TAB

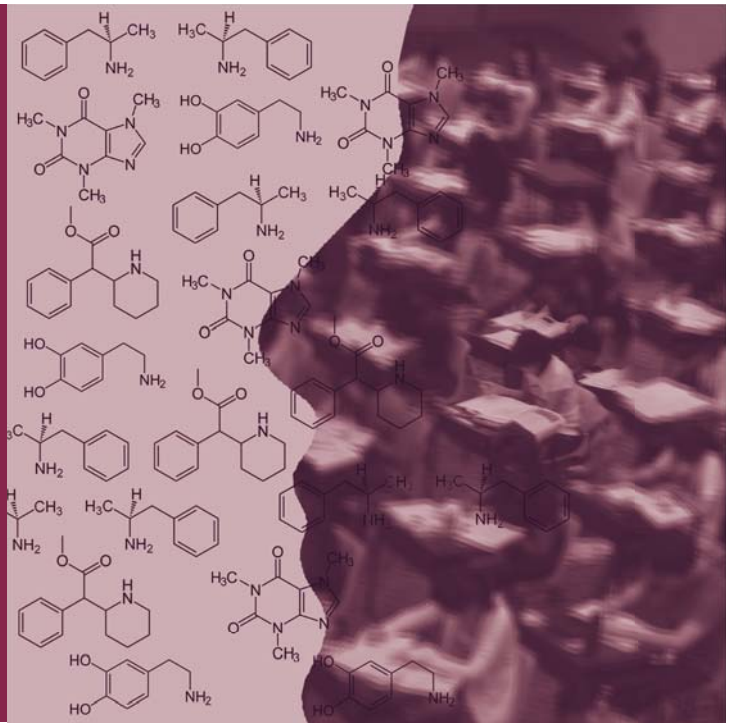
OFFICE OF TECHNOLOGY ASSESSMENT
AT THE GERMAN BUNDESTAG

Arnold Sauter
Katrin Gerlinger

The Pharmacologically Improved Human

Performance-Enhancing Substances as a Social Challenge

Final Report



Technology Assessment Studies Series, No 5

THE PHARMACOLOGICALLY IMPROVED HUMAN

TECHNOLOGY ASSESSMENT STUDIES SERIES, NO 5

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

TAB is operated by the Institute for Technology Assessment and Systems Analysis (ITAS) at the Karlsruhe Research Centre. In executing its working programme the Karlsruhe Research Centre cooperates with the Fraunhofer-Institut für System- und Innovationsforschung (ISI), Karlsruhe.

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).

Arnold Sauter
Katrin Gerlinger

THE PHARMACOLOGICALLY IMPROVED HUMAN

PERFORMANCE-ENHANCING SUBSTANCES AS A SOCIAL CHALLENGE

Report for the Committee on Education, Research and Technology Assessment of the German Bundestag

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NOTE

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

A PDF-Version of the report is currently available on the Internet at the address http://www.tab-beim-bundestag.de.

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THE COMMITTEE' S PREFACE

For some years now, in response to the rising challenges of global socioeconomic competition, both the scientific community and the public have been debating whether the improvement of individuals' performance with the help of technical or biomedical interventions in the human body – termed enhancement – is a welcome, inevitable or undesirable vision of the future.

The report on brain research by the Office of Technology Assessment at the German Bundestag (TAB) (Bundestag printed paper 16/7821) also presented evidence of a growing trend towards the use of pharmaceuticals and other medical interventions to specifically influence mental states and capacities.

Following publication of the highly respected TAB report »Gene Doping«, an analysis of physical performance enhancement in sport, the Committee for Education, Research and Technology Assessment commissioned the TAB to undertake a technology assessment project on »pharmacological and technical interventions to improve performance – prospects for more widespread use in medicine and everyday life« (»Enhancement Project«).

The TAB's final report analyzes the areas of development and use with the greatest social and political relevance now and in the foreseeable future, i.e. current developments and plausible trends regarding the use of psychopharmaceuticals and other drugs to enhance performance in working and everyday life. It provides a comprehensive analysis of the current status of possibilities to influence human performance by pharmacological means and of the classification of those agents within the framework of laws regulating medicines, foods and healthcare. This will facilitate a realistic discussion of future developments that clearly stands out from previous hypothetical and visionary descriptions of enhancement. The report shows that the targeted development and use of pharmacological substances for nontherapeutic performance enhancement is incompatible with the current objectives of the medical innovation system and the remit of doctors. A change in this situation would require a far-reaching public and political opinion-forming process. At the same time, the systematic analysis of the scientific approach to the doping problem in elite and competitive sport undertaken in the TAB report points to the need for a thorough public debate on how to deal with growing demands for performance and innate differences in abilities among individuals.

The report examines the options for action in the fields of research, regulation, healthcare consumer protection and prevention.

This report places in the hands of the Bundestag an up-to-date and highly detailed informational basis for parliamentary debate on this important aspect of research, health, legal, economic and social policies.

Berlin, November 22, 2011

The Committee on Education, Research and Technology Assessment

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INHALT

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SUMMARY

»Doping for the brain«, »Cosmetics for gray cells«, »Pills to improve human beings« – for some years headlines such as these have reflected public interest in a scientific and social development that aims to improve human performance and that is mostly referred to in debates about bioethics as »enhancement«. However, considerable uncertainty prevails as to the extent of development and use, the possible physical and mental effects and side effects, and the nature and extent of the possible socioeconomic consequences of the various enhancement methods.

In order better to assess the present and medium-term societal and political significance of the topic »Enhancement«, the Committee on Education, Research and Technology Assessment (*Ausschuss für Bildung, Forschung und Technikfolgenabschätzung*) of the German *Bundestag* commissioned the Office of Technology Assessment at the German *Bundestag* (*Büro für Technikfolgen-Abschätzung beim Deutschen Bundestag*, TAB) to undertake a technology assessment project on the topic »Pharmacological and technical interventions to improve performance – prospects for more widespread use in medicine and everyday life« (»Enhancement«). The final report of this project focuses on developments to date and plausible projections of trends in the use of (psychotropic) medicines for performance enhancement in working and everyday life. Technical (neuroimplants and the like) and biomedical (e.g. genetic manipulation) interventions are not considered in the report, since widespread use of such methods for performance enhancement in healthy individuals seems a possibility only in the long term, if ever.

HUMAN PERFORMANCE AND ATTEMPTS TO INFLUENCE IT BY PHARMACOLOGICAL MEANS

Statements to the effect that enhancement is of special societal relevance are generally made with reference to the possibility of individual and/or collective performance improvement. Only rarely, however, is it stated what precisely is meant by the term »human performance« or why improving human performance might be useful.

Unlike performance as a physical-technical concept defined on the basis of effort made, *human performance* refers also to the result achieved. The necessary effort can be made by means of a variety of individual capabilities (or organ functions) and targeted use of these. As the various effort and result components can be highly diverse, human performance must be regarded as a qualitative entity that is only slightly amenable to quantification by means of parameters and measure-

ment approaches based on these. The use of such approaches thus runs a »risk« of reducing human performance to what can be defined and measured using such parameters. A basic distinction needs to be made between physical and mental achievements.

Many types of sport are based on precise and comparative measurement of the physical performance that results from a particular action. The skeletal muscles and the physiological processes that take place in them play a special role in the effort component. The more a defined process can be attributed to a particular muscular activity, the greater the extent to which individual substances and methods can be used to interfere with relevant processes. Doping – in the sense of pharmacological enhancement of a defined sporting performance – can therefore work to some extent, though it also has many side effects.

By comparison, the situation with regard to mental, and in particular cognitive, performance is far more complex. This is true both of the underlying biological processes and of the measurement techniques used, in particular the assessment of the results achieved. This assessment is highly context-dependent, depending among other things on specific demands made in the person's educational and working environment. Comparative measurement and assessment techniques exist above all at a highly aggregated level, e.g. in the form of occupational performance appraisals and educational credentials.

As far as the physiological effort component is concerned, a central role is played by the brain and its diverse abilities and functions. Notwithstanding the great advances that have been made in neurological science, it remains true that only partial processes of brain function have been explained. A variety of strategies to influence the highly complex and still only partially understood processes of the brain have been adopted. However, the function of the brain is far more complex than that of a muscle, and the possibility of specifically influencing performance-relevant brain functions in a way comparable to doping in sport is at least questionable. Even if it were to prove possible to specifically stimulate individual functions, this would not mean that any effects thus achieved would be of practical relevance, since it must be assumed that it is only when acting in conjunction with one another that different cognitive abilities, and likewise different mental abilities of an emotional or social nature, make possible a mental achievement, especially in the working environment. Whether pharmacological enhancement can achieve an improvement in performance that is of practical relevance thus remains an open question.

When claims about performance-enhancing effects of substances and methods are made, the objectives to which these claims relate and the baseline from which the improvement concerned was achieved must always be specified. The methods by means of which the abilities of an individual can potentially be in-

fluenced are many and varied. The strategies referred to below appear to be of particular relevance to the field of enhancement.

CONDITIONING OF THE ORGANISM BY LEARNING AND TRAINING

It is beyond question that pedagogically and psychologically well-founded learning methods can strengthen and broaden the range of a person's abilities and thereby fundamentally improve the individual abilities that form the basis for human performance. Measures of this kind are not intended to interfere with individual biochemical/neurological self-regulatory mechanisms, even though these may well be affected. The effectiveness of teaching and learning methods is scarcely called into question in the debate about enhancement. Rather, there is much speculation about the extent to which these methods can be supplemented, reinforced, improved, or even replaced.

EFFECT OF NUTRITIONAL COMPONENTS

Whether nutritional components present at the concentrations that are permitted in foods can exert specific performance-enhancing effects above and beyond their effects on nutritional physiology is unclear and a matter of dispute. To date, claims made by food suppliers to the effect that nutritional components have beneficial effects beyond those attributable to correction of deficiencies have not been corroborated by scientific studies.

Coffee and tea are commonly cited as examples of performance-enhancing substances that have been available for a long time and are effective and relatively free of side effects; as such, they form a partial exception to this rule. It is beyond dispute that consumption of coffee or tea can increase physical alertness during periods of tiredness. This effect is attributed in particular to caffeine, a psychostimulant which, as a natural constituent of various plants, may be present in certain concentrations in foods. On the other hand, caffeine is regarded as an active substance rather than as a nutrient, and products that contain caffeine at concentrations above those at which consumption of the substance is associated with increased side effects are regarded as medicinal products (see below). This historically evolved special status of caffeine cannot be meaningfully conferred on new substances with potentially performance-enhancing properties. Recent debates in the German *Bundestag* about the Health Claims Regulation (HCR) indicate a broad political consensus that pharmacologically active substances should not be approved for use as food ingredients.

PROFILES OF ACTION OF PHARMACOLOGICALLY ACTIVE SUBSTANCES IN HEALTHY SUBJECTS

Pharmacologically active substances act on a variety of endogenous control processes. Especially in combination with training, they can influence individual di-

mensions of physical (e.g. endurance or strength) or motor abilities (e.g. dexterity or precise movements). Based on the many years of experience available with the use of such substances for performance enhancement in sport – and notwithstanding the low level of transparency that prevails in this field –, neither their effects nor their diverse, and in some cases serious, side effects are in dispute.

In attempts to improve mental abilities a number of different strategies are followed with the aim of increasing the activity of nerve cells, especially in the brain, primarily by interfering with processes in which the activating neurotransmitters dopamine and norepinephrine are involved. Where brightening of mood is desired, the chain of biochemical processes involving serotonin is also targeted. In the case of substances from the field of medicinal plants and natural medicine (e.g. ginkgo extracts) there is as yet no generally accepted proof of efficacy in terms of performance enhancement. Proof that specifically acting psychoactive medicines can bring about performance-relevant improvement in individual abilities in healthy subjects is generally regarded as lacking. On the other hand, the side effect potential of such substances has been shown to be substantial. This fact, which became fully apparent only after many years of experience with the use of such substances, led in many cases to a revision of the benefit-risk assessment and to the imposition of corresponding restrictions on the approval and use of such substances. To date, claims of performance enhancement in healthy individuals have been made in particular for the following psychostimulants:

Amphetamines: A number of reviews of published studies suggest that amphetamines can improve cognitive, and in particular executive, abilities (attention, reaction time). Positive effects occurred especially after sleep deficits and/or in individuals with a less well developed working memory. On the other hand, under good baseline conditions (no sleep deficit, good working memory performance) amphetamines were more likely to impair performance.

Methylphenidate: A variety of studies have yielded conflicting results on the effects of methylphenidate. Even on the question of whether this medicine can counteract fatigue-related impairment of abilities, different conclusions have been reached. Whether the medicine, as well as causing increased alertness, can bring about a specific improvement in cognitive abilities in healthy individuals is still a matter of dispute. There is some evidence that individuals with a poorer working memory can improve certain abilities to some extent by consuming this substance. In individuals whose working memory was already good, consumption of this substance led to an increased frequency of errors and worse results in performance tests.

Like caffeine, *modafinil* can reduce the symptoms of fatigue. Whether consumption of this substance can also improve cognitive performance is unclear. There

is some evidence that individuals with a lower IQ are more likely to benefit from modafinil.

Beta-blockers can make it easier for an individual to perform activities that call for specific fine motor skills while in states of agitation such as stage fright.

There is some evidence that *levodopa*, a medicine used to treat dopamine deficiency in Parkinson's disease and other conditions, can bring about improvements in simple associative learning tasks and that the similarly used substance *tolcapone* can selectively improve executive abilities and episodic memory in individuals with a genetically determined tendency to metabolize dopamine more rapidly. By contrast, *anti-dementia medicines* – the therapeutic effect of which is in any case weak – and *antidepressants* have not been shown to have any effects on mental abilities or performance in general in healthy subjects.

Overall, it can be asserted that there is no proof that any presently available substance can enhance human performance without at the same time causing significant side effects. All that can be demonstrated are effects on individual cognitive abilities (e.g. attention, reaction time) that are to some extent thought to be of special relevance to present-day occupational training and working environments.

It must nevertheless be pointed out that efficacy studies on medicinal products are not generally performed on healthy subjects (see below) and that the available knowledge base in that population is therefore extremely small. Despite this, there is some evidence that the physical and mental state of study participants defined as being healthy is an important determinant of the efficacy of a variety of pharmacological agents. There is some reason to believe that presently available substances have shown performance-relevant effects – insofar as they have done so at all – only in cases in which the subjects concerned suffered from some kind of deficit at baseline. There is also some evidence that in subjects with a high level of wakefulness at baseline any additional activation of general wakefulness or increase in neurotransmitter concentrations leads if anything to a deterioration in cognitive performance.

PERFORMANCE-ENHANCING SUBSTANCES: LEGAL DEFINITION, REGULATORY TREATMENT, AND EXTENT OF USE

The precepts of the present regulatory system exert a decisive influence on the future development, spread, and use of potentially performance-enhancing substances. Even though such substances will in all probability be covered by medicinal products legislation, it is necessary, in order to understand the issue of enhancement in all its complexity, to look at the interface between performance-enhancing substances and foods, since this interface is likely to function as a pathway and »wish intensifier« to the use of performance-enhancing substances.

REGULATORY TREATMENT OF FOODS

Foods may legally contain substances other than nutrients, however such substances may not exert any special effects – i.e. effects above and beyond normal nutritional effects – on the organism. Foods are therefore expected not to have any harmful effects or to pose any risk to health, and consumers are expected to exercise discretion in their use of them. Foods may be marketed almost without restriction, and based on their occurrence in nature they do not require marketing authorization.

Nevertheless, restrictions may be imposed in the interests of health. As a result of the ever-increasing possibilities by means of which individual substances can be added to, or removed from, a foodstuff, the intake of such substances can greatly exceed, or fall below, the level that is appropriate for a balanced diet. As a result, there is an increasing trend for foodstuffs to contain mixtures of substances that possess not only nutritional, but also more specific health-promoting or health-endangering, properties. In some cases new categories (e.g. food supplements) have been created for such substances and the regulatory treatment of them has shifted in the direction of medicinal products law (e.g. imposition of dose limits, linking of market access to licensing).

Food law does not require proof of efficacy of food ingredients. Manufacturers bear a degree of responsibility for the information they provide, e.g. a responsibility not to mislead and, with some exceptions, not to make claims about illness. Since the Health Claims Regulation (HCR) came into effect, claims about effectiveness or health generally have to be supported by sufficiently well-founded scientific data and are subject to approval. In Europe, manufacturers are not required to provide information on possible health risks arising from the consumption of foodstuffs.

At present an increasing amount of research is being directed at specific mechanisms of action of individual foods and food ingredients, since foods with additional health benefits are considered to have great market potential. The requirement for proof of health-related efficacy – in particular with regard to psychological and behavioral functions – coupled with the prohibition of claims about illness may promote the development of concepts regarding how an (additional health) benefit in the sense of enhancement can be demonstrated in the absence of a disease state.

REGULATORY TREATMENT OF MEDICINAL PRODUCTS

Medicines are defined as substances or mixtures of substances that exert a specific (pharmacological, immunological, or metabolic) action on the human organism. In view of the potency of such substances and in order to protect human health (from harmful effects), medicinal products law is based on a »principle of

prohibition subject to exemptions«. The manufacture and marketing of medicinal products is subject to authorization based upon proof of efficacy of the substance concerned, whereby the burden of proof rests with the manufacturer. In the case of a new marketing authorization the manufacturer is required to investigate and demonstrate, by means of scientifically recognized methods (clinical studies), both the tolerability and safety (risk dimensions) and the medical (in most cases therapeutic) efficacy (benefit dimension) of the product. Marketing authorization is then granted for treatment of the specific illness-relevant state for which the manufacturer has demonstrated a therapeutic benefit. The obligatory items of information on the effects and side effects of the medicinal product are likewise examined and stipulated in the marketing authorization procedure.

Not only medicinal products themselves, but also the studies that are required for the licensing of these, are subject to approval. Independent ethics committees and the regulatory authorities assess such studies on the basis of internationally accepted ethical standards the essence of which is a weighing of potential benefits against the risks to which study participants will be exposed. The usual procedure for establishing a criterion of benefit is to define an illness-relevant state as a baseline from which a therapeutic effect of the substance to be studied can be demonstrated. In other words, therapeutic efficacy is demonstrated by treatment of ill subjects.

The case-specific, illness-specific nature of this benefit-risk analysis forms an obstacle to targeted research into possible enhancing properties of pharmacological agents. Nevertheless, this barrier is by no means insurmountable, since at least in some cases therapeutic benefit can be defined in broad terms. Thus, the pharmaceutical industry is already conducting research at the fringes of illness-relevant states, e.g. on essentially preventive treatment of mild forms of dementia.

In the marketing authorization procedure the regulatory authority inspects the study results and weighs the proven therapeutic efficacy of the substance against identifiable health risks. This precludes the granting of marketing authorization for use of a substance for enhancement purposes. Rather, marketing authorization is granted for use of a substance in a medical indication in which it has been shown to be effective, provided that compliance with prescribed standards of safety and quality of manufacture can be assured.

The path by which the substance subsequently reaches the user depends on the specific conditions imposed as part of the marketing authorization. Depending on the risk potential of the particular substance, access to the market is regulated by means of a graded »gatekeeper« system (pharmacies, doctors). Special attention is paid to the dissemination of information about active ingredients. This information must be made available in full to medical research and to »gatekeepers«, while users must be protected in particular from one-sided claims of

effectiveness (which can result in restriction or prohibition of advertising). Since claims of effectiveness must be scientifically proven whereas enhancing effects are not directly investigated, it would at present not be permissible to include claims about enhancing effects in the obligatory information about medicinal products.

In practice, however, many strategies are adopted to circumvent the ban on direct advertising. These aim in particular to create a demand for, among other things, performance-enhancing substances. This is seen most clearly when advertising material is used to systematically »medicalize« physical and mental states and to suggest the possibility of improvement. Among an abundance of advertising material the consumer finds it difficult or even impossible to distinguish unbiased, scientifically well-founded information from one-sided, incomplete, or incorrect information.

Unlike in food legislation, in medicinal products legislation it is not assumed that consumers are able to make autonomous and full decisions about the – in this context, health-promoting – use of medicines. Instead, they can and should make use of and seek advice from the public health system. Prescription medicines are available only via doctors, whose highest priority is the preservation and restoration of their patients' health. The gatekeeper system is intended to ensure that the use of medicines is associated with the lowest possible risk to the user. However, it cannot guarantee that a medicine will be used only in its approved indication. Instead, a substance can also be used outside of its approved indications (»off-label« use), e.g. for enhancement purposes. Early analyses of prescriptions for methylphenidate and modafinil suggest that off-label prescription of these medicines is by no means rare.

When a person falls ill the costs of treatment are borne largely by the statutory health insurance (SHI) funds (primary healthcare market). The increasing restrictions now being placed on provision of SHI benefits in accordance with the principle that treatment must be »adequate, appropriate, and necessary« greatly limit the potential for unintended financing of possible »enhancement prescriptions«. This exclusion from the primary healthcare market could shift enhancement to the secondary healthcare market (self-paying patients), the economic importance of which, especially for gatekeepers (pharmacists and doctors), is now increasing. Nevertheless, the substantial range of side effects possessed by many potentially enhancing substances and the prohibition of doping enshrined in the German Medicinal Products Act *(Arzneimittelgesetz,* AMG) constitute major obstacles to more widespread prescription of enhancement substances as a favor to the patient.

Where either appropriate or inappropriate consumption of foods or medicines leads to impairment of health, treatment of this impairment falls – at present

regardless of the cause of the impairment – within the area of responsibility of doctors and within the benefits catalog of the SHI funds and other social service providers. Assuming that the present principles of German social legislation remain in place, it is difficult to see how cost bearers can avoid having to pay benefits specifically in the case of enhancement. As a result, the cost of the treatment of increasing damage to health possibly attributable to enhancement behavior would probably be borne by the public purse.

USE AND HANDLING OF ENHANCEMENT SUBSTANCES

Within the framework of the German legal system, the consumption of particular substances, including substances that are harmful to health (e.g. doping agents and illegal drugs), cannot be prohibited by law; rather, all that can be prohibited is the handling of such substances and actions by third parties that could promote such handling. In Germany around 1.4 to 1.9 million people are dependent on prescription psychotropic medicines and another 1.7 million people are classified as being at moderate to high risk of such dependence. It may be assumed that a proportion of the latter group are presently developing dependence behavior despite having originally wanted »only« to at least maintain, or perhaps even improve, their performance in occupational settings. The first empirical studies to be performed on this topic have provided evidence on the extent to which pharmacological agents are used for performance enhancement in educational and occupational settings. In a survey on doping at work commissioned by the German Employees' Health Insurance Fund (*Deutsche Angestellten-Krankenkasse*, DAK), 5% of respondents stated that they had taken potent medicines when there was no medical need to do so and 2.2% said that they had done this often to regularly. In a survey of schoolchildren and students in Germany, 1.5% of the schoolchildren and 0.8% of the students stated that they had taken prescription medicines for enhancement purposes on at least one occasion. Similar figures have been obtained in surveys of students in other European countries. In the USA about 7% of respondents admitted such behavior.

Compared to doping in sport, which is condemned by a large proportion of the population, the use of potentially performance-enhancing substances in everyday and occupational settings appears to be less frowned upon by society. Though in the survey commissioned by the DAK a majority of respondents rejected »doping behavior at work«, approximately one respondent in four accepted a wish for a general increase in attention, memory, and concentration, and a smaller proportion a wish to reduce tiredness during working hours or to extend working time in order to meet deadlines, as a justification for such behavior. Many presently available pharmacological agents can make some contribution towards achieving at least the last two of these objectives.

THE DEBATE ON ENHANCEMENT IN ETHICS AND SOCIAL SCIENCES

To date scarcely any pharmacological agents have been shown to be able to significantly improve cognitive performance in healthy individuals (unlike enhancement of physical performance in sport by means of doping) and all of the substances that have at least the potential to do this cause side effects that cannot be ignored. Little is known about the extent to which allegedly performance-enhancing substances are consciously and intentionally used in everyday life. Philosophers and ethicists commonly respond to these gaps in our knowledge of enhancement by discussing hypothetical performance-enhancing substances, while social scientists locate enhancement within the broader topic of medicalization.

AGENTS – OBJECTIVES – CONSEQUENCES

The bioethical debate about enhancement focuses on three principal questions:

- What is enhancement? What agents are used and what objectives are pursued? How does enhancement differ from other behaviors and the pursuit of other objectives?
- Where does enhancement stand in relation to the »classical« principles of medical bioethics?
- What are the potential implications of enhancement for our understanding of human nature and our notions of humanity and society?

Problems of definition and demarcation are a feature of the bioethical debate about enhancement. There is no broad agreement regarding either the substances to be considered or the objectives of enhancement. Alongside extremely broad definitions (e.g. »all mechanisms which make possible better life«) are attempts to draw more precise distinctions between doping, improvement, and alteration. Of particular importance for an ethical evaluation of enhancement would be the drawing of a distinction between enhancement and treatment in the sense of medically indicated measures, however the existence of such a distinction is often disputed in the individual case and moreover the drawing of such a distinction is theoretically and conceptually almost impossible, since there exist no precise definitions of illness or health, but rather a plurality of terms referring to illness.

One approach adopted by many participants in the debate about enhancement is ethical evaluation of hypothetical – specifically acting, relatively side-effect-free – performance-enhancing substances that are not simultaneously used as medicines. However, conclusions derived from such evaluations are not directly applicable to presently available psychopharmaceuticals or other substances of relatively nonspecific action and/or with substantial side effects.

As a result, ethical considerations are generally abstract in nature (as indicated by the terms »speculative« or »exploratory« ethics). Thus, in the absence of an empirical basis, a study of, for example, the »quality of happiness« that could be made possible by pharmacological enhancement as compared with traditional forms of mental self-transformation such as concentration techniques, meditation, or psychological coaching would perforce be purely hypothetical. The same would apply to any ethically problematic impairment of identity or authenticity brought about by enhancing (in the narrow sense of the word) substances if these were to cause major or irreversible changes in users' personality.

By contrast, the question of the voluntariness of use of enhancement agents can be discussed in more substantive fashion even without knowledge of the specific effects and side effects of performance-enhancing pharmacological agents. The principle of personal autonomy is discussed mostly in terms of resistance to a covert or insidious pressure, or even obligation, to practice pharmacological performance enhancement. It is necessary to ask whether ostensibly individual and autonomous use of enhancement substances can set in motion a spiral of competition in which decision-making can no longer be assumed to be autonomous.

The principle of fairness is sometimes said to impose an obligation on society to provide and pay for enhancement agents in order to prevent unfair competition, e.g. in examinations and job applications, or to compensate for economically determined differential access or congenital disadvantages and inequalities. However, these situations too are inapplicable to known substances with uncertain effects and significant side effects.

Along with ethical considerations regarding the possible concrete individual and social consequences of the use of biomedical technologies, fundamental concerns about the »future of human nature« are commonly expressed in the debate about enhancement. These relate either to far-ranging visions of biotechnical manipulation or to scenarios of wholesale »pharmacologization« of everyday life. Whereas there is little evidence that specific transformation of the human body and its abilities, e.g. by means of genetic modification, is likely to become a reality within the foreseeable future, the phenomenon of pharmacologization as part of the medicalization of psychosocial problems has been observed and studied for some time in the social sciences.

ENHANCEMENT AS A MANIFESTATION OF MEDICALIZATION

The increase in the range of medical treatment options that resulted from the multiplicity of biomedical research and development lines pursued in the twentieth century has led both to an enormous expansion and differentiation of the healthcare system and to a spreading of what were once purely medical technologies and perspectives into neighboring fields. This »medicalization« encompasses a number of different processes, including an expansion of medical diag-

nosis (pathologization), an expansion of medical therapy beyond its former boundaries into everyday life (»routinization«), a detemporalization of illness (prediction), and »improvement« of human nature (»enhancement«). Outstanding examples of the expansion of medical diagnosis include the introduction of the diagnosis »attention deficit hyperactivity disorder« (ADHD) and the pathologization of declining libido or pronounced shyness. Typical of many of these boundary changes is a shift of emphasis from psychosocial to somatic explanations of causality.

The most important differences between the four types of boundary shift and medicalization referred to above relate to the social role played by the various players involved (from medicine and industry, the media, science, politics, and not least patients or new customers). For example, the routinization of medical interventions in the case of cosmetic surgery is driven to a considerable extent by self-help literature, media reports, and cosmetic surgery customers themselves – at a certain remove from the »classical« medical profession, which sees its mission as that of curing illnesses. Predictive genetic diagnosis, on the other hand, which can be seen as a prime example of the »detemporalization« of illness, is driven more by basic research in the biosciences – research which is now linking an ever-increasing number of diseases with genetic risk factors.

The case of ADHD, in turn, the historical development of which is seen by many observers as a paradigm of the medicalization of a type of socially deviant behavior that can be associated with difficulties in cognitive performance, is characterized by quite different constellations. The question as to what can be regarded as falling within the bounds of »healthy« behavior and what must be considered to have entered the realm of »pathological« behavior can be answered only in part by use of biomedical measurement techniques. Moreover, such a diagnosis is based also on an assessment of the individual's environment and self-perception. Especially in adults diagnosed as having ADHD, the clinical picture appears to be interpreted, and even seized upon, as an opportunity insofar as it provides access to medicines that are perceived and experienced at least by many users as means of achieving specific and perceptible performance enhancement and self-optimization. This thus constitutes one of the few examples of apparently successful enhancement, albeit in a gray area on the fringes of »classical« therapy.

Especially multifaceted is the field of »anti-aging«, which as a hybrid of pathologization and routinization represents what is probably the most important and diverse area of medicalization. In it, declining hormone levels are seen as a medical indication for concrete »therapeutic« measures, and a multitude of substances with completely unknown and unproven effects are promoted for this purpose. Given their fear of an inevitable waning of their abilities, many elderly people with declining hormone levels may well have lower expectations of the

effects of anti-aging measures, and may experience more pronounced placebo effects, than do young people who use purportedly performance-enhancing substances. In many cases they may be satisfied simply if they have the impression that the waning of their abilities would have been more pronounced if they had not used the substances concerned. It therefore seems possible that use of questionable »neuroenhancement agents« may be most likely to increase in this segment of the population.

PERFORMANCE-ENHANCING AGENTS OF THE FUTURE – A SCENARIO OF EXPANSION

Underlying the ethical debate about enhancement is the assumption that substances with specifically performance-enhancing effects in healthy individuals but with few side effects may be developed in the future. The TAB report therefore considers a scenario of expansion and asks how such substances might arise via the medical-pharmacological innovation system. Though it seems fundamentally unlikely that a substance could exert potent, specific effects on relevant mental abilities without at the same time exerting harmful effects on other physical or mental processes, this is no more than an – albeit scientifically plausible – assumption and by no means a certainty.

PERFORMANCE-ENHANCING DRUGS IN THE PRESENT SYSTEM OF RESEARCH AND INNOVATION

The (presently) available range of supposedly performance-enhancing substances is derived from discoveries made via the biomedical research system and development work undertaken either individually or jointly by public (e.g. universities) or private (e.g. pharmaceutical manufacturers) scientific institutions. At both the national and the international level there is now a trend towards a graduated model of medical-pharmacological research. This involves

- largely public financing of basic, healthcare, and other specific areas of research;
- the creation of small and in many cases highly specialized companies (»spinoffs«) for the early stages of product development; and
- increasingly large pharmaceutical companies that can provide the resources required for product development up to the marketing authorization stage.

The activities undertaken by these various R&D players are determined to a significant extent by the requirements of research sponsors (especially in the noncommercial field), by the conjectured sales prospects and market potential of possible new products, and consequently also (especially in the commercial field) by marketing authorization criteria, adherence to which is the responsibility mostly of national and international licensing and regulatory authorities. Along

with these legal structures there also exist illegal structures via which supposedly performance-enhancing substances can be placed on the market.

Basic research into cognitive performance or emotional disposition and possible means of influencing this has already become a scientifically interesting and potentially rewarding area of activity. Scarcely any application-oriented approaches – e.g. specific analysis of performance-enhancing effects of pharmacologically active substances in healthy individuals or even direct development of such substances – exist to date, and possible joint projects with the pharmaceutical industry seem unlikely to be genuinely appealing to public research institutions in the absence of a relaxation of the criteria for the marketing authorization of neuroenhancers.

It is clear that up to now, scarcely any pharmacologically active substances with an assumed potential for performance enhancement have been sought or discovered with that potential in mind. Rather, most such substances had been licensed for the treatment of a variety of symptoms of illness for many years before their (supposedly) performance-enhancing effects in healthy people came to light more or less by chance in the course of routine use. It also seems that any future increase in the use of performance-enhancing substances is more likely to come about via an »accidental broadening of indications« than to result from specific (basic) medical research and development – at least for as long as current precepts of medical ethics remain the same and the present clinical trials and marketing authorization procedures remain unchanged, since to date these have severely restricted any specific search for performance-enhancing effects of pharmacologically active substances in healthy subjects.

Nevertheless, even today some R&D activities that are situated at the margins of what is permissible in terms of medical ethics and the law are to be observed (e.g. studies by armed forces on performance-enhancing effects of presently available medicines, pharmaceutical research on the retention of abilities at advanced age). Furthermore, specific research and development of performance-enhancing drugs could occur in countries with well-developed scientific infrastructure but different regulatory standards (e.g. China, India, Brazil). Substances of this kind could be approved for use in these countries and from there spread to other countries.

ELEMENTS AND IMPLICATIONS OF A SCENARIO OF EXPANSION

In considering a scenario of expansion, the TAB report explores the question of what would be required to make the present logic and procedures of the major pharmaceutical markets compatible with the investigation and development of pharmaceutical agents and medicines for »performance enhancement in healthy individuals«. To date nobody has dealt in any depth with this question or the

question of the potential consequences that such an expansion might have on the healthcare and innovation system.

Existing legislation forms an obstacle to the licensing of medicinal products for performance enhancement in healthy individuals (hereinafter »HPEDs«: hypothetical performance-enhancing drugs). Access to the market via a broadening of food categories seems unlikely because HPEDs – by definition – exert biological effects beyond those permitted by food legislation. The term »medicinal product«, on the other hand, refers to all substances used to influence physiological functions – regardless of the presence or absence of illness. Since, however, a connection with illness is a prerequisite for marketing authorization, licensing of HPEDs would require changes to marketing authorization regulations.

All in all, the rate of research and development of performance-enhancing drugs is unlikely to increase to any significant extent without interaction between scientific developments and the political decision-making process. The regulatory basis for legalizing the use of performance-enhancing drugs would have to be an acceptance of performance enhancement in healthy individuals as a benefit dimension of pharmacological R&D both in the framework of medicinal product licensing and in the framework of present medical ethics assessment procedures.

Even if performance enhancement in healthy individuals were to come to be regarded as useful to the individual and/or society, the safety testing and the entire benefit-risk assessment of HPEDs would need to be stricter than in the case of products licensed for therapeutic use. One likely prerequisite for marketing authorization would be exclusion of the possibility of serious side effects. Greater attention would presumably also be paid to rare and long-term side effects and to indirect side effects and consequences of a psychosocial nature. Since these are by their nature especially difficult to detect, a fundamental and protracted scientific, social, and political dispute about how to approach such risks would be likely to ensue.

If only to facilitate detection of harmful after-effects, it would be expedient for access to approved HPEDs to be restricted by means of a gatekeeper system, i.e. such drugs could be issued only by authorized persons subject to notification and documentation obligations and available for user feedback. Restriction of the gatekeeper role to doctors would seem appropriate in this regard. In such a scenario the concept of medical discretion would need to undergo a fundamental rethink, and presumably be expanded, in doctors' codes of professional conduct.

RISK ASSESSMENT AND PROOF OF EFFICACY

Compared to the development of therapeutic medicines, the development of HPEDs brings new challenges and difficulties in relation both to proof of effica-

cy and to risk assessment – which together form the basis for a robust benefit-risk assessment for the purpose of marketing authorization.

In the case of therapeutic studies the social value of a drug is regularly regarded as having been established. Even nontherapeutic research in humans is generally justified on the basis that it promotes medical progress and thus may bring medical benefit at some time in the future. The extent to which the objective of performance enhancement in healthy individuals can be legitimized in this way is yet to be determined.

Phase I clinical trials on HPEDs would probably differ little from those on substances being developed as medicines. Unlike in the case of medicine candidates, however, in the case of HPEDs questions of efficacy could also be addressed initially in phase I studies. At present, actual proof of efficacy of medicines used for therapeutic purposes is obtained in phases II and III. In the case of HPEDs a different type of proof would be required, therefore proof of efficacy would have to be established in a different way. As with safety requirements, requirements for proof of efficacy are likely to be more stringent with HPEDs than with medicines intended for therapeutic use.

NEW DEMANDS ON THE HEALTHCARE SYSTEM

Since they act on central functions of the brain, HPEDs could potentially cause undesirable psychosocial effects (e.g. on abilities, range of abilities, and personal identity). In the development of HPEDs particular attention would therefore need to be paid to such effects during the clinical trials phase, which would thus evolve into a clinical-social trials phase. In some cases completely new assessment criteria and procedures would need to be developed for this purpose, and many parameters might prove very difficult to test in advance. Systematic long-term monitoring would therefore be crucially important and consideration would need to be given not only to possible individual, but also to social, ramifications. How and by whom this could be achieved is entirely unclear. What does seem beyond question is that requirements for provision of information to users of HPEDs would need to be very stringent. The need for special labeling requirements would have to be discussed and demarcation problems between the labeling requirements that applied to HPEDs and those that applied to doping substances would have to be anticipated.

It must be assumed that a proportion of users of HPEDs would develop problematic patterns of use. Harmful effects on individual health would presumably be treated – and costs reimbursed – in much the same way as are harmful effects on health due to other substances. Abuse of an HPED could lead at any time to a reassessment of the benefit-risk relationship and to withdrawal of marketing authorization.

REPERCUSSIONS ON THE SYSTEM OF INNOVATION

The following changes to the present system of research and innovation could potentially occur as longer-term consequences of increasing development and spread of HPEDs:

- Once the granting of marketing authorization for HPEDs became a realistic possibility, especially in the European Union or the USA but perhaps also in the growing markets of emerging economies, pharmaceutical companies would be likely to embark on an intensive R&D program aimed at gaining access to new markets. Such expansion would require the sort of major investment that tends to be possible only for large companies with a global presence.
- The opening up of these new markets would lead to at least a temporary slowdown in R&D activity in the core area of medical pharmacology, since some of the limited resources available to this industrial sector would be redirected to the field of enhancement.
- Healthcare providers would find new opportunities for growth. Specially trained doctors could care for users of HPEDs. Given that HPED-related services would have to be financed privately and that doctors' fees are lower for services provided via the SHI scheme than for those provided privately, medical care could change in some ways. The shortage of doctors that has already become apparent in some areas of treatment would be exacerbated.
- Social security systems would incur treatment costs arising from incorrect use – or at the very least would find themselves enmeshed in expensive legal disputes about liability to reimburse the cost – of HPEDs. The pressure to establish more precise procedures for limiting and excluding cost reimbursement would intensify.

DOPING AND ENHANCEMENT: COMMONALITIES AND DIFFERENCES BETWEEN SPORT AND WORKING LIFE

The parallels between (neuro)enhancement and doping in sport are strikingly obvious: in both cases people take pharmacological agents in order to improve their performance. There is therefore a need for a systematic analysis of the extent to which information derived from scientific study of doping in competitive and recreational sport can be extrapolated to the intentional and widespread use of performance-enhancing substances in everyday and working life.

PATTERNS OF JUSTIFICATION AND BEHAVIOR

Especially in relation to questions of ethical acceptability – the right of self-determination and the right to harm oneself, equality of opportunity, and fairness – the debate about doping in the sense of pharmacological performance

enhancement has much in common with, and in fact can be seen as a forerunner of, the debate about enhancement. One difference is that in the case of doping only a minority of the population is seeking explicit approval to use certain substances, whereas in the case of enhancement a large number of people are arguing against a general prohibition of the use of potentially performance-enhancing substances. As a result, bioethical analyses of enhancement often come to the conclusion that in a rational and liberal society doping in sport should likewise not be prohibited. In both these areas of debate, however, benefits are described only in vague terms and risks are either downplayed or said to be the responsibility of the individual user. This emphasis on individual autonomy of action, together with a denial that the »deviant« behavior has any systemic context or supra-individual pathological significance, is an obvious common feature of the debate about doping and that about enhancement.

Two intrinsic features that drive the phenomenon of doping in competitive sport are especially useful for acquiring an understanding of performance enhancement: the »quantity law« of doping and the tendency of athletes who choose not to engage in doping to drop out. The former feature is derived from the observation that even assuming that a form of doping that is harmless to health can be achieved by use of medicines within a low, »therapeutic«, dosage range, over the course of their careers athletes almost inevitably move up into a »nontherapeutic« dosage range that is increasingly harmful to health while offering only the prospect of progressively smaller increments in performance. Dropping out, in the sense of the premature withdrawal from competitive sport both of athletes themselves and of athlete support personnel and officials who do not wish to engage in pharmacological performance enhancement, is seen as a systemic consequence of the spread of doping behavior of which the public is scarcely aware. In this way sport loses many of its most thoughtful, self-aware, and strong-willed people. In addition, athletes who fail to meet doping-based standards are »weeded out« at a later stage. All of this suggests that »moderate, controlled« pharmacological »optimization« of human beings is not a realistic possibility with any prospect of success.

Overall, doping in sport can be seen as a form of behavior which, though officially frowned upon, is tacitly accepted and in some areas of sport may well be more the rule than the exception. Central to individual and social acceptance of doping is an exclusively result-oriented view of performance. In working life the value placed on performance, under whatever conditions it occurs, appears to be far more unreservedly positive, since in this sphere, unlike in sport, performance is generally measured not in terms of the defeat of competitors by pharmacological manipulation, i.e. »doping at the workplace«, but rather in terms of the achievement of corporate objectives. The positive connotation of performance – and of performance enhancement – presumably also has the result that in many cases the question of whether pharmacological intervention actually brings

about any measurable improvement in performance is not even discussed in any substantive way.

Sports sociology has shown how misleading it is to regard doping behavior as no more than a form of misconduct for which the individual concerned bears sole responsibility. Rather, doping is always shaped by the values and norms of the individual's sociocultural frame of reference. Deviation from explicitly permitted forms of behavior occurs when legitimate means are no longer sufficient to meet the demands of the system. Rule violators can then rationalize their infractions as an expression of conformity and willingness to integrate. Deviant behavior is also facilitated when official norms that prohibit doping coexist with informal norms that countenance doping by reclassifying it as a form of treatment or a means of promoting wellbeing or avoiding disadvantages.

Neuroenhancement can likewise be seen as a deviant, »innovative« form of behavior, an attempt by individuals to adapt to excessively demanding social structures. The more uncertain a person is of being able to perform as required and the greater the risk they perceive of losing their job or failing to achieve important training objectives, the more likely they are to respond by resorting to medicines that they believe may help them.

The argument that if enhancement products were freely available everybody could decide for themselves whether to use them or not is unconvincing. In such a scenario the structural pressure to use such substances would not decrease, but if anything increase, since the pressure to perform must be expected to increase further. At the same time, willingness to take medicines or other substances to enhance performance appears to be a sign of a lack of confidence in one's own abilities. It is scarcely plausible that a person of high intellect would experience a pharmacologically induced improvement in performance as an improvement in their personal sovereignty or autonomy. Studies on substance abuse among secondary and tertiary students suggest that – as in doping in sport – it is not primarily the most talented, but rather »second-tier« individuals subject to high expectations, who use prescription medicines in an attempt to achieve their educational and competitive objectives.

PATHOLOGICAL ASPECTS OF HIGH PERFORMANCE AND QUESTIONS OF PREVENTION

Many people who are not elite athletes use doping substances (e.g. an estimated one million people in Germany). This suggests the presence of a social orientation towards high performance that is at least increasingly problematic, and possibly even pathological. People whose occupation orients them towards high performance strive tenaciously to exert as much control as possible over their own body. Along with the increasingly common phenomenon of eating disorders, the little-discussed problem of sports addiction can be seen as a member of a widespread group of disturbances of bodily perception and management.

There is no clarity, however, with regard to the determinants of these conditions, e.g. with regard to the interactions between performance orientation, substance use, and addiction. French experts on addiction have found (elite) competitive athletes to be at substantially greater risk for drug addiction than people who do not engage in sport or do so only occasionally. To what extent this is attributable to the pre-existing personality structure of the persons concerned, and what contributions are made by substance use *per se* and by the structure of competitive sport, are research questions that are of relevance also to the debate about enhancement. Study is needed on the question of to what extent intellectual work can have harmful effects similar to those that appear to occur with physical hyperactivity. Specifically, we need to find out whether consumption of neuroenhancement products or other forms of medication abuse do or do not constitute an additional risk for such effects.

Social setting exerts a major – either moderating or intensifying – influence on addiction and dependence behavior in athletes. It is not substances or modes of behavior *per se* that cause addiction, but rather the manner in which a particular personality deals with substances in a particular sociocultural setting. As far as the potential for abuse of medicines beyond sport is concerned, there is little doubt that behaviorally oriented approaches to prevention should be directed not towards prohibition and punishment, but rather towards general education about health. Especially in adolescents, efforts at prevention based simply on warnings about possible harm to health have proved to be of little use. Of far more use are efforts to promote protective factors and skills, whereby the individual background and social milieu of children and adolescents (e.g. parental home, schools) should be taken into account when formulating preventive strategies. At the same time, the most important structures that provide opportunities for undesirable behavior (e.g. routes of access to medicines) should be shaped in such a way that this type of behavior is not facilitated (situational prevention).

SIGNIFICANCE FOR WORKING LIFE

The use of enhancement agents in the working environment is sometimes portrayed as a rational response to increasing psychological demands in working life. It appears to be a measure aimed at reducing unmanageable complexity and coping with situations in which excessive demands are being made. From a short-term perspective such expectations of benefit may seem realistic, however the historical development of doping suggests that the concept of pharmacological manipulation of human beings offers little prospect of success in the long term.

The pressure to use performance-enhancing substances that is apparent in the world of sport now appears to be gaining ever more ground also in the working world, especially among highly qualified people. Increasing stresses and strains jeopardize not only the health of affected individuals, but in the long term also

the successful further development of companies as a whole. In accordance with the »quantity law of training« known from sports science, ever greater efforts are required in order to achieve ever smaller increments in performance. Further escalation, whether by doping, by abuse of medicines, or perhaps in the future by means of effective neuroenhancement, neither reverses this process nor makes it any more bearable. It must therefore be in companies' self-interest to monitor, and where appropriate take countermeasures against, the rampant growth of pharmacological boosting.

A number of brain researchers and psychopharmacologists have put forward the view that the performance of a brain that has been well endowed by nature and its environment cannot be improved, and in fact can only be impaired, by pharmacological influences, since it is already working optimally. Should this view be correct, »enhancement« would bring only disadvantages, above all to particularly susceptible high-achieving professionals. The feeling of being overburdened would presumably not be alleviated, but rather intensified, since the persons concerned would find that the substances that they had felt no option but to take had in the long run brought them no benefit at all.

POTENTIAL AREAS OF ACTIVITY

The results of the TAB report suggest some options for action in the fields of research, regulation, consumer health protection and prevention, and public debate.

RESEARCH

There is a need for research especially in relation to the various social forms of the deliberate use of medicines for performance enhancement. The empirical analyses that have been published to date provide a starting point that could be expanded by studies on the following questions, in particular:

- What proportion of people who do not feel ill – broken down by social group, occupation, and life situation – deliberately take medicines (or illegal substances) in order to improve their performance, and what substances do they take?
- How is this influenced by educational and working environment? Are the persons concerned satisfied with their situation, or would they prefer alternative options for action that did not involve consumption of substances?
- What economic and social factors and developments influence concrete patterns of use and acceptance of the use of substances in principle?
- What health effects and psychosocial consequences are to be observed?
- Starting with doping in sport: What interactions exist between performance orientation, substance use, and addiction?

› Can intellectual work have harmful effects similar to those that appear to be observable in physically hyperactive sports-addicted people?

It would be helpful if the presently available body of knowledge on observed and conceivable effects of supposedly performance-enhancing substances could be evaluated – insofar as is permitted by present regulations governing research and medical ethics – more thoroughly than it has been to date.

Since pharmaceutical research and development is distinctly global in orientation and performance-enhancing drugs could easily gain a foothold outside of Europe, there is a need for periodic monitoring of international developments in this field.

REGULATION

No pressing need for regulation of, or modification of the laws pertaining to, pharmacological (neuro)enhancement is apparent at present. All the purportedly enhancing substances known to date are covered by pharmaceutical, narcotics, or food legislation. Therefore, the question of whether to prohibit substances or substance consumption does not arise at present.

Nevertheless, it seems reasonable to request some clarification of the prohibition of doping enshrined in the German Medicinal Products Act *(Arzneimittelgesetz,* AMG). In order to protect health (§ 6 AMG), this prohibits the placing on the market, prescription, or administration of medicinal products to others for the purpose of doping in sport (§ 6a AMG). Were it to become apparent on the basis of detailed empirical surveys that abuse of medicines for the purpose of enhancing mental/cognitive performance constitutes a problem of similar magnitude to that of physical performance enhancement, it would be appropriate to consider putting these two practices on an equal footing for the purposes of the AMG.

Some regulatory fuzziness also exists with regard to the use of the concept of therapeutic benefit as a justification for clinical research and subsequent licensing of medicinal products. For example, a substance can be licensed but at the same time excluded from the benefits catalog, especially that of the SHI funds. As a result, an increasing number of substances seem likely to be sold mostly in the secondary (private) healthcare market, the documentation and control mechanisms of which are less stringent than those of the primary healthcare market. Assessment of possible trends in enhancement would require a systematic, transparent, and detailed survey of prescriptions and sales. In addition, the independent benefit-risk assessment would need to be strengthened and provision of reliable, easily accessible, and comprehensible information for patients/clients receiving individual health services or off-label prescriptions would need to be ensured. The present practice by doctors – a practice which is opaque

and of unknown extent – of providing off-label prescriptions or prescriptions of convenience at the borderline between treatment and performance enhancement requires careful consideration by medical associations and society as a whole.

With regard to food legislation it would be useful to assess the extent of goal attainment that has resulted from implementation of the Health Claims Regulation and if appropriate to review the regulations governing the advertising of purportedly performance-enhancing foods in order to restrict practices that create or reinforce a wish for performance enhancement.

CONSUMER HEALTH PROTECTION AND PREVENTION

There are many grounds for believing that the use of pharmacologically active substances is not an appropriate or socially desirable option for coping with highly or even excessively demanding performance expectations and objectives. The observation that despite the threat of a myriad of nontrivial side effects this form of behavior is of relevance to medical practice suggests the need for broad-based promotion of health-conscious individual lifestyles, among other means by provision and dissemination of reliable information and by establishing a health-promoting environment as envisaged in the WHO's Ottawa Charter for Health Promotion.

Preconditions for this would include construction of a counterweight to interest-driven advertising claims and confusing internet information and provision of clear, comprehensive, and reliable information to consumers on claims about effects, lack of effects, and side effects both of foods and of medicines.

When working to establish health-promoting educational and working environments we must distinguish between the general question of the formulation and enforcement of demands for performance – which is a basic question for society as a whole (see below) – and concrete measures to promote health in working and educational environments. Occupational health promotion including the establishment of decent working conditions is a responsibility mostly of the employer, whereas the situation with self-employed and bogus self-employed people, unemployed people, and secondary and tertiary students is either less clear or completely different. Particular attention should be paid to the phenomenon of increasing mental stress (due to increasing pressure of time and rapid switching between tasks), which appears to lead to more frequent illness in all segments of the population.

SOCIAL AND POLITICAL DEBATE

The principal social and political relevance of the topic »Enhancement« arises not because enhancement is perceived as contributing towards a scientifically and technically based »improvement of human beings«, but rather because

pharmacological interventions to improve performance form part of the »medicalization of a performance (enhancement)-oriented society«. The social and political debate about this issue should therefore focus on the likely future status of pharmacological and other (bio)medical strategies and measures for coping with performance targets and demands in a globalized educational and working environment and on the consequences of demographic change. To this end, rather than assuming at the outset that adoption of strategies designed to maximize individual and collective performance is inevitable, we need to look into conditions in secondary and tertiary education and at the workplace, and where appropriate adjust performance indicators. Commercial and economic considerations also favor such an approach, at least in the medium and long term. In this regard the example of doping in sport shows how a system of competition could potentially self-destruct as a result of unlimited expectation of ever-improving performance.

One substantial argument for pharmacological enhancement that is cited in many bioethical submissions is that it is of particular benefit to less highly achieving individuals, especially in working life, and thereby provides greater equality of opportunity and fairness. An analysis of the effects of presently available substances suggests that people who suffer from some kind of deficit at baseline may be more likely to benefit. Confirmation of this hypothesis would intensify discussion of the difficult question of boundaries that has arisen as a result of the increasing pathologization of normal conditions, a trend to which social security systems too must constantly adapt. At the same time, surveys conducted to date suggest that performance-enhancing substances are most likely to be used by very well educated and highly motivated people who nevertheless feel unable to cope with the demands placed upon them. All in all, therefore, occupational »enhancement« seems unlikely to be experienced as an autonomous action with beneficial consequences.

If, at some time in the distant future, more solid evidence than is presently available should emerge of performance-enhancing effects unaccompanied by significant side effects, there are likely to be pressing calls for more systematic research into enhancement agents. Given the paradigm shift in medical research that this would entail, a public opinion-forming process would need to be initiated by that time at the latest in order to give the public the opportunity to decide whether it really wished to allocate public funds to such research.

However, the findings of the present report do not suggest that performance-enhancing substances are likely to exert a beneficial influence on public wellbeing, the social fabric, or individual happiness in the longer term.

INTRODUCTION I.

For some years the term »enhancement« – a term that lacks a satisfactory German equivalent – has been used, especially in the fields of sociology and bioethics, to refer both to developments in biotechnology and medical technology and to the changing practices of growing segments of the population in relation to pharmacologically active substances. The term refers to »interventions in the human body« that are intended to bring about a subjective or objective improvement in performance. In its broadest sense it can therefore also refer to mood control and cosmetic alterations. Among the many views expressed, there have been calls from bioethicists and natural scientists for intensified systematic research into performance-enhancing substances and methods, while health and social professionals have mostly warned about the increasing internal and external pressures exerted on people to engage in pharmacological »everyday doping« in the context of the growth of customer service medicine and wish-fulfilling medicine in the secondary healthcare market.

BACKGROUND AND CENTRAL ASPECTS OF THE TOPIC 1.

To an increasing extent, particular mental, and in many cases also physical, abilities are seen as a precondition for professional and personal success in modern industrial societies. This social trend is apparent in various areas of life and is influenced by a number of different economic, social, and scientific developments. With regard to the scientific basis of attempts to influence performance, increasing attention is being paid to research in pharmacology and medical technology and to the discoveries and products that result from this research – products that were developed and are used primarily for the purpose of treating diseases. Some of these substances and technologies could potentially be used not only to treat mental or physical ailments, but also to improve specific aspects of an individual's mental or physical abilities (e.g. ability to concentrate, muscular strength) beyond »normal« limits. It is widely assumed that this would make it increasingly difficult to draw boundaries between use of pharmacological and (neuro)technical interventions that is definitely indicated, use that is at least medically justifiable (off-label use), and use that is not medically indicated and that may constitute abuse. Similarly, it is predicted that the improvement in individual abilities made possible by such interventions will come to permeate more and more areas of life, whereas, it is said, the implications of such a trend towards »everyday enhancement« are not sufficiently recognized.

This development is considered to be driven not only by the increasing possibilities offered by science and technology, but also by changes in the way in which society and individuals perceive health and illness and by new dissemination structures for products and information (worldwide availability not subject to traditional regulatory structures, e.g. for medicines). Evidence of increasing development and diffusion of drugs and other medical techniques including (neuro)technical interventions to improve individual performance in specific everyday situations has been identified in a number of TAB projects, namely »Brain Research« (Hennen et al. 2008 and TAB 2007), »Converging Technologies« (TAB 2008a), and »Gene Doping« (Gerlinger et al. 2008 and TAB 2008b). Over the past few years the topic of enhancement has also been dealt with by other German and European technology assessment institutes including the European Academy for Research on the Consequences of Scientific and Technical Developments (Merkel et al. 2007); the European Technology Assessment Group on behalf of STOA (»Scientific and Technical Options Assessment«, the TA institute of the European Parliament) (Coenen et al. 2009); TA-SWISS, the TA institution of the Swiss Parliament (project completed in 2011; www.ta-swiss.ch); and ITAS (»Institut für Technikfolgenabschätzung und Systemanalyse«), which focuses on nano- and neurotechnologies and converging technologies (e.g. Fiedeler 2008; Grunwald 2008; ITAS 2009).

2. COMMISSION, OBJECTIVE, AND APPROACH

Notwithstanding the trend referred to above, much uncertainty remains about many scientific and technical possibilities and about the developmental stage and resulting time frames for greater diffusion, the possible effects and side effects, and the nature and intensity of the societal ramifications of these possibilities. For this reason the Committee on Education, Research and Technology Assessment (*Ausschuss für Bildung, Forschung und Technikfolgenabschätzung*) at the German *Bundestag* commissioned the TAB to undertake a project on the topic »Pharmacological and technical interventions to enhance performance – prospects for more widespread use in medicine and everyday life« (short title: »Enhancement«).

Based on an analysis of identifiable trends, the project aims to discuss the use of pharmacological and technical interventions for performance enhancement, the potential ramifications of such use, and resulting issues for politics and society. The challenge of this TA project was to describe and analyze the multiplicity of scientific developments, relevant fields of technology, and potential societal impacts in detail while at the same time focusing on politically relevant questions. To this end the project was divided into two phases, namely an exploratory and an in-depth phase.

RESULTS OF THE EXPLORATORY PHASE

The exploratory phase served for the acquisition of a broader perspective on the topic. In addition to a survey and evaluation of completed and ongoing studies on the topic of enhancement by the TAB's own project team, six expert reports were commissioned, namely on the current state of research and development of relevant psychopharmaceuticals, on a comparison between cognitive enhancement training programs and pharmacological and technical interventions, on foods advertised as being able to enhance performance, and on the sociological, ethical, and legal debates surrounding this issue (Section I.3). An interim assessment of the findings of the expert reports was discussed in detail with the reporting experts at an internal workshop. The following conclusions were used as starting points for establishing areas of enquiry in the in-depth phase.

WORKING DEFINITION OF »ENHANCEMENT« AND SYSTEM CLASSIFICATION

Even after years of scientific debate, the contours of the study object »enhancement« remain fuzzy. This term, which lacks a satisfactory German equivalent, has been used by many experts in a multitude of contexts, projects, and publications to refer to »interventions in the human body« of a broader or narrower kind. The focus in the project title on »prospects for more widespread use of pharmacological and technical interventions to enhance performance in medicine and everyday life« excludes certain interventions, e.g. purely cosmetic procedures, but still permits a broad area of investigation. There are at least four reasons for this fuzziness, namely:

- a lack of clarity regarding the concept and measurability of »performance enhancement« in the transitional area between doping (within the »normal« limits to human performance), improvement (beyond these limits), and alteration (qualitative extension of performances or abilities);
- difficulties in establishing boundaries between illness and health, in determining the start and end of a medical (deficit) treatment (including preventive measures), and in distinguishing between use that is definitely medically indicated, use that is at least medically justifiable (off-label use), and use that is not medically indicated and that may constitute abuse;
- subsuming of extremely heterogeneous agents and methods (at very different stages of development) into the same term;
- a paucity of empirical data on the pervasiveness of use of different enhancement agents and methods.

A precise definition of enhancement is therefore scarcely achievable. Based on a consideration of short- and medium-term social and political significance, the *in-depth phase* of the TAB project was *limited to pharmacologically active substances*, that is to say that strictly technical (neuroimplants and the like) and biomedical (e.g. genetic manipulation) interventions were excluded. Most such ap-

proaches are at such an early stage of development that the question of their possible future use for performance enhancement in professional and everyday life could be answered at best only speculatively.

PRELIMINARY FINDINGS ON THE USE OF ENHANCEMENT AGENTS

The project was focused on plausible projections of observable scientific and social trends in the use of medicines as enhancement agents in professional and everyday life. Most of the medicines considered were psychopharmaceuticals that influence – or are intended to influence – mood, wakefulness, and attention or memory. Typical agents used for physical performance enhancement are familiar especially from doping in competitive, fitness, and recreational sport. The preliminary findings on the use of pharmacological enhancement agents obtained in the exploratory phase of the study were as follows:

- Scarcely any evidence-based knowledge on the performance-enhancing effects of medicines in healthy individuals is available, since such effects are not investigated (benefit aspect). Because of this there has likewise been no investigation of the side effects, not to mention the possible long-term effects, of such use (risk aspect).
- Despite this, segments of society use certain medicines with the intention of improving their performance in educational, occupational, and private settings.
- Access to such agents is obtained by legal purchase, prescription, or illegal acquisition, depending on the substance.
- Driving factors appear to include firstly the growth in the secondary healthcare market by self-financing of services that has resulted from increasing non-reimbursement of medicines and treatments by SHI funds, and secondly the existence of new means of accessing information via the internet.
- Patients appear to be active seekers of information, however they encounter basic problems of orientation and trust as a result of unclear or misleading information.
- Enhancement trends are accompanied by a shift in the self-image of the medical profession and medicine towards service provision and wish fulfillment in the context of an increasingly competitive »performance improvement society« and as a consequence of economic, political, and legal developments and precepts.

TOPICS OF THE IN-DEPTH PHASE

In the in-depth phase of the TAB project two paths of development of the future use of medicines for performance enhancement were considered in detail, namely:

- the »business-as-usual scenario«, in which diffusion of enhancement within the healthcare system and society proceed in accordance with existing circumstances and developmental trends, and
- on the other hand, a scenario of regulatory requirements and constraints and the consequences of a »scenario of expansion« of use of enhancement agents such as could result from targeted scientific development efforts and political decisions.

In addition, in order to explore the causes of and motives for enhancement behavior in more depth, an attempt was made to determine which of the behavioral patterns and system conditions that prevail in doping in (competitive and recreational) sport could also be relevant to enhancement in occupational and everyday settings. Three additional expert reports were commissioned on these topics (Section I.3).

The results of the expert reports and literature analyses from both phases of the project are presented in this final report.

3. COOPERATION WITH REPORTING EXPERTS

The following expert reports were commissioned in the exploratory phase:

- Neuro-Enhancement – Die Argumente (»Neuroenhancement – the arguments«). Centrum für Bioethik, Westfälische Wilhelms-Universität Münster (authors: Dr. Johann S. Ach, Dr. Benedetta Bisol)
- Marktangebot von Lebensmitteln, die mit Aussagen zur Leistungssteigerung oder über die Beeinflussung des optischen Erscheinungsbildes beworben werden (»Market supply of foods that are advertised via claims of performance enhancement or effect on appearance«). Christina Rempe, Berlin
- Psychopharmakologisches Neuroenhancement – Aktuelle Möglichkeiten, Risiken und Perspektiven (»Psychopharmacological neuroenhancement – current possibilities, risks, and outlook«). Klinik und Hochschulambulanz für Psychiatrie und Psychotherapie, Charité-Universitätsmedizin Berlin (authors: Dimitris Repantis, Prof. Dr. Isabella Heuser)
- Der Stand der psychologischen Forschung zu Enhancement-Trainings im Vergleich zu pharmakologischen und technischen Interventionen (»The present state of psychological research into enhancement training methods compared to pharmacological and technical interventions«). Dr. Ralph Schumacher, Prof. Dr. Elsbeth Stern, Berlin/Zürich
- Enhancement in Medizin und Alltag: Eine erste Sondierung der ethischen Implikationen und des rechtlichen Regulierungsbedarfs (»Enhancement in medicine and everyday life: an initial study of the ethical implications and the need

for legal regulation«). Prof. Dr. Jürgen Simon, Ass. Jürgen Robienski, Dr. Rainer Paslack; Bardowick, Lüneburg, Bielefeld

- Die Entgrenzung der Medizin und die Optimierung der menschlichen Natur – Biopolitische Strategien und Praktiken des Enhancements und ihre Aneignung durch die Individuen, illustriert anhand der Beispiele ADHS und Anti-Aging-Medizin (»The expansion of medicine beyond its former boundaries and the optimization of human nature – biopolitical strategies and practices of enhancement and adoption of these by individuals, illustrated using ADHD and anti-aging medicine as examples«). Dr. Willy Viehöver, PD Dr. Peter Wehling, Fabian Karsch, Dr. Stephan Böschen; Augsburg

The following expert reports were commissioned in the in-depth phase:

- *Das Gesundheitssystem und seine derzeitige und zukünftige Rolle bei der Diffusion von Enhancementmitteln* (»The healthcare system and its present and future role in the diffusion of enhancement agents«). IGES Institut GmbH, Berlin (authors: Hans-Holger Bless, Dr. Katrin Krämer, Hans-Dieter Nolting)
- *Forschungs- und Innovationssystem: Medikamentöse Leistungssteigerung – ein künftiges Entwicklungsfeld?* (»Research and innovation system: pharmacological performance enhancement – a future area of development?«). risicare GmbH, Zürich (authors: Dr. Anne Eckhardt, Dr. Andreas Bachmann, Dr. Gordon Gundert, Michèle Marti, Dr. Juliane Neuss Münzel, Dr. Harry Telser)
- *Doping und Medikamentenmissbrauch in Sport und Beruf. Soziologische und psychologische Aspekte des Dopings und ihr Projektionspotential für das Enhancementproblem* (»Doping and abuse of medicines in sport and at work. Sociological and psychological aspects of doping and the potential relevance of these to the problem of enhancement«). Dr. Andreas Singler, Prof. Dr. Gerhard Treutlein, Mainz

Close cooperation was maintained with all the reporting experts both during and after the preparation of the expert reports. Prof. Klaus Lieb, of the University of Mainz, kindly agreed to comment on parts of the draft report. We offer our sincere thanks to all those involved for their commitment and patience. We are particularly indebted to our TAB and ITAS colleagues Dr. Christoph Revermann, who worked on the project right through to the release of the final report, and also Christopher Coenen and in particular Dr. Thomas Petermann, who made decisive contributions to improving the report by counter-checking and providing detailed comments. Special thanks are also due to our colleagues B.-Ulrike Goelsdorf, for her thorough revision of the manuscript and for the final layout, and to Johanna Kniehase, for preparing the illustrations. Any remaining deficiencies are the responsibility of the authors, Dr. Arnold Sauter and Dr. Katrin Gerlinger.

4. STRUCTURE OF THE REPORT

Section II (*Human performance and attempts to influence it by pharmacological means*) starts with a discussion of the concept of human performance and abilities and of the extent to which these can be assessed. It then goes on to provide a brief review of the current state of biological knowledge on this subject. The principal aim of the section is to provide an account of relevant substance groups and individual substances, of the proven effects, side effects, and uses of such substances, and of the presumed and proven effects of such substances in the context of performance enhancement. Psychologically based cognitive training measures and noninvasive technologies such as electrical or magnetic fields are compared and contrasted.

Section III (*Enhancement substances: foods or medicines? Legal definition, regulatory treatment, and routes of diffusion*) is devoted to the legal situation with regard to the licensing and placing on the market of medicines and foodstuffs with particular reference to provision of information and advertising by suppliers and gatekeepers (doctors and pharmacists). The known and presumed routes of diffusion of performance-enhancing substances in the primary and secondary healthcare markets and via other channels are discussed. Finally, the present state of knowledge about the diffusion of drugs for the purpose of mental/cognitive and physical performance enhancement is summarized.

Section IV deals with the *debate about enhancement in ethics and the social sciences* from the particular perspective of the concrete social and political relevance of the questions that have been raised and the conclusions that have been reached. The debate about ethics is presented in somewhat abbreviated form, since many of the pertinent analyses are based less on empirical observations or plausible assumptions than on speculative cases of hypothetical enhancement agents. A more detailed discussion is devoted to the question of what findings in sociology suggest that the use of substances for the purpose of performance enhancement can or must be understood in the context of a medicalization of psychosocial problems in an increasingly competitive society.

Section V (*Performance-enhancing agents of the future – a scenario of expansion*) fills what has until now been a central gap in the entire debate about pharmacological enhancement, namely: Is the objective of performance enhancement at all compatible with the present logic and R&D procedures of pharmaceutical agents and medicines, in particular with regard to the applicable legal precepts? What scientific, social, and political developments would be required in order to make it possible for enhancement substances to actually play the major future role that is foreseen for them, especially in bioethical discussions? The scenario that emerges is suggestive not of a predominantly science-driven dynamic, but rather of a great deal of scope for political and social influences.

Also analyzed in Section VI *(Doping and enhancement: commonalities and differences between sport and working life*) is an aspect of the problem which – astonishingly – appears scarcely to have been dealt with in any depth to date, namely the possible lessons to be learned from pharmacological performance enhancement in the social subsystem of sport when this is projected onto working life. The conclusions that can be derived from research conducted in the natural sciences and sociology on the problem of doping (e.g. on motives, drivers, system influences, pathological after-effects, possibilities for prevention) are discussed insofar as they are applicable to enhancement as a pharmacological solution to the problem of growing demands for performance in educational and occupational settings.

Finally, in Section VII *(Résumé and potential areas of activity)* conclusions are drawn with regard to the scientific, social, and political relevance of the phenomenon of pharmacological enhancement and about the consequent need for action in the fields of research, regulation, consumer health protection, and public debate.

5. USE OF THE TERM »ENHANCEMENT«

As explained in Section I.2, the term »enhancement« is used to mean very different things. On the one hand it is used in a very broad sense to refer to, among other things, any one of a multitude of technical and biomedical interventions intended to influence and mold the human body in a given way. On the other hand, a substantial part of the specialist and public debate refers in particular, via the terms »cognitive enhancement« and »neuroenhancement«, to enhancement (or »improvement«) of the *intellectual* or *mental* capacities of humans as distinct from enhancement of physical abilities. One reason for this is that intellectual performance is regarded as a critical determinant of economic and social success, whereas physical ability is often seen only as a basis for mental and intellectual performance, that is to say that specific manipulation of physical abilities, e.g. by means of cosmetic procedures or substance-assisted muscle building, is assigned to the realm of self-expression or an experience of authenticity in one's private life. Moreover, pharmacological enhancement of physical abilities in the form of doping in competitive sport is generally regarded – at least ostensibly – as socially taboo and is formally prohibited, with the result that trade in performance-enhancing substances is explicitly punishable by law (Section III.3). The negative image of doping appears to have created thematic »no-go areas« in the enhancement debate, with the result that physical effects tend not to be discussed.

The highest level of public awareness of the topic »cognitive enhancement« or »neuroenhancement« to be seen in recent years was reached at the international level in late 2008 in response to a plea by six well-known brain researchers and the editor-in-chief of the journal *Nature* for responsible use of enhancement substances (Greely et al. 2008) and in Germany in the fall of 2009 in response to the *Memorandum zu Chancen und Risiken des Neuro-Enhancements: Das optimierte Gehirn* (»Memorandum on the opportunities and risks of neuroenhancement: the optimized brain«) issued by an interdisciplinary working group put together by four well-known research institutes (Galert et al. 2009). The German authors favor a critical, but open, debate on the potentials and effects of potentially performance-enhancing psychopharmaceuticals and warn against any prejudgment of the topic as »doping of the brain« – and above all against any prophylactic prohibition that might follow from such a prejudgment. Precisely that term, however, forms the title of an article that is to date the most comprehensive popular science account of the subject by a German expert in the field (Lieb 2010), though the author of the article concerned does not deal with hypothetically possible specifically performance-enhancing substances with few side effects, and still less with illicit drug consumption, but rather regards doping of the brain as being »the improper use of prescription medicines to improve mental performance«. Similarly, a study commissioned by the German Employees' Health Insurance Fund (*Deutsche Angestellten-Krankenkasse*, DAK) that is to date the most extensive survey on the use of performance-enhancing substances by working people in Germany bears the title »Doping am Arbeitsplatz« (»Doping at work«) (DAK 2009, pp. 37ff.; see also Section III.4.1). Other (groups of) scientists have used the term »mental enhancement« (Merkel et al. 2007), while others prefer the term »cognitive enhancement« to »neuroenhancement«, since the intention is said to be to improve not neuronal structures, but thought (Metzinger 2009).

As, however, will be shown in the following sections on the biological foundations and dimensions of action of known enhancement substances, the effects that have been proven to date are small, and in many cases no clear distinction can be drawn between intellectual, psychological, cognitive, mental, and emotional effects on the one hand and physical effects on the other. The present report is therefore not explicitly limited to »neuroenhancement« or the like, though the focus of discussion is on the influencing of mental capacity by pharmacological means.

References to enhancement or to enhancement agents or substances in the present report do not imply that a performance-enhancing effect has actually been observed and documented in the case in question, but only that a »pharmacological intervention« has been carried out with the *intention* of enhancing performance. The significance of this seemingly rather awkward distinction should become quite clear in the following sections.

HUMAN PERFORMANCE AND ATTEMPTS TO INFLUENCE IT BY PHARMACOLOGICAL MEANS II.

The enhancement debate deals with the possibilities and limits of attempts to modify human characteristics, abilities, and performance. As stated in the Introduction (Section I), the topic of enhancement is very broad, extending even to certain aspects of reproductive medicine, gene therapy, cosmetic surgery, and slowing of aging processes (Coenen et al. 2009; President's Council on Bioethics 2003; Simon et al. 2008). It is generally considered to become particularly socially contentious when it relates to modifications that can lead to improved individual performances that can be exploited for the purpose of meeting demands by peer groups and/or society as a whole or achieving individual social or economic objectives. In this regard two interconnected levels are recognized: firstly, the level of the individual, with his or her potential and limitations in terms of achieving objectives and making individual decisions; and secondly, the level of the peer group or society as a whole, at which the results of enhancement are assigned value and exploited insofar as certain demands are made, certain achievements are required, and the boundaries within which individual decisions have to be made are set.

The following discussion deals with the benefit dimension of pharmacological interventions for performance enhancement in terms of human achievements that be exploited within a peer group. Discussions of the phenomenon of enhancement often deal with the societal benefit dimension of enhancement in rather vague terms. This is not unproblematic, especially in relation to the ethical and political assessment of enhancement (for details, see Section IV). In addition, concepts at the level of the individual (characteristics, personality traits, abilities, achievements) are generally not precisely defined and are sometimes used inconsistently or interchangeably.

The following discussion of relevant concepts (Section II.1) makes no claim to provide comprehensive descriptions of, and still less to unify, various specialized concepts. Rather, it aims to make it possible for these concepts to be used in as consistent a manner as possible. Section II.2 deals with various procedures and possibilities that can be used with the intention of enhancing the abilities of healthy individuals. Section II.3 deals with the state of scientific knowledge about pharmacological substances and their actions especially in relation to ability and performance dimensions in healthy individuals. This is followed by a discussion of other, mostly plant-based, substances, and their actions (Section II.4) and a discussion of cognitive training and noninvasive techniques (Section II.5).

1. CONCEPTS AND BIOLOGICAL FOUNDATIONS

1.1 HUMAN PERFORMANCE

Performance is an abstract concept that can be defined in different ways depending on its context and the precise perspective from which it is viewed. Basically, »performance« can be understood to mean a value created by an effort. In the context of natural science the effort component of a performance is the focus of attention. This is seen most clearly in the physical definition of performance, according to which a performance is the ratio of energy expended (or work performed) to the time required for that purpose. The possible result of this effort lies outside of the scope of observation of physics. Similarly in medicine, in which the focus of investigation is on the ways in which individual organs and their metabolic processes function, it is the effort component of human performance that is investigated in the first instance and it is only subsequently, if at all, that any attempt is made to draw conclusions as to possible applications or results of the performance. As a result, the concept of (human) performance has little currency in medicine other than in industrial medicine, in which it refers mostly to an abstract target value of medical action or treatment (e.g. achievement of the ability to perform) (e.g. Landau/Presse 2009).

A different perspective prevails in behavioral research and psychology, in which *human* performance is understood to mean a specific result or objective (result component) of an action undertaken by an individual in order to satisfy demands imposed either by the individual himself/herself (i.e. from within) or from without. In contrast to the medical perspective, behavioral research focuses on the demands that an individual wishes, or is required, to satisfy and asks what behavior and what abilities – in short, what individual effort – is required for that purpose. In general a result is considered to have value only if it is achieved by means of a certain effort. In this sense human performance can be seen as a measure of quality on the basis of which an individual effort and a result are put into relationship with each other and assessed (Lück et al. 1984) (Fig. 1).

The following discussion draws on this view of performance. Similarly, it deals only with those aspects of alteration of individual abilities that have the potential to bring about assessable or exploitable human performance.[1] Where an action has a result that is regarded as a human performance, that result arises from the exercise of various abilities (characteristics) in a particular setting (Schumacher/Stern 2008, p. 3). Figure 1 illustrates this conceptual distinction.

1 Medical specialties such as cosmetic surgery and reproductive medicine are not associated with the concept of human performance that is used here and consequently are not dealt with here, even though various studies locate them within the concept of enhancement (Coenen et al. 2009; President's Council on Bioethics 2003).

FIG. 1 HUMAN PERFORMANCE: SCHEMATIC REPRESENTATION OF CONCEPTUAL CATEGORIES

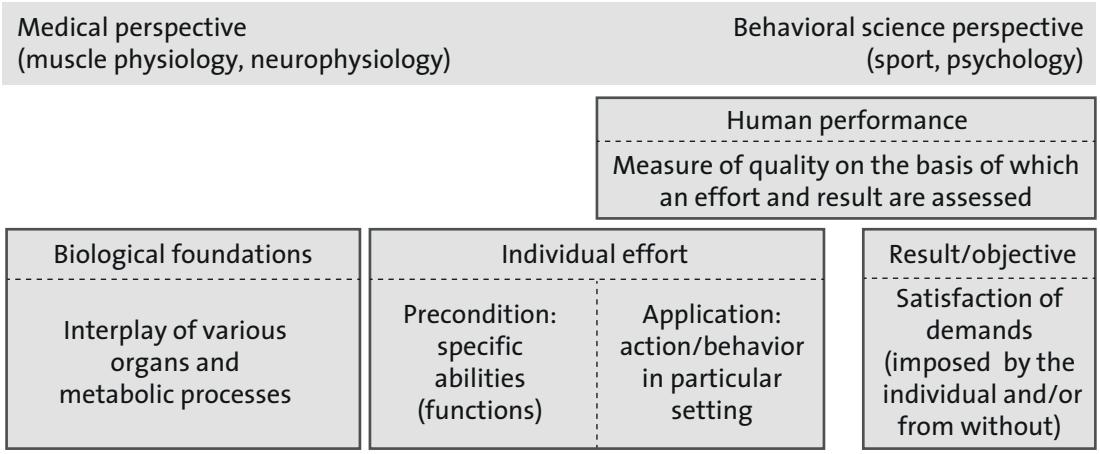


Figure devised by authors

To summarize the above, the natural science perspective can be seen as a kind of effort-focused consideration of costs, whereas the behavioral science perspective can be seen as a kind of result-focused consideration of benefits. As to date only individual dimensions of human performance can be quantified, only certain concepts related to human performance can be empirically founded. A distinction is made between physical (bodily) and mental (intellectual) performance.

PHYSICAL PERFORMANCE DIMENSIONS

Physical performances by human beings can in some respects be understood in a narrow physical sense. For example, the speed at which an individual can cover a certain distance or lift a certain object is regarded as a performance. The individual's muscles are the organ by means of which a physical performance can be achieved.

Depending on the particular externally imposed demands that were to be satisfied or tasks that were to be accomplished, physical performances used to be highly valued especially within peer groups and even in society as a whole provided that they could not be achieved by mechanical means. In the wake of increasing industrialization and mechanization their perceived value fell, especially in the occupational setting. In the modern world physical performances can be exploited for economic and social, and in some cases even political, purposes above all in the »special world of sport« (Franke 2007, pp. 7ff.). Sport has spawned a great variety of concepts for measuring and comparing physical performances. These range from competitions in CGS sports[2], in which results achieved by individual athletes

2 CGS: »centimeters, grams or seconds« (Emrich et al. 2004, p. 227).

are measured and compared directly in physical units, through to competitions that call for a greater variety of abilities, such as team ball sports, in which results are quantified not in physical units but instead in terms of abstract, though measurable and comparable, constructs (e.g. goals scored).

Since CGS sports are based on the performance of relatively simple individual actions, specific parts of the skeletal musculature and the metabolic processes that are relevant to them can be specifically conditioned to such an extent by training measures as to result in a measurable improvement in performance. The result that an individual can achieve in a CGS sport is therefore to a large extent predictable on the basis of that individual's physical condition. For example, the body's maximum oxygen uptake in liters per minute (VO_2 max) is a reasonably good physiological predictor of performance in endurance sports: less than 25 mL is regarded as abnormal, while more than 75 mL is achieved only by elite endurance athletes. Training plans, both for rehabilitation and for sport, are increasingly being put together with the aid of performance physiologists from the fields of industrial medicine and sports medicine.

In the case of team ball sports the result is likewise measurable, however the actions that lead to the result call for a multiplicity of individual abilities. Environmental factors are considerably more important, therefore the effort component is far more complex. Though here too individual physical abilities such as speed are a prerequisite, the physical condition of the individual is of only limited predictive value for the team result.

At the level of society, the combination of intense idealization and commercialization of individual sports has led to the best results (both in CGS and in team sports) becoming exploitable, especially for financial gain. Though the value that society places on top sporting performances is determined by a multiplicity of factors, there is general agreement that the sporting performance must have some kind of authenticity in that the result must bear some kind of relationship to the effort. Any loss of this authenticity – i.e. any loss of validity of the basis on which the effort and the result can be put into context with one another – can have negative consequences for the value that society puts on the performance (e.g. the situation of professional cycling in recent years in Germany).

MENTAL PERFORMANCE DIMENSIONS

Mental performances – which are brought about by the brain – can be very diverse, therefore various dimensions of mental performance are often distinguished. In particular, an individual's mental, cognitive, and intellectual achievements – terms that are often used interchangeably – can be exploited for personal gain and therefore are associated with the concept of performance.

The gradual decline in the value placed by different peer groups and society as a whole on physical performance that has occurred especially in occupational set-

tings has been accompanied by a parallel rise in the exploitability of, and thus also in the value placed on, various dimensions of mental performance. This too, however, is subject to change over time. For example, the extent to which human computational achievements can be exploited has been reduced by the advent of computers with their constantly increasing computational power, whereas the exploitability of foreign language skills is increasing as a result of globalization. Though the regulations that govern mental performance are not as standardized as those that govern sport, various quantitative indices of results and goals exist by means of which certain dimensions of mental performance can be assessed (e.g. learning performance, educational achievements). However, the concrete tasks that must be performed for this purpose are not fixed in the way that they are in individual sports (e.g. running 100 meters), but instead are continually being adapted to changing circumstances (for example, a »good grade in math« is no longer evidence of any particular skill in mental arithmetic). The value of mental performance dimensions is assessed in the most diverse learning, occupational, and everyday settings. A variety of environmental influences, past experiences, and learning processes play important roles as joint determinants of concrete performance.

A variety of approaches have been developed in psychology and behavioral research for the measurement of mental, and in particular cognitive, performance dimensions on the basis of a (performance) result (Schumacher/Stern 2008 p. 3). These approaches range from the most precise possible recording of individual events (e.g. counting, recall of words or terms) through to abstract parameters that include as many dimensions as possible (e.g. intelligence quotient, working memory) and can be determined by means of specific tests. These parameters are theory-based constructs which, with the aid of statistical techniques, can be used on the one hand to draw conclusions about various mental abilities and on the other hand to predict the likelihood of occurrence of certain future events (e.g. graduation from high school). Nevertheless, the results of simple cognitive tests often permit the drawing of only limited or no conclusions about complex and moreover future performance, e.g. at school or work.

With a view to achieving a particular result, a variety of learning and training concepts have been developed for the purpose of extending or maintaining abilities so that certain mental tasks can be performed. These concepts show some relatedness to medical and neurological knowledge of the function of the brain. However, our limited knowledge of the functional relationships that exist between neurophysiological observations and behavioral psychological effects, together with the powerful influence exerted on the performance of complex tasks by environmental factors, has so far at least made it impossible to find a firmer foundation in natural science for learning and training concepts – the brain, after all, is not a muscle.

HUMAN ABILITIES 1.2

Individual abilities are the product of both biological circumstances and specific environmental factors. They are subject to change as a result of continuous learning and application processes acting in concert with environmental factors. Because of the multiplicity of ways in which human abilities can be changed, the extent of these abilities shows marked individual variability. For this reason individual abilities are also referred to in the behavioral sciences as competences or characteristics of a human being, while the medical literature often refers to different organ functions rather than to abilities.

Like human performance, human abilities are divided into two main categories, namely physical and mental abilities, each of which can be further subdivided. One possible classification system is as follows (Jost 2008, pp. 61ff.):

- *Bodily abilities* (by means of which bodily activities can be performed)
  - physical abilities (e.g. endurance, strength, speed, fitness)
  - motor abilities (e.g. manual skills, dexterity, mobility)
- *Mental abilities* (by means of which mental/intellectual activities can be performed)
  - cognitive abilities (abilities/functions that are associated with perception, learning, memory, and thought, i.e. with the processing of human knowledge and information, and that are generally referred to jointly as a person's intelligence); these can be further subdivided into
    - operational, i.e. executive, abilities (e.g. attention, concentration, processing speed, memory, ingenuity, processing capacity) and
    - content-related abilities (e.g. numerical, verbal, or figurative thought)[3]
  - emotional abilities (e.g. motivation, volition, feelings such as anxiety, anger, pleasure, and disgust, ambition, self-discipline, mental resilience)
  - social abilities (characteristics that make interaction with other people possible, e.g. ability to work in a team, willingness to help)

It is apparent from this list that apart from physical abilities and the activities that they make possible, most of the dimensions that make up the spectrum of human abilities are qualitative in nature, i.e. not amenable to direct measurement in physical units.

One way of approaching these categories is to break them down into different factors or elements. Various theories and approaches have been proposed for the purpose of further differentiation, however no scientific consensus about the internal structure of the individual categories has been reached. In the case of

3 This enumeration is based largely on the »Berliner Intelligenzstrukturmodell« (Berlin intelligence structure model) (Kubinger/Jäger 2003); other models and approaches use different terms for individual dimensions.

cognitive abilities a multidimensional approach is commonly adopted, with operational/executive ability dimensions on one level and content-related ability dimensions on another level. It is likewise assumed that social and emotional ability dimensions are important influencing factors that can facilitate or inhibit performance-producing processes. A variety of models are used to investigate the internal structure of mental ability dimensions and to try to find an empirical basis for classifying them.

POSSIBILITIES AND LIMITS OF ATTEMPTS TO QUANTIFY PERFORMANCE AND ABILITIES 1.3

Apart from directly measurable physical performance dimensions, human performance and the abilities that make it possible are quantified by means of models and statistical procedures. To this end the actual qualitative situation (which is not directly measurable as an absolute value) is described in terms of a larger or smaller number of measurable proxy variables that are subsequently quantified. This makes it possible to identify changes and to determine the influence of measures taken to bring about change or development. Values obtained by repeated use of the same procedures and measurement methods permit comparison with a control group (cross-sectional comparison) or a baseline value (longitudinal comparison). Like any model-based representation, this procedure is always liable to obscure the phenomenon actually under consideration by reducing it to a series of measurable parameters. Nevertheless, it is often the only way of obtaining empirical substantiation of specific assertions.

INTELLIGENCE – ASSESSMENT OF A COMPLEX SET OF FACTS BY BREAKING IT DOWN INTO INDIVIDUAL DIMENSIONS

Attempts to break mental performances and abilities down into individual dimensions and to quantify them and their interplay have been made for many years in the discipline of psychology (psychometry). The first important attempts to quantify mental performance dimensions and draw conclusions about corresponding abilities were made by C. Spearman about a hundred years ago. Spearman proposed a »two-factor theory of intelligence« in which the first factor was the totality of cognitive abilities and the second factor was other mental abilities. Subsequently a number of different multifactorial approaches and structural models involving larger or smaller numbers of vectors, factors, and dimensions were developed. Ever more diverse cognitive tasks intended to measure ever more specific individual abilities were incorporated into intelligence tests. The range of these different cognitive ability dimensions is increasing continuously. Jäger et al. (1982) compiled a list of more than 2000 intelligence test tasks that had been described in the literature up to that time, while Carroll

(1993) reanalyzed about 400 intelligence test datasets. Based on their analyses, each of these authors developed tests intended to provide an empirical basis for conclusions about the internal structure of intelligence. Though there is no scientific consensus about the internal structure of individual ability dimensions, certain hierarchical concepts and rankings are accepted. For example, the ability to process complex information, which involves the ability to combine various thought processes and draw appropriate conclusions, is given a much higher weighting for the purpose of assessing intelligence in the sense of the totality of an individual's cognitive abilities than is, for example, simple associative learning (e.g. learning of terms). When effects are compared by means of individual measures, attention must always be paid to the question of what psychological ability constructs these effects represent and at what level of complexity the effects have been demonstrated.

On the basis of model performance tasks, performance is measured in standardized fashion in order to draw conclusions in particular about individual cognitive ability dimensions (or their constituent parts). However, whether these cognitive abilities actually result in corresponding performances in real life is determined also by reinforcing and inhibiting factors such as the extent of noncognitive mental abilities (e.g. self-discipline, motivation) and prevailing environmental conditions (Vock 2004, p. 5).

Intelligence tests and models represent the phenomenon »mental performance«, which is actually qualitative in nature, by means of quantifiable components. In other words, they reduce intelligence to what they measure and deem it to be (Asendorpf 2009, p. 80). Intelligence tests generally assess intelligence by breaking it down into individual dimensions, however these individually determined dimensions are then recombined to give an overall value, the intelligence quotient (IQ). The IQ is not an absolute measure of cognitive abilities, but rather a relative value that indicates the extent to which an individual deviates from the mean value of a control group in terms of ability to perform certain cognitive tasks (where 100 is the mean value). Parameters such as the IQ are psychometric constructs which nevertheless are mostly assumed to possess a certain validity as indicators of the extent to which an individual can cope with the demands with which he or she is faced in present-day life.

WORKING MEMORY – A PSYCHOLOGICAL CONSTRUCT FOR OVERALL ASSESSMENT

In contrast to approaches in which mental ability dimensions are broken down into ever smaller components so as to permit quantitative determination, other approaches strive for an overall assessment.

Over the past 20 years attempts have been made in the field of psychology to incorporate various individual dimensions such as intelligence, attention, ability

to concentrate, self-discipline, and motivation into a comprehensive theory of working memory so that the individual effort component of a mental performance can be assessed in its totality (with regard to this and the following discussion, see Schumacher/Stern 2008, pp. 6ff.).

A central aspect of the theory of working memory is the way in which information is processed in the brain. This is based on a distinction between information which at least in theory is available from long-term memory and memory content which is activated on a situational basis, i.e. short-term memory. In working memory, information obtained via the senses is combined with information from long-term memory to produce purposeful behavior. The capacity of working memory is limited in terms of both these sources of information in that only a fraction of all the external information that is available can be perceived and only a small part of the content of long-term memory can be activated. This limitation serves a purpose in that only in this way can purposeful behavior be pointed out. In a functioning working memory all incoming information that is not required for purposeful behavior is blocked out. Openness to new information is restored only after the objective has been achieved.

However, as well as playing a role in the performance of cognitive tasks, working memory coordinates emotional processes and social behavior. Development of the ability to regulate one's emotions and of self-discipline in the sense of the ability to defer objectives that are satisfying in the short term in favor of longer-term objectives is based to a large extent on the functioning of working memory. Thus, a functioning working memory coordinates presently pursued objectives, suppresses any information from long-term memory that is incompatible with the achievement of these objectives, and blocks off irrelevant external stimuli. This complex system of behavioral control is susceptible to disturbances arising from the world outside, long-term memory, or conflicts between objectives.

Though various aspects (e.g. the internal structure) of working memory have yet to be fully elucidated, the basic assumption that working memory capacity forms the basis and limiting factor of a person's intellectual abilities is accepted by a number of researchers (Vock 2004, p. 2). Test procedures based on this assumption are used both for the diagnosis of high intellectual potential (giftedness) in childhood (Vock 2004) and to detect disturbances of working memory in psychiatric conditions such as attention deficit hyperactivity disorder (ADHD), schizophrenia, and dementia (Barkley 2006; Frith/Frith 2007; Lindenberger et al. 2006). Individuals with these disorders are often unable to keep sight of, and to direct their behavior towards, their objectives.

The psychological construct »working memory« is thus used to represent the individual effort component of human performance (i.e. the sum of specific abilities and the purposeful use of them) in its totality. It therefore occupies a hierar-

chical position similar to that occupied by tests of general intelligence. According to Schumacher/Stern (2008, p. 8) general intelligence quotient as measured by intelligence tests is concretely related to the ability to solve working memory-related problems.

In the techniques that it has developed for measuring intelligence and working memory, psychological research provides tools that permit precise description and quantification of mental performances and the abilities that underpin them. These tools can be used to determine whether changes in medical or neurological parameters (e.g. a rise in dopamine level) are accompanied at the behavioral level by improvements in performance as evidenced by an improved ability to perform certain tasks (Schumacher/Stern 2008, p. 3).

From the perspective of psychology, specific abilities are seen as necessary, but not sufficient, preconditions for human performance (Schumacher/Stern 2008, p. 32), since it is only when they are used purposefully and in a particular setting that they produce results that are considered to constitute human performance.

The concepts presented here for assessing highly specific and also general abilities are genuinely psychological constructs that were developed in the field of behavioral research as means of explaining differences in human behavior. They are not medical or neurological concepts that describe any neurologically measurable activity or the performance of any specific parts or areas of the brain.

BIOLOGICAL FOUNDATIONS 1.4

From the perspective of biology, abilities are based essentially on an individual's ability to take in, convert, transmit, select, and store information (stimuli/signals) and to induce a biochemical or motor reaction in another organ. Information processing for this purpose takes place within the nervous system and its subsystems, whereas the action that results from this process is performed by other organs. A human performance thus results from an interplay between mental and physical ability dimensions in varying proportions.

Notwithstanding the major advances that have been made in the neurosciences, many gaps remain in our understanding of information processing and process control, especially in the central nervous system (CNS). Though it is undisputed that mental performances always result from an interplay between various parts of the nervous system, there is general agreement that the most anterior part of the cerebral cortex (the prefrontal cortex) plays a special role in more complex thought processes. The »supreme control center« for ordering situationally appropriate actions is located in the prefrontal cortex, since it is there that preprocessed sensory signals are received and related to thought contents and emotional judgments and that actions are initiated. The prefrontal cortex also plays a

role in the regulation of emotional processes. Because it is believed to have these functions and abilities, the prefrontal cortex is seen as forming a link to the psychological theory of working memory. Disturbances of the prefrontal cortex make purposeful behavior difficult or impossible, since incoming information is not adequately filtered and the contents of long-term memory are only partly activated (Schumacher/Stern 2008, p. 7).

Findings in neurophysiology have shown that the prefrontal cortex develops at a much slower rate than do other parts of the brain and that even in adulthood it continues to develop in response to learning and experience (Neubauer/Stern 2007). This explains why young children perform very badly in tasks that involve working memory and why even older children show specific deficits in terms of coordination of objectives (Schumacher/Stern 2008, p. 9).

There is a general consensus that information processing in the brain occurs not on an all-or-nothing basis, but rather in fine increments at different levels of attention (Schumacher/Stern 2008, p. 14). There is much evidence to suggest that different brain functions and abilities should not be categorized simply as either simple or complex, but rather should be located along a continuum between unconscious-reflexive and conscious-reflective processes. Individual processes result from interaction between conscious and unconscious components. In this regard the limitations of working memory, in particular, can be offset by factors such as automation and efficient knowledge building, and the capacities made available in this way can be used for parallel activities and thought processes (Schumacher/Stern 2008, p. 10).

At the cellular level a variety of neurotransmitters (messenger substances of the nervous system) play an important role in the transmission and processing of information. These substances play a role in a multitude of processes that take place on both sides of the blood-brain barrier (in both the peripheral and the central nervous system), however they cannot cross that barrier. Important neurotransmitters include glutamate and acetylcholine (the most common neurotransmitters), dopamine and norepinephrine (also referred to as activating neurotransmitters because by increasing the state of excitation of nerve cells they strengthen impulses), and serotonin, which has a particularly broad range of actions.

Important roles in various processes in the brain are also played by inhibitory neurotransmitters (e.g. gamma-aminobutyric acid [GABA] and glycine) and by cotransmitters (e.g. adenosine, which blocks the release of activating neurotransmitters). Neurotransmitters are converted and broken down with the aid of cofactors such as vitamin C (in the conversion of dopamine to norepinephrine in the

CNS) and COMT (catechol-O-methyltransferase)[4], an enzyme that inactivates and breaks down dopamine in the synaptic cleft between adjacent nerve cells.

Psychoactive substances, which increase brain activity (Section II.2), interfere in particular with the metabolism of neurotransmitters and the way in which these act (see box).

Transmission of information/signals within nerve cells occurs via changes in electrical potential at the cell membrane, whereas that between cells occurs by biochemical means (Fig. 2): When an electrical signal reaches, for example, the dopamine-containing vesicles of the synapses of the information-transmitting (presynaptic) neuron, these vesicles release dopamine into the synaptic cleft and this dopamine binds to specific receptors of the information-receiving (postsynaptic) cell membrane. If this process results in activation of a sufficient number of receptors on the information-receiving side of the synapse, another electrical potential is produced and then conducted along the nerve cell membrane to the next set of synapses.

EXAMPLES OF DIMENSIONS OF ACTION OF NEUROTRANSMITTERS

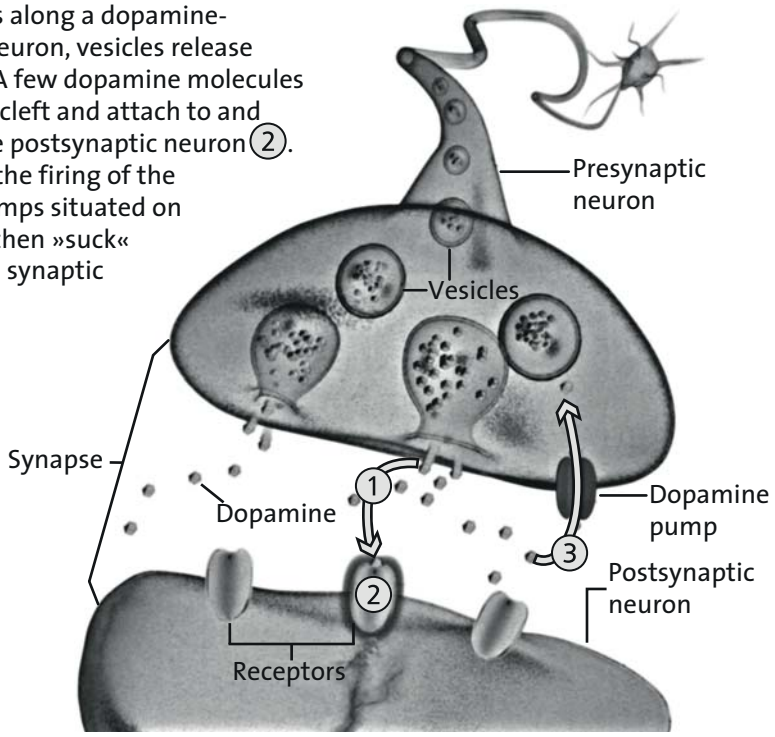
- *Acetylcholine* mediates signal transmission throughout the nervous system and is thought to play an important role in learning processes. In Alzheimer's disease acetylcholine-producing nerve cells gradually die off.
- *Dopamine* plays an important role in the brain, especially in the prefrontal cortex, influencing cognitive and executive abilities such as motivation and also controlling motor function. Because dopamine plays a role in many different processes, changes in dopamine levels influence many different organs. Dopamine is formed from the amino acid tyrosine via the intermediate product levodopa (L-Dopa), which can cross the blood-brain barrier. Dopamine is also the precursor of norepinephrine.
- *Norepinephrine* regulates mental adaptation to stress in the central nervous system by increasing attention and mental readiness and at the same time temporarily suppressing immune functions (as does epinephrine in the blood). Prolonged stress can lead to a deficit of norepinephrine and thereby to a decrease in mental ability and to depression. Increased concentrations of dopamine and norepinephrine in certain parts of the brain have also been linked to the development of substance dependences (Fatke/Förstl 2010, p. 28).

4 The activity of COMT is genetically determined and thus varies with a person's genotype. Low activity of this enzyme (in met/met genotypes) is associated with higher levels of dopamine (Repantis/Heuser 2008, p. 8). Some studies suggest that met/met individuals have greater working memory capacity (Egan et al. 2001), however only 0.1% of differences in intelligence can be attributed to the variants of this gene that have been identified to date (Stern 2010, p. 38).

› *Serotonin* likewise influences many brain functions, as it plays a role in the regulation of perception, behavior, sleep, and other processes. The broad range of these effects is explained by the large number of different serotonin receptors that exist. The best-known action of serotonin is the inhibition of impulsiveness and aggressive behavior that it causes by stimulating certain parts of the cerebral cortex that are responsible for emotional processes.

FIG. 2 SYNAPTIC ACTIVITY

When an impulse travels along a dopamine-producing presynaptic neuron, vesicles release neuro-transmitter (1). A few dopamine molecules pass across the synaptic cleft and attach to and activate receptors on the postsynaptic neuron (2). In this way they control the firing of the postsynaptic neuron. Pumps situated on the presynaptic neuron then »suck« dopamine back from the synaptic cleft into the cell (3).



Source: Stix 2010, p. 50

After releasing the dopamine the presynaptic neuron uses a type of pump (»reuptake transporter«) to »suck up« some of the dopamine that remains in the synaptic cleft and conduct it back into the vesicles. This prevents overstimulation of nerve cells by excessive concentrations of dopamine and permits restimulation of the postsynaptic nerve cell by further release of dopamine. In addition, some dopamine is inactivated and gradually broken down in the synaptic cleft.

The more frequently a synapse is stimulated, the more neurotransmitter is released and the more receptors are formed. This reinforcement is a learning process in that it causes incoming stimuli to be conducted more readily than before.

Attempts to influence learning processes by technical means target the electrical mechanisms by which information is transmitted (Section II.5.2).

So far, however, our knowledge of how learning processes occur and of how information is stored (i.e. memory formed) at the molecular and cellular levels is extremely limited and in fact still at the stage of basic research. With the aid of new imaging techniques we are now learning more and more about the anatomy and the function of individual parts of the nervous system at different levels and about the biochemical and electrical mechanisms by which information is transmitted. By means of a complex, finely regulated balance, these processes give rise to specific mental functions (Stix 2010, p. 48). Our present level of knowledge is still nowhere near sufficient to give us a detailed understanding of the various levels at which information and information processing are biologically significant, e.g. with regard to the question of how the development of various memory contents is influenced by emotional states.

Similarly, the considerable research efforts that have been made to elucidate and find treatments for mental illnesses and mental degenerative processes have so far yielded only strategies with limited success. The phenomenon whereby improvements in one ability dimension lead to deterioration in other dimensions has been shown to occur also in the case of cognitive abilities. This has been demonstrated by studies in which the ability of genetically modified mice to register new information and to store this information in long-term memory was improved, but only at the expense of a simultaneous deterioration in the performance of complex tasks (Stix 2010, p. 52).

Based on the present state of medical knowledge, some researchers working in the fields of neurobiology and memory research see no immediate potential for their research results to be abused for the purpose of cognitive performance enhancement in healthy individuals and describe the neuroenhancement debate as essentially speculative (e.g. Langlitz 2010a). Other scientists, however, see a potential for pharmacological neuroenhancement in areas such as the synthesis, release, and reuptake of neurotransmitters, stimulation or blockade of receptors, and improvement of the energy supply of the brain (e.g. Lieb 2010; Quednow 2010).

2. APPROACHES AND LIMITS TO IMPROVEMENT OF HUMAN ABILITIES

As outlined in Section II.1, the interplay between different organs and their respective metabolic processes confers upon human beings certain abilities by means of which they can perform in many different ways. The range of abilities varies between individuals and can change over time. A person's performance

status can be individually assessed and classified as either above average, average, deficient, or even pathological.

It must also be noted that an individual's range of abilities is not constant, but rather subject to periodic fluctuation. The body's individual abilities depend on the waking state, which is limited in time, since every individual needs regular phases of regeneration. The extent to which individual abilities can be used depends crucially on wakefulness, i.e. the degree of alertness of the organism. This ranges from states of extreme agitation (e.g. due to threats or anxiety) in which normally unavailable reserves are mobilized through phases of »normal« wakefulness, tiredness, or exhaustion to deeply unconscious states (e.g. deep sleep). Degree of alertness is of central importance for many bodily processes. In the context of performance-enhancing effects of psychopharmaceuticals »wakefulness« is described as a functional state of the nervous system that is a prerequisite for attention and concentration.[5]

Many different options are available for influencing the various abilities of an individual in order to make that individual capable of performing better. These options can be classified on the basis of their proximity to, or depth of intervention in, the human body. The regulatory approach to products and substances is likewise oriented to some extent towards depth of intervention, both in the case of substances that are consumed, swallowed or injected (foods and medicines; Section III) and also in the case of material artifacts that are not intended for consumption (»normal« marketable goods and medical devices including implants). By contrast, non-material-based conditioning and training techniques (training and learning strategies) – which can likewise be quite invasive – have yet to be regulated in any way. The following approaches seem relevant:

- *Conditioning of the organism by training and learning*: Conditioning measures are directed more or less specifically at individual ability dimensions. Though not intended in the first place to interfere with the body's self-regulatory mechanisms, they sometimes bring about extensive changes at the cellular or organ level.[6]
- *Special diets*: These are intended to ensure an optimal supply of substances required for specific metabolic processes, firstly in order to build up the relevant organs in the training phase and secondly so that when performance is required energy conversion in those organs will be optimal. The purpose of a

5 Lieb (2010, pp. 68ff.) groups the dimensions »wakefulness« (*Wachheit*) and »attention« (*Aufmerksamkeit*) together and classifies tiredness as a different dimension.

6 The proportion of fast muscle fibers can be increased to as much as 70% by specific sprint and strength training and reduced to as little as 20% by specific endurance training (in the absence of any specific training human muscle contains approximately equal proportions of slow and fast fibers). In the case of mental performance it is assumed that learning processes reinforce neuronal networks.

specific diet is to ensure an optimal supply of nutrients without thereby interfering directly in endogenous metabolic control processes.

- *Use of pharmacological substances*: Pharmacological substances do not supply nutrients, but influence endogenous control processes. Especially in combination with training, they can influence individual dimensions of physical (e.g. endurance or strength) or motor abilities (e.g. dexterity or precise movements). Major pharmacological methods of improving physical abilities include the building up of skeletal muscle and improvement of the metabolic processes that take place in skeletal muscle (oxygen and energy supply), in the case of motor abilities by reducing the effects of stress hormones. Only in organized sport is the use of pharmacological substances outside of any medical indication in order to improve individual abilities and thereby enhance physical performance, i.e. doping, explicitly prohibited. As the name indicates, the purpose of psychopharmaceuticals is to influence metabolic processes in the brain. In attempts to improve mental abilities a number of different strategies are followed with the aim of increasing the activity of nerve cells, primarily by interfering with processes in which the activating neurotransmitters dopamine and norepinephrine are involved. Where brightening of mood is desired, the chain of biochemical processes involving serotonin is also targeted. Because such substances act at a variety of sites in the human body, their desired specific effects are often accompanied by numerous side effects.
- *Use of technical aids*: Depending on their proximity to, or depth of intervention in, the human body, »normal« utility objects and various categories of medical devices are distinguished (summary in Fiedeler 2008; update in, e.g., Stieglitz 2010). To date there is no evidence that technical aids implanted into healthy individuals (e.g. as in deep brain stimulation) can improve individual abilities other than in pathological states (Stieglitz 2010, p. 789). Therefore, they are not discussed further in this report.
- *Alteration of genetic disposition*: So far more than 300 genes are known which if defective can cause severe mental disabilities (Stern 2010, p. 38). At present there is no reliable evidence of any relevant genetic differences within the normal range of cognitive abilities. All presently available evidence indicates that the development of mental abilities results from the combined action of a large number of genes distributed over all the chromosomes (Stern 2010, pp. 37–38). Similarly, the TAB's project on gene doping found knowledge of physical high performance gene variants to be extremely limited, imprecise, and contradictory and therefore concluded that »promising« techniques for inducing specific alterations in an individual's genetic disposition were extremely unlikely to be developed in the foreseeable future. Nor was any evidence found to suggest that any strategies based on human selection or breeding for enhanced sporting ability are likely to become technically feasible within the foreseeable future (Gerlinger et al. 2008, p. 8; TAB 2008b, p. 4).

It is largely undisputed that training and learning techniques can substantially improve the range of a person's abilities. Also undisputed is that performances in keeping with these abilities can be achieved only if an adequate supply of nutrients is maintained throughout the entire process (development of abilities and performance of a task). The question of whether special diets can bring about additional effects is already a controversial topic in relation to physical performance. The topic of mental performance dimensions is similarly controversial (Section III.2.4).

It can be assumed that individual dimensions of physical ability can be temporarily augmented by means of a combination of training and use of pharmacological substances, but that such effects are accompanied by numerous side effects and long-term effects. Whether this is true also of mental performance dimensions is an open question, since the biological processes that underpin mental abilities are vastly more complex and diverse than are those that underpin physical abilities and performances. Though our understanding of brain functions is improving all the time, it is generally agreed that mental abilities cannot be explained purely on the basis of brain structure and biological processes. Rather, environmental and context dependency are so pronounced that these processes differ in almost every human being. This should be borne in mind in relation to future possibilities for influencing mental abilities.

PHARMACOLOGICALLY ACTIVE SUBSTANCES 3.

Most, but not all, pharmacologically active substances, i.e. substances that act on and influence endogenous control processes, fall within the regulatory category of medicines (Section III). Medicines are recognized as having therapeutic effects, that is to say that they bring some kind of benefit in the treatment of illnesses. The range of actions of most pharmacological substances has been investigated and analyzed in relation to the treatment of pathological states. At least in the case of prescription medicines, the existence of a therapeutic benefit is established via appropriate studies that are a prerequisite for regulatory approval of the substance as a medicine. Nevertheless, the efficacy of the substance does not need to be explicitly linked to an illness-relevant state. A few substances are assumed to have performance-enhancing effects, including in healthy individuals.

As the use of medicines to enhance performance in sport is prohibited in Germany (§ 6a AMG[7]), as in many other countries, methods of enhancing physical performance are explicitly excluded as subjects of pharmacological research. Nevertheless, information about them may arise as incidental findings of other studies. For example, research into better methods of detecting doping with

7 *Arzneimittelgesetz* (German Medicinal Products Act)

erythropoietin also yielded information on the performance-enhancing effects of this substance (Thomsen et al. 2007). This led to a lively debate in which many opinions and counter-opinions were expressed.

Though not covered by the prohibition of doping, use of medicines to enhance performance outside of sport violates the basic ethical principles of medical research (Section III.3.2). As a result, questions relating to the performance-enhancing effects of pharmacologically active substances in healthy individuals are at present not systematically investigated in accordance with the usual standards that apply to clinical trials. Despite this, studies on extended dimensions of action of presently licensed medicines occasionally also yield information on performance-enhancing effects in healthy volunteers. As will be shown below, however, our knowledge of possible enhancement of mental ability dimensions by pharmacological substances remains extremely limited.

Repantis/Heuser (2008) performed a systematic review of the scientific literature looking for information about whether use of psychopharmaceuticals influences mental ability dimensions in healthy individuals. Their results were compared with those of similar review articles (e.g. Lieb 2010; Schumacher/Stern 2008, pp. 15ff.). The following discussion deals with various substance classes, namely psychostimulants (Section II.3.1), antidepressants (Section II.3.3), and anti-dementia drugs (Section II.3.4), plus a few substances that do not fall within any of these groups (Sections II.3.2 and II.3.5).

PSYCHOSTIMULANTS 3.1

(Psycho)stimulants are substances that increase the activity of certain nerve cells in the brain. Their principal effects are reduction of sleep requirement and hunger, increase in level of motivation and vigilance (sustained attention), and euphoria and hyperactivity (Repantis/Heuser 2008, p. 7). The list of such substances is long and can be subdivided in different ways, for example into

- *amphetamines and amphetamine-like substances*, the use of which is severely restricted or prohibited (narcotics, some illegal drugs),
- *xanthines* (e.g. caffeine, theophylline, theobromine), which are naturally present in small concentrations in various plants (e.g. coffee, tea, cocoa) and may be present in small amounts in foods, and
- *other substances*, which are not further subdivided and the use of which is governed by very diverse regulations, e.g. nicotine (legal drug), cocaine (illegal drug), modafinil (medicine).

AMPHETAMINES

The word »amphetamine« is used on the one hand to refer to a specific substance (chemical name: 1-phenylpropane-2-amine) and on the other hand as a generic term for a number of different psychotropic substances including the naturally occurring substance ephedrine and the synthetic substance methamphetamine. The illegal drugs known as »speed« and »ecstasy« are also amphetamine derivatives.

MODE OF ACTION – SIDE EFFECTS

Amphetamines act on dopamine- and norepinephrine-related processes in the CNS and activate the »reward system« in the brain. It is believed that amphetamines not only promote direct release of dopamine and norepinephrine from nerve cells but also block dopamine and norepinephrine transporters and thereby prevent reuptake of these neurotransmitters from the synaptic cleft. As a result of this disturbance of the reuptake process that normally follows release of the neurotransmitters, the cell receives no signal to stop and consequently continues to release dopamine and norepinephrine in unchecked fashion. As a result, the extracellular concentration of neurotransmitters rises independently of the presence of a nerve impulse (Repantis/Heuser 2008, p. 8) (Fig. 3). The increased concentrations of neurotransmitters in the synaptic cleft lead to increased neuronal activity. By increasing dopamine and norepinephrine levels, amphetamines increase wakefulness, attention, and concentration. These effects are highly dose-dependent. At excessive doses a feeling of agitation can occur and the ability to concentrate can decrease (Lieb 2010, pp. 66–67).

Use of these substances by healthy individuals is associated with a high potential for the development of mental and physical dependence, especially with intranasal or intravenous administration, since with these forms of administration dopamine is released in the brain in sudden surges, causing euphoria. At high doses amphetamines can cause life-threatening hypertension and cardiac arrhythmias and precipitate psychotic states. Repeated use of amphetamines may promote the death of nerve cells.[8]

USE

Amphetamine was first synthesized in 1887. Large-scale manufacture of amphetamine started in 1929 and medical use of amphetamines in 1932. In the 1930s and 1940s amphetamines were used as over-the-counter remedies for

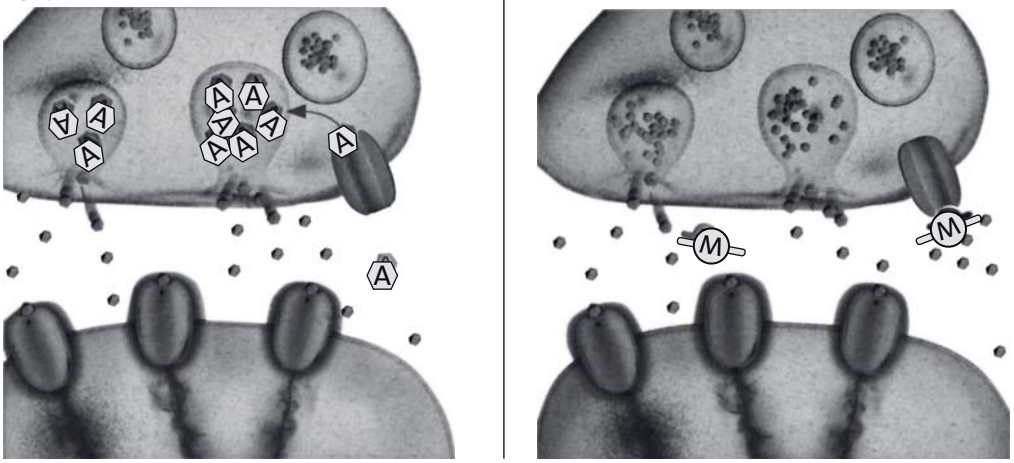
8 Unlike with the other substance groups discussed here, no table of side effects of amphetamines is provided, since the ephedrine-containing medicines that are presently licensed for use in Germany are substance mixtures whose side effects therefore cannot be ascribed to their individual active constituents.

colds and overweight and also (because of a lack of alternatives) to treat severe mental and neurological illnesses (Lieb 2010, p. 64).

FIG. 3 PHARMACOLOGICAL INTENSIFICATION OF SYNAPTIC ACTIVITY

Amphetamines (A)
are transported by means of the pump mechanism into the presynaptic neuron, where they increase the release of dopamine into the synaptic cleft. As a result, more dopamine is available for the receptors of the postsynaptic neuron.

Methylphenidate (M)
blocks the reuptake of dopamine. This too results in more dopamine being available for binding to a postsynaptic neuron. As a result, the intensity of the transmitted signal increases.



Source: Stix 2010, p. 50

At the start of the Second World War the stimulant and concentration-improving effects of amphetamines were discovered. This led among other things to soldiers being given amphetamines as »go pills« (Emonson/Vanderberek 1995; Kenagy et al. 2004). In 1941, in response to cases of addiction, trade in amphetamines was regulated in Germany by means of the Opium Act of the Reich (*Reichsopiumgesetz*). In parallel with the observed abuse of amphetamines, a majority of clinical studies failed to demonstrate the supposed effectiveness of these substances. As a result, ever more restrictions were placed on the use of them. For example, amphetamines are now licensed in the USA only for the treatment of ADHD and narcolepsy. Based on the great discrepancy between the quantities of amphetamines sold and the prevalence of these conditions, it must be assumed that some healthy Americans are using amphetamines without any medical indication, i.e. abusing them. In Germany amphetamine itself (1-phenylpropane-2-amine) is now classified as a non-marketable narcotic (Anlage I BtMG[9]), whereas methamphetamine and ephedrine (along with norpseudoephedrine) are classified as marketable and prescribable narcotics

9 *Betäubungsmittelgesetz* (Narcotics Act)

(Anlage III BtMG). In Germany the latter drugs can be used, for example, for second-line treatment of narcolepsy, a neurological condition in which a disturbance of the sleep-wake cycle results in frequent episodes of sleep during the day (DGN 2008, pp. 5–6). Amphetamines are included in the WADA (World Anti-Doping Agency) Prohibited List (category S6, stimulants) (WADA 2011 p. 7). Their use for performance enhancement in sport is therefore prohibited (Section III.3.3).

EFFECTS RELEVANT TO PERFORMANCE ENHANCEMENT

The first report of »enhancement of human performance by means of amphetamines« appeared in 1962 (Weiss/Laties 1962). Since then various studies on this subject have been performed with different amphetamines. Most of the studies performed in the absence of an illness-relevant state at baseline have shown an improvement in cognitive abilities, especially executive ability dimensions and, at a similar hierarchical level, working memory. Repantis/Heuser (2008, p. 8) consider that the improvement in the cognitive abilities of healthy individuals, in particular working memory and executive functions, that has been found in a majority of the studies performed since 1962 can now be regarded as having been established. Similarly, in a review of medical studies Lieb (2010, pp. 69–70) concludes that amphetamines bring about dose-dependent improvements in wakefulness and attention and shorten reaction times, these effects being seen especially when abilities are impaired by tiredness.

Studies in which no illness-relevant state was present at baseline yielded the following findings: It was suggested that the increase in dopamine level brought about by amphetamines, and the consequences of this increase, may depend on working memory capacity, since those study subjects whose working memory capacity was in the lower part of the normal range benefited from use of an amphetamine whereas those whose working memory capacity was in the upper part of the normal range experienced no improvement or even showed a deterioration (Mattay et al. 2000). These differences in effects were also apparent when the subjects were grouped by genetic makeup (genotype). Individuals who because of their genotype have relatively low concentrations of dopamine in the prefrontal cortex (val/val genotypes) showed an improvement in working memory in response to amphetamine, whereas individuals who because of their genotype have high concentrations of dopamine (met/met genotypes) showed a deterioration of working memory at the highest level of task difficulty (Mattay et al. 2003). In subjects in whom they compensated for low, if not strictly pathological, baseline concentrations of dopamine, amphetamines were found to have positive effects on cognitive ability dimensions, whereas in subjects with high baseline concentrations of dopamine they resulted in, if anything, a deterioration (Repantis/Heuser 2008, p. 8).

METHYLPHENIDATE – AN AMPHETAMINE-LIKE SUBSTANCE

EFFECTS – SIDE EFFECTS

Methylphenidate (MPH) is an amphetamine-like substance that blocks reuptake of norepinephrine and dopamine into the presynaptic neuron but which, unlike amphetamines, does not directly promote the release of these substances (Figs. 2 and 3). This blockade causes the concentrations of these neurotransmitters in the synaptic cleft to rise only if the neuron is already active and the neurotransmitters have already been released. Therefore, unlike amphetamines, which by directly releasing the neurotransmitters exert a stimulant effect independently of cell activation, MPH exerts a stimulant effect only if mental tasks are already being performed (Lieb 2010, p. 72).

Table 1 lists the possible side effects of MPH based on the user information texts of medicines that contain MPH as their sole active constituent.

TABLE 1 METHYLPHENIDATE: POSSIBLE SIDE EFFECTS* WITH THERAPEUTIC USE

Frequency	Potentially serious	Other
≥ 10%		Headache, nervousness, insomnia
1–10%	Irregular heartbeat; mood fluctuations, personality changes	Joint pain; dry mouth; elevated temperature; hair loss; drowsiness, dopiness; reduced appetite; pruritus, rash; cough, nose and throat inflammation; high blood pressure, rapid heart rate; dizziness, uncontrolled movements, hyperactivity; aggressiveness, agitation, anxiety, depressed mood, irritability, abnormal behavior
0.1–1%	Suicidal thoughts; seeing, feeling, or hearing things that do not exist; uncontrolled talking and bodily movements; signs of allergy	Constipation, blood in the urine; tremor; double vision, blurred vision; muscle pain and twitching; shortness of breath, chest pain; increased liver values; rage, restlessness, sadness, heightened perception of surroundings, sleep disturbances

* Side effects are unintended adverse reactions occurring in association with use of a medicine in accordance with instructions. Serious side effects are side effects that are fatal or life-threatening, necessitate hospitalization or prolongation of hospitalization, or lead to lasting or serious impairment, invalidity, congenital anomalies, or birth defects (§ 4 Subsection 13 AMG).

Source: User information texts of medicines that contain methylphenidate as their sole active constituent (www.pharmnet-bund.de, 15/04/2011)

Because of differences in dosage and methods of administration (smoking, snorting, injecting), abuse of MPH can lead to side effects not listed in Table 1. As no long-term studies are available, no reliable statements can be made about dependence potential or tolerance development in healthy individuals. The available studies suggest that oral dosing of MPH is unlikely to lead to gross euphoria (Repantis/Heuser 2008, p. 9).

USE

MPH was first synthesized in 1944 and was first approved for use as a medicine (proprietary name: Ritalin®) in 1954. Its stimulant effect was recognized at a very early stage and as a result it soon came to be used to treat chronic fatigue, disturbances of drive, depression, and age-related behavioral disturbances. Since 1971 MPH has been subject to the German Narcotics Act (*Betäubungsmittelgesetz*). MPH is indicated for the treatment of ADHD in children and is also used off-label to treat attention deficit disorders in adults (Lieb 2010, p. 71).

Since the 1990s there have been regular reports of increasing prescription figures and sales volumes of MPH. This can be attributed to various causes. Along with an increase in ADHD diagnoses, an increase in treatment with medicines in general, and increased off-label use of MPH, use of MPH for performance enhancement or as a recreational drug because of its supposedly intoxicating effect is cited as a possible cause of rising sales figures (Hennen et al. 2008, pp. 153ff.).

In June 2006, on the basis of a European risk assessment procedure, the indications for the use of MPH were restricted throughout Europe. According to this ruling, exclusively pharmacological treatment of ADHD with MPH is inappropriate and multimodal therapy is indicated in its place (for details, see Table 11, Section III.3.5 and Section IV.2.2.1). In September 2010 the Federal Joint Committee (*Gemeinsamer Bundesausschuss*, G-BA) adopted this restriction and stipulated in its pharmaceutical guideline that MPH may be prescribed at the cost of the SHI scheme only when used as intended in its approved indication (*Bundesanzeiger* no. 181 of November 30, 2010, p. 3975).

MPH is included in the WADA Prohibited List. Use of it for performance enhancement in sport is therefore prohibited (WADA 2011).

EFFECTS RELEVANT TO PERFORMANCE ENHANCEMENT

As long ago as 1973 MPH was tested over a prolonged period in a group of healthy volunteers over 60 years of age. The subjects in the treated group felt less tired than those in the control group, however no measurable changes in mental ability dimensions could be found (Gilbert et al. 1973). Lieb (2010, p. 72) concluded that although effects related to wakefulness occurred, consequent effects on certain executive abilities such as improved attention and shortened

reaction time were weaker than with use of amphetamines. Repantis/Heuser (2008, p. 9) point out that weak effects on cognitive abilities have been found only in older studies, whereas no such effects have been found in more recent studies and overall there is no evidence of performance enhancement. Many subjects who took the drug nevertheless reported a subjective impression of improved ability. This could explain the persistence of the widespread belief that MPH improves performance-relevant abilities (Repantis/Heuser 2008, p. 10). It is also possible, however, that MPH was compared to a placebo that was itself effective. In that case some subjects might indeed experience potent effects, however these would be pure placebo effects which controlled studies would not find to be attributable to the substance.

In the studies referred to above no positive effects were found in relation to either wakefulness, executive abilities such as attention, or mood (as a dimension of emotional ability). On the other hand, a positive effect on memory was found after a single dose of the substance (Repantis/Heuser 2008, p. 11). Continuous intake over a week or six weeks produced no significant effects (Gilbert et al. 1973; Gobbi et al. 2003).

Nor were deficits resulting from sleep deprivation correctable by means of MPH. Studies in which a deficiency state was deliberately induced by sleep deprivation showed no improvement in attention even though the subjects reported a subjective improvement (Bishop et al. 1997; Roehrs et al. 1999 and 2004) that extended in some cases to overestimation of their own abilities (Bray et al. 2004).

As with amphetamines, a careful assessment of the available evidence suggests that individuals whose working memory is poor are more likely to benefit from use of MPH than are individuals whose working memory is good (Mehta et al. 2000). There is evidence to suggest that study subjects whose working memory at baseline is good make more errors after using MPH because – due to impulsiveness and even overestimation of their own abilities – they react before fully processing all the necessary information (Schumacher/Stern 2008, p. 16).

CAFFEINE – A MEMBER OF THE XANTHINES

EFFECTS – SIDE EFFECTS

Caffeine has a relatively broad range of actions both on various organ systems and on the nervous system. Via a biochemical cascade it promotes release of the stress hormone epinephrine and prolongs the actions of this hormone in the body. Caffeine crosses the blood-brain barrier almost without hindrance. In the CNS it interferes with the self-regulatory mechanisms by means of which neurons are prevented from exhausting themselves. Active neurons release transmitter substances such as dopamine, consuming energy in the process, and simulta-

neously release the cotransmitter adenosine, which binds to specific receptors. As the cell becomes more active, more adenosine is produced, more receptors are occupied by adenosine, and the resulting signal to reduce cellular activity becomes more powerful. Caffeine has a chemical structure similar to that of adenosine and can occupy the same receptors as adenosine but without activating them and thereby triggering an inhibitory signal. As a result, the neurons remain active despite a rising concentration of adenosine and dopamine activity remains high (Lieb 2010, p. 144; Wyatt et al. 2004).

Most of the caffeine-containing medicines that are licensed for use in Germany are mixtures of substances, e.g. caffeine is a common constituent of analgesic combinations. The side effects listed in Table 2 as occurring in association with therapeutic use of caffeine are based on available user information texts of medicines that contain caffeine as their sole active constituent.

TABLE 2 CAFFEINE: POSSIBLE SIDE EFFECTS WITH THERAPEUTIC USE

Frequency	Side effects*
Not specified	Side effects depend on individual substance sensitivity and dose. Low doses: increased heart rate, insomnia, internal restlessness, gastrointestinal symptoms. Higher doses and/or greater sensitivity: irritability, headache, exacerbation of naturally present but normally imperceptible muscle tremor.
	More prolonged use of caffeine, especially at higher dosage, leads to the development of tolerance to most of the effects and side effects of the substance. On abrupt discontinuation after prolonged use: headache, tiredness, muscle pain, nervousness, and autonomic phenomena (e.g. sweatiness, dizziness, tremor, palpitation, chest tightness).

* The information about side effects provided in user information texts for medicines is not fully standardized, e.g. it does not always include information about frequency and severity. The structure of the tables of side effects included in this section therefore varies to some extent.

Source: User information texts of medicines that contain caffeine as their sole active constituent (www.pharmnet-bund.de, 15/04/2011)

USE

Caffeine is a naturally occurring substance that is present in the leaves, fruit, or seeds of more than 100 species of plant, e.g. tea and coffee bushes. It is therefore present in small amounts in tea and coffee – drinks that have been consumed in Europe for hundreds of years and in Asia (in the case of tea) for thousands of years. Caffeine is the world's most commonly consumed pharmacologically active substance. Because of its stimulant effect, consumption of it spread quite rapidly. Regionally limited bans in the 18th and 19th centuries were imposed mostly for sociological or economic reasons and could not be sustained for long in the

face of popular opposition (Maritsch/Uhl 1989, pp. 6ff.). Caffeine may legally be present in small amounts in foods, whereas formulations containing larger amounts of caffeine (e.g. caffeine tablets) are subject to the Medicinal Products Act (*Arzneimittelgesetz*, AMG). For example, one Coffeinum® tablet contains 200 mg of caffeine (equivalent to about two cups of coffee) and is available only in pharmacies.

As a stimulant, caffeine consumed in amounts above a certain limit – a limit that permitted normal consumption of caffeine-containing drinks – was for some time included in the WADA Prohibited List. However, the available detection methods were not sufficiently specific and findings could be contested. In 2004 the World Ant-Doping Agency removed caffeine from its Prohibited List.

EFFECTS RELEVANT TO PERFORMANCE ENHANCEMENT

Coffee, or more precisely the caffeine that it contains, is often cited in the enhancement debate as an example of an effective and relatively side-effect-free substance for performance enhancement, since although the liberal approach to its use was questioned for some time, it is now known to be essentially safe.

At low doses caffeine reduces the effects of tiredness. Its almost exclusively stimulant action is observable in executive ability dimensions such as attention and concentration and also in emotional ability dimensions such as drive and mood. These effects are attributed to increased dopamine activity. Caffeine stimulates the respiratory center and the circulation and influences motor centers in the brain. In this way reaction times can be reduced. Probably as a result of increased secretion of epinephrine, which tends to replace cognitive abilities with reflex actions, caffeine can also improve physical endurance (Grebe 2010). Tasks that call for specific cognitive abilities (e.g. complex visual-motor coordination) are believed to be if anything impaired by high doses of caffeine.

The effects of caffeine in healthy individuals are particularly apparent in sleep deprivation (Lieb 2010).

MODAFINIL

EFFECTS – SIDE EFFECTS

Modafinil belongs to a group of psychostimulant substances whose molecular structure differs substantially from that of amphetamine-like stimulants. Not only the pharmacological properties, but also the physiological and behavioral effects, of this substance suggest that its mechanism of action differs from that of amphetamine-like stimulants. It is believed that modafinil both increases the activity of the stimulating neurotransmitters dopamine and norepinephrine and decreases the activity of the inhibitory neurotransmitter gamma-aminobutyric

acid (GABA) (Lieb 2010, p, 74). According to the manufacturer, modafinil promotes wakefulness by selectively activating the cerebral cortex via the wakefulness center, however to date no consensus exists regarding the precise neurochemical mechanism of action of the drug.

Modafinil does not cause euphoria and does not appear to have any dependence potential, however in the absence of long-term studies in healthy subjects the possibility of dependence potential, in particular, cannot be ruled out. Similarly, no conclusions about long-term side effects can be drawn at present (Repantis/ Heuser 2008, p. 12).

TABLE 3 MODAFINIL: POSSIBLE SIDE EFFECTS WITH THERAPEUTIC USE

Frequency	Potentially serious	Other
≥ 10%		Headache
1–10%		Dizziness, drowsiness, insomnia; awareness of an unusually rapid heartbeat; chest pain; flushing; mouth dryness; appetite loss, nausea, abdominal pain, digestive disturbances; weakness; numbness or tingling in the hands or feet; blurred vision; elevated liver enzyme levels
0.1–1%		Back pain, neck pain, joint pain, swelling of feet and hands, muscle problems (cramps, twitching, tremor, coordination); rotatory vertigo; hay fever-like symptoms (nose, airways, mouth, eyes, skin); nosebleeds, sore throat or paranasal sinusitis; visual disturbances; sweating; changes in blood pressure or heart beat; difficulty swallowing; severe flatulence; reflux; altered urine, frequent micturition; elevated blood glucose and cholesterol levels; changes in appetite, weight, thirst, and taste; vomiting; migraine; speech and sleep disturbances, abnormal dreams; loss of sexual desire
Not specified	Sudden breathing difficulties, swelling of face, mouth, or throat; skin rash or itch, especially affecting the entire body; changes in mental state and wellbeing	

Source: User information texts of medicines that contain modafinil as their sole active constituent (www.pharmnet-bund.de, 15/04/2011)

USE

Modafinil-containing medicines have been approved for use in France since the 1980s and in the USA since 1998 (US proprietary name: Provigil®; German proprietary name: Vigil®). Since 2008 modafinil has not been subject to the German Narcotics Act (*Betäubungsmittelgesetz*) (because of its low addiction potential).

Modafinil was originally approved, i.e. medically indicated, for the treatment of diseases associated with pronounced daytime tiredness, e.g. narcolepsy, in sleep apnea, and in chronic shift work sleep disorder. According to Lieb (2010, p. 74) modafinil has also been used outside of this approved indication and in the absence of any proof of clinical efficacy to treat ADHD and illnesses accompanied by tiredness and a lack of drive, e.g. depression. The latter off-label use, in particular, appears to be especially risky. In February 2011, as a result of a new risk assessment of modafinil by the European Medicines Agency (EMA) that found the benefit-risk relationship to be favorable only in adult patients with narcolepsy, the indications for use of the drug were severely restricted in that marketing authorization for all indications other than adult patients with narcolepsy was withdrawn. It was also ruled that modafinil must be used with particular caution in patients with a history of psychosis, depression, or mania or abuse of alcohol, medicines, or illegal drugs and that patients in these categories must be carefully monitored (Cephalon 2011).

Modafinil is included in the WADA Prohibited List. Its use for performance enhancement in sport is therefore prohibited (WADA 2011).

EFFECTS RELEVANT TO PERFORMANCE ENHANCEMENT

Both patients and healthy individuals consider modafinil to exert positive effects on cognitive abilities, presumably by increasing wakefulness and reducing the need for sleep. According to Repantis/Heuser (2008, pp. 11–12) the action of modafinil as a neuroenhancer is now being intensively investigated. The results of studies in which modafinil has been used in the absence of any baseline deficit are described by Repantis/Heuser (2008, p. 12) as being inconsistent. Schumacher/Stern (2008, p. 22) are likewise of the opinion that the available studies on the cognitive effects of modafinil do not reveal any uniform picture and do not establish that modafinil can improve cognitive performance in healthy individuals. Lieb (2010, p. 74) estimates the potency of effect of modafinil in »unstressed adults« to lie approximately between that of methylphenidate and that of amphetamines.

Subjects with no illness-relevant state at baseline have been further analyzed in two different ways: firstly by being subjected to a sleep deficit (i.e. an overall reduction of the waking state), and secondly by being grouped on the basis of their individual cognitive ability (as measured by IQ).

Most of the available studies on the effects of modafinil in healthy subjects after sleep deprivation have been sponsored by the military, in particular the US, French, and Canadian militaries. Studies in which subjects were subjected to periods of sleep deprivation (on average 36 hours) and took a single dose of modafinil showed that modafinil could restore wakefulness to the level that prevailed before sleep deprivation. After sleep deprivation, memory performance was better in a group treated with modafinil than in a placebo group. Results for attention varied. Mood appeared to be unaffected. After prolonged sleep deprivation wakefulness was better maintained by repeated doses of modafinil than by placebo, whereas executive abilities such as attention were not. Instead, these abilities deteriorated both in the subjects who took modafinil and in those who took placebo (Repantis/Heuser 2008, pp. 11–12).

In two studies subjects were asked to estimate their own cognitive performance before and after administration of modafinil (Baranski et al. 2002; Baranski/Pigeau 1997). The subjects' prospective estimates proved to be accurate, whereas retrospectively they tended to overestimate their cognitive performance after taking modafinil.

In an analysis in which subjects were grouped by IQ, two groups were defined, namely a group with an IQ of 106 ± 0.6 (a level above the average IQ of 100) and a group with an even higher IQ (115.5 ± 0.5) (Randall et al. 2005). The subjects took modafinil in a normal waking state and then underwent extensive testing of a broad range of cognitive abilities. The only positive effect they showed after taking modafinil was more rapid recognition of visual stimuli, and an analysis by group showed this effect to be present only in the group with an IQ of 106 (Schumacher/Stern 2008, p. 22). The authors of the studies came to the tentative conclusion that the ability of modafinil to improve cognitive abilities may depend upon IQ, i.e. the individual's baseline level of cognitive ability (Repantis/Heuser 2008, p. 12).

AMPHETAMINE, CAFFEINE, MODAFINIL, AND PLACEBO COMPARED

In a double-blind randomized study commissioned by the US Army, 48 healthy young adults were kept awake for 85 hours. After 64 hours of sleep deprivation groups of 12 volunteers were given either 20 mg d-amphetamine, 400 mg modafinil, 600 mg caffeine, or placebo. The three active substances had approximately equal effects on alertness and performance of simple psychomotor tasks tested over two to four hours. The placebo group performed worse in these tests (Wesensten et al. 2005).

NICOTINE

EFFECTS – SIDE EFFECTS

Nicotine acts very rapidly on the nervous system on both sides of the blood-brain barrier. It binds to and activates nicotinergic acetylcholine receptors. These specific receptors are closely related to the prefrontal cortex and the dopaminergic reward system. Nicotine promotes the release of a variety of neurotransmitters (epinephrine, dopamine, serotonin, norepinephrine, endorphins) and thereby initiates, among other things, a cascade of positive feelings in the brain's reward center. Regular consumption of nicotine leads to the development of tolerance, as the number of receptors increases and the receptors simultaneously become less sensitive.

The dependence potential of nicotine is very high when the substance is inhaled, but very low when it is taken orally or administered via the skin (nicotine patches). Smoking (which results in absorption not only of nicotine but also of various other substances including tar) is one of the most important risk factors for chronic nontransmissible diseases such as cardiovascular and chronic airways diseases, cancer, and type 2 diabetes. Smoking damages almost every organ in the body and reduces life expectancy by ten years (DKFZ 2010).

In order to reduce the health risks of smoking, nicotine may be administered in a variety of ways over a limited period as a form of replacement therapy.[10] User information texts for nicotine refer to side effects such as insomnia, dizziness, headache, and nausea that also occur in association with cessation of smoking. Also reported are side effects that are specific to the method of administration. In the case of patches, these include skin irritation at the site of administration; in the case of oral administration, mouth and throat irritation, nausea, and vomiting; and in the case of inhalation, airways diseases (www.pharmnet-bund.de, 15/04/2011).[11]

USE

Pure nicotine is classified as a highly toxic dangerous substance. Nicotine is present in small amounts in tobacco, which has been consumed by various means in many cultural settings for thousands of years. Despite the serious risks to health that it poses, tobacco is an established part of everyday culture and is classified both in Germany and internationally as a legal drug which may therefore be

10 Nicotine dependence is recognized as a disease both in Germany and internationally. In the WHO International Classification of Diseases (ICD) it is described as »mental and behavioral disorders due to tobacco« (ICD-10: F17) with a multifactorial web of causality representing the sum of internal and external factors.

11 Because of the variety of available dosage forms of nicotine and the fact that some side effects are related to dosage form, no table of all side effects mentioned in user information texts is provided here.

marketed. In Germany the market in tobacco products is largely unrestricted, though societal attitudes to the substance are changing substantially. The legal position of the substance is unique (governed in Germany by the Provisional Tobacco Act [*Vorläufiges Tabakgesetz*]). A shift away from the present emphasis on consumer rights towards a greater emphasis on the rights of nonconsumers (to be protected from passive smoking) is apparent at present. The principal reason for this shift is the ever greater ability of science to prove the health consequences of nicotine consumption. Though at present there are no plans to ban consumption of nicotine, considerable efforts are being made to discourage consumption as much as possible.

Nicotine has not been shown to possess any therapeutic value as such. Rather, it may be used in the form of nicotine patches, chewing gum, or spray only for the purpose of combating dependence by facilitating the withdrawal process (nicotine replacement therapy). Most of these nicotine preparations for the treatment of dependence are classified as pharmacy-only nonprescription medicines (Section III.3.3).

EFFECTS RELEVANT TO PERFORMANCE ENHANCEMENT

At low doses nicotine has a brief stimulant action. Notable among its performance-enhancing effects are an increase in psychomotor abilities and improved attention. Whether nicotine directly improves memory or learning is disputed. In one study 16 nonsmoking pilots each chewed one piece of nicotine-containing or placebo gum on two different days, in each case before doing a test flight on a flight simulator. The pilots' performance in the test flight was found to be significantly better on the nicotine day (Mumenthaler et al. 2003).

SUBSTANCES USED TO COMBAT DOPAMINE DEFICIENCY 3.2

Two strategies are adopted at present for the treatment of neurodegenerative diseases characterized by, among other things, a deficiency of dopamine in the CNS (e.g. Parkinson's disease):

- Increasing the concentration of dopamine in the CNS (e.g. by administering the dopamine precursor levodopa)
- Preventing the breakdown of dopamine (e.g. by inhibiting the enzyme COMT, which plays a role in the breakdown of dopamine)

LEVODOPA (L-DOPA)

Via the influence of dopamine on various processing pathways in the brain, levodopa activates the reward system and improves working memory and executive functions. Dopamine also plays an important role in the regulation of motor function.

EFFECTS – SIDE EFFECTS

Levodopa is a precursor of dopamine, which in turn can be converted into epinephrine or norepinephrine. Levodopa is the only one of these substances that is able to cross the blood-brain barrier. The desired pharmacological effect in the CNS is brought about not by levodopa, but by its metabolic products.

USE

Levodopa has been approved for use as a medicinal substance since the 1970s. In combination with carbidopa it was included in the World Health Organization's list of essential medicines (WHO 2010) for the treatment of diseases that result from dopamine deficiency (e.g. Parkinson's disease, restless legs syndrome). At present a total of 250 different medicinal products that contain levodopa in combination with other active constituents are licensed for use in Germany (www.pharmnet-bund.de).

TABLE 4 LEVODOPA: POSSIBLE SIDE EFFECTS WITH THERAPEUTIC USE

Frequency	Side effects
≥ 10%	Nausea, vomiting, diarrhea, reduced appetite; abnormally sad moods, depression (which however can be part of the clinical picture of Parkinson's disease); sleep disturbances With prolonged treatment and/or high dosage: involuntary movements, severe fluctuations in mobility; transient changes in certain liver enzyme and blood levels
1–10%	Irregular heartbeat, low blood pressure (consequence: dizziness, fainting); headache, mouth dryness, altered taste sensation; misperceptions; anxiety; sniffling, bronchitis, febrile infections
0.1–1%	Loss of taste

Source: User information texts of medicines that contain levodopa 100 mg and benserazide 25 mg as their active constituents (www.pharmnet-bund.de, 15/04/2011)

EFFECTS RELEVANT TO PERFORMANCE ENHANCEMENT

When the effects of levodopa that are relevant to performance enhancement are discussed, reference is regularly made to a study by Knecht et al. (2004). In that study 20 healthy young subjects were given either a placebo or a low daily dose (100 mg) of levodopa in double-blind fashion over a period of five days (40 probands all in all). After each dose the subjects were to memorize a set of nonsense words. Compared to the placebo group, the levodopa group learned more and faster and was better able to recall the words both at the end of each treatment day and one month after the final dose. In another study (Flöel et al. 2008b) the effect of levodopa on fine motor abilities (e.g. speed of movement of the hands) was investigated. A significant improvement was found in the 20 el-

derly subjects but not in the young subjects. Repantis/Heuser (2008, p. 13) conclude that a dopaminergic deficit is generally present in elderly people and that levodopa could be used to improve fine motor abilities in this population.

TOLCAPONE

The therapeutic effect of levodopa can be enhanced by tolcapone.

EFFECTS – SIDE EFFECTS

Tolcapone acts at various levels. In the CNS it inhibits the enzyme COMT, which inactivates and breaks down dopamine especially in the prefrontal cortex. This reduces the decline in dopamine concentration. However, this effect has been observed only in individuals with the val/val genotype, in whom COMT is fully active (Lieb 2010, p. 109). In individuals with met/met or val/met genotypes, in whom COMT is only very slightly active, the disruption of the cascade of action does not increase the concentration of dopamine.

TABLE 5 TOLCAPONE: POSSIBLE SIDE EFFECTS WITH THERAPEUTIC USE

Frequency	Potentially serious	Other
≥ 10%		Psychiatric illnesses (sleep disturbances, excessive dreaming, sleepiness, confusion, hallucinations), nervous system disturbances (disturbances of the sequence of movements, headache, dizziness), vascular disturbances (orthostatic disturbances), gastrointestinal disturbances (nausea, vomiting, diarrhea)
1–10%		Infections of the upper airways, influenza, hypokinesia, syncope, vomiting, constipation, discoloration of urine, abdominal and chest pain, increased sweating
0.01–0.1%	Acute liver damage, possibly with fatal outcome	

Source: Prescribing information text of Tasmar film-coated tablets (www.rote-liste.de, 17/04/2011)

EFFECTS RELEVANT TO PERFORMANCE ENHANCEMENT

Because of its mechanism of action, tolcapone is thought to be most likely to exert effects on mental ability dimensions in individuals in whom the dopamine-catabolizing enzyme COMT is fully active in the prefrontal cortex (val/val genotypes). In a proof-of-concept study (phase IIa clinical trial) performed in 2007, a working group of the US National Institutes of Health compared the effects of

tolcapone with those of placebo in a group of 47 healthy volunteers (Apud et al. 2007). The subjects were stratified by genotype, there being 15 val/val genotypes (COMT fully active), 11 met/met genotypes (COMT only slightly active), and 21 val/met genotypes. The three groups were found to be similar in terms of IQ (mean IQ between 107 and 108) and the subjects completed various cognitive tests. The reported side effect profiles of tolcapone and placebo were similar. The study did not involve pharmacological treatment of a baseline deficit (due to lack of sleep) or of differences in cognitive abilities (IQ). It was also shown that the COMT variants (genotype groups) did not differ in terms of IQ or educational level (Apud et al. 2007, p. 1012). The study showed a significant genotype-dependent substance effect. Tolcapone selectively improved executive functions, verbal episodic memory, and the efficiency of information processing in the prefrontal cortex (which is associated with the construct of working memory) only in those healthy subjects with the val/val genotype, whereas in the subjects with the met/met genotype it resulted in poorer test results. The authors regard this as the first evidence of pharmacological enhancement of cognitive ability dimensions in »normal« individuals to be achieved without use of psychostimulants (Apud et al. 2007, p. 1016).

ANTIDEPRESSANTS 3.3

EFFECTS – SIDE EFFECTS

Antidepressants are intended to combat symptoms such as depression of various degrees of intensity, loss of interest and pleasure, increased fatigability, and impaired concentration and attention. They do this by interfering with various neurotransmitter systems. First-generation antidepressants acted both on transmitter systems and receptors and for this reason often caused substantial side effects, whereas more recently developed antidepressants act in more specific fashion and are generally better tolerated. Antidepressants are classified as follows (Repantis/Heuser 2008, p. 6):

- *Selective serotonin reuptake inhibitors* (SSRI) including fluoxetine (proprietary name in the USA: Prozac®) and many other substances with similar profiles of action
- *Selective norepinephrine reuptake inhibitors* (SNRI)
- Selective serotonin-norepinephrine reuptake inhibitors (SSNRI)
- *Monoamine oxidase inhibitors* (first-generation antidepressants with a relatively unfavorable side effect profile)

Different antidepressants have different profiles of action. Along with their mood-brightening action in depressed patients they may also, depending on their receptor-binding profile, increase, have no effect on, or decrease drive, i.e. exert a sedative effect. In clinical use their therapeutically desirable effects occur only after repeated dosing, in many cases over several weeks. The side effects men-

tioned in the user information texts for SSRIs, the most important antidepressants in the context of performance enhancement, are listed in Table 6.

TABLE 6 SSRI-TYPE ANTIDEPRESSANTS: POSSIBLE SIDE EFFECTS WITH THERAPEUTIC USE

Frequency	Potentially serious	Other
> 10%		Mostly at the start of treatment, then diminishing: nausea, mouth dryness, appetite loss, diarrhea, constipation, vomiting, abdominal pain, flatulence, taste alterations, difficulty swallowing Transient: head and limb pain, insomnia, nervousness, tiredness, anxiety/dizziness, tremor, dopiness, disturbances of sexual function (e.g. impotence, reduced libido, prolonged to persistent erection), disturbances of sensation or thought, nightmares, confusion, restlessness, weakness, excessive sweating, visual disturbances, itch, palpitations, chest pain, hot flushes; weight loss
1–10%		Allergic reactions including bronchospasm, swelling of the skin or mucous membranes, urticaria, skin rashes, in some cases with itch or blistering, accompanied by general symptoms such as fever, increased numbers of white blood cells (leukocytosis), joint pain, breathlessness or tissue swelling (edema); impairment of concentration, yawning, disturbances of micturition
0.1–1%	Severe systemic reactions in the lungs, kidneys, or liver (in some cases with inflammation of vessels) in combination with skin reactions	
Not specified	Suicidal thoughts, suicidal behavior, worsening of depression/anxiety	

Source: User information text of the medicinal product Fluoxetin AbZ (20 mg hard capsules)[12] (www.pharmnet-bund.de, 15/04/2011)

12 According to pharmnet-bund.de, 44 different fluoxetine-containing medicinal products are currently licensed for use in Germany. The user information text for Fluoxetin AbZ 20 mg hard capsules was used as a source for this table because it is one of the very few user information texts for these products that lists not only side effects but also the frequency of occurrence of these.

USE

Over the past two decades the range of indications for the therapeutic use of antidepressants has extended beyond the narrow field of depressive illnesses. Antidepressants are now indicated for the treatment of anxiety disorders (generalized anxiety disorders, phobias, and panic disorders), obsessive-compulsive disorders, post-traumatic stress disorders, pain syndromes, eating disorders, and premenstrual dysphoric syndrome. Various studies and clinical experience have also provided evidence of a therapeutic action of antidepressants in somatoform disorders and chronic fatigue syndrome (Repantis/Heuser 2008, p. 5).

This broadening of indications has been favored by the introduction of new substance classes of similar therapeutic efficacy but markedly reduced side effect profile and a consequent greater willingness on the part of both doctors and patients to try pharmacological therapy.

Critics see this development as a softening of the diagnostic criteria of mental illness (Healy 2004) as a consequence of which a proportion of prescriptions are made out not to patients as such but instead to individuals faced with everyday problems rather than with an illness (Section IV.2).

EFFECTS RELEVANT TO PERFORMANCE ENHANCEMENT

Duration of administration is important for the action of antidepressants. Thus, no effect is observed after a single dose even in individuals with no medical condition at baseline. Only a few studies involving administration to healthy subjects over a number of weeks are available. Based on the criterion of statistical significance, Lieb (2010, pp. 81–82) considers the results of these studies to be clear: »Considering the studies as a whole, none of the substances improves mood in healthy individuals compared to placebo.«

Similarly, Repantis/Heuser (2008, p. 6) come to the conclusion that findings on the effects of antidepressants on individual cognitive abilities such as attention and reaction time and on overall memory are inconsistent. At least as many studies were found that showed no effect at all as that yielded positive results.

Aside from the inconsistent findings on direct effects, Repantis/Heuser (2008, p. 6) conjecture that even if they have no demonstrable direct effect on mood, antidepressants may act indirectly by exerting a positive influence on people's frame of mind (influence on emotionally charged information processing: increased threshold for rage and anxiety, improved memory for words with positive connotations; influence on social ability dimensions: subjects were more cooperative, less hostile, and less inclined to criticize). Lieb (2010, p. 82) nevertheless points out that the fact that a substance is effective at treating symptoms of depression does not mean that it should be expected to improve mood in healthy individuals. Antidepressants probably work only in the presence of a deficiency of transmitter substances such as serotonin or norepinephrine, which they correct.

ANTI-DEMENTIA AGENTS 3.4

Substances that are licensed at present for the treatment of dementia fall into the following categories:

- *Acetylcholinesterase inhibitors* (second-generation substances: donepezil, galantamine, and rivastigmine), which increase the concentration of acetylcholine in the CNS
- *Memantine derivatives*, which antagonize glutamate receptors of the N-methyl-D-aspartate type

EFFECTS – SIDE EFFECTS

Anti-dementia drugs exert their effects only when taken over a prolonged period. Even then their beneficial effect on existing symptoms of dementia is relatively minor. In a proportion of patients they can temporarily halt further deterioration of various mental abilities (Lieb 2010, p. 78), however they cannot slow down, much less halt, the underlying disease process. The dimensions of action of anti-dementia agents are being investigated at present in patients with mild cognitive impairment (e.g. incipient Alzheimer's dementia), however no definite results are available as yet (Repantis/Heuser 2008, pp. 14–15).

TABLE 7 DONEPEZIL: POSSIBLE SIDE EFFECTS WITH THERAPEUTIC USE

Frequency	Potentially serious	Other
> 10%		Diarrhea, nausea, headache
1–10%		Colds, loss of appetite, delusions, agitation, aggressive behavior, fainting, dizziness, insomnia, vomiting, abdominal pain, itch, skin rash, muscle cramps, urinary incontinence, tiredness, pain, tendency to fall
0.1–1%	Gastric or duodenal ulcers Gastric or intestinal bleeding Convulsions	Slow heart rate; slight rise in concentration of muscle creatine kinase in blood
< 0.1%	Hepatic impairment/hepatitis	

Source: User information texts of medicines that contain donepezil hydrochloride as their sole active constituent (www.pharmnet-bund.de, 15/04/2011)

USE

In Germany the first acetylcholinesterase inhibitor was introduced in 1995. Second-generation substances are now available on prescription for the treatment of mild to moderately severe Alzheimer's disease.

Memantine too is available only on prescription. It is licensed in Europe and the USA for the treatment of moderate to severe Alzheimer's disease. Its therapeutic value has been investigated and assessed several times over the past few years by the German Institute for Quality and Efficiency in Health Care (*Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen*, IQWiG). An inadequate assessment of the value of memantine in terms of preservation of cognitive abilities from the year 2009 (IQWiG 2009) was followed by a revised assessment in 2011. As a result of this, memantine may once again be prescribed at the expense of the SHI scheme for the purpose of delaying progression of Alzheimer's disease (IQWiG 2011). To date there is no proof that prophylactic use of antidementia agents can prevent the development of Alzheimer's disease (Lieb 2010, p. 80).

EFFECTS RELEVANT TO PERFORMANCE ENHANCEMENT

Repantis/Heuser (2008, pp. 14–15) assessed nine studies on the use of acetylcholinesterase inhibitors. They refer to several commonly cited but in some respects conflicting studies:

- Yesavage et al. (2002): In a randomized placebo-controlled double-blind study with two parallel groups, 18 middle-aged pilots trained on a flight simulator and then performed a series of maneuvers in which individual performances were measured. They then took either donepezil or placebo for 30 days before repeating the maneuvers. The pilots in the donepezil group performed at the same level as they had in the training maneuvers, whereas the pilots in the placebo group performed worse than they had in the training maneuvers.
- Gron et al. (2005): Thirty healthy young men took either donepezil or placebo over a period of 30 days. At the end of this period an improvement in verbal and visual episodic memory was found only in the donepezil group. However, the improvements were selective, i.e. there was no improvement in other cognitive abilities such as attention, working memory, or semantic memory.
- Beglinger et al. (2005): Twenty-six healthy elderly subjects (age range 55–75 years) took either donepezil or placebo over a period of 14 days. In a battery of tests at the end of the period of treatment the donepezil group performed worse in terms of reaction time, attention, and short-term memory. Neither then nor at any time subsequently were any improvements in performance observed. These observations were largely consistent with the findings of a similar preliminary study performed by the same authors in 2004.

Repantis/Heuser (2008, pp. 14–15) came to the overall conclusion that the available evidence is insufficient to justify the assumption that donepezil, in particular, has any positive effect in healthy individuals. Nor have the five studies available to date in which memantine has been administered to healthy subjects

(in each case as a single dose) shown any definite positive effects. Repantis/Heuser (2008, pp. 14–15) therefore conclude that at present few conclusions can be drawn about the neuroenhancement potential of anti-dementia agents, that regular consumption may be more likely to lead to positive effects, and that such effects may depend also on the age of the subject. They consider, however, that the available data are not sufficient to permit any reliable conclusions as to possible beneficial effects of anti-dementia agents on cognitive abilities.

Lieb (2010, p. 80) likewise calls into question the supposedly positive effects found in the »pilot study« (Yesavage et al. 2002). He considers the results of the use of anti-dementia agents in healthy subjects to be »at best contradictory« and sees no evidence at present that these substances are effective in healthy individuals.

BETA-BLOCKERS 3.5

EFFECTS – SIDE EFFECTS

Beta-blockers bind to specific norepinephrine and epinephrine receptors (beta-adrenoceptors). In this way they interfere with the actions of these substances and block the adrenergic stress system. In stress situations more norepinephrine and epinephrine are formed. By directing resources towards certain central processes, these transmitter substances cause short-term activation of certain physical and mental reserves. An increase in heart rate and blood pressure in order to improve energy supply, a strengthening of emotional learning processes, and a focus on important mental abilities are accompanied by, among other things, a brief decline in peripheral abilities (e.g. fine motor functions) and immune function and a slowing of digestive processes (Wehling, M. 2005, pp. 52ff.).

Beta-blockers can also activate specific receptors, dilate vessels, and reduce memory storage of traumatic material (Cahill et al. 1994). Because of these specific properties, beta-blockers have long been used to treat specific conditions (e.g. hypertension, various heart conditions, and also anxiety and migraine). Lieb (2010, p. 85) also suggests that because they inhibit memory storage of traumatic experiences, beta-blockers also have a potential for use to prevent post-traumatic stress disorders.

USE

The first beta-blockers were developed in the 1960s. Because of their favorable ratio of desired effects to side effects and the many different indications that exist for their use, beta-blockers are among the most commonly prescribed of all medicines. In 2006 1.98 billion daily doses of them were prescribed in Germany alone (Schwabe/Paffrath 2008, p. 9).

Beta-blockers are included in the WADA Prohibited List, however they are not prohibited in all sport, but only in certain types of sport that call for precise fine motor function (WADA 2011).

TABLE 8 BETA-BLOCKERS: POSSIBLE SIDE EFFECTS WITH THERAPEUTIC USE

Frequency	Side effects
0.1–1%	Especially at the start of treatment: tiredness, depressed mood, dizziness, confusion, headache, sweating, nightmares or increased dream activity, sleep disturbances, and hallucinations
	Transient gastrointestinal symptoms (nausea, vomiting, abdominal pain, constipation, diarrhea)
	Allergic skin reactions (reddening, itch, rashes, skin rashes on exposure to light)
	Abnormal sensations, sensation of coldness in the limbs

Source: User information texts of medicines that contain metoprolol tartrate as their sole active constituent (www.pharmnet-bund.de, 15/04/2011)

EFFECTS RELEVANT TO PERFORMANCE ENHANCEMENT

As beta-blockers reduce peripheral symptoms of anxiety such as palpitations and tremor even when used at low doses (Lieb 2010 p. 85), they make it easier to perform tasks that are accompanied by high levels of excitement or even extreme anxiety and that call for specific fine motor skills. Areas of human activity in which beta-blockers are repeatedly rumored to be used include, in sport, shooting disciplines such as the biathlon, and, in music, instrumental music. Lieb (2010, p. 86) states that musicians commonly take beta-blockers before performing on stage.

Use of beta-blockers in the field of music, in particular, is a subject of constant speculation. In this regard musicians whose instruments are extremely demanding in terms of fine motor skills are sometimes suspected of using beta-blockers, especially when the demand for absolute precision becomes difficult to satisfy because of an age-related waning of abilities in settings in which the collective rewards for achievement are very great. In this situation the use of beta-blockers may be euphemized as a way of dealing with nervousness or stage fright or of compensating for an age-related decline in fine motor skills, especially of the fingers. Though use of medicines outside of sport is not classified as doping, little is ever said about this kind of use. This at least suggests that such use is at the margins of accepted medical use and is not uncontroversial.

Use of beta-blockers to improve specific cognitive abilities does not appear plausible, since blockade of the adrenergic stress system would tend to have the opposite effect (Lieb 2010, p. 85).

POSSIBLE NEUROENHANCERS OF THE FUTURE 3.6

The following discussion deals with a number of substances whose presumed or intended mechanism of action suggests a potential for use for neuroenhancement purposes but whose actual effects in healthy individuals are scarcely known at present because they are still at an early stage of development and have yet to be approved for use (Repantis/Heuser 2008, pp. 15–16).

A variety of new substances are being investigated at present, especially for the treatment of Alzheimer's disease. Strategies for the development of new antidementia agents aim to provide symptomatic treatment and/or treatment that acts directly at the molecular site of pathogenesis. Since agents developed using the latter approach interfere with processes that do not occur in healthy individuals, their effects may not simply be assumed to occur also in healthy individuals. Experts assume that forms of treatment that are aimed at delaying the development of illness will not bring about any improvement in individuals with no baseline deficit and consequently are unlikely to have any performance-enhancing effects in healthy individuals (Vellas et al. 2007).

Research is also being conducted on therapeutic use of substances to improve existing symptoms of cognitive impairment. An example of such a substance is Dimebon, which has been claimed to possess, among other things, potentially performance-enhancing properties but about whose effects in healthy individuals little is actually known (Bachurin et al. 2001). Dimebon was initially approved for use in Russia as an antihistamine but was later withdrawn from the market for commercial reasons. Though this substance is no longer marketed, its »blockade of neurological signaling pathways« (as a possible therapeutic approach to neurodegenerative diseases) continues to be investigated. When the biotech company Medivation and its drug development partner Pfizer initiated phase III trials, analysts predicted that if the trials were successful annual sales of the drug would reach two billion US dollars by 2015. In March 2010, however, Pfizer and Medivation announced that neither the primary nor the secondary endpoints of the clinical trial had been met.[13]

Other new substances of a number of different classes are being investigated for use in various psychiatric indications. These substances include ampakines, which strongly stimulate excitatory neurons by modulating glutamatergic AM-

13 http://investors.medivation.com/releasedetail.cfm?releaseid=448818, 14/10/2010

PA receptors. Increased excitatory neurotransmission promotes long-term potentiation, a process that forms the basis of memory and learning at the cellular level. Many ampakines have shown positive effects also in studies in healthy subjects. For example, Ampalex (the first ampakine to be developed) improved memory in healthy elderly subjects (Ingvar et al. 1997). The main focus of research at present, however, is on other, more potent, ampakines with longer half-lives (e.g. CX-717, Farampator). CX-717 has been tested in, among other groups, sleep-deprived subjects, however it failed to reverse the impairments that resulted from sleep deprivation in this population (Wesensten et al. 2007). Though farampator improved short-term memory in elderly subjects, it impaired the episodic memory of those subjects who reported side effects (e.g. headache, sleepiness, nausea) (Wezenberg et al. 2007).

Another group of substances presently under discussion as possible cognitive enhancers is that of CREB modulators. The transcription factor CREB (»cAMP response element binding protein«) plays a role in the formation of long-term memory. Following the awarding of the Nobel Prize in Physiology or Medicine for the year 2000 to Eric Kandel for his work on the mechanism of action of CREB, great expectations were placed on CREB modulators, however these expectations have yet to be fulfilled (Section V.1.1).

Many other pharmacological agents developed especially for indications such as mild cognitive disturbance or illnesses associated with reduced cognitive abilities could also become relevant as possible cognitive enhancers. The existing registers of commercially sponsored clinical trials provide a means of checking the state of progress of such R&D activities (Section III.3.2).

OTHER SUBSTANCES: PLANT-BASED SUBSTANCES 4.

The following discussion gives a number of examples of substances whose potency (bioactivity) in terms of their influence on endogenous control processes is considered to be less than that of pharmacologically active substances but which nonetheless are said to be able, or at least advertised as being able, to improve various performance dimensions. For regulatory purposes they are classified as food additives, and when added to foods they are regarded as food supplements (Section III.2.2). Rempe (2008) examined the »NEM-Liste 2008« (»Food Supplement List 2008«) published by the *Apothekergenossenschaft Essen* (Essen Association of Pharmacists) for products said to be able to influence cognitive abilities and »neuro performance«. A search performed using the search terms »performance enhancement«, »ability to concentrate«, »difficulty concentrating«, and »memory« and a subsequent inspection of the resulting list of hits

identified 13 such products. The advertising claims about the ingredients of these products are listed in Table 9.

It is clear from Table 9 that ginkgo, B vitamins, and polyunsaturated fatty acids, in particular, are claimed to be able to influence cognitive ability dimensions. These and selected other substances will be used here as a basis for a discussion of methods of assessing the value of such claims. In the following discussion, which makes no claim to completeness, claims made by various groups of players about possible performance-enhancing effects are described in brief and where appropriate compared. The players involved include on the one hand manufacturers and their associations (Federal Association of the German Food Trade [*Bundesverband des deutschen Lebensmittelhandels*, BVL], Confederation of the Food and Drink Industries of the EU [*Confédération des Industries Agro-Alimentaires*, CIAA]), which draw up and approve lists of health-related advertising claims made for their members' products, and on the other hand regulatory and inspecting authorities, e.g. at the national level the German Federal Office of Consumer Protection and Food Safety (*Bundesamt für Verbraucherschutz und Lebensmittelsicherheit,* likewise abbreviated as BVL) and the British Food Standards Agency (FSA), and at the European level the European Food Safety Authority (EFSA).

TABLE 9 ADVERTISING CLAIMS ABOUT FOOD INGREDIENTS IN THE CONTEXT OF COGNITIVE PERFORMANCE ENHANCEMENT

Indications	Ingredients
To assist memory and ability to concentrate when mental fatigue is present	Ginkgo, ginseng, Rhodiola rosea, phospholipids, lecithin, amino acids (L-glutamine, L-phenylalanine)
Mental and physical performance, nerves, nervousness, memory	B vitamins, magnesium
Learning curve capsules	B vitamins, lithothamnium, ovophospholipids
Stress	B vitamins, magnesium, selenium, bioflavonoids
Nutrition of brain cells, neurons, and vascular cells; performance and ability to concentrate, memory	Omega-3 and omega-6 fatty acids (DHA, EPA)
Optimized/optimal performance enhancement	L-carnitine, creatine

Source: Rempe 2008, p. 16

SUBSTANCES FROM THE FIELDS OF MEDICINAL PLANTS AND NATURAL MEDICINE 4.1

Extracts of medicinal plants (e.g. ginkgo, ginseng) are situated at the fringes of pharmacologically active substances. Many such preparations are licensed as medicines purely on the basis of the many years of experience available with their use (hence their status as traditional medicines), i.e. without any scientifically based proof of their effectiveness having ever been obtained. There have been many legal disputes as to whether pharmacological effects can be ascribed to such substances or whether such substances are added purely for reasons of nutrition or taste. Recent jurisdiction in this area has inclined increasingly towards treating these substances as foods. This relieves manufacturers and regulatory authorities from the time-consuming and expensive licensing procedures that would be required if such products were classified as medicines. This approach may be justified in some respects, however at the same time it provides easy market access – albeit only to the foods sector – to products of questionable value (Rempe 2008, p. 41) (Sections III.2 and III.3).

GINKGO BILOBA

The drug information system pharmnet-bund.de lists 121 licensed medicinal products that contain ginkgo extracts. User information and prescribing information texts are available for some of these, however products in which the substance is licensed as a homeopathic medicine contain no information either on therapeutic efficacy or on side effects. The November 2010 user information texts of products containing ginkgo leaf extracts that are licensed as ordinary medicinal products state that the substance is indicated for the symptomatic treatment of performance impairments of organic cerebral etiology as part of an overall treatment plan in patients with deterioration or loss of acquired cognitive abilities (dementia syndrome); the list of side effects included in the user information texts is reproduced in Table 10.

TABLE 10 GINKGO LEAF EXTRACTS: POSSIBLE SIDE EFFECTS WITH THERAPEUTIC USE

Frequency	Side effects
Not specified	Bleeding from individual organs (especially when taken concomitantly with anticoagulants); in hypersensitive individuals: allergic skin reactions and possibly severe hypersensitivity reactions (allergic shock); mild gastrointestinal symptoms, headache, dizziness

Source: User information text of ginkgo leaf extract 120 mg (www.pharmnet-bund.de, 15/04/2011)

Manufacturers and their associations regard the efficacy of ginkgo leaf extracts as established even when these extracts are used as food additives. The CIAA regards the claim that ginkgo has a beneficial effect on cognitive functions as permissible (Rempe 2008, pp. 24–25). Various manufacturers claim, for example, that their ginkgo extracts

- are licensed for use in the treatment of disturbances of memory and concentration in patients with dementia and protect against further deterioration,[14]
- can be used in disturbances of memory, age-related disturbances of concentration, ringing in the ears, and dizziness and can improve memory, learning ability, and concentration,[15]
- are useful in people with poor memory and impaired concentration associated with waning of mental performance due to increasing functional impairment of neurons in the brain, vary in potency depending on dosage form, and improve concentration, mental balance, and resilience.[16]

Two systematic reviews that reanalyze and compare a large number of scientific studies on the efficacy of Ginkgo biloba are available. In the first of these, the IQWiG found highly disparate results for the therapeutic objective »cognitive abilities« in the treatment of mild cognitive impairment or dementia and therefore concluded that no conclusion can be reached about the magnitude of a possible effect (IQWiG 2008, p. vii). The second review likewise came to the conclusion that the available results are contradictory and that the assertion that Ginkgo biloba provides a significant benefit to people with cognitive impairment or dementia is without foundation (Birks/Grimley Evans 2009).

In relation to claims made about individuals with no baseline deficit, Schumacher/Stern (2008, p. 23) refer to a placebo-controlled study in which 115 subjects over 60 years of age received either a ginkgo preparation as per the manufacturer's instructions or else placebo (230 probands all in all), in each case over a period of six weeks. By means of an extensive battery of standardized tests the subjects' abilities in terms of learning, memory, attention, concentration, and expressive language were investigated. In none of these cognitive functions was any significant difference found between the ginkgo and the placebo group (Solomon et al. 2002). Lieb (2010, p. 150) likewise sees no evidence that either therapeutic or preventive use of ginkgo extracts is effective in cognitive impairment and therefore considers there to be no reason to consider using Ginkgo biloba to enhance performance either in subjects with or in subjects without a cognitive deficit at baseline.

14 www.hexal-natuerlich.de/arzneimittel/arzneimittel.php, 05/10/2010
15 www.stada.de/gesundheitundmehr/produkte/PRODUKT_UEBERSICHT/produkt/details. asp?AGID=168, 05/10/2010
16 www.tebonin.de/schwabe/Arzneimittel/Tebonin/index.php, 05/10/2010

B VITAMINS 4.2

B vitamins are present naturally (as micronutrients) in foods. They can also be added to foods to increase the naturally occurring concentration of them. For regulatory purposes, the resulting products are considered to be a subcategory of foods (Section III.2.2).

VITAMIN B_1 – THIAMINE

Ingested vitamin B_1 must first be converted into its biologically active forms, which act primarily as coenzymes in various processes of carbohydrate metabolism. After about two weeks with no dietary intake of thiamine the body's reserves of the vitamin are depleted by 50%. Deficiency results in, among other things, tiredness and disturbances of the nervous system. According to the German Federal Institute for Risk Assessment (*Bundesinstitut für Risikobewertung*, BfR) there is no evidence either that any side effects occur, even with excessive consumption, or that oversupply brings any benefit to the consumer. It considers the few studies that have come to contrary conclusions to be of questionable relevance (Domke et al. 2004, pp. 119ff.).

Suboptimal intake or frank deficiency of thiamine has been found in only a small proportion of the German population (especially in people whose alcohol intake is excessive), whereas most people in Germany have an adequate intake of thiamine (Domke et al. 2004, p. 124). Thiamine supplements are used for prophylaxis or treatment of deficiency states. The effects of thiamine, e.g. on mental abilities and in Alzheimer's disease, have been investigated, however the European Expert Group on Vitamins and Minerals (EVM) considers the results obtained in the studies concerned to be contradictory overall and has identified no beneficial effects of the vitamin other than its nutritional effects (EVM 2003, p. 74).

Based on the CIAA/BVL list of health-related advertising claims, the following statement about vitamin B_1 is regarded as permissible: »Thiamine supports the normal function of the nervous system« (Rempe 2008, p. 18). However, advertising claims made by many manufacturers, dealers, and users go far beyond this. For example, the following statement appears in the »Naturheilkundelexikon« (Lexicon of Natural Healing): »However, the outstanding characteristic of vitamin B_1 is its ability to positively influence a person's frame of mind. For this reason it has been dubbed ›the morale vitamin‹. For many people vitamin B_1 is an indispensable aid to coping with stressful situations such as illness, anxiety (examination nerves, phobias), traumatic situations, e.g. after operations, etc. In such situations it promotes the sort of positive attitude that is a precondition for,

or at least greatly facilitates, a favorable outcome.«[17] In no way can claims such as these be justified on the basis of the available scientific studies (Domke et al. 2004, p. 122; EVM 2003, p. 74).

VITAMIN B_6 – PYRIDOXINE

Vitamin B_6 plays a role in the biosynthesis of various neurotransmitter substances including serotonin, gamma-aminobutyric acid (GABA), dopamine, and norepinephrine and thus plays an indirect role in the regulation of mental processes and moods (EVM 2003, pp. 80ff.; Rempe 2008, p. 18). Vitamin B_6 deficiency is very rare and scarcely occurs in individuals with a balanced diet. Severe vitamin B_6 deficiency manifests itself as, among other things, neurological disturbances (e.g. disturbances of sensation, confusion). In Germany vitamin B_6 intake is generally well above the amount considered to be necessary. Risk groups for suboptimal intake include in particular individuals who are underweight or whose food intake is low and individuals with chronically high alcohol consumption (Domke et al. 2004, p. 159).

No safe daily doses or upper limits for intake of vitamin B_6 can be derived from the presently available studies. Neurotoxic effects can occur when vitamin B_6 is taken by itself in high doses. Based on its biological activity it can be regarded as a medicinal substance when taken in pure form. The EVM (2003, p. 80) confirms that vitamin B_6 is therapeutically effective in certain metabolic disorders and can improve symptoms in, among other conditions, peripheral neuropathies. Pyridoxine is scarcely marketed by itself, but instead forms part of mixtures of various B vitamins.

VITAMIN B_9 – FOLIC ACID

Vitamin B_9 is essential for the organism. Like thiamine, ingested folic acid must first be converted into a form (tetrahydrofolic acid or other folates) that can be used in the body. This conversion is limited by a saturation process, with the result that any folic acid ingested thereafter is not metabolized, but instead circulates in unchanged form and is eliminated from the body (Bailey/Ayling 2009). The function of folates is in some respects closely related to that of vitamins B_6 and B_{12}. Tetrahydrofolic acid acts as a coenzyme in many metabolic processes, including in the brain, e.g. in the breakdown of the metabolic product homocysteine in the blood.

Low folic acid and high homocysteine concentrations in the blood have been linked to impaired cognitive abilities. In a three-year case-control study involving

17 www.naturheilkundelexikon.de/uv/vitamin-b1.html, 05/10/2010

more than 800 subjects aged between 50 and 70 years, cognitive abilities (memory and information processing) that tend to decline with increasing age were shown to improve significantly when elevated homocysteine concentrations were reduced by folic acid supplementation (Durga et al. 2007). Critics state that these beneficial effects are at least partially offset by the increased risk of cancer that also accompanies high folic acid intake (e.g. the risk of breast cancer has been found to increase by 50%). They therefore doubt whether folic acid supplementation brings any additional health benefit in humans. Instead, they argue, all that happens is that because of the rapidity with which the processes by which folic acid is converted are saturated, an increased amount of unconverted folic acid circulates in the body (Bailey/Ayling 2009). In the view of the BfR the risk of adverse effects on health associated with the addition of synthetic folic acid to foods must be regarded as moderately high (Domke et al. 2004, p. 184).

Folic acid may be added to foods for normal consumption (»Regulation on the addition of vitamins and minerals and certain other substances to foods« [COM(2003) 671 final of 10/11/2003]). Surveys of consumption in Germany show that 80 to 90% of the population (in all age groups) do not achieve the recommended intake of folate equivalents by consumption of normal, unfortified foods. Nevertheless, uncertainties persist regarding the extent to which fortified foods actually help adults to meet their dietary requirements (Domke et al. 2004, p. 177).

VITAMIN B_{12} – COBALAMIN

Vitamin B_{12} plays a role in the formation of the sheath of nerve fibers and in the entry of folic acid into human cells. As the liver stores enough vitamin B_{12} to meet the body's requirements for about three years, vitamin B_{12} deficiency takes several years to develop. Severe vitamin B_{12} deficiency can cause tiredness, confusion, dementia, and depression, among other things. The EVM (2003, pp. 93ff.) recognizes that a high intake of vitamin B_{12} can be beneficial by influencing biorhythms in individuals with sleep disturbances and other symptoms.

According to the BfR the average intake of vitamin B_{12} in the population may be substantially higher than the amount considered to be necessary to meet requirements. There is no evidence of deficiency in the population. The BfR considers that use of vitamin B_{12} as a food additive may be associated with a small health risk to the user. To date there have been no reports of adverse effects that could be attributed to excessive intake of vitamin B_{12} via foods or food supplements (Domke et al. 2004, p. 211).

MANUFACTURERS' CLAIMS ABOUT B-GROUP VITAMINS

A variety of food supplements, mostly combined preparations of various B-group vitamins, minerals, and trace elements, are offered for sale in pharmacies and drugstores and over the internet. Although deficiency of B-group vitamins other than folic acid is relatively rare in Germany and is largely restricted to high-risk groups, manufacturers of vitamin B combination products advertise their wares in the following ways, among others:

- »B vitamins for strong nerves, including in stress situations«[18]
- »B vitamins – for more energy, better concentration, and improved performance (the combined product containing vitamins B_{12}, B_1, B_2, and B_6 influences natural energy metabolism in the body, improves mental ability, and significantly assists memory, concentration, and mental performance).«[19]

These advertising claims are not supported by any scientific studies.

UNