization suspects with a sufficient degree of certainty that a violation of anti-doping rules has been committed, it is not required to provide proof of culpable behavior on the part of the athlete concerned. The athlete can rebut this reasonable suspicion by demonstrating how the prohibited substance came to be in his/her body and that the violation occurred without culpability on his/her part. The re-

quired standard of proof is a high probability (*überwiegende Wahrscheinlichkeit*) (NADA 2006b, pp. 12 and 34).[14]

(GENE) DOPING: RULE-BREAKING BEHAVIOR BY PERSONS WHO FORM PART OF AN ATHLETE'S MILIEU

Persons who form part of an athlete's milieu are classified as either athlete support personnel[15] or other association employees. Only athlete support personnel are fully subject to the NADA Code, since this was designed exclusively for questions of sports law. Anti-doping regulations applicable to association employees should be agreed at the level of labor law (BMI 2007b, p. 27).

Tampering or attempted tampering with any part of doping control, possession, trafficking, administration or attempted administration of doping agents, and any other participation in prohibited acts are prohibited both by the WADC and by the NADA Code (Table 5). It is true also of these violations that sports organizations bear the burden of proof, that evidence permitted by the code of civil procedure is admissible, and that the sports organization must demonstrate *objective elements* of a violation as well as *subjective guilt*. Where a sports organization succeeds on this basis in demonstrating culpable participation in a prohibited act, it can impose sanctions on persons who form part of an athlete's milieu in accordance with the law of associations (provided that the person concerned is a member of the sports organization).

No standardized procedures for demonstrating culpable participation in a prohibited act exist. Some of the offenses specified in the NADA Code are also governed by public law (Section IV.3). The Federal Government stipulates that when a sports organization that it supports becomes aware of a positive analytical result in an athlete it must check for involvement of any athlete support personnel and where there is an initial suspicion of criminal behavior must inform the responsible public prosecutor's office of this fact (BMI 2007b, p. 78).

DOPING CONTROL PROCEDURES 2.2

Doping controls need to demonstrate the presence of a prohibited substance or its metabolites or markers in specimens of an athlete's bodily tissues or fluids, or the use of a prohibited substance or a prohibited method, with a sufficient de-

14 The Federal Supreme Court (*Bundesgerichtshof*) came to a similar decision: In order for *prima facie* evidence of doping to be overturned it is sufficient that there exist a serious possibility of an atypical sequence of events (Simon et al. 2007, S. 27).

15 »Athlete support personnel: any coach, trainer, manager, agent, official, team member, or medical or paramedical personnel who works with or treats athletes who participate in or are preparing themselves for sports competitions.« (NADA 2006b, p. 46)

gree of certainty. They are the most important source of proof of violations of the NADA Code. From the perspective of sports law, a rebuttable presumption of a violation of anti-doping regulations must be established (*objective element)*. This objective is linked to other objectives such as deterring athletes from doping and demonstrating to the public that sports organizations are fighting doping.

According to the NADA Code, the doping control process comprises

- organization of doping tests,
- sample collection and handling,
- laboratory analysis, and
- hearings, appeals, and imposition of sanctions (NADA 2006b).

Many parts of the sport-internal doping control process that are specified by the NADA Code and the WADA standards could in principle also detect gene doping – assuming that it is detectable at all (Section III). In some respects, however, the existing procedure based upon these codes is already coming up against its limits, or else gaps or needs for clarification are becoming apparent.

Given the crucial role that doping testing and sanctions structures play also and particularly in gene doping, they are described in somewhat more detail in the following section.

ORGANIZATION OF DOPING TESTS

Doping tests were originally performed only during competitions, however from the second half of the 1980s out-of-competition testing was gradually added. In addition, tests to qualify an athlete to compete are now being performed occasionally. In principle, in-competition testing and the financing thereof are the responsibility of competition organizers, whereas out-of-competition testing is the responsibility of sports associations. According to the WADC this responsibility can be transferred to national anti-doping agencies. In Germany such a transfer of responsibility for out-of-competition testing has largely occurred in the case of sports organizations that have adopted the NADA Code.

OUT-OF-COMPETITION TESTING

The NADA Code and the WADA International Standard for Testing (IST) specify the procedure for out-of-competition testing in detail. According to the IST, out-of-competition testing should be performed only in a »testing pool« of elite athletes. Individual sports associations nominate their national- and international-level athletes for this testing pool. No criteria for identifying such elite athletes on an internationally uniform basis have been established. As a result, there are substantial international differences in this regard.

Along with a need to increase the number of doping tests performed, other major challenges are to eliminate errors in the performance of tests and to increase the efficiency of testing. The IST states that in order to be able to test efficiently for doping, national anti-doping agencies need to develop a test distribution plan that takes into account at least the potential doping risk and possible doping patterns in each type of sport based among other things on the physical demands of the particular sport, the possible performance-enhancing effects of doping, and available research on doping trends (WADA 2004b, p. 13).

In order to comply with this requirement, NADA has announced its intention of introducing »intelligent« doping testing in 2008. To this end athletes are to be divided into the following groups and tested more intensively during periods of high doping risk as indicated by their competition plans (NADA 2007b):

- National testing pool (NTP): generally A-squad athletes[16], national A teams, athletes in the international testing pool, and members of the top team for the Olympics. According to NADA this group includes about 1500 athletes, in whom a total of 6000 tests are to be performed in 2008. NTP athletes are subdivided into three risk groups. Athletes in the highest risk group are each to undergo five urine tests and two blood tests, those in the second risk group four urine tests and one blood test, and those in the third risk group one urine test (BMI 2007b, p. 105 ff.).[17]
- General testing pool (*Allgemeiner Testpool*, ATP): From 2008 this pool is to be further subdivided into ATP I (B-squad athletes of Olympic associations and A-squad athletes of non-Olympic associations), comprising about 2000 athletes, who are to undergo a total of 1500 doping tests in 2008, and ATP II (C-, D/C-, and D-squad athletes), comprising about 4500 to 5500 athletes, who are likewise to undergo a total of 1500 doping tests in 2008 (BMI 2007b, pp. 105 ff.).

In order to permit out-of-competition testing of athletes with as little notice as possible, athletes' whereabouts must be known. The IST states that athletes are obliged to file their whereabouts information and keep this information current at all times. NTP athletes have a 24-hour deadline for notification of change of whereabouts, ATP I athletes a 72-hour deadline, and ATP II athletes no such deadline (BMI 2007b, pp. 105 ff.). The imposition of these deadlines for notification presupposes a forwarding of personal data by athletes that can be regulated only by means of a voluntary undertaking by the individual concerned. Failure to meet these deadlines for notification constitutes a doping violation in accordance with the WADC and the NADA Code (Table 5).

16 Each sports association assigns athletes to a particular squad on an individual basis and exclusively on the basis of performance figures.

17 The factual bases on which identification of periods of high doping risk and risk groups of athletes are based are not specified.

At least for the national testing pool, NADA is at present switching from its own data collection system (»NADA Xtra.NET«) to the database management tool developed by WADA (»ADAMS«). Discussions are being held about compliance with nationally applicable requirements for data protection. No more precise information about this is available at present.

NADA's new system of intelligent out-of-competition testing can be expected to close a number of loopholes that have existed up to now. As before, however, participation in this system is basically voluntary, however nomination for the 2008 national Olympic team presupposes participation. Federal support for sport, which flows via the sports associations, is likewise tied to participation in this out-of-competition testing system. Nevertheless, this procedure does not extend to all branches of sport. Most sports organizations that are not members of the German Olympic Sports Confederation (DOSB) and/or that fall within the realm of professional sport do not participate.

The need for specific control concepts, efficient doping tests, and concepts for monitoring will become greater as detection of gene doping drives the cost of testing even higher. One major challenge will be how to include special risk groups for gene doping in the system (Section V.1).

IN-COMPETITION TESTING

Each organizer (mostly national sports associations), on the basis of its individual position, experiences, and financial possibilities, independently determines the extent and type of in-competition testing. The extent of testing ranges from complete absence of in-competition testing (a few professional sports events, but also most regional competitions) to full testing of prizewinners and random testing of other participating athletes. Testing is generally performed immediately after competitions and in some cases also before competitions (in which case it overlaps with out-of-competition testing). As with out-of-competition testing, the general structure of testing and the testing procedure can be specified by reference to the NADA Code and the IST, however these documents make no recommendations as to the extent of testing[18] or specific substances to be tested for.

Though the organizer is in principle responsible for the planning and performance of testing, WADA and NADA offer assistance internationally and in Germany, respectively. The Federal Ministry of the Interior's »Special Doping Testing« (*Sonderprüfung Doping*) project group already recommends that in the present situation testing should be entrusted to NADA (BMI 2007b, p. 8). NADA itself states that in the medium term it would be able to take on this responsibility (BMI 2007b, p. 42). Joint development of concepts for in-competition

18 As organizers generally allocate funds for in-competition testing on an annual basis, increased costs per test generally lead to a reduction in the extent of testing. This has already had the result that testing can only be performed at the national level.

testing by competition organizers and anti-doping organizations would also be beneficial in relation to possible gene doping.

In a few cases, organizers of endurance sports competitions make permission to participate conditional upon compliance with norms for certain performance-relevant parameters – such as the hematocrit or hemoglobin[19] level of the blood – that can be determined at relatively low cost in all competition entrants. This approach is technically and analytically simpler than the use of tests that must provide evidence of doping that will stand up in court. It is not intended to detect a multiplicity of possibly used prohibited substances or methods. If the values obtained are marginally above the specified limit, the athlete is not allowed to participate but is not at risk of any other sanctions. Temporary »protective bans« of this kind are intended to protect the athlete from possible health damage and the competition from a loss of credibility. In conjunction with other methods, this approach could prove useful for combating new forms of doping.

Even today, any doping test that can demonstrate doping violations with a satisfactory degree of certainty is logistically and analytically complex and therefore expensive. The planning of doping controls is rendered more complex by the need to take account of each athlete's pre-competition training plans and by the limited time frame available for detection of the various substances. In the event that individual tests cease to be sufficient by themselves for the detection of gene doping, but instead more or less regular measurement of yet-to-be-determined performance-relevant parameters becomes necessary, the level of complexity will increase even further. It is doubtful whether all countries will be willing or able to go down this road. If they are not, national differences in terms of control of doping violations will become even more pronounced than they already are.

COLLECTION AND HANDLING OF DOPING SAMPLES

A sample as per the WADC is any biological material that is provided by or collected from athletes for the purposes of doping control. In practice, urine and blood samples are virtually the only types of sample used at present.

According to the WADC, only accredited persons or companies may perform doping tests. In Germany the organizers of national competitions often accredit these persons or companies themselves. To date very little use has been made of the possibility of having the tests performed by NADA (BMI 2007b, p. 40 ff.). The WADC stipulates that in the case of out-of-competition testing the planning

19 Hematocrit: red blood cells as a proportion of total blood volume; hemoglobin level: the amount of the oxygen-carrying molecule hemoglobin as a proportion of total blood volume.

of random testing must be kept organizationally and legally separate from the collection of samples.

In Germany legally correct sample collection in the world of sport is at present offered essentially by only one independent, specialized company. This company performs this service both in Germany and abroad and at present employs about 70 freelance anti-doping testers (PWC 2008). NADA uses this company exclusively. This market segment is similarly uncomplicated worldwide. In each country there is a more or less large group of testers operating in a variety of corporate structures. There appears to be some international cooperation. Quality assurance can be based upon international certification 9001.2000 of the International Organization for Standardization (ISO), however this is not an absolute requirement at present.

Anti-doping testers who have been working for many years assert that the quality of sample collection has improved greatly over the past 20 years (Steiner 2007; Teufel 2006). Despite this, not all athletes are tested with the same degree of precision either in Germany or abroad, and in many places compliance with standards is still inadequate. Were consideration to be given to obtaining blood profiles or genetic profiles of individual athletes as part of possible testing for gene doping, the demands placed upon testers would most definitely increase. They would then need medical training and their equipment would need to be adapted to perform an increased number of invasive interventions.

TRANSPORT OF DOPING SAMPLES

Following correct sample collection, the biological material is divided into two samples of equal size (A- and B-sample), sealed, anonymized, encoded, and labeled with the address of the entity commissioning the test. According to the NADA Code, details of the transport of urine samples need to be recorded only formally at present, and no time or temperature standards are stipulated (NADA 2006b, p. 52). According to Kindermann/Steinacker (2007), as a result of the present transport arrangements »in more than 50 percent of all urine samples no hormone at all is detectable, i.e. the samples are unsuitable for their purpose.« Even now they require cold transport and storage. In the case of blood samples this is stipulated by the NADA Code (NADA 2006b, p. 59).

The transport and storage requirements depend upon the biological material and the substance to be detected. Where a substance is to be detected via RNA or DNA components, which are more stable than many substances and their metabolites, no additional transport or storage requirements are expected. However, precise statements cannot be made until detection methods have been developed (Section III).

LABORATORY ANALYSIS

The WADC stipulates that the laboratory analysis must also be kept organizationally and legally separate from the planning of random testing and the collection of samples. The result of the laboratory analysis of the bodily tissue or bodily fluid sample is the most important, and normally also the only, item of evidence that supports the presumption of a violation of a doping prohibition. For this reason the requirements that apply to the various laboratories are stipulated by means of a special standard and the analytical procedures are precisely defined.

In order to perform detection procedures, laboratories require a special WADA accreditation. The accreditation process is stipulated via the standard for doping laboratories (WADA 2004c). Not all of the 34 laboratories that are accredited worldwide (Section IV.2.3) are technically equipped to perform all procedures. For the detection of gene doping the requirements placed on laboratories will become even more demanding. In principle, other, unaccredited laboratories can perform specific, legally sound analyses in accordance with the ISO certification both neutrally and correctly. Without accreditation, however, they may be commissioned to perform tests to detect doping only in countries that have no accredited laboratory. The question of whether only WADA-accredited laboratories or also specifically ISO-certified laboratories will be allowed to perform gene doping tests will need to be decided at the appropriate time.

Laboratory analyses that can provide evidence of a particular doping violation that will stand up in court are based on standardized and scientifically tested analytical procedures that have been authorized by WADA (WADA 2004a, p. 19). The same will be true of tests for gene doping (Section III). In order not to facilitate the development of doping strategies that take account of the detection possibilities of tests, the descriptions of the various analytical procedures that are used have not been released into the public domain. This policy of secrecy means that accredited laboratories enjoy a monopoly of information. Many laboratories that perform standardized doping analyses simultaneously conduct research into new methods of detection. The greater the monopoly of information, the higher is the value of the information and the greater are the possibilities for, and risk of, abuse. Kekulé (2007, p. 25 ff.) expresses the view that restriction of access to certain information is unlikely to prevent the spread of specialized knowledge. Rather, restriction of access creates possibilities for the development of lucrative black markets in which doping networks (e.g. such as that described in Donati [2007]) act as buyers and distributors.

In response to this situation WADA has developed a code of ethics for doping control laboratories on the basis of which directors and employees undertake not to pass on to outsiders any information that could facilitate doping (WADA

2004c, p. 56). The extent to which this code of ethics and monitoring of laboratories by WADA can prevent possible abuse of knowledge worldwide is an open question. A possible – though also problematic – alternative would be transparent description of test procedures. This too could remove the basis for the black market in information so that individual employees of laboratories would have no incentive to pass on their knowledge illegally. In this way the principle of the *transparent athlete* would be extended into a principle of the *transparent laboratory*.

According to the NADA Code (NADA, 2006b, p. 45), samples of bodily tissues or bodily fluids that are collected on instructions from NADA are the property of NADA. The sample material *may*, and all associated documents *must*, be retained until the limitation time of eight years (even in the case of tests that had a negative result). NADA has the right to examine these samples again. The question of ownership and rights in relation to samples that were not collected on instructions from NADA (in-competition tests) was not considered in the present TAB project, however this question will need to be clarified at some time in the future. As far as gene doping is concerned, the prospect of analysis at a later time could have a deterrent effect, since it would mean that »abusers« could be retrospectively exposed and penalized in a few years' time on the basis of prohibitions that are in place today.

In Germany the analytical laboratory reports any positive test results (results that justify a suspicion of doping actions) obtained in out-of-competition testing only to NADA, in its capacity as the commissioner of the test. NADA then forwards this information to the sports association. In the case of in-competition testing the competition organizer and NADA are informed.

THERAPEUTIC USE EXEMPTIONS

Before the sports association concerned comes to a decision about sanctions, consideration is given to whether a therapeutic use exemption (TUE) is present. TUEs permit athletes and their treating physicians to use prohibited agents and methods for the treatment of illness. TUEs are an example of the growing complexity of the doping question. This complexity has now reached the point at which

- WADA has developed its own standard containing criteria for assessment, forwarding of information, composition of the group of physicians, and the recognition procedure, and
- only accredited persons (TUE Committee) can now make decisions on the issue of a TUE.

The number of athletes in Germany with a TUE is growing. In 2004 a total of 2462 athletes in Germany had a TUE, in 2005 the number was 2880, and in

2006 3513 (NADA 2005, 2006a and 2007a). Without going into the details of this complex subject here, it is worth pointing out that TUEs illustrate the fact that the increasing number of possibilities offered by modern medicine make it increasingly difficult to define the limits of what is permissible, express these limits in terms of procedural norms, and implement such norms in a practicable way.

In general, TUEs can be issued only for licensed substances and methods. A substance or method the abuse of which is classified as gene doping (Section II) cannot be the subject of a TUE unless it is licensed for use in the country concerned. Especially in the field of anti-aging therapies, however, problems of differentiation may arise in relation to licensing (Sections II.4.2 and V.2.2).

DECISION-MAKING AND IMPOSITION OF SANCTIONS

Where a positive analytical result is obtained and there is no TUE, the commissioner of the test checks the correctness of the testing procedure; the athlete is then informed and has the opportunity to respond in writing. Where the positive analytical result was obtained in an out-of-competition test, the athlete can be suspended (temporarily barred from competing). A positive analytical result obtained in an in-competition test leads automatically to disqualification and annulment of competition results. The athlete has the right to have the B-sample analyzed in order to rebut the result of the analysis of the A-sample (NADA 2006b, p. 27 ff.). Where there is no TUE, analysis of the B-sample confirms the result of analysis of the A-sample, or the athlete opts not to have the B-sample analyzed, a process is initiated. In Germany responsibility for this lies with the relevant national sports association or the competition organizer, provided that the latter has not assigned this task to NADA (NADA 2006b, p. 26). As from 2008 it will also be possible to commission the German Sports Arbitration Tribunal (*Sportschiedsgericht*), operated by the Cologne-based German Institution of Arbitration (*Deutsche Institution für Schiedsgerichtsbarkeit e.V*), to undertake this result management.

A hearing is then held by the responsible sports law tribunal of the sports association concerned. At this hearing the affected athlete has the opportunity to use other individual means of demonstrating the occurrence of a different sequence of events and can explain how the prohibited substance came to enter his/her body. If he/she is unable to rebut the presumption that he/she committed the violation at least as a result of negligence, a sanction is imposed – in Germany on the basis of the NADA Code. A synopsis of the catalog of measures specified in the NADA Code, starting with annulment of results and disqualification from competing, is shown in Table 7.

TABLE 7 VIOLATIONS AND RANGE OF SANCTIONS SPECIFIED IN THE NADA CODE

Violation	Proof	Culpability	1st violation (period of ineligibility)	2nd violation (period of ineligibility)	3rd violation (period of ineligibility)	4th violation (period of ineligibility)
1) Presence of a prohibited substance or its metabolites or markers in the doping sample 9) Participation in competition despite suspension	Doping test (observation in conjunction with doping test)	culpable	two years	lifelong		
		neither intentional nor negligent	min. one year	min. eight years		
		not culpable	min. one year	min. eight years		
2) Use or attempted use of prohibited substance(s) or method(s)		culpable	two years	lifelong		
		not culpable	min. one year	min. eight years		
3) Refusal or failure to submit to sample collection		culpable	two years	lifelong		
5) Tampering or attempted tampering with doping control		neither intentional nor negligent	min. one year	min. eight years		
4) Violation of availability rules (out-of-competition testing)		culpable	public warning	min. three months	one year	two years
6) Possession of prohibited substance(s) or method(s)	Observation/admission	culpable	two years	lifelong		
		neither intentional nor negligent	min. one year	min. eight years		
7) Trafficking in prohibited substance(s) or method(s)		culpable	min. four years to lifelong			
8) Administration or attempted administration of prohibited substance(s) or method(s) or other complicity		not culpable	ineligibility can be revoked			

Ineligibility of an athlete means that he/she is barred for the specified period of time from participating in any capacity in any competition or activity (other than preventive or rehabilitation measures) of any national or international sports organization.
Ineligibility of athlete support personnel means that they suffer withdrawal of accreditation, i.e. are prohibited from participating in any (supporting) capacity in any competition or performing any official function for the sports association or federation or the athlete. Athlete support personnel are referred to in the NADA Code only in connection with trafficking, administration or attempted administration of prohibited substances, or other complicity.

Source: NADA 2006b, p. 35 ff.

The catalog applies also to doping violations committed by persons in the athlete's milieu. Only a partially regulated procedure is available for detecting doping violations by persons in the athlete's milieu. This states that whenever an athlete is under reasonable suspicion a check must be made for involvement of any persons in the athlete's milieu. Where there is sufficient suspicion that an offense against public law has been committed, the sports association must inform the public prosecutor's office of this fact (NADA 2006b, p. 37).

Based on the present legal situation, this catalog of measures is fully applicable also to gene doping, assuming that it can be detected. As the effect of some gene doping techniques is presumed to be very long-lasting, account must be taken of the fact that the effect could persist beyond a period of ineligibility. Overall it must be expected that with gene doping the entire doping control process (both objective elements of a violation and subjective guilt, e.g. of an athlete) will impose greater requirements on sports jurisdiction.[20]

LIMITS TO THE DOPING CONTROL PROCESS 2.3

The WADC and the NADA Code contain the rules for doping control processes at the international and German levels, respectively. Each sports organization is responsible for incorporating these rules into its internal regulations and for implementing these. The extent to which this has occurred varies between and within countries. According to the WADC, independent national anti-doping organizations (NADOs) should play a leading role in implementing the rules in their respective countries. Of the 202 countries that presently participate in the Olympic Games, 68 have an NADO that recognizes the WADC and 19 have an NADO that does not recognize the WADC. In Germany, NADA states that by 2008 it will be able to offer an extensive range of services, especially with regard to out-of-competition testing as per the IST.

Testing of doping samples should be performed only in accredited analytical laboratories. In 2007 there were 34 accredited laboratories worldwide, of which 20 were located in Europe, five in Asia, three in North America, three in Central and South America, two in Africa, and one in Australia (WADA 2007).

On the basis of the data published to date it is scarcely possible to draw comparisons (in terms of activity and effectiveness) even between countries that have an independent NADO and recognize the WADC. Isolated data, e.g. for 1997 (dsj

20 Expensive lawsuits could occur. This could become a problem especially for sports associations with a small budget. WADA already refers to this problem in relation to conventional doping (WADA 2004a, p. 11).

2004) and for 2000 (KPMG 2002), have been compared.[21] Because of a lack of background information, however, such comparisons are of very limited value. And because of the different ways in which reports are prepared in different countries, even detailed figures on doping are generally not directly comparable. Based on Striegel (2007) – and with reservations – all that can be said is that testing is performed about three times more frequently in Germany and the United Kingdom than in the USA and 2.5 times more frequently in Switzerland than in Germany (in relation to the population of these countries).

Since NADA commenced its work in 2003 it has issued an annual *Dopingbilanz* (doping report). This relates the number of tests performed to the number of rebuttable reasonable presumptions of a violation of anti-doping regulations (based on doping tests, i.e. A-samples that tested positive and other violations such as failure to submit to sample collection).[22] In a proportion of the A-samples that tested positive there was a TUE. In 2004 this was true of 22 cases, equivalent to 24% of the reasonable presumptions of a doping violation (out-of-competition and in-competition testing considered together). The corresponding figures for 2005 and 2006 were 40 cases (37%) and 42 cases (42%), respectively (NADA 2005, 2006a, and 2007a).

Table 8 provides a summary of the tests analyzed by the two accredited laboratories in Germany in the years 2004 to 2006 and the sanctionable results of these tests (positive A-sample and violation of doping control rules) separately for out-of-competition and in-competition testing.

Though it is generally not doubted that doping is started in the out-of-competition phase in order to achieve a performance-enhancing effect during competition, the present control process cannot detect out-of-competition doping in the same way as it can detect in-competition doping. The proportion of positive A-samples found in out-of-competition tests was between 0.25% and 0.4%, compared to between 1.2% and 1.3% in in-competition tests. If these published annual doping reports are complete, four to five times as many positive A-samples are found in in-competition tests as in out-of-competition tests. There are many possible reasons for this that are not apparent from the data. It remains to be seen whether and to what extent the NADA concept of intelligent out-of-competition testing will alter this situation.

21 According to *dsj* (*Deutsche Sportjugend* [»German Sports Youth«]) (dsj 2004, p. 15), in 1997 the number of positive doping samples as a proportion of all samples varied from more than 4% (doping laboratories in Montreal, Ghent, and Paris) to 0.5% and less (doping laboratories in Oslo, Seoul, Kreischa, and Rome). Data published by the accountancy consultancy KPMG (KPMG 2002, p. 85) lie within the same range (France 3.7%, United Kingdom 2.5%, Denmark 0.6%).

22 In accordance with the NADA recommendation, the 2003 doping report is not used as a basis for comparison, since it was significantly influenced by changes in the legal framework that resulted from introduction of the WADC (NADA 2005)

TABLE 8 DOPING TESTS AND SANCTIONABLE RESULTS REPORTED BY NADA FROM 2004 TO 2006

Year	Organization	Out-of-competition tests			In-competition tests		Other*
		Number	A-sample positive	Other	Number	A-sample positive	
2004	NADA	4282	9 (0.2%)	2 (0.05%)	–	–	
	WADA	64	–	–	–	–	
	Assoc.Germany	–	–	–	–	53 (1.5%)	
	Abroad	71	–	–	898**	5 (0.6%)	
	Total	*4417*	*11 (0.25%)*		*4468*	*58 (1.3%)*	*3 (4%)*
2005	NADA	4482	12 (0.27%)	6 (0.13%)	–	–	
	WADA	197	–	–	–	–	
	Assoc. Germany	–	–	–	3839	49 (1.3%)	
	Abroad	–	–	–	153	–	
	Total	*4679*	*18 (0.4%)*		*3992*	*49 (1.2%)*	–
2006	NADA	4415	10 (0.2%)	–	–	–	
	WADA	219	–	–	–	–	
	Assoc. Germany	102	2 (2.0%)	–	3679	44 (1.2%)	
	Abroad	–	–	–			
	Total	*4736*	*12 (0.3%)*	–	*3679*	*44 (1.2%)*	*1 (2%)*

* Reported violations which according to annual doping reports could not be assigned either to out-of-competition testing or to in-competition testing.

** International associations (764) and the International Olympic Committee (134).

Out-of-competition testing was performed on German athletes both in Germany and abroad; in-competition testing was performed in Germany and on German athletes abroad (Olympic Games)

Source: NADA annual doping reports (NADA 2005, 2006a, and 2007a)

It cannot, however, be concluded on the basis of the apparently small number of positive doping tests that doping is only a minor problem overall.[23] For one thing, only a disappearingly small proportion of competitive athletes are ever tested. In Germany each sports association independently determines the scope

23 In 2006 the US track-and-field athlete Marion Jones admitted in court that she had doped herself, yet 160 doping tests had failed to detect this. According to triathlete Faris Al-Sultan, »People only get caught when there's a raid on somewhere. If anybody gets caught in a urine test, it's mostly juniors or people from fringe sports who don't have enough money to dope themselves professionally.« (reported in *Berliner Zeitung*, December 12, 2006)

of in-competition testing in its sport. In practice, in-competition testing is largely limited to the national championship level. For its part, out-of-competition testing is largely limited to the national testing pool and – because of limited resources – occurs far less at the level of the general testing pool. As a result, up-and-coming athletes, even those performing at an above-average level, remain outside of the existing testing and sanctions structures for a very long time. For another thing, like all diagnostic procedures, analytical tests to detect doping do not correctly identify all positive (doping) cases as such. As mentioned in Section IV.2.2, Kindermann/Steinacker (2007) believe that about half of all doping samples are unusable because of inadequate cooling during transport to the laboratory. By contrast with diagnostic tests used for medical purposes, the sensitivity and specificity of the doping tests that are used are not published. It is therefore not possible to estimate the frequency of doping on the basis of the presently available information.

The few empirical studies that have been performed (by means of anonymous or indirect questioning) on the frequency of doping in competitive sport have thrown up sobering figures on the extent of doping in elite sport. In an indirect survey[24] of more than 1000 Italian competitive athletes and more than 200 trainers and physicians, Scarpino et al. (1990) found the rate of regular consumption of amphetamines or anabolic steroids to be 10% and that of blood doping to be 7%. Rates for occasional doping were two to three times higher, i.e. between 20% and 30%. Pitsch et al. (2005), using an anonymous internet survey of 448 squad athletes and allowing for the likelihood of false responses, estimated a doping rate of 26% (plus 22% probably false responses and an estimated 52% of athletes who genuinely had not doped themselves at any time in their sports career). There were substantial differences between men and women and between different sports. In 2007, using a model it had developed for determining the rate of blood doping, a team from the Swiss Antidoping Laboratory estimated cycling to be 75% doping-free. This, it was concluded, made 2007 one of the cleanest years for a long time (Geisser 2007). By comparison, according to their own estimate 80% of competitive cyclists took EPO in 1996. Revelations about German cyclists in 2007 also suggest that EPO doping is fairly widespread. Doping tests for EPO are shown separately in NADA's annual doping reports. A total of 698 tests were performed in 2004, 800 in 2005, and as many as 900 in 2006. Despite assumptions about the use of EPO for doping purposes, none of these tests detected EPO.

Moreover, abuse of various new EPO agents which since the expiry of patent protection in 2007 have been licensable as medicines, and of other substances such as growth hormone, cannot even be detected at present (Donati 2007).

24 The question was worded: »How widespread do you consider doping to be in your sporting environment?«

Bearing in mind the original objective of doping tests (Section IV.2), it must be reaffirmed that in practice, doping tests remain the most important, and in many cases the only, source of evidence that can justify a rebuttable presumption of an anti-doping rule violation. In some cases they are able to prove the existence of an anti-doping rule violation and a legally valid sanction can be imposed. On the other hand, the converse conclusion, namely that all other athletes are doping-free, cannot be drawn. In view of the relatively low rate of detection, it must also be doubted whether the secondary objectives of testing, namely to deter athletes from doping themselves and to show the public that sports organizations are fighting doping, are achievable.

(PARTIAL) LEGALIZATION – AN ALTERNATIVE?

Given also the assumed, though so far neither proven nor disproven, discrepancy between the actual rate of doping and the number of proven (and penalized) cases of doping, there are more or less regular calls for (partial) legalization of doping. Other arguments put forward in favor of this approach are that, as with drug abuse, some health risks may be made greater by criminalization than by controlled issue of substances, and arguments based on ethical principles such as (re)establishment of a »level playing field«. In relation to gene doping, authors such as Miah (2004) and Savulescu et al. (2004) have argued that athletes with »better« genes enjoy an unfair advantage in competitive sports. Though this advantage may not directly ensure victory, there can be little doubt that it increases the likelihood of victory. Savulescu et al. (2004) therefore argue that instead of performing doping tests in order to detect abuse of a multitude of substances and methods, we should look for quantifiable evidence that an athlete is jeopardizing his/her health by ingesting substances. It may prove possible to quantify and assess the risk to an athlete's health in very approximate terms on the basis of the athlete's hematocrit level, however it remains to be seen how this can be achieved with other forms of doping (e.g. those aimed at strengthening skeletal muscle).

Given the existence and broad recognition of the WADC, however, this approach is decisively rejected on both ethical and political grounds based on different interpretations of similar considerations to those used in favor of legalization. According to this view, athletes who reject doping would be disadvantaged, as their likelihood of winning would be reduced (Knoeppfler/Albrecht 2007, p. 28). As a result, athletes who rejected doping in principle would have no choice but to dope themselves in order to give themselves an equal chance, and the principle of respecting the health of one's opponents would be rendered obsolete. Legalization of doping would deprive athletes of the possibility of »combining equality of opportunity in play with health in competitive sport« (Knoeppfler/Albrecht 2007, p. 28).

Even assuming it could be confined to elite sport, legalization of doping would transform the entire system of sport and rob sport of any value content or social function. In the presence of unrestricted doping, the sport-following public would, to an even greater extent than it already does, attribute sporting success less to athletes and their achievements than to the scientific apparatus that supports them: »Legalization of doping would largely rob successful athletes of their personal aura.« (Bette/Schimank 2006b, p. 366) Furthermore, a broad new field of experimentation would be opened up, sport would become an ongoing study in which athletes, as the subjects, would be subjected to high risks. Medical ethics and the physicians who are beholden to it would be unlikely to be able to control this development. Eventually the role model function that elite sport fulfils for children's sport, youth sport, and recreational sport in general would be lost. Since it is certain that if doping were legalized few parents would encourage their children to embark upon a career in competitive sport, the basis for recruitment in competitive sport would be lost. Finally, legalization of doping would not only undermine the »credibility of real competition as compared to a choreographed show« and the possibility of »meaningful identification with the athlete«, but also remove the central structural pillars of the system of competitive sport (Franke 2007, p. 16).

For all the above reasons and notwithstanding the deficiencies of the present system, there is no real alternative to the prohibition of doping and a system of doping tests and sanctions, and the only viable pathway is that of continuous improvement of the effectiveness of testing. In addition to the system of testing and sanctions implemented within the world of sport, however, there is a need for many other entities to undertake complementary and supportive anti-doping measures. A factually and normatively based discussion of the emphasis given to ever greater development of control structures and the effectiveness of these compared to other anti-doping measures focused not just on individual doping actions of athletes needs to be held, and not just within the world of organized sport.

OTHER APPROACHES TO DOPING CONTROL 2.4

In 2007 the DOSB introduced a declaration/undertaking by physicians, veterinarians, physiotherapists, trainers, and athlete support personnel. By signing this the person asserts that he/she has »at no time passed on to, made available to, prescribed for, or administered to athletes substances, or used methods, that violate currently applicable anti-doping regulations«. A violation can have the following consequences: withdrawal of accreditation, demand for reimbursement of dispatch costs, payment of up to 10,000 euros to the NADA-supporting association, and reporting of an offense as per the German Drug Law

(*Arzneimittelgesetz*, AMG) (BMI 2007b, p. 79 ff.). This declaration covers gene doping. In conjunction with the long retention period for doping samples, it opens up the possibility of applying sanctions at some time in the future to doping violations that are undetectable at present but may become detectable later.

In principle, a similar, organization-internal declaration could be made by athletes. Were such a declaration to be modeled on the NADA Code, it would likewise cover gene doping. Violations would result in imposition of sanctions under service law. The German Sports Foundation (*Stiftung Deutsche Sporthilfe*) likewise makes its support conditional upon the making of a declaration whereby each athlete undertakes never to dope himself/herself (Stiftung Deutsche Sporthilfe 2007). In the event of a violation any financial support provided over the past two years must be repaid. Individual sports associations such as the International Cycling Union (*Union Cycliste Internationale*, UCI) and the German Ski Association (*Deutsche Skiverband*, DSV) are presently developing similar approaches and are making team membership and participation in competitions conditional upon the making of such a declaration. Franke (2007, p. 30) is also in favor of a voluntary undertaking by competitive athletes that commits them in principle not to jeopardize the specialized world of competitive sport and that can be developed from a behavioral maxim into a set of guidelines.

However, the potential effectiveness of such measures remains linked to that of the doping control system, since the imposition of sanctions beyond those of the World Anti-Doping Code presupposes proof of doping that will stand up in court.

A few anti-doping organizations and sports organizations have announced their intention of performing regular doping tests on elite athletes in order to issue athletes with »athlete passports« or »biological passports« on the basis of the results obtained. Both the technical and the procedural feasibility of such approaches are currently being investigated.[25] The use of »intelligent« biomonitoring as a means of detecting gene doping could be linked to such developments (Section III.2).

3. (GENE) DOPING IN THE CONTEXT OF PUBLIC LAW

In Germany doping (and thus gene doping) is not a defined term in public law (BMI 2007a). A variety of legal norms deal both with the topic of doping in general and – by recognition of international conventions and reference to appropriate lists – with the topic of gene doping as a special form of doping that

25 The UCI announced that in 2008 it would introduce a biological passport as a precondition for participation in competitions, but has now put this off until 2009.

may arise in the future. In the following, a description of the legal situation in Germany is therefore preceded by a summary of relevant international agreements that have been incorporated into German law.

INTERNATIONAL AGREEMENTS 3.1

ANTI-DOPING CONVENTION OF THE COUNCIL OF EUROPE

The parties to this convention dated November 16, 1989 undertook »with a view to the reduction and eventual elimination of doping in sport, within the limits of their respective constitutional provisions, to take the steps necessary to apply the provisions of this Convention.« (Council of Europe 1989).

In Article 2.1 of the Convention, *doping in sport* is defined as »the administration to sportsmen or sportswomen, or the use by them, of pharmacological classes of doping agents or doping methods«. Article 2.1.c defines *sportsmen and sportswomen* as »those persons who participate regularly in organized sports activities«. The Council of Europe thus defines doping as a behavior that occurs only in competitive sport. In Article 2.1.b *pharmacological classes of doping agents or doping methods* are defined as »those classes of doping agents or doping methods banned by the relevant international sports organizations and appearing in lists that have been approved by the monitoring group under the terms of Article 11.1.b« (Council of Europe 1989). This list has now become the WADA Prohibited List. The most recent amendment to the Appendix was incorporated into German law in June 2007 (*Bundesgesetzblatt* 2007 Part II No. 18, p. 812 ff.). This covers gene doping.

ADDITIONAL PROTOCOL TO THE ANTI-DOPING CONVENTION OF THE COUNCIL OF EUROPE

The Additional Protocol of September 12, 2002 was incorporated into German law in 2007. This protocol forms the legal basis for performing doping controls in accordance with the WADC in the territory of other contracting parties. Regarding doping definitions, it refers to the Anti-Doping Convention of the Council of Europe.

UNESCO CONVENTION AGAINST DOPING IN SPORT

The UNESCO Convention of October 19, 2005 was likewise incorporated into German law in 2007. This obliges Germany to enshrine the regulations and principles of the WADC in corresponding laws. In this way the basis for a uniform worldwide approach to doping is meant to be established. The Convention is based partly on the WADC. As gene doping is covered by the Prohibited List to which the WADC refers, it is also prohibited by the UNESCO Convention.

GERMAN LAW 3.2

Within the framework of constitutional law referred to above, the German Federal Government can take legal measures to fight doping more effectively. In the past the possibilities that exist in this regard have been a matter of controversy.[26] The present outcome of these debates is the Law to Improve the Fight against Doping in Sport (*Gesetz zur Verbesserung der Bekämpfung des Dopings im Sport*), which came into effect on November 1, 2007 (*Bundesgesetzblatt* 2007 Part I No. 54, p. 2510 ff.).

LAW TO IMPROVE THE FIGHT AGAINST DOPING IN SPORT

The law envisages an amendment of the German Drug Law (*Arzneimittelgesetz*, AMG) and the Federal Criminal Office Act (*Bundeskriminalamtsgesetz*, BKAG). In the introduction to the bill it is stated that the Federal Government (*Bundesregierung*) considers itself to be committed to the ethical-moral values of sport and to public health and that these are damaged by doping in that participants in competitive sport, the public, and organizers of sports events are deceived and the health of athletes is jeopardized (Bundesregierung 2007). This law too thus relates doping directly to competitive sport. Because of the role-model function exerted by elite athletes, however, effects on the protection of the health of the population at large are also seen.

GERMAN DRUG LAW (*ARZNEIMITTELGESETZ*)

The subpenal German Drug Law (AMG) defines doping actions as falling within environmental law and there relates them exclusively to medicinal products (*Arzneimittel*) (§ 2 AMG) and sport. Though reference is made to »doping in human beings« and »doping purposes in sport«, doping itself is not defined. Since it is stated that the lawmaking body considers itself to be committed to public health, a broad understanding of sport must be assumed.

Potential agents for gene doping are largely substances for the transfer of genes or gene components. They are regarded by the lawmaker as medicinal products if they are intended for use in humans. In § 4, no. 9 AMG gene transfer medicinal products are defined as »medicinal products intended for human use within the meaning of § 2, no. 1 which, for the purpose of the genetic modification of somatic cells by means of the transfer of genes or gene segments, are or contain specific naked nucleic acids, viral or non-viral vectors, genetically modified human cells, or recombinant microorganisms, without the purpose being, in the

26 For example, the suggestion that doping be deemed to constitute anticompetitive behavior according to the criminal code failed to find a parliamentary majority (Bundesregierung 2007; ReSpoDo 2005).

case of the latter, to prevent or treat the infectious diseases caused by them«. Other potential agents for gene doping in the broad sense, such as antibodies and transcription regulators (Section IV.3.2), fall within the substance definition given in § 3 AMG.

Even without special reference to doping, medicinal products may be manufactured for the purpose of dispensing to others in Germany only with the permission of the responsible authority (§ 13, no. 1 AMG). In the case of gene transfer medicinal products this permission is given by agreement with the Higher Federal Authority (§ 13, no. 4 AMG). This norm could be used as a basis for taking action against illegal laboratories (Section IV.3.2), provided they are located in Germany, and also against trainers, athlete support personnel, or other third parties that place gene transfer medicinal products on the market. Infractions can be penalized with a period of imprisonment of up to one year or with a fine (§ 96 AMG). Use in others and possession of agents cannot, however, be prohibited in accordance with § 13, no. 4 AMG.

In § 6a (»Prohibition of medicinal products for doping purposes in sport«) the AMG also explicitly defines punishable doping actions insofar as the doping is to be performed in humans:[27]

- »The placing on the market, prescribing, or administering of medicinal products to others for the purpose of doping in sport is prohibited.« (§ 6a, no. 1 AMG) For the specification of medicinal products, reference is made in § 6a, no. 2 AMG to the law of March 2, 1994 on the Anti-Doping Convention of the Council of Europe of November 16, 1989. As mentioned above, the named list is the WADA Prohibited List, the most recent amendment of which was incorporated into German law in June 2007 (*Bundesgesetzblatt* 2007 Part II No. 18, p. 812 ff.).[28] Section 6a, no. 1 AMG applies only to medicinal products that contain substances that belong to the listed groups of prohibited substances or substances that are intended for use with the listed prohibited methods. The incorporation of the WADA Prohibited List into German law thus makes gene doping a prohibited method in Germany, and substances used for this purpose may not be placed on the market, prescribed, or used for doping purposes.
- It is also prohibited »to possess non-small amounts of medicinal products that are or that contain substances named in the Appendix to this Law for doping purposes in sport insofar as the doping is to be performed in humans« (§ 6a, no. 2a AMG). The substances concerned and the »non-small« amounts are specified in the Doping Agents Amounts Ordinance (*Dopingmittel-*

27 Doping of animals is not covered by the AMG.

28 The question (referred to in Section IV.1) of the precision and scope of the definition of gene doping used in the WADA Prohibited List applies also to the AMG.

Mengen-Verordnung, DmMV) of the Federal Ministry of Health (BMG 2007)[29]. The substances listed in this appendix to the law largely correspond to those of substance classes S1, S2, and S4 of the WADA Prohibited List (Table 6). *Possession* of substances for use in gene doping is thus not prohibited in itself.[30]

According to the German Drug Law (AMG), substances required for gene doping that are medicinal products may not be placed on the market, prescribed, or used for doping purposes. Even an attempt to perform any of these actions is a punishable offense that in accordance with § 95 AMG may result in imprisonment for up to three years or a fine. In particularly serious cases[31] the punishment may be increased to between one and ten years. This norm is directed mostly against trainers, physicians, and athlete support personnel rather than against the athlete who commits the act on himself/herself.

FEDERAL CRIMINAL OFFICE ACT

In accordance with the Law to Improve the Fight against Doping in Sport (*Gesetz zur Verbesserung der Bekämpfung des Dopings im Sport*), the Federal Criminal Office (*Bundeskriminalamt*, BKA) is responsible for launching prosecutions in cases of internationally organized illegal actions involving narcotics or medicinal products that call for investigation beyond the borders of Germany and of criminal offenses committed in association with such actions.

OTHER (LEGAL) NORMS

Where use of doping methods without the consent of the athlete results in damage to health, a criminal assault as per the German penal code (§ 223 ff. *Strafgesetzbuch*, StGB) may have been committed. Where, as with gene doping, serious damage to health is to be expected, use even with consent could be regarded as immoral and would be punishable despite the consent. The severity of the punishment is determined by the severity of the bodily injury (Simon et al. 2007, p. 40).

29 Substances included in the WADA Prohibited List formed a starting point. The equivalent of a one-month therapeutic supply was defined as a »small amount«. By comparison, the Norwegian anti-doping law prohibits possession only of more than a year's supply, such as is issued in sport or bodybuilding (Reinsch 2007).

30 In order for possession to be prohibited, a »small amount« would also need to be defined.

31 For example, when the health of a large number of people is jeopardized, when the action exposes another person to a risk of death or serious physical injury or damage to health, when the action is performed in a professional way or by a gang, or when the actions are performed on minors.

As well as on the basis of actions prohibited by the German Drug Law, gene doping could be punishable under criminal law in cases in which deception or falsification of documents occurred because of or in connection with gene doping. For this to occur, the relevant association- or federation-internal legal norms, employment contracts, and/or declarations of principles and obligations would need to be suitably formulated. In conjunction with the existing prohibition of gene doping and the existing rules on retention, later analysis, and limitation periods, this could have a deterrent and consequently a preventive effect (Section IV.2.4).

Where a person who performs gene doping on another person is a physician registered in Germany, his/her actions could be punished by the responsible state medical association (*Landesärztekammer*). According to the Federal Ordinance for Physicians (*Bundesärzteordnung*, BÄO), registration as a physician is conditional upon recognition of the ordinance governing the profession and membership of the relevant state medical association. By recognizing the ordinance governing the profession the physician undertakes »to serve the health of the individual human being and of the entire nation« (§ 1, no. 1 BÄO).

The financial support of sport (as an area of public law) is another area in which there is scope for action to combat doping. »Direct financial support by the Federal Government in the realm of elite sport is provided via federal sports associations, Olympic support centers, and federal performance centers. In this way athletes, physicians, trainers, and other athlete support personnel benefit only indirectly from grants of budgetary funds.« (BMI 2007b, p. 8) Recipients of this financial support are required to observe the applicable anti-doping regulations of WADA and NADA (BMI 2007b, p. 12). In addition, by the end of 2007 all elite athletes employed by the Federal Police, the Federal Armed Forces, or Federal Customs had signed an undertaking never to dope themselves. They accept that if they breach this undertaking they will be excluded from financial support and will be subject to additional measures under civil service law. In addition, they receive documented annual instruction (BMI 2007b, p. 115 ff.). According to the WADC and the NADA Code, gene doping is covered by decisions on allocation of grants. A precondition for demands for repayment of grants and in particular for the taking of measures under civil service law, e.g. dismissal, is completion of an investigation under sports law and proof of a statutory offense that will stand up in court (BMI 2007b, p. 72).

CRIMINAL PROSECUTION AND IMPOSITION OF SANCTIONS

Though prosecuting authorities have more extensive investigative powers than do sports organizations, they are required to ensure proportionateness of measures. They are empowered to have specific investigations performed on a

compulsory basis, but may do so only if such investigations are appropriate and necessary for establishing the facts of the case. In the absence of a suitable test procedure such investigations are not permitted.

A (gene) doping violation in the sense of self-harming by an athlete is not punishable under German law. Such an athlete may nevertheless be prosecuted if he/she has made a statutory declaration or documented undertaking not to dope himself/herself (§ 267 *Strafgesetzbuch* [German penal code, StGB], *Urkundenfälschung* [falsification of documents]; § 274 StGB, *Urkundenunterdrückung* [suppression of documents]) (Simon 2007, p. 35). However, in accordance with the principle of »no punishment without guilt«, sanctions for gene doping may be imposed only if proof that will stand up in court can be established by means of a suitable method. No such methods are apparent at present.

In order to prove the occurrence of (gene) doping actions in the milieu of the athlete (placing on the market, prescribing, and administering), the principle of clarity and definiteness must likewise be satisfied and either objective and subjective elements of a rule violation or the intention »for the purpose of doping« must be established. Where bodily harm occurs as a result, proof of intention is not required, however objective and subjective elements of a rule violation must be demonstrated. Violations fall within the area of medicinal product crime[32]. Up to now, prosecuting authorities have generally regarded violations of the German Drug Law as falling within the area of environmental crime and therefore not as a priority area of activity (Sürmann 2007). Responsibility lies with the German *Lands*. There have been calls for the establishment of specialized public prosecutor's offices, however as far as is known no such offices have been established as yet.

To date, criminal offenses as per the German Drug Law (*Arzneimittelgesetz*, AMG), and thus doping offenses, are not identified as such in police crime statistics. Some retrospective data have been obtained by means of questionnaires, however according to Sürmann (2007) the information provided by these is not representative. As from 2008 criminal offenses as per § 6a AMG are to be identified as such and reported to the Federal Criminal Office (*Bundeskriminalamt*, BKA). Along with analysis of crime statistics, surveys of experts have been conducted in order to provide a basis for developing methods of combating the growing phenomenon of medicinal product crime. The resulting proposals could probably also help to combat gene doping.

32 The study »Arzneimittelkriminalität – ein Wachstumsmarkt« (»Medicinal product crime – a growth market«), issued by the Federal Criminal Office (*Bundeskriminalamt*, BKA) (Sürmann 2007), is the first attempt to provide information on the state of medicinal product crime in Germany from the perspective of the police.

DOPING BEHAVIOR IN ITS SOCIAL SETTING V.

Compared to those of other countries, Germany's doping control and sanctions structures are certainly well developed. Despite this, they have not succeeded in preventing the use and spread of doping in elite sport. Like other deviant, rule-breaking behavior in society that cannot be prevented by the threat of punishment, doping may result from individual developmental processes in the course of which pro-doping attitudes, mentalities, and behavioral patterns are acquired. A situation in which these attitudes prove to be largely resistant to the threat of testing and sanctions, and in which athletes often fall into a »biographical trap« in which doping is integrated into their life plan as a matter of course, can arise only if social structures and people in the athlete's milieu promote and reinforce individual doping.

The following observations are intended to take account of this interconnectedness between individual decision-making and the social setting in which it occurs. In the context of the present report this cannot, however, take the form of a comprehensive sociological (systems) analysis of the »links between the individual and cooperative interests of the protagonists« (Bette/Schimank 2006b, p. 26). The objective is more modest than this. The following discussion is intended to demonstrate at least in outline that the subject matter of the present report cannot be meaningfully considered purely in biomedical terms. Rather, (gene) doping can be understood only if it is analyzed and considered as individual behavior in a social setting (rather than as autonomous behavior).

To this end Section V.1.1 considers how doping behavior can arise during the career of a competitive athlete, with particular reference to the role of medical support personnel. As important elements in the »support milieu« (Bette/Schimank 2006b), these individuals can contribute substantially to the development of a doping mentality among athletes and to reinforcement of the practice of doping. Other people who form part of the athlete's milieu are referred to in Section V.1.2. By reference to sports organizations and individuals and entities that support sport, it is pointed out that athletes act and make decisions not autonomously, but under the influence (even if undetermined) of their social milieu.

Using bodybuilding and sport in the elderly as examples, Section V.2 considers the question of how doping behavior typically arises in individual sport. In Sections V.2.1 and V.2.2, under the heading »Points of entry«, there is a discussion of the factors that the athlete is likely to take into account when deciding for or against gene doping and that could tend to promote or prevent the spread of gene doping.

COMPETITIVE SPORT 1.

Athletes are generally health-conscious and determined people. They are motivated to engage in sporting activity by wishes related to enjoyment of movement, play and competition with others, physical health and/or strength, stamina, and a will to achieve. Many of these wishes are linked either consciously or unconsciously to athletic bodies as *image bearers*. Sporting activity can mean great subjective success for oneself and a degree of recognition by one's social milieu that can act as an impetus to further physical development. In this way »shaping of human nature« by training and sporting activity also provides »an opportunity for a life plan and the associated endowment of life with meaning« (Fuchs et al. 2007, p. 31).

ATTITUDES AND BEHAVIOR 1.1

Experience shows that during their sporting development athletes can develop attitudes and modes of behavior that lead to doping actions. The decisions that an athlete makes in the course of his/her sporting development are not just isolated individual decisions, they are also the result of the individual and combined influence of a variety of people who form part of the athlete's milieu (parents, trainers, sponsors, media, physicians). It seems very likely that use and spread of gene doping in competitive sport will be possible only if athletes are able to get help of one kind or another from the medical profession. The following discussion therefore focuses on the development of the athlete and on the role of medical support personnel and physicians.

INDIVIDUAL DEVELOPMENTAL PHASES

Most people who achieve success in elite sport nowadays have been playing sport since their early childhood. Those who eventually reach the top level started out simply as talented children who loved sport. In most cases they have no realistic idea of where a move into competitive sport might take them and are therefore unable to take this question into account when making decisions. To sport-loving children, elite athletes are important role models who significantly influence their opinion-forming and decision-making processes.

Children play sport for a variety of reasons, for instance because they enjoy bodily movement or in order to be with friends. Success in their sporting activity often puts them on a path that leads towards a career in sport. Those who do not drop out, e.g. because they are not prepared to spend the required amount of time or are afraid of failing or not reaching the top level, have fallen into a »biographical trap« (Bette/Schimank 2006b, p. 126) in that they have found an effective means of achieving social status. The subsequent path of their life plan

in sport is largely without alternatives, leads in many cases to excessive ambition, and can gradually give rise to doping behavior (Singler/Treutlein 2007, p. 16 ff.). The final step from being a non-doping to a doping athlete is generally preceded by a lengthy process in which barriers are gradually broken down and mental acceptance of doping is developed (Laure/Treutlein 2006). In some cases this *doping mentality* develops before any actual doping actions occur, and in some cases it becomes more pronounced as further doping actions are committed.

Referring to people in the athlete's milieu such as physicians, trainers, and sports officials, Singler/Treutlein (2007, p. 16 ff.) speak of a »staircase of seduction into doping«. This staircase already leads athletes to blood doping and doping with growth hormone, for example, and assuming unchanged conditions and availability it could in the future lead to the decision to practice gene doping. »This staircase of seduction into doping is an illustrative model. In reality the path can be shorter. It is also possible for someone to take a few steps on this staircase but then, fortunately, not reach the stage of doping.« (Singler/Treutlein 2007, p. 17)

Figure 9 shows the gradual development of doping behavior in schematic form. In the first phase, namely the discovery of the type of sport to play as a recreational activity, the amount of time spent training is still relatively small. Young athletes who observe casual and even everyday use of medicines or similar substances in their sporting environment can start to develop pro-doping attitudes at an early stage.

The second phase of sporting development generally coincides with the physical and mental upheavals that accompany adolescence in the young athlete. If this phase is marked by success and social recognition, sport can become the young person's principal means of establishing his/her identity. The motive of achieving social recognition now increasingly takes over from the earlier motive of finding pleasure in play. As the degree of social recognition increases and possible alternatives disappear, the athlete is drawn into a vortex from which it is increasingly difficult to escape. Increasing demands on the athlete's time and progressive marginalization of peer groups other than those associated with sport are accompanied by the increasing physical burden imposed by ever more intensive training. Exhaustion and over-exertion occur, injuries occur more frequently and increasingly are treated with medicines prescribed by specialist physicians. In some cases performance-enhancing substances are recommended supposedly as preventive measures to maintain health. As a result of all this, even young athletes can become receptive to the idea of taking substances as an »aid« before they reach the point at which they have to make decisions both about their further development in sport (which can occur only via even longer training times) and about their professional future. The decision – if taken – to make a career out of sport, the moment of »going professional« (Brissonneau 2004), represents a fundamental turning point in the life of the athlete.

FIG. 9 DEVELOPMENT OF DOPING BEHAVIOR IN COMPETITIVE SPORT

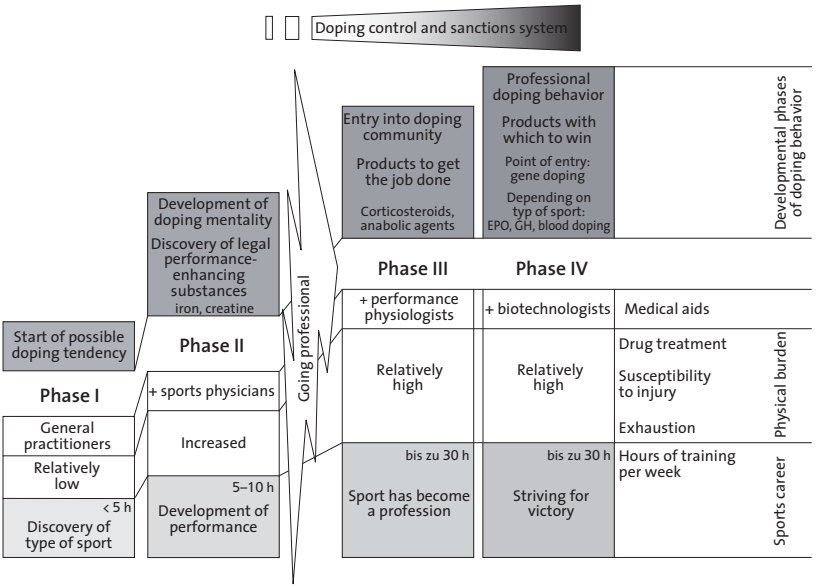


Figure 9 shows in schematic form the preliminary and developmental phases of doping behavior that can occur in parallel with a life in sport. The figures on training times are intended only to give a general idea of how sport takes up more and more of the athlete's time.

Own illustration, from Brissonneau 2004

In the third phase, the development of sporting prowess largely determines daily routine and displaces other activities. Increasingly, the athlete trains to the limit of his/her physical capacity in accordance with methods optimized by performance physiology for 25 or more hours per week, depending on the type of sport, in order to be able to participate successfully in the large number of competitions that finance the ever-growing competitive sport industry. The milieu in which the athlete moves is progressively reduced to a narrow, success-oriented world of sport in which expectations, incentives, and rewards are determined by sporting achievement. This development is characterized by a continuous »maximization of economic income and career opportunities« (Bette/Schimank 2006b, p. 129). The athlete has to measure himself/herself against other athletes who may or may not be doping themselves. He is now caught in the *doping trap*, and in the absence of alternatives he joins the doping community. He is now subject to the doping control system. The risk of being caught is greatest at the start of a doping career.

After joining the doping community an athlete becomes even more result-oriented and single-minded. From there it is a relatively small step to the fourth phase, in which »all that matters is winning« and increasingly subtle doping agents that must be undetectable (or that are not detected) are used because the athlete's whole career depends on their use.

EMPIRICAL STUDIES ON DOPING AT DIFFERENT PHASES OF SPORTING DEVELOPMENT

A small number of quantitative studies have been performed on the extent and types of doping practiced in the early stages of sporting development. Laure/Treutlein (2006) analyzed the results of 39 empirical studies on doping in adolescents in North America and ten studies from Europe that also attempted to quantify doping behavior during the early phases of sporting development. The North American studies from the 1990s found that doping often started before the age of 14 years and that adolescent competitive athletes made use of doping agents far more commonly than did noncompetitive athletes. Doping with anabolic steroids formed the focus of the studies. Only Rickert et al. (1992) studied doping with growth hormone. In that study 5% of male interviewees from two schools in Chicago (mean age 15 years) stated that they had used growth hormone for doping purposes.

Two empirical studies on doping in competitive sport were performed in France in 1991 and 1998. The 1991 survey of 2425 children aged between 12 and 20 years likewise found that age and involvement in competitive sport influence doping behavior. Overall, 2.9% of the boys and 1.4% of the girls admitted to having used doping agents. Of the boys who played sport, 2.4%, 2.5%, and 7.7% took part in sports competitions at the local, regional, and national level, respectively. The 1998 study was based on a survey of 2000 amateur athletes from all types of sport in Lorraine. »9.5% had taken doping agents at some time during the preceding 12 months. Most affected were the 20–29 and 35–39 year age groups. 10.8% of competitive athletes, but only 4.9% of recreational athletes, had taken doping agents. Most at risk were athletes performing at a high level (17.5% compared to 10.3% of athletes performing at a lower level).« (Laure/Treutlein 2006, p. 53)[33]

In a direct survey of 480 squad athletes performed using a randomized response technique, Striegel (2007, p. 51) found an overall doping rate of 6.8%. There was no breakdown by type of sport, age, or gender, nor was any information provided on probably incorrect answers.

33 Similarly, the German Federal Government's health report for 2006 included a summary of published studies on doping in recreational and mass sports (Müller-Platz et al. 2006), however the state of organized sport was scarcely referred to and no quantitative information on it was provided.

In an internet survey of 448 squad athletes that likewise used a randomized response technique, Pietsch et al. (2005) found a doping rate of 26% (plus an estimated 22% probably incorrect answers) (Section IV.2.3).

RISK-BENEFIT CONSIDERATIONS AND JUSTIFICATION STRATEGIES

On the basis of the available scientific literature on the life courses of performance-oriented athletes, it is possible to identify certain common behavioral patterns and also certain time-points or phases in an athlete's career when the risk of doping is particularly high. These include:

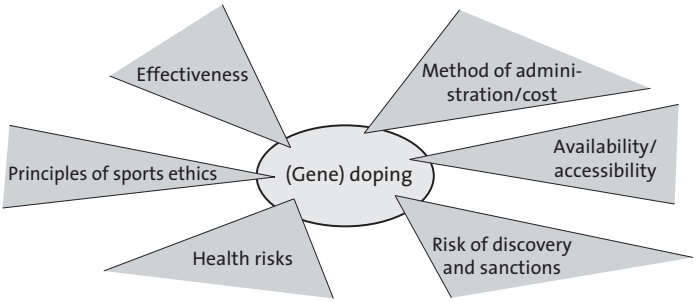
- transitions between one level of sporting performance and the next (often associated with changes of trainer, support personnel, and sports team or association; phase transitions in Fig. 9);
- times at which the limits of training possibilities are being approached (when intensification of training at an already high level results in progressively smaller increases in performance);
- times of crisis (which become more frequent because of the increasing physical, mental, social, and financial risks that can result from accidents, chronic injuries, and long-term damage);
- the twilight of the athlete's career (when the athlete's physical performance has passed its peak and younger athletes are posing an increasing threat).

Nevertheless, competitive athletes are not a homogeneous group. Differences related to type of sport and to gender, for example, have yet to be studied to any great extent either qualitatively or quantitatively.

It is reasonable to assume that all groups of athletes consider both the benefits and the risks of doping (Fig. 10). Various criteria are included, weighted, and balanced against each other so as to come to an overall assessment of the risk-benefit relationship. This balancing of risks against benefits doesn't necessarily occur before the decision to dope or not to dope is made, but can just as easily occur later. From the point of view of the doping athlete (and of his/her support personnel), this process of balancing risks against benefits can lead to a rational decision. This can be illustrated by imagining a simple thought process of this kind (Knoepffler/Albrecht 2007, p. 20): If from the point of view of a performance-oriented athlete the expected improvement in performance is great and the health risk is low, doping is a rational strategy, whereas if doping is likely to bring only a minor improvement in performance but its health risk is high, it is an irrational strategy. This process in which the athlete weighs benefits against risks will be discussed again later in relation to potential points of entry for gene doping.

However, as well as basing their decision-making behavior on the utility principle, athletes often have to consider rules and regulations if their doping actions are to be stable and consistent. Bette/Schimank (2006b, p. 226 ff.) coined the term »neutralization rhetorics« to refer to typical arguments used by athletes to render deviation from rules plausible to themselves and others.

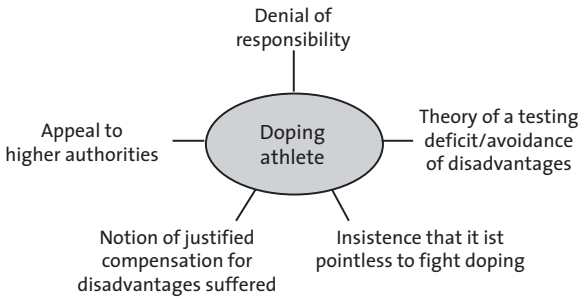
FIG. 10 FACTORS IN THE SUBJECTIVE RISK-BENEFIT ANALYSIS IN (GENE) DOPING



Own illustration

Justification strategies include the argument that since other athletes dope themselves, one must do the same in order to avoid disadvantages. Also used as justifications are inconsistencies in doping testing (»testing deficit«) and the assertion that the fight against doping is pointless in any case. Another line of argument is that doping can be an aid to overcoming the risks, in some cases to one's very existence, associated with a career in sport. Finally, reference is made to the massive pressure exerted by the sports industry, which supposedly leaves athletes with no option but to dope themselves (Fig. 11).

FIG. 11 ARGUMENTS USED BY DOPING ATHLETES TO JUSTIFY THEIR ACTIONS



Source: adapted from Bette/Schimank 2006b, p. 226 ff.

Arguments such as these also have effects that extend beyond the individual athlete to doping athletes as a group. Taken together, the various justifications constitute a sort of »counter-morality« that attempts to justify doping and refute contrary norms and precepts (Bette/Schimank 2006b, p. 244).

MEDICAL SUPPORT

The notion of health that is accepted in the world of elite sport is not the same as that which prevails in the early stages of a sports career or outside of the world of competitive sport (Brissonneau 2004). This is because the health of someone who plays sport five hours per week is not comparable with that of athletes who train at the limit of their physical capacity for 25 or more hours per week (Fig. 9). A workload of this kind results in certain physical deficits that call for rest periods to permit recovery from physical exhaustion. Rapid succession or long duration of competitive sporting events often leaves no time for such rest periods during the competition season. The logic of elite sport »systematically brings its principal protagonists, i.e. athletes, to the brink of injury and illness« (Bette/ Schimank 2006b, p. 55). The athlete comes to experience the limits of his/her physical capacity. This creates a need for a network of professionals who, for example, advise their athletes to apply for Therapeutic Use Exemptions (TUEs, Section IV.1.3) so that they can use specific drugs to mitigate the effects of overexertion and exhaustion. The increasing intensity of drug therapy reduces athletes' »pharmacologic barrier«.

As athletes move in the direction of elite sport they come into increasingly close contact and work ever more closely with the medical profession. Producing an optimal performance at precisely the right time now calls for precise medical planning. As a result of the commercialization of elite sport, some sports physicians now specialize in this area. According to the German Society for Sports Medicine and Prevention (*Deutsche Gesellschaft für Sportmedizin und Prävention e.V.*, DGSP) there are now about 11,000 sports physicians practicing in Germany and between 150 and 200 of these specialize in elite sport.

According to Brissonneau (2004), when the question of the relationship between doping and sports physicians is considered a distinction needs to be drawn between clinicians, who are in very close contact with athletes and provide them with medical care, and researchers, to whom athletes are essentially objects of investigation. Specific to clinicians is the fact that many of them are former athletes who share their passion for sport with their patients. They are fascinated by these people and want to help them. Health is an important consideration for them. They care for elite athletes whose training volume and methods are increasingly risky and harmful to health and who as a result are often exhausted and sometimes injured. Prescription of pharmacologic products rises accordingly

and is justified with the argument that the products concerned are intended to help keep the athlete's body healthy despite the extreme demands that are being placed on it.

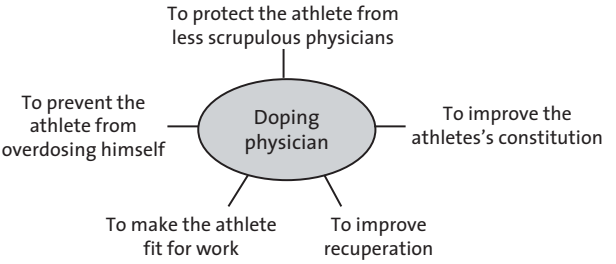
Those sports physicians who care mostly for elite athletes who train for up to 30 hours per week have to some extent become performance physiologists and tend towards research. The medical care that they provide serves the purpose of enhancing athletes' performance and optimizing their performance-to-risk ratio. Using training methods in which individual physiology and the monitoring thereof occupy an increasingly important role and using improved techniques for recuperation, they help athletes to get ever closer to the limits of their potential. Actions are increasingly determined by the credo of elite sport, namely to win at any cost. Aids developed in the fields of sports medicine, biomechanics, and pharmacology help to make the athlete's overtaxed body fit to withstand the demands of elite sport in which the only thing that matters is winning. An »unwell body« is undesirable (Bette/Schimank 2006b, p. 54).

Like many other people who are directly or indirectly involved in doping, physicians and medical support personnel reflect upon their behavior, want it to have a purpose, and try to justify it. They develop their own ideas about what is right and wrong because they are troubled by the fact that they are using illegal substances to help athletes achieve certain physiological objectives. By either tolerating or actively assisting in the practice of doping, physicians are exceeding their traditional role of curing, alleviating, or preventing illnesses on the basis of medical indications. They also know that they may be harming the athlete's health (Fuchs et al. 2007, p. 35). The ethical principles of the medical profession are especially relevant to any physician who participates in the doping of an athlete: In order to avoid inconsistencies in their actions, those who are sworn to the dictum »first, do no harm« must be able to justify their behavior on the basis of the intention to preserve health or minimize harm (Singler/Treutlein 2007, p. 18). Doping is therefore portrayed either as a means – where no other means are available – of improving the constitution, or promoting the recuperation, of an athlete more rapidly and intensively than would otherwise be possible or as a means of preventing the athlete, in his/her own interest, from using doping agents at his/her own initiative (Fig. 12).

Given the likely effectiveness of such arguments, which are directed also at athletes and to some extent at the public, Singler and Treutlein (2007, p. 20) correctly point out that the success of preventive strategies is crucially dependent on awareness of such arguments: »Such lines of argument must be denounced as unacceptable at the outset in prevention processes ranging from athlete education and the training of sports trainers and sports teachers through to medical school curricula. Athletes need an 'early warning system' for this purpose so that on the basis of the common euphemisms they can identify possible pro-doping

attitudes in persons in their milieu. For there's no doubt that such euphemisms will continue to play an important role.«

FIG. 12 ARGUMENTS USED BY DOPING PHYSICIANS TO JUSTIFY THEIR ACTIONS



Source: Singler/Treutlein 2007, p. 19

ELITE SPORT AS A POINT OF ENTRY FOR GENE DOPING

Elite sport seems the most likely point of entry of gene doping into competitive sport. Even if gene doping turns out to be no more effective than conventional doping methods, in its case

- the pharmacologic barrier is especially low,
- the pressure to use undetectable doping methods is greatest[34],
- the willingness to run risks is greatest,
- because of the high degree of commercialization, relatively large amounts of money are available, and
- international structures (laboratories, personnel, transport)[35] are already in place to some extent.

As is already the case with conventional doping, the types of sport most likely to be affected by gene doping are firstly those in which success is associated with clearly defined physiological performances (»cgs« sports: centimeter, gram, second; Emrich et al. 2004) and with great intangible and tangible benefits, and

34 Though doping with growth hormone is assumed to be less effective than doping with anabolic steroids, doping with growth hormone could spread because abuse of anabolic agents has now become relatively easy to detect.

35 Specialized laboratories already supply the existing doping networks in elite sport. Depending on cost and availability (Section II), the range of doping products could be kept within certain limits or further expanded by means of even more specialized laboratories. Because of the high degree of specialization in biotechnology, individual substances could either be acquired abroad or else, at greater expense, manufactured locally.

secondly sports in which doping behavior is not much discussed and not very efficiently combated. The rate at which gene doping spreads will depend on a number of factors that can be seen by the athlete as either obstacles or incentives.

At present, the biggest and most effective obstacle to gene doping is nonavailability or nonaccessibility. As far as abuse of gene therapy methods (gene doping in the narrow sense, Section II.1.) is concerned, this obstacle will probably persist for some time yet because of the early state of development of such methods. The obstacles to abuse of specific gene regulatory methods (gene doping in the broad sense, Section II.1.) are rather less, since some therapeutic methods of this kind have already reached the stage of clinical development (Section II.2). Nonavailability can also mean that an agent or method exists – e.g. has reached or completed the clinical trials stage – but has not yet been licensed. Spinoffs from clinical trials would be illegal, but possible. This illegality would not be a real obstacle to all potential abusers. Current doping practice is not limited to substances that are licensed only for use in animals (e.g. clenbuterol, an agent used in calf feed) (Striegel 2007) or even to untested substances that were developed specifically for doping purposes and have never been licensed (e.g. the synthetic steroid hormone THG manufactured by the American company Balco).

Another obstacle to gene doping is unknown health risks (Section II.3). Here again, the perception of this risk on the part of potential users and their advisers and support personnel differs considerably according to the willingness of those concerned to take risks. Information on possible health consequences is imparted mostly in milieus that support or approve of doping. These milieus are largely closed circles that filter out alternative, critical information. This is one reason why elite athletes are so willing to take risks and so impervious to contrary arguments. Thus, in a survey conducted by Bamberger/Yeager (1997), 50% of the elite athletes who were surveyed stated that they would take undetectable performance-enhancing substances if this meant that they would win all the competitions in which they participated over the next five years and then die. Though this result should perhaps not be given too much importance, it certainly suggests the existence of a heavily skewed cost-benefit calculation. In competitive sport top performances are achieved by division of labor. This means that responsibility for the athlete's health, including health risks and side effects, is delegated.[36] In this respect the behavior of elite athletes does not differ from that of the overwhelming majority of the population: they have faith in the competence and the sense of responsibility of those who provide them with medical care.

36 Little empirical knowledge is available as yet on the willingness of athletes, and even less on the willingness of physicians, to take risks in these contexts. Information of this kind could be useful for the development of target-group-specific measures against gene doping.

The third obstacle to gene doping relates to the way in which it is used. For as long as gene therapy continues to call for very specialized knowledge, specific skills, and special aids, abuse of it for gene doping purposes and the spread of gene doping are likely to face substantial obstacles. In medicinal product development great efforts are made to ensure that use is as simple as possible, since – along with efficacy and side effects – simplicity of use is a central determinant of whether a new product is granted a product license and thus acquires market potential. Before a dosage form can be simplified, however, the method that underlies it must be shown to work safely. One reason why experts consider the risk potential of gene doping in the broad sense to be much greater than that of gene doping in the narrow sense is that administration of agents of the former kind is simpler than that of agents of the latter kind (Section II.2)

Finally, an athlete's views and decisions about doping are influenced by his/her perception of the effectiveness of the control system and the severity of the sanctions system. As previously stated (Section IV), gene doping is prohibited both to athletes and to athlete support personnel in competitive sport and is punishable by periods of ineligibility and loss of accreditation, respectively. Since the substances that are emerging as possible candidates for gene doping are covered by the German Drug Law, all manufacture for the purpose of issue to others without permission is prohibited. Placing on the market, prescription, and use in others for the purpose of doping are also punishable by law. However, as long as violation of these prohibitions cannot be detected,[37] the risk of discovery is low and this obstacle is probably of little value.

THE ATHLETE'S MILIEU 1.2

From a sociological perspective, doping is far more than just an action by individuals (Bette/Schimank 2006a and 2006b; Franke 2007; Knoepffler/Albrecht 2007). Consequently, the phenomenon of doping cannot be properly understood purely on the basis of an analysis of individual deviant behavior. Instead, social structures and the athlete's milieu must also be considered, since via specific motivating structures, supporting measures, and omitted actions, these have contributed to the rise of doping. Singler/ Treutlein (2007, p. 10 ff.) make the following statement in this regard: »Doping on its present scale would be inconceivable as a phenomenon that goes beyond individually deviant behavior if it did not receive some kind of support from many quarters. This support does not

37 As odd as it may sound, the non-detectability of present doping agents and methods is an important obstacle to the use of gene doping. As long as presently practiced doping methods cannot be detected, the pressure to switch to new undetectable methods of unknown risk is relatively low. Even conventional blood doping underwent a renaissance when doping with EPO stopped being »safe« because the risk of detection increased.

need to be active in the sense of direct participation in doping. Support is also given precisely via the omission of actions.« The present Section of this report therefore deals with institutional motivating structures insofar as these could become relevant to gene doping.

COMMERCIALIZATION

It is a commonplace, but nonetheless true, that sport, which was originally play, has long since become a business. Its economic potential in a globalized, media-driven world is based on its entertainment value, its image value, and its ability to act as a vehicle for product information. Sport as a business provides elite athletes with the possibility of participating in the value creation of this economic sector. The more important is winning, the more tangible are the economic consequences of success or failure (KPMG 2002, p. 9). Almost universal adherence to the principle that only winning counts leads to a »winner-take-all rat race« (KPMG 2002, p. 13) that by its nature is open to any means that help to improve performance.

The imperative to perform has thus become a defining characteristic of sport, however it applies also to society as a whole, in which »in association with simultaneous economization of resource conditions« performance and competition are the dominant principles of action. Competitive sport has thus become »a reflection of the achievement-oriented society« in which »everyday life and competitive life« have become structurally linked (Franke 2007, p. 2).

Over the past few decades many involved parties (e.g. sports organizations, media, industry) both in Germany and abroad have gradually developed sport, especially elite sport, into a kind of *trademark*. The particular feature of the brand *sport* is that it can function as an *image bearer* to represent a large variety of quite different things, e.g. performance, team spirit, stamina, and health, in all cases closely linked to success and as far as possible not linked to unfair or deceitful behavior. The public projects authenticity of performance onto the system of competitive sport as a wish and a demand.

One of the pillars that finance elite sport – sponsorship – is based on this construct of sport as an *image bearer*. Sport itself is also an almost universal medium through which an enormous international target group can be reached, the »ultimate communication vehicle for sponsors and the core business for many media companies« (KPMG 2002, p. I). On this is based another pillar of sports financing – advertising revenue. The resulting mutually reinforcing exploitability of only the *results* of competitive sporting efforts has led to a situation in which the rewards, both material and non-material, for these results are in some cases extravagant. This also puts athletes under greater economic pressure (KPMG 2002, p. 9 ff.). The prospect of high earnings at the top of the performance ladder influences all of competitive sport and has the result that even in the early

stages of their career many athletes are strongly motivated to work their way to the top so as to reap some of these rewards.

Global commercialization of sport has led to an increasingly specialization-based optimization process in which a variety of participants help the individual athlete to produce outstanding performances in order to maintain and develop the *trademark*. As a result, the various participants and beneficiaries, including sports associations and federations, media, and the public at large, each have specific expectations with regard to the performance of the athlete. They are focused on outstanding performances, records, and victories along with an expectation of »naturalness of achievement« (Franke 2007). These demands can be quite contradictory, as illustrated by the attitude of society: »On the one hand, society shows a growing willingness to use powders and pills for health and good looks. On the other hand, we continue to condemn athletes taking substances to cope with the physical pressures of top sports.« (KPMG 2002, p. II)

SPORTS ORGANIZATIONS

Sports organizations can be regarded as mediators between the athletes whom they support and on whom they place demands on the one hand, and the demands imposed by the athlete's environment – politics, sponsors, the media, the public – on the other hand. As guardians and developers of the trademark »sport«, they help athletes to develop and improve their physical performance and they organize competitions. Their position and their influence, both in absolute terms and in relation to other sports organizations, therefore depend upon the achievements of athletes and the fascination with competition generated by these achievements (Bette/Schimank 2006b, p. 432).

Sports organizations finance both individual people (talent scouts, trainers, therapists, psychologists – i.e. athlete support personnel as per the NADA Code [NADA 2006b, p. 46]) and infrastructures (sports academies, performance centers, Olympic support centers) in order to help athletes optimize their performance. The individual developmental phases on the path to a career in sport (Fig. 9), to which the would-be athlete increasingly has to make a commitment in early childhood in order to have any chance of rising to international level, are accompanied and shaped by specialized athlete support personnel working in special facilities. The transition from one developmental phase to the next is almost exclusively result-oriented, i.e. dependent on the achievement of certain performance figures. Athlete support personnel are likewise dependent on the sporting achievements of athletes, since – depending on their contract – their entire income is directly or indirectly linked to the sporting achievements of athletes. As a result of this interdependency, the incentives to perform that are set by sports organizations and their athlete support personnel are accompanied by

heavily result-oriented expectations in terms of athletes' sporting development and achievements.

By organizing tournaments, sports organizations drive the development and spread of the trademark »sport«. Over the past few years there has been a noticeable trend towards more and more tournaments, closer links between individual competitions, increasing performance requirements, and expansion to include ever larger numbers of athletes.[38] This means that athletes are required to produce top performances that subject them to extreme physical strain at an ever younger age and at ever closer intervals (Section V.1.1). Substantial sources of income that finance large parts of the entire system are therefore available in elite sport, which consequently functions largely independently of public subsidies.

At the same time, however, competitions have to have a degree of credibility, which is a component of the trademark »sport«. Both in its self-perception and in the perception of others (the media and the public), competitive sport is a »particularly ethical system of conduct« (Franke 2007, p. 10) – though as such, also a fragile construct. This fragility is evident in the form of a certain tension between the »precept of outdoing«, i.e. absolute striving for victory, and the »precept of equality«, i.e. the principle of fairness and equality of opportunity. Whereas the latter precept calls for cooperativeness, the »precept of outdoing« calls for »authentic« achievement[39], i.e. rule-compliant achievement not based on deceit (Franke 2007, p. 11). It is therefore only natural that sports associations and competition organizers should attempt to portray doping as a peripheral issue. In order to sustain the belief that competitions are fair, the problem of doping is played down and at the same time critical observers and athletes who report the existence of doping practices in the environment of competitions or teams are marginalized via accusations of »letting the team down« or »general suspicion« (Singer/Treutlein 2007, p. 13).

However, it is by no means just by smoothing things over and by marginalizing whistleblowers that sports organizations react to the risk that doping could

38 This is illustrated by the continuous increase in the number of world cups that require participation in a number of competitions, e.g. the *Tour de Ski* (eight cross-country skiing races over ten days), the *ProTour* (27 cycling road races per season), and the Youth Olympic Games (for athletes 14 to 18 years of age), the creation of which was approved by the IOC in 2007 and which are to be held for the first time in the summer of 2010 and the winter of 2012 with the participation of 3000 and 1000 young athletes, respectively.

39 Widespread use of gene doping would make the expectation of authentic achievement even lower than it has already become due to the increasing medicalization of sport. »Gene doping would spark a competition between biotechnologists ... Competition would no longer be between athletes, but between biotechnologists; the athlete would be reduced to a biotechnological agent.« (Fuchs et al. 2007, p. 6)

eventually make the whole world of sport seem dishonest and unattractive – especially in the eyes of the mass media, the public, and private and public sponsors. In response to growing disillusionment, especially on the part of the sport-loving public, with the »special world« of sport (Franke 2007) with its supposed attributes of honesty and fairness, they are forced to take a position on the question of doping, since otherwise sponsors could terminate their contracts and politicians could cut their funding. Since their very existence depends on this support (Bette/Schimank 2006b, p. 313), sports associations become active in the fight against doping. Their repertoire of anti-doping measures includes pedagogic strategies and informational campaigns that provide relevant information, e.g. on the health damage that can result from doping. Another important area of action is that of control and sanctions structures. It is here, however, that the ambivalent situation in which sports associations find themselves is especially clear: controls and sanctions could indeed make elite sport somewhat »cleaner«, however this could jeopardize its very success. Like athletes, sports associations are thus caught in a »doping trap«. Again as with athletes, the situation is exacerbated by the risk that other associations, either domestic or international, are unable or unwilling to cooperate by imposing systematic controls.

This constellation of elements that form part of, and result from, the »systems logic« of competitive sport largely explains the much-criticized tardiness and inconsistency of sports organizations that fail to combat doping in systematic fashion, but instead merely »simulate« a commitment (Bette/Schimank 2006b, pp. 380 and 395).

STATE SUPPORT – RECREATIONAL SPORT, TALENT DEVELOPMENT, ELITE SPORT

Support of sport by the German *Lands* is directed at recreational sport and talent development right up to the elite level. This support is intended to contribute to, among other things, preventive health, prevention of antisocial behavior, and a reduction in violent behavior (Bundesregierung 2006). The responsibility of the *Lands* is limited to the developmental phases of sport in which doping mentalities arise but punishable doping actions have generally not yet occurred (Fig. 9, phases I and II). Because of Germany's federal structure, the individual *Lands* are able to fashion their sport support programs autonomously. Approaches vary with regard to both support of sporting achievements and actions

to influence doping behavior.[40] The Sports Ministers Conference (*Sportministerkonferenz*, SMK) of the German *Lands* has so far been restrained in its statements about doping. In 2006 it called for harsher penalties for doping violators, and in 2007 it expressed the view that those entrusted with the task of combating doping should be provided with all necessary means to do so (www.sportministerkonferenz.de/dateien/PM%20300707.pdf). So far, however, anti-doping measures have scarcely been discernible as a topic. Doping is seen mostly as a problem of elite sport. To date, the attitude of the *Lands* scarcely suggests that they see themselves as having any specific responsibilities in the fight against doping.

The German Federal Government continues what the *Lands* have started. Its support of sport is intended to reinforce positive signals both inside and outside of competitive sport. Its support is explicitly directed at elite sport and tied to performance figures such as squad membership and medal chances at international tournaments. This applies both to direct support of individual athletes and to support of sports organizations. When providing support the Federal Government respects the sense of responsibility and the autonomy of sport and places its trust in sport's »self-cleaning« capacity, however it demands observance of the World Anti-Doping Code (WADC).

As well as supporting sport, the German Federal Government still largely finances the anti-doping activities of NADA and other preventive anti-doping research up to the level of WADA. Up to now this financial support has gone almost exclusively to the system of doping controls and sanctions. In 2007 legal measures relating to the fight against doping were strengthened. These are directed mostly at persons in the athlete's milieu (Section IV.3.2). Doping control remains a responsibility of the *Lands*. The powerful incentives to strive to reach the top level in sport are still present.

The finding that the world of athletes and sports organizations is structurally linked to the world of doping is true also of the world of politics. The state supports sport because it is interested in success. However, since this success is supposed to be achieved in conformity with rules, the state also supports doping con-

40 In Baden-Württemberg, for example, the Ministry for Culture, Youth, and Sport does not deal with doping as a topic in itself. However, in 2005 a general survey of state support of sport was conducted and the current situation, state of development, and outlook were assessed. The *Land* Sports Association (*Landessportverband*, LSV) performed a stocktaking and review of its anti-doping activities (LSV 2007). Similarly in Berlin, the subject of doping is not referred to in direct connection with the support of sport. Neither on the web pages of, or in any other informational material on the support of sport in Berlin provided by, the Berlin Senate Administration for the Interior and Sport (*Senatsverwaltung für Inneres und Sport*) nor on the web pages of the Berlin Sports Federation (*Landessportbund Berlin*) do the terms »doping« or »anti-doping« appear.

trol and sanctions systems in sport and establishes its own rules in the form of laws. Success in the fight against doping could, however, mean failure on the part of national athletes, especially as the doping practices of competitors from other countries may be opaque and the doping control and sanctions systems of some countries may be largely symbolic and ineffective.

PRIVATE SPONSORS

As a result of the marketing of sport and the development of sport into an *image bearer* and *trademark*, sporting performances and competitions in various types of sport have become exploitable for financial gain and of increasing interest to private sponsors. Over the past few years the resulting opportunities for major commercialization of some types of sport have led the German Federal Government to limit its support to a single rung of the sports career ladder and leave other levels to private sponsors.

Private sponsors get involved in order to use sport to draw attention to themselves and their products. Sports competitions and individual elite athletes permit a transfer of image to companies' products and companies themselves. They hope that characteristics associated with competitive sport such as youthfulness, dynamism, and motivation will be projected onto the company. Within certain limits, public discussion of doping in the type of sport concerned does not jeopardize this objective[41] provided that doping cannot be linked directly to the sponsor. When these limits have been exceeded in the past, the resulting threats by industry to withdraw from sports sponsorship have at least led to an intensification of efforts to fight doping. As yet, however, there has been little evidence of the adoption of any coordinated anti-doping policy by involved companies or of any concerted action against doping, e.g. involving cooperation between private companies and anti-doping organizations or public authorities.

CONCLUSION: DOPING AS A STRUCTURAL EFFECT

Elite sport is part of a global market phenomenon in which athletes and the people in their milieu have, by their actions and omissions, created a system of which doping behavior is an integral part. Bette/Schimank (2006b, p. 149 ff.), for example, regard doping as a structural effect. Knoepffler/Albrecht (2007) conclude that in the presence of the existing motivating structures in sport only a very strong and determined personality can resist the temptation to engage in doping. It would therefore be a mistake to attempt to change the present situa-

41 In 2006 the Gerolsteiner racing team conducted a survey of people who watched cycling races. Only 7% of those surveyed stated that they had stopped watching cycling on television because of the problem of doping in cycling. The rest were unconcerned. This phenomenon is apparent not just from survey results and viewing figures, but also from spectator behavior at sporting events.

tion by working only with athletes using methods such as provision of information, explanation, and education. Rather, the whole situation that has led to doping needs to be examined and consideration given to the responsibility of those who have contributed to the development of the institutional motivating structures: »Only as a result of the failure of many people to take action against doping has the spread of doping firstly to elite sport, and over the past few decades also far beyond this into the realm of fitness and recreational sport, been able to assume such wildfire-like proportions. ... Germany's federal system has facilitated this failure to act by a variety of people and institutions both inside and outside of sport. When asked to take the initiative in the fight against doping, decision-makers at all levels have been able to deny responsibility and pass the buck to other institutions. These likewise did not consider themselves to bear responsibility for dealing with the problem. This led to a *system of organized lack of responsibility*. A particular feature of this system of institutional encouragement of doping is that it was able to come into being with only a minimum of conspiratorial communication. As a result, there are scarcely any people or institutions who can be held concretely responsible for the wrong turns that were taken. Such a system develops and becomes established as if by itself.« (Singer/Treutlein 2007, p. 7 ff.)

According to Singer/Treutlein (2007, p. 13), the making of changes to the entire system of sport and a breaking down of the tangled network of benefits involving athletes, sports associations, industry, and the media will require immense efforts and a »Copernican change« in the sense of responsibility of office-holders at all levels of public and political life both inside and outside of sport. Doping is a »collectively created« problem and as such (like global environmental problems) can be solved only by joint activities at multiple levels (Bette 2006, p. 87).

As another turn in the vortex of doping, gene doping could signify both a real risk to sport and an opportunity to break down the system of »institutional encouragement of doping«. Gene doping could act as a warning sign. Public debate about gene doping could make clearer what is to a large extent already known, namely that doping undermines the public's interest in and willingness to identify with athletes, »dupes politicians whose task it is to allocate public funds, prevents the image transfer that is the objective of sponsoring arrangements, and disillusions sport's recruitment base in schools and families« (Bette/Schimank 2006b, p. 308). As a new wave of doping could further devalue not only the intangible values of sport but also the concrete material interests of all those involved at all levels of sport, gene doping could prove to be a signal for a change of course.

2. INDIVIDUAL SPORT

For most people the motivation to engage in individual sport arises mainly from a desire to maintain health and physical performance. Because in many cultural milieus these aims imply an athletic physique, which is also associated with several other stereotypes such as success and recognition, the desire for an athletic body or increased strength is deeply rooted. As in competitive sport, many people who strive to achieve an athletic body are health-conscious and remain so throughout their active athletic phase.

Sport at the individual level is based on the rejection of organized settings and the association of athletic activity with certain norms and rules. Fitness studios see themselves as unbiased, neutral providers of services tailored to the wishes of athletically active people. The rules in fitness studios do not define self-doping as a violation. Hence, controls and sanctions under civil law cannot be applied. Everyone is free to indulge in self-harming behavior if they so desire: in some cases it is overlooked, in other cases it is actively supported.[42] Consequently, fitness studios or their milieus can become marketplaces at which professional, well organized doping drug traffickers and consumers meet. Analogies to the »system of organized irresponsibility« described by Singler/Treutlein (2007) should therefore not be dismissed out of hand.

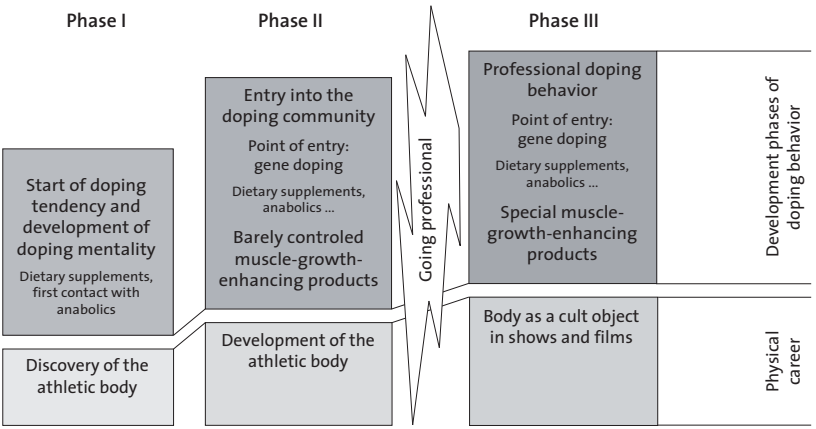
2.1 BODYBUILDING

As long as the basic motivation for athletic activity is to maintain physical health, the obstacles to the emergence of doping behavior among individual athletes are probably relatively high, especially if the athletes are able to obtain information from independent sources. However, if the underlying motivation becomes the »building« of an athletic body with associations of energy, strength, and success (image projection), doping behavior can quickly develop. Such behavior is bolstered by social trends such as the increasing medicalization of everyday life, the declining importance of traditional virtues (e.g. diligence, discipline, abstinence), and the rising importance of hedonistic values of self-realization (happiness, communication, pleasure).

42 It is not known whether fitness studios pass anti-doping conduct rules in agreement with their users. In Germany they are not subject to any specific civil sports jurisprudence but only the laws of the state. In some cases it is therefore argued that behavior in fitness studios should not be referred to as doping but rather as drug abuse.

The emergence of a doping mentality and doping practice depends on numerous factors[43] but is not necessarily a drawn-out process. The initial encounter with doping substances can occur in the early phase of discovery of the athletic body. Many adolescents embark on the problematic use of drugs relatively early, as studies in the USA have shown: before the age of 17 or 15 (Giebing 2002, p. 24) or even earlier (Feigenbaum et al. 1998). At this age the potential for harm is especially great, and the side effects are often more severe than for example in male adults. On the bodybuilding scene the development of doping behavior is ushered in by the misuse of muscle-growth-enhancing drugs in adolescents (Bätzing 2007; Laure/Treutlein 2006, p. 54 ff.) (Figure 13, phases I and II).

FIG. 13 DEVELOPMENT OF DOPING BEHAVIOR IN THE BODYBUILDING SCENE



Own illustration

Giebing (2002, p. 24) points out that according to some US studies »nearly one in ten male adolescents has already used anabolics«. A noteworthy finding is that adolescents who do not use anabolics do not by any means reject them and in fact evince a willingness to take them. This is compounded by poor knowledge of the side effects (Giebing 2002, p. 24) and the ready availability of anabolic drugs (via the internet, professional structures that also serve the general drug market, pliant physicians, or counterfeit prescriptions coupled with inattentiveness of pharmacies) (Boos et al. 1998; Donati 2006 and 2007).

43 An international literature review conducted for WADA showed that doping behavior tends to be influenced by gender, age, training frequency, type of sport, consumption of other drugs, and familiarlization with other doping athletes as well as by the individual's body perception and self-image (Backhouse et al. 2007, pp. 10 ff.).

If the desire for an athletic body and its exhibition grows stronger (Fig. 13, Phase II), the internet with its communication possibilities provides an ideal setting for finding like-minded people and exchanging information on, for example, sales channels – even without fixed organizational structures. In many cases the motivation to engage in doping stems from a lack of training success and/or time. According to Boos et al. (1998), 12% of individual athletes who indulge in doping have less than two years' training experience, and another 16% only train two to three years before resorting to doping agents. If the athlete then wants to exhibit his/her physical fitness thus achieved, national and international amateur competitions provide a stage for this. However, it is reasonable to assume that the use of performance-enhancing drugs is motivated only in small part by a desire to participate in competitive events (Giebing 2002, p. 25).

If the body is developed to an extreme degree, practitioners can become professional – even in the body building arena. This is phase III (Fig. 13). Performance pressure and economic dependencies mount, giving rise to motivating structures for doping. Giebing (2002, p. 23) reports that in the performance-oriented sport of bodybuilding, doping is used on an extensive scale.

EMPIRICAL KNOWLEDGE OF DOPING IN FITNESS STUDIOS

It has now been relatively well documented by numerous studies that the use of doping substances has developed into an »epidemiologically significant phenomenon« in Western industrialized countries (Striegel/Simon 2006, p. 63). Increasingly, not only elite sport but also recreational and fitness sport are affected. EU studies from 2002 indicate that at least 6% of the 16 million members of approximately 23,000 fitness studies use doping substances (Donati 2006, p. 22).

The 2006 health report by the German federal government summarized surveys on doping in recreational and popular sport (Müller-Platz et al. 2006). In one of the documented studies in which members of 58 fitness studios were surveyed (454 evaluated questionnaires; return rate 35%), 22% of the men and 8% of the women admitted misusing drugs. The following points were clear:

- Misuse commenced well after the individuals started training.
- Those who admitted to drug misuse for doping purposes were less well educated on average than those who denied misusing drugs.
- The misuse of anabolic drugs was associated relatively frequently with the use of other stimulants and drugs (Boos/Wulff 2001, from Müller-Platz et al. 2006, p. 16).

A 2001 study conducted among 113 fitness studios in southern Germany produced the following results based on 1,802 anonymized questionnaires

(return rate 34.5%) (Striegel/Simon 2006): 13.5% of the respondents (19% of the men and 4% of the women) had already taken doping substances (Striegel 2007, p. 111). 98.5% of these cases involved the use of anabolic drugs. Unlike the study by Boos/Wulff (2001), this investigation found a negative correlation between the use of doping substances and alcohol consumption. Moreover, the group of doping-substance users tended to be health-conscious and socially well integrated, i.e. they were not a »group of socially deprived individuals with a tendency towards generalized drug use« (Striegel/Simon 2006, p. 65).

According to Müller-Platz et al. (2006, p. 17) doping substances were detected in 39% of urine samples at bodybuilding events in Germany in the period from 1995 to 2000. Control tests detected not just anabolic substances but in most cases all the usual doping agents.

BODYBUILDING AS A POINT OF ENTRY FOR GENE DOPING

Ambitious bodybuilding is likely to be the main point of entry for gene doping in individual sport. In this context gene doping – like conventional doping in individual sport – focuses mainly on the formation of skeletal muscle. The stronger the personal fixation on the development of a muscular physique, the greater is the individual's willingness to accept risks and experiment, including offering him/herself as a test subject – and this does not apply only to the relatively small group of professionals. Thus gene doping could be used in ambitious bodybuilding at the same time or even earlier than in competitive sport (unlike in the past where doping drugs were first used in competitive sport and only later in the fitness arena). The scope, speed, and form of diffusion will probably depend on a number of restrictive and promotional factors, as in organized competitive sport.

In individual sport too the greatest barrier to the use of gene doping is currently its unavailability or inaccessibility. As in the case of elite athletes, this barrier is probably greater for gene therapy methods than for specific gene-regulating methods. However, unavailability as such is a relative quantity whose effectiveness depends on the willingness to take risks by procuring and using untested drugs and methods. As soon as these drugs are available (in the sense that they exist), misuse is likely to occur. All the forms of drug crime that currently exist (illegal imitation products; impure, unknown, and uncontrolled substances; illegal trafficking) can occur, as described in the report of the German Federal Bureau of Investigation on drug crime (Sürmann 2007). Criminal infrastructures and distribution networks (Donati 2006) are able to supply new untested substances, especially if they do not involve increased demands with regard to their use and handling compared to previous drugs. With the help of the internet,

criminal supply structures meet organized demand structures (specific forums, blogs, chatrooms). However, these distribution structures probably do not yet include special laboratories at which individual athletes willing to engage in doping can be »treated«.

Bodybuilders as a group already seem to have poorer health-risk perception than other population groups. Knowledge about potential side effects of doping drugs is often generated from milieus that favor doping (Striegel 2007, pp. 115 ff.). Overall, this results in the supposed effectiveness being overstated and the risks understated. Because the risks are glossed over, side effects do not have much of a deterrent effect. Relevant internet pages show that a willingness to experiment is present.

In addition, the gene doping barrier in the ambitious bodybuilding scene will be determined by the efficacy, dosage forms, and costs. The relevant frame of reference are the anabolic steroids. For new drugs to prevail in this »marketplace«, the balance between muscle-building effects, complexity of use, and costs must be better than that of anabolic steroids. Hence, techniques that can only be exploited with the help of specialists may find use in professional bodybuilding, but the danger of them spreading further is less likely. Based on the current state of knowledge, gene doping in the broad sense, especially in relation to the blockade of myostatin, must be seen as an immediate danger (Section II.4).

EXCURSUS: OLDER ATHLETES 2.2

In individual as well as in organized sport, supply and demand among older people are growing apace. This trend is expected to continue unabated due to the increasingly prevalent view that preventive health maintenance brings about a gain in quality of life particularly for older people and is probably also more cost-effective than the curative approach. This trend is being driven by a demographic shift with the »aging of society«. Sport is a keystone of the preventive health maintenance approach. Many sports associations, sports clubs, and fitness studios cater separately to older people with a growing number of events and competitions, especially in the endurance area.[44] The motivation for older people to engage in sport is usually intimately linked to the aim of maintaining health, coupled with a desire to slow the progression of age-related physical changes. But age is no guarantee against excessive athletic ambition. Many older athletes wish to achieve top athletic performance and tend to deny physical aging processes.

44 Take marathon running as a recreational sport, for example: In 1979 there were 50 events with approximately 10,000 runners. In 2005 there were 153 marathon events with an estimated hard core of approximately 100,000 active runners, whose mean age is steadily rising (http://de.wikipedia.org/wiki/Marathonlauf).

The growing importance of sport for older people is coupled with a changing understanding of medical science, which increasingly pursues not only curative but also preventative goals. Thus, it is becoming more and more an aim of medical science to offer interventions in functional body processes. A growing and to a large extent wealthy segment of the population is becoming an interesting target group for commercial medicine. Analysts regularly predict a huge market potential for pharmaceutical products for preventive health maintenance. The licensing of a drug, which is granted on the basis of proof of efficacy in a specific indication, opens up possibilities for other uses. The principle of freedom of treatment in Germany grants physicians broad discretionary powers in the choice of treatment. Physicians may not traffic in, prescribe, or use drugs for doping purposes (§ 6a no. 1 AMG, Section IV.3.2). However, in order to counter the age-related loss of skeletal muscle, for example, physians can suggest certain measures to their patients based on their medical competence (age, indication, form of treatment [preventative or curative treatment, training, a healthy diet, and/or »anti-aging« or »lifestyle« therapies]). On the basis of age or a condition-related indication, it could then also be possible to treat deficiencies that have no pathogenic value in order to improve the individual's well-being (comparable in some respects to the marketing strategy for the PDE-5 inhibitor Viagra® or the use of the amphetamine derivative Ritalin®). This development will be favored by an overall high level of social acceptance of efforts to slow the rate of physical aging processes by pharmacologic means.

Even if such use does not constitute doping as defined by association and criminal law because it does not explicitly aim to enhance performance in sport, this form of application of new therapeutic options will influence and shape sport. The trends described above also show that doping in older or unhealthy individuals is becoming increasingly difficult to define and delineate and has led to a growing controversial debate on medical enhancement in general.

NEED FOR INFORMATION AND ACTION VI.

Gene doping means entering a political sphere characterized by incomplete and uncertain knowledge about future developments coupled with an urgent need for action due to its considerable potential for misuse. The possible timeframe for doping in sport (and beyond) is likely to be extended by gene doping. This could lead to another turn of the doping spiral or it could negate successes already achieved. The following examples of options for action take this situation into account. Together, these options can form the backbone of a specific anti-gene doping strategy.

OBSERVING DEVELOPMENT PROJECTS WITH REGARD TO THEIR RELEVANCE TO GENE DOPING

Gene doping misuses knowledge from basic and/or applied research in the life sciences that was intended to lead to new therapeutic strategies. Continuous predictive monitoring of biomedical and pharmaceutical development projects and of the potential demand side could provide strategically important information about trends relevant to doping. Screening need not cover the entire range but could concentrate on those areas of development expected to be highly relevant to gene doping. This report points out some developments along these lines (Section II). Continuous monitoring could become a kind of early warning system, providing guidance for those involved in the fight against doping and insights into preventive doping research. Close cooperation between preventive doping research, existing control and monitoring institutions and drug research would be required.

RESEARCHING DETECTABILITY, DEVELOPING TESTS, DESIGNING INTELLIGENT MONITORING

There is a great need for research and development work to devise gene doping detection methods and suitable validated tests. A two-step approach within the control system currently appears to be the most promising. It covers intelligent monitoring and, where there are grounds for suspicion, specific tests for verification. This kind of monitoring must aim to measure specific performance-relevant physiologic parameters of athletes that could provide evidence of manipulation. It calls for specialized knowledge, i.e. what parameters measured at what intervals can provide evidence of doping-induced developments and abnormalities? In addition, numerous details of so-called results management must be considered (e.g. storage periods). At the same time, there is a need for legal clarification with regard not only to proportionality and suitability but also data protection and personal protection. If this approach can be refined into a practicable con-

cept with suitable validated tests, the prospects for countering the expected rise in new doping practices, including gene doping, are good.

DEVELOPING CONCEPTS AND ACTIVITIES FOR PUBLIC INFORMATION CAMPAIGNS SPECIFIC TO GENE DOPING (BEHAVIOR PREVENTION)

In parallel with the further development of testing and sanctioning structures, independent public information campaigns focusing on gene doping must be devised. Given the current early stage of development, these could certainly have a preventative and behavior-modifying effect. For them to work, however, a broad design is needed which covers the whole process of individual sports development during which mentalities and behavioral patterns favorable to doping can gradually arise. Such an approach should take into consideration both the athlete's immediate milieu (trainer, manager, physician) and the role of sponsors and the media.

A key topic could be the unknown health risks involved. The potential and in some cases probable consequences should be presented in relation to the athlete type and the relevant circumstances. Where health is a strong motivator in sport, an attitude critical of doping could be fostered or developed. However, such education campaigns meet their limits where attitudes favoring extreme performance prevail. Here one must be realistic with regard to the target group of top-level athletes who have already embarked on their athletic careers. The practical application of concepts would have to be accompanied by interdisciplinary research that provides a stimulus for refining the concepts on the basis of critical evaluation. However, public awareness of the fact that gene doping is a real danger must be awakened and heightened. The political debate can highlight the fact that gene doping could be a trend intensifier for doping practice in competitive sport and beyond.

ADAPTING FUNDING POLICIES

Sport in general and elite sport in particular is shaped by a large number of actors. In the context of the public funding of sport, those receiving financial support are now required to adhere to the rules set down by WADA and NADA. In this respect, gene doping is covered. Repayment of financial support in the event of violations, however, requires proof that will stand up in court. Here again detection proves to be the Achilles heel. Nevertheless, the demand for compliance with anti-doping rules should be upheld in any case and, indeed, applied even more stringently to gene doping. To this extent, the state could serve as a role model for private sector sponsorship in its funding activities.

GERMAN DRUG LAW: CHECKING ITS APPLICABILITY AND FURTHER STATUTORY OFFENCES

The German *Gesetz zur Verbesserung der Bekämpfung des Dopings im Sport* (Law to Improve the Fight against Doping in Sport) has created better conditions for the prosecution of doping, particularly in the athlete's own milieu. It is a jurisprudential and legislative challenge to review and if necessary refine suitable legislative norms in the light of further development. For example, gene doping could be more clearly defined as a prohibited act in order to satisfy the principle of clarity and definiteness. Given the recent extension of the definition of doping to include any substance intended for use in conjunction with prohibited methods, it should be possible to include substances relevant to gene doping. To this end reference could be made in § 6a, nos. 2 and 2a AMG to § 4, no. 9a, AMG. In this way, the use of gene transfer agents for the purpose of gene doping could be prohibited.

In the light of further development, it should also be considered whether the constituent element »*nicht geringe Menge*« (= more than a small amount) is even valid for gene doping or whether instead any medically unindicated use of gene transfer agents in humans should be made a punishable offence. Given a specific risk potential, in due time it could be examined whether gene doping substances reasonably suspected of carrying a risk should be equated with narcotic drugs. This would afford an opportunity to make possession a punishable offence under the *Betäubungsmittelgesetz* (Narcotics Law).

The state has the capacity to assist organized sport in the pursuit of cases of gene doping. The setting up and training of special police units and specialized public prosecutor's offices for the effective criminal prosecution of offenders, clearly defined contact routes and contact persons, and closer cooperation between prosecuting authorities and other relevant entities and individuals (science, sport, pharmaceutical manufacturers) are already important means for combating conventional doping and will be indispensable in the fight against gene doping.

PARLIAMENTARY TECHNOLOGY IMPACT ASSESSMENT, PUBLIC DEBATE

The relevance of gene doping stems not only from its significance as a factor that will probably intensify the problem of doping in sport. Rather, the potential diffusion of gene doping options reflects another highly relevant problem: a growing social trend towards the use of pharmaceutical agents or (neuro-) technical methods to manipulate physical and psychological performance beyond sports. »Routine doping« or »enhancement« is a topical subject that will continue to be relevant to technology impact evaluation and the select committees of the German Bundestag in the future.

Like a lens, gene doping focuses the overarching aspects of doping in sport. The field of gene doping will allow the German Bundestag and its select committees to take a pioneering role in the political and social debate. Proactive positioning that is visible to the public could also include an initiative to establish further impact and prevention research as a basis for political and legal measures. The problems that gene doping might pose in the future for sport in general and competitive sport in particular are a strong argument for the responsible actors, especially policymakers, not to relent in their antidoping activities.

BIBLIOGRAPHY

COMMISSIONED EXPERT REPORTS 1.

Diel, P., Friedel, U. (2007): Gendoping: Techniken, potenzielle biologische Ziele und Möglichkeiten des Nachweises. Deutsche Sporthochschule Köln

Franke, E. (2007): Doping – ein nicht zufälliges Dilemma: Die (traditionelle) Athletenverantwortung in der (globalen) Systemwelt des Sports. Berlin

Fuchs, M., Lanzerath, D., Sturma, D. (2007): Natürlichkeit und Enhancement. Zur ethischen Beurteilung des Gendopings. Bonn

Kekulé, A.S. (2007): Gendoping – Potenzielle Anbieter und Möglichkeiten der Kontrolle. Halle

Knoepffler, N., Albrecht, R. (2007): Das Täter-Opfer-Verhältnis in seiner ethischen Dimension und damit verbundene Grenzen und Möglichkeiten von Antidopingstrategien. Jena

Simon, J., Robienski, J., Paslack, R. (2007): Rechtliche Aspekte des Gendopings im Sport. Lüneburg

Singler, A., Treutlein, G. (2007): Doping in demokratischen Gesellschaftssystemen. Heidelberg

Striegel, H. (2007): Dopingstrukturen im Sport unter besonderer Berücksichtigung der Möglichkeiten und Grenzen des Dopingnachweises. Bietigheim-Bissingen

Wolfarth, B., Scherr, J., Pertl, A. (2007): Stand und Perspektiven dopingrelevanter Ergebnisse der Genomforschung und entsprechender gentherapeutischer Verfahren. TU München / Klinikum rechts der Isar

OTHER SOURCES 2.

Andersen, J.L., Schjerling, P., Saltin, B. (2000): Muscle, genes and athletic performance. In: Scientific American 9, pp. 30–37

Arsic, N., Zacchigna, S., Zentilin, L., Ramirez-Correa, G., Pattarini, L., Salvi, A., Sinagra, G., Giacca, M. (2004): Vascular endothelial growth factor stimulates skeletal muscle regeneration in vivo. In: Molecular Therapy 10(5), pp. 844–854

Backhouse, S., McKenna, J., Robinson, S., Atkin, A. (2007): International literature review: attitudes, behaviours, knowledge and education – drugs in sport: past, present and future. Prepared for World-Anti-Doping Agency. www.wada-ama.org/rtecontent/document/Backhouse_et_al_Full_Report.pdf; accessed in March 2008

Bamberger, M., Yaeger, D. (1997): Over the edge. In: Sports Illustrated 14, pp. 62–70

Barandon, L., Leroux, L., Dufourcq, P., Plagnol, P., Deville, C., Duplaa, C., Couffinhal, T. (2004): Gene therapy for chronic peripheral arterial disease: what role for the vascular surgeon? In: Annals of Vascular Surgery 18(6), pp. 758–765

Baserga, R. (1999): The IGF-I receptor in cancer research. In: Experimental Cell Research 253, pp. 1–6

Bätzing, S. (2007): Drogen- und Suchtbericht. Bericht der Drogenbeauftragten der Bundesregierung. www.bmg.bund.de/nn_603372/SharedDocs/Publikationen/Drogen-und-Sucht/g-602,templateId=raw,property=publicationFile.pdf/g-602.pdf; accessed in June 2008

Bette, K.H. (2006): Doping als transintentionales Konstellationsphänomen. In: Knörzer, W., Spitzer, G., Treutlein, G. (eds.): Dopingprävention in Europa. Erstes internationales Expertengespräch in Heidelberg. Aachen, pp. 75–91

Bette, K.H., Schimank, U. (2006a): Die Dopingfalle. Bielefeld

Bette, K.H., Schimank, U. (2006b): Doping im Hochleistungssport. Frankfurt a.M.

BISp (Bundesinstitut für Sportwissenschaft) (2003): Gendoping. Die Dopingbekämpfung rüstet sich. Bonn

BMG (Bundesministerium für Gesundheit) (2007): Verordnung zur Festlegung der nicht geringen Menge von Dopingmitteln (Dopingmittel-Mengen-Verordnung – DmMv). Bundesrat, Drucksache 677/07, Berlin

BMI (Bundesministerium des Innern) (2007a): Doping. www.bmi.bund.de/cln_012/ nn_122688/sid_356152B911D7BB2E1C9DAAFE15C2BABE/Internet/Content/Common/Lexikon/D/Doping__Id__20137__de.html; accessed in December 2007

BMI (2007b): Abschlussbericht Projektgruppe Sonderprüfung Doping. Bonn

Bogdanovich, S., Krag, T.O., Barton, E.R., Morris, L.D., Whittemore, L.A., Ahima, R.S., Khurana, T.S. (2002): Functional improvement of dystrophic muscle by myostatin blockade. In: Nature 420, pp. 418–421

Boos, C., Wulff, P., Kujath P., Bruch, H.–P. (1998): Medikamentenmissbrauch beim Freizeitsportler im Fitneßbereich. In: Deutsches Ärzteblatt 95(16), pp. 953–957

Boos, C., Wulff, P. (2001): Der Medikamentenmissbrauch beim Freizeitsportler im Fitnessbereich. Öffentliche Anhörung zum Doping im Freizeit- und Fitnessbereich. Protokoll der 38. Sitzung des Sportausschusses, 14. Wahlperiode, pp. 115–152

Brissonneau, Ch. (2004): Dopage: Le rôle des médicins. In: Le Monde, 16-Jan-2004. www.lemonde.fr/web/imprimer_element/0,40-0@2-3242,50-1301,0.html; accessed in March 2008

Bundesregierung (2006): Unterrichtung durch die Bundesregierung. 11. Sportbericht der Bundesregierung. Deutscher Bundestag, Drucksache 16/3750, Berlin

Bundesregierung (2007): Entwurf eines Gesetzes zur Verbesserung der Bekämpfung des Dopings im Sport. Deutscher Bundestag, Drucksache 16/5526, Berlin

Callinan, P.A., Feinberg, A.P. (2006): The emerging science of epigenomics. In: Human Molecular Genetics 15(1), pp. 95–101

Chargé, S.B., Rudnicki, M. A. (2004): Cellular and molecular regulation of muscle regeneration. In: Physiological Reviews 84, pp. 209–238

Chenuaud, P., Larcher, T., Rabinowitz, J.E., Provost, N., Cherel, Y., Casadevall, N., Samulski, R.J., Moullier, P. (2004): Autoimmune anemia in macaques following erythropoietin gene therapy. In: Blood 103(9), pp. 3303–3304

Chi, N., Epstein, J.A. (2002): Getting your Pax straight: Pax proteins in developement and disease. In: Trends in Genetics 18, pp. 41–47

Clarke, D. C., Miskovic, D., Han, X.X., Calles-Escandon, J., Glatz, J.F., Luiken, J.J., Heikkila, J.J., Bonen, A. (2004): Overexpression of membrane-associated fatty acid binding protein (FABPpm) in vivo increases fatty acid sarcolemmal transport and metabolism. In: Physiological Genomics 17(1), pp. 31–37

Council of Europe (1989): Anti-Doping Convention. http://conventions.coe.int/Treaty/en/Treaties/Html/135.htm

Coussens, L.M., Fingleton, B., Matrisian, L.M. (2002): Matrix metalloproteinase inhibitors and cancer: trials and tribulations. In: Science 295(5564), pp. 2387–2392

Deems, R.O., Evans, J.L., Deacon, R.W., Honer, C.M., Chu, D.T., Burki, K., Fillers, W.S., Cohen, D.K., Young, D.A. (1994): Expression of human GLUT4 in mice results in increased insulin action. In: Diabetologia 37, pp. 1097–1104

DFG (Deutsche Forschungsgemeinschaft) (2006): Entwicklung der Gentherapie. Stellungnahme der Senatskommission für Grundsatzfragen der Genforschung. Mitteilung 5, DFG, Bonn

Donati, A. (2006): Zur Situation des internationalen Schwarzmarktes. In: Knörzer, W., Spitzer, G., Treutlein, G. (Hg.): Dopingprävention in Europa. Erstes internationales Expertengespräch in Heidelberg. Aachen, pp. 17–29

Donati, A. (2007): World traffic in doping substances. www.wada-ama.org/rtecontent/document/Donati_Report_Trafficking_2007-03_06.pdf; accessed in March 2007

dsj (Deutsche Sportjugend im Deutschen Olympischen Sportbund e.V.) (2004): Sport ohne Doping! Argumente und Entscheidungshilfen (authors: Arndt, N., Singler, A., Treutlein, G.), Frankfurt a.M.

Ehrenreich, H., Aust, C., Krampe, H., Jahn, H., Jacob, S., Herrmann, M., Siren, A.-L. (2004): Erythropoietin: novel approaches to neuroprotection in human brain disease. In: Metabolic Brain Disease 19(3/4), pp. 195–206

Emrich, E., Klein, M., Papathanassiou, V., Pitsch, W., Schwarz, M., Urhausen, A. (2004): Soziale Determinanten der Freizeit- und Gesundheitsverhaltens saarländischer Schülerinnen und Schüler – Ausgewählte Ergebnisse der IDEFIKS-Studie (Teil 3). In: Deutsche Zeitschrift für Sportmedizin 55(9), pp. 222–231

Feigenbaum, A. D., Zaichkowsky, L. D., Gardner, L. E., Micheli, L. J. (1998): Anabolic steroid use by male and female middle school students. Pediatrics, 101(5), pp. 1–6

Friedman, J.E., Dudek, R.W., Whitehead, D.S., Downes, D.L., Frisell, W.R., Caro, J.F., Dohm, G.L. (1991): Immunolocalization of glucose transporter GLUT4 within human skeletal muscle. In: Diabetes 40(1), pp. 150–154

Geisser, R. (2007): Die Blutspur des Radsports. In: NZZ–Online, 15-Aug-07. www.nzz.ch/nachrichten/sport/aktuell/die_blutspur_des_radsports_1.536876.html; accessed in September 2007

Gervois, P., Fruchart, J.C., Staels, B. (2007): Drug insight: mechanisms of action and therapeutic applications for agonists of peroxisome proliferator-activated receptors. In: Nature Clinical Practice Endicrinology Metabolism 3(2), pp. 145–156

Giebing, J. (2002): Fitness-Studios und Muskelpillen: Doping als Phänomen des Breitensports. In: dvs-Informationen 17(4), pp. 23–25

Goldspink, G., Yang, S.Y. (2004): The splicing of the IGF-1 gene to yield different muscle growth factors. In: Advances in Genetics 52, pp. 23–49

Gould, G.W., Holman, G.D. (1993): The glucose transporter family: structure, function and tissue-specific expression. In: Biochemical Journal 295(2), pp. 329–41

Grimberg, A., Cohen, P. (2000): Role of insulin-like growth factors and their binding proteins in growth control and carcinogenesis. In: Journal of Cellular Physiology 183(1) pp. 1–9

Haas, U. (2002): Die rechtlichen und organisatorischen Grundlagen der Dopingbekämpfung in der Bundesrepublik Deutschland. Baden-Baden

Hamilton, J.A., Kamp, F. (1999): How are free fatty acids transported in membranes? Is it by proteins or by free diffusion through the lipids? In: Diabetes 48, pp. 2255–2269

Huet, C., Li, Z.F., Liu, H.Z., Black, R.A., Galliano, M.F., Engvall, E. (2001): Skeletal muscle cell hypertrophy induced by inhibitors of metalloproteases; myostatin as a potential mediator. In: American Journal of Physiololgy - Cell Physiology 281, pp. 1624–1634

Idris, N.M., Haider, H.K., Goh, M.W., Sim, E.K. (2004): Therapeutic angiogenesis for treatment of peripheral vascular disease. In: Growth Factors 22(4), pp. 269–279

Ishizuka, K., Usui, I., Kanatani, Y., Bukhari, A., He, J., Fujisaka, S., Yamazaki, Y., Suzuki, H., Hiratani, K., Ishiki, M., Iwata, M., Urakaze, M., Haruta, T., Kobayashi, M. (2007): Chronic TNF{alpha} treatment causes insulin resistance via IRS-1 serine phosphorylation and SOCS3 induction in 3T3-L1 adipocytes. In: Endocrinology 148(6), pp. 2994–3003

Jackson, A.L., Bartz, S.R., Schelter, J., Kobayashi, S.V., Burchard, J., Mao, M., Li, B., Cavet, G., Linsley, P.S. (2003): Expression profiling reveals off-target gene regulation by RNAi. In: Nature Biotechnology 21(6), pp. 635–637

Jones, D., Round, J., De Haan, A. (2004): Skeletal muscle from molecules to movement. Elsevier, London

Kawamoto, A., Murayama, T., Kusano, K., Li, M., Tkebuchava, T., Shintani, S., Iwakura, A., Johnson, I., von Samson, P., Hanley, A., Gavin, M., Curry, C., Silver, M., Ma, H., Kearney, M., Losordo, D. W. (2004): Synergistic effect of bone marrow mobilization and vascular endothelial growth factor-2 gene therapy in myocardial ischemia. In: Circulation 110(11), pp. 1398–1405

Kayano, T., Burant, C.F., Fukumoto, H., Gould, G.W., Fan, Y.S., Eddy, R., Byers, M.G., Shows, T.B., Seino, S., Bell, G.I. (1990): Human facilitative glucose transporters. Isolation, functional characterization, and gene localization of cDNAs encoding an isoform (GLUT5) expressed in small intestine, kidney, muscle, and adipose tissue and an unusual glucose transporter pseudogene-like sequence (GLUT6). In: Journal of Biological Chemistry 265(22), pp. 13276–13282

Kindermann, W., Steinacker, J.M. (2007): Unser Anti-Dopingsystem muss einfacher und besser werden! In: Deutsche Zeitschrift für Sportmedizin 58(6), pp. 151–152

Kollek, R., Feuerstein, G., Schmedders, M., van Aken, J. (2004): Pharmakogenetik: Implikationen für Patienten und Gesundheitswesen. Anspruch und Wirklichkeit der »individualisierten Medizin«. Baden-Baden

KPMG (2002): Aren't we all positive? A (socio) economic analysis of doping in elite sport. http://ec.europa.eu/sport/action_sports/dopage/studies-reports/2002-study-socioeconomic_en.pdf; accessed in June 2007

Kramer, D.K., Ahlsen, M., Norrbom, J., Jansson, E., Hjeltnes, N., Gustafsson, T., Krook, A. (2006): Human skeletal muscle fiber type variations correlate with PPAR alpha, PPAR delta and PGC-1 alpha mRNA. In: Acta Physiollgica 188(3-4), pp. 207–216

Laure, P., Treutlein, G. (2006): Studien zum Doping von Jugendlichen und Ansätze zur Prävention. In: Knörzer, W., Spitzer, G., Treutlein, G. (eds.): Dopingprävention in Europa. Erstes internationales Expertengespräch in Heidelberg. Aachen, pp. 48–62

Lee, S.J., McPherron, A.C. (2001): Regulation of myostatin activity and muscle growth. In: Proceedings of National Academy of Sciences of the U.S.A. 98(16), pp. 9306–9311

Levetan, C. (2007): Oral antidiabetic agents in type 2 diabetes. In: Current Medical Research Opinion 23(4), pp. 945–952

LSV (Landessportverband) (2007): Anti-Doping Informationen. Präsentation auf der Geschäftsführertagung des LSV am 8.5.2007

Ma, K., Mallidis, C., Bhasin, S., Mahabadi, V., Artaza, J., Gonzalez-Cadavid, N., Arias, J., Salehian, B. (2003): Glucocorticoid-induced skeletal muscle atrophy is associated with upregulation of myostatin gene expression. In: American Journal of Physiological Endocrinological Metabolism 285(2), pp. 363–371

McMahon, J.M., Wells, K.E., Bamfo, J.E., Cartwright, M.A., Wells, D.J. (1988): Inflammatory responses following direct injection of plasmid DNA into skeletal muscle. In: Gene Therapy 5, pp. 1283–1290

McPherron, A.C., Lawler, A.M., Lee, S.J. (1997): Regulation of skeletal muscle mass in mice by a new TGF-beta superfamily member. In: Nature 387(6628), pp. 83–90

Melman, A., Bar-Chama, N., McCullough, A., Davies, K., Christ, G. (2006): hMaxi-K Gene Transfer in Males with Erectile Dysfunction: Results of the First Human Trail. In: Gene Therapy 17(12), pp. 1165–1176

Miah, A. (2004): Genetically modified athletes. New York

Mitchell, P. (2007): Critics pan timid European response to TeGenero disaster. In: Nature Biotechnology 25(5), pp. 485–486

Müller-Platz, C., Boos, C., Müller R.K. (2006): Gesundheitsberichterstattung des Bundes Heft 34; Doping beim Freizeit- und Breitensport. Robert Koch Institut/Statistisches Bundesamt (eds.), Berlin

NADA (Nationale Anti-Doping Agentur) (2005): Doping-Bilanz der NADA. Für den Deutschen Sport 2004. www.nada-bonn.de/fileadmin/user_upload/Downloads/Dopingbilanzen/NADA_Doping-Bilanz-2004.pdf; accessed in November 2007

NADA (2006a): Doping-Bilanz der NADA. Für den Deutschen Sport 2005. www.nada-bonn.de/fileadmin/user_upload/Downloads/ Dopingbilanzen/NADA_Doping-Bilanz-2005.pdf; accessed in November 2007

NADA (2006b): NADA-Code. www.nada-bonn.de/fileadmin/user_upload/nada/Downloads/Regelwerke/NADA-Code_2006.pdf; accessed in February 2008

NADA (2007a): Jahresbericht 2006 der NADA. www.nada-bonn.de/fileadmin/user_upload/Downloads/Dopingbilanzen/20070712_Jahresbericht-NADA_2006.pdf; accessed in November 2007

NADA (2007b): Trainingskontrollen. www.nada-bonn.de/t2/dopingkontrollen/trainings kontrollen/; accessed in December 2007

NECEDO (Netherlands Centre for Doping Affairs) (2004): Gene Doping (Haisma, H.J.). Rotterdam

Olguin, H.C., Olwin, B.B. (2004): Pax7 up-regulation inhibits myogenesis and cell cycle progression in satellite cells: a potential mechanism for self-renewal. In: Developmental Biology 275, pp. 375–388

Ustanina, S. (2005): Pax7 directs postnatal renewal and propagation of myogenic satellite cells, but not their specification. Dissertation, Martin Luther University, Halle-Wittenberg

Peroni, C.N., Gout, P.W., Bartolini, P. (2005): Animal models for growth hormone gene therapy. In: Curr Gene Therapy 5(5), pp. 493–509

Pitsch, W., Emrich, E., Klein, M. (2005): Zur Häufigkeit des Dopings im Leistungssport. Ergebnisse eines www-surveys. In: Leipziger Sportwissenschaftliche Beiträge 46(2), pp. 63–77

PWC (PWC GmbH – Medizinische Testverfahren im Sport) (2008): www.pwc-doping kontrolle.de/unternehmen.html; accessed in February 2008

Ramazanov, Z., Jimenez del Rio, M., Ziegenfuss, T. (2003): Sulfated polysaccharides of brown seaweed Cystoseira canariensis bind to serum myostatin protein. In: Acta Physiol Pharmacol Bulg 27, pp. 101–106

Reinsch, M. (2007): Doping – Straffrei mit 8 EPO-Spritzen. Frankfurter Allgemeine Zeitung, 29-Nov-07 p. 32

Relaix, F., Rocancourt, D., Mansouri, A., Buckingham, M. (2005): A Pax3/Pax7-dependent population of skeletal muscle progenitor cells. In: Nature 435(7044), pp. 948–953

Relaix, F. (2006): Visions & Reflections – Skeletal muscle progenitor cells: from embryo to adult. In: Cellular and Molecular Life Sciences 63, pp. 1221–1225

Ren, J.M., Marshall, B.A., Mueckler, M.M., McCaleb, M., Amatruda, J.M., Shulman, G.I. (1995): Overexpression of Glut4 protein in muscle increases basal and insulin-stimulated whole body glucose disposal in conscious mice. In: Journal of Clinical Investigation 95, pp. 429–432

ReSpoDo (Rechtskommission des Sports gegen Doping) (2005): Abschlussbericht der Rechtskommission des Sports gegen Doping zu möglichen gesetzlichen Initiativen für eine konsequentere Verhinderung, Verfolgung und Ahndung des Dopings im Sport. Bonn

Rickert, V.I., Pawlak-Morello, C., Sheppard, V., Jay, M.S. (1992): Human growth hormone: a new sustance of abuse among adolescents? In: Clinical Pediatrics 31(12), pp. 723–726

Rodnick, K.J., Piper, R.C., Slot, J.W., James, D.E. (1992): Interaction of insulin and exercise on glucose transport in muscle. In: Diabetes Care 15(11), pp. 1679–1689

Savulescu, P., Foddy, B., Clayton, M. (2004): Performance enhancing drugs. Why we should allow performance enhancing drugs in sport. In: Journal of Sports Medicine 38, pp. 666–670

Scarpino, V., Arrigo, A., Benzi, G., Garanttini, S., La Vecchia, C., Bernardi, L.R., Silvestrini, G., Tuccimei, G. (1990): Evaluation of prevalence of »doping« among Italian athletes. In: Lancet 336(8722), pp. 1048–1050

Schakman, O., Gilson, H., de Coninck, V., Lause, P., Verniers, J., Havaux, X., Ketelslegers, J. M., Thissen, J. P. (2005): Insulin-like growth factor-I gene transfer by electroporation prevents skeletal muscle atrophy in glucocorticoid-treated rats. In: Endocrinology 146(4), pp. 789–797

Schertzer, J.D., Lynch, G.S. (2006): Comparative evaluation of IGF-I gene transfer and IGF-I protein administration for enhancing skeletal muscle regeneration after injury. In: Gene Therapy 13(23), pp. 1657–1664

Schneider, A.J., Friedmann, Th. (2006): Gene doping in sports: the science and ethics of genetically modified athletes. San Diego

Schulz, Th., Smolnikar, K., Diel, P., Michna, H. (1998): Gendoping im Sport: Fakt oder Fiktion. In: F.I.T. Wissenschaftsmagazin der Deutschen Sporthochschule Köln 1, pp. 13–18

Seale, P., Rudnicki, M.A. (2000): A new look at the origin, function, and »stem-cell« status of muscle satellite cells. In: Dev Biol 218, pp. 115–124

Seale, P., Ishibashi, J., Scimè, A., Rudnicki, M.A. (2004): Pax7 is necessary and sufficient for the myogenic specification of CD45+:Sca1+ stem cells from injured muscle. In: PLOS Biology 2(5), pp. 664–672

Sledz, C.A., Holko, M., De Veer, M. J., Silverman, R.H., Williams, B.R.G. (2003): Activation of the interferon system by short-interfering RNAs. In: Nature Cell Biology 5, pp. 834–839

Stahl, A. (2004): A current review of fatty acid transport proteins (SLC27). In: Pflugers Arch. 447(5), pp. 722–727

Steiner, J.(2007): Ansichten eines Kontrolleurs. In: Berner Zeitung, 25-Aug-07

Stiftung Deutsche Sporthilfe (2007): Sporthilfe-Eid. www.sporthilfe.de/servlet/index?page=57; accessed in February 2008

Striegel, H., Simon, P. (2006): Doping im Fitnesssport zu Beginn des neuen Jahrtausends. In: Knörzer, W., Spitzer, G., Treutlein, G.: Dopingprävention in Europa – Grundlagen und Modelle. Heidelberg, pp. 63–69

Sürmann, H. (2007): Arzneimittelkriminalität – ein Wachstumsmarkt? Bundeskriminalamt (ed.), Wiesbaden

Sweeney, H.L. (2004): Gene Doping. In: Scientific American 7, pp. 36–43

TAB (2007): Hirnforschung (Autoren: Hennen, A., Grünwald, R., Revermann, C., Sauter, A.). Endbericht, TAB-Arbeitsbericht Nr. 117, Berlin

Takahashi, T., Ishida, K., Itoh, K., Konishi, Y., Yagyu, K.I., Tominaga, A., Miyazaki, J.I., Yamamoto, H. (2003): IGF-I gene transfer by electroporation promotes regeneration in a muscle injury model. In: Gene Therapy 10(8), pp. 612–620

Teufel, F (2006): Der Dopingjäger. In: Tagespiegel, 30-Aug-06, p. 3

The President's Council on Bioethics (2003): Beyond therapy: biotechnology and the pursuit of happiness. A report of The President's Council on Bioethics, Washington D.C.

Treadway, J.L., Hargrove, D.M., Nardone, N.A., McPherson, R.K., Russo, J.F., Milici, A.J., Stukenbrok, H.A., Gibbs, E.M., Stevenson, R.W., Pessin, J.E. (1994): Enhanced peripheral glucose utilization in transgenic mice expressing the human GLUT4 gene. In: Journal of Biological Chemistry 269, pp. 29956–29961

Tsao, T. S., Burcelin, R., Katz, E.B., Huang, L., Charron, M.J. (1996): Enhanced insulin action due to targeted GLUT4 overexpression exclusively in muscle. In: Diabetes 45, pp. 28–36

UCI (Union Cycliste Internationale) (2007): Information on the biological passport. www.uci.ch/Modules/ENews/ENewsDetails.asp?source=SiteSearch&id=NTQzOA&MenuId=MTI1ODA&CharValList=&CharTextList=&CharFromList=&CharToList=&txtSiteSearch=biological+pass; accessed in February 2008

van Hilvoorde, I., Pasveer, B. (Hg.) (2005): Beter dan goed: over genetica en de toekomst van topsport. Diemen

WADA (World Anti-Doping Agency) (2004a): World Anti-Doping Code. www.wada-ama.org/rtecontent/document/Code_deutsch.pdf; accessed in May 2007

WADA (2004b): International Standard for Testing. www.wada-ama.org/rtecontent/document/testing_v3_a.pdf; accessed in August 2007

WADA (2004c): International Standard for Laboratories. www.wada-ama.org/rtecontent/document/lab_aug_04.pdf; accessed in August 2007

WADA (2004d): International Standard for Therapeutic Use Exemptions. www.wada-ama.org/rtecontent/document/international_standard.pdf; accessed in August 2007

WADA (2005): play true – Gene Doping. www.wada-ama.org/rtecontent/document/Play_True_01_2005_en.pdf; accessed in August 2006

WADA (2007): Accredited Laboratories. www.wada-ama.org/en/dynamic.ch2?pageCategory.id=333; accessed in September 2007

WADA (2008): The Prohibited List 2008. www.nada-bonn.de/fileadmin/user_upload/nada/Downloads/Listen/2008_List_En.pdf; accessed in January 2008

Waldbröl, H.J. (2006): Repoxygen haben wir im Kühlfach. In: Frankfurter Allgemeine Zeitung, 31-Jan-06

Wang, L., Dobrzynski, E., Schlachterman, A., Cao, O., Herzog, R.W. (2005): Systemic protein delivery by muscle-gene transfer is limited by a local immune response. In: Blood 105(11), pp. 4226–4234

Wang, Y.X., Zhang ,C.L., Yu, R.T., Cho, H.K., Nelson, M.C., Bayuga-Ocampo, C.R., Ham, J., Kang, H., Evans, R.M. (2004): Regulation of muscle fiber type and running endurance by PPAR-delta. In: PLoS Biology 2(10), e294, pp. 1532–1539

Wassarman, P. (2002): Advances in developmental biology and biochemistry. In: Sassoon, D. (ed.) Stem cells and cell signalling in skeletal myogenesis. Vol. 11, New York

Whittemore, L.A., Song, K., Li, X., Aghajanian, J., Davies, M., Girgenrath, S., Hill, J.J., Jalenak, M., Kelley, P., Knight, A., Maylor, R., O'Hara, D., Pearson, A., Quazi, A., Ryerson, S., Tan, X.Y., Tomkinson, K.N., Veldman, G. M., Widom, A., Wright, J. F., Wudyka, S., Zhao, L., Wolfman, N.M. (2003): Inhibition of myostatin in adult mice increases skeletal muscle mass and strength. In: Biochemical and Biophysical Research Communication 300, pp. 965–971

APPENDIX

LIST OF TABLES 1.

Table 1	Doping violations and the regimen of sanctions in Germany	16
Table 2	Gene doping techniques: modulation of energy supply	54
Table 3	Gene doping techniques: structure/properties of skeletal muscle	54
Table 4	Gene doping techniques: modulation of oxygen supply	56
Table 5	Anti-doping rule violations as per the WADC	85
Table 6	Summary of forbidden substance classes and methods of the WADA Prohibited List	86
Table 7	Violations and range of sanctions specified in the NADA Code	100
Table 8	Doping tests and sanctionable results reported by NADA from 2004 to 2006	103

LIST OF FIGURES 2.

Fig. 1	Methods of modifying the body's gene activity	30
Fig. 2	Principle of ex vivo gene therapy	32
Fig. 3	Possible foundations for gene doping: gene therapy and modulation of gene expression	39
Fig. 4	Structure of skeletal muscle consisting of individual bundles composed, in turn, of individual muscle fibers	41
Fig. 5	Clinical gene therapy studies by country (1989–2007)	57
Fig. 6	Indications of clinical gene therapy studies (1989–2007)	57
Fig. 7	Clinical gene therapy vectors used (1989–2007)	58
Fig. 8	Genes transferred to clinical gene therapy techniques (1989–2007)	59
Fig. 9	Development of doping behavior in competitive sport	118

Fig. 10 Factors in the subjective risk-benefit analysis in (gene) doping 120
Fig. 11 Arguments used by doping athletes to justify their actions 121
Fig. 12 Arguments used by doping physicians to justify their actions 123
Fig. 13 Development of doping behavior in the bodybuilding scene 135

Just like a phantom, the topic of »gene doping« keeps haunting the debates regarding the future of competitive sports for years. Very often, corresponding fantasies and visions culminate in the imagination of super athletes who are permanently manipulated with regard to their genetic disposition. However, the application scenarios to be expected will be far more unspectacular, but more probable and more obvious at the same time. Very soon, we will have to expect the use of new substances as well as of methods in gene and cell therapy for targeted manipulation of gene activity. Their use promises a highly efficient performance enhancement and will be difficult to prove, if at all. This book provides comprehensive answers to the key questions of the further development: Which scientific results could cater to the needs of potential gene doping? Where are the future gateways in top-level and popular sports? And how can prohibitions and monitoring be used in responding to this? Another question will be which individual behavioural patterns of athletes and which social contexts will play a role with regard to the potential »career« of gene doping.

TAB

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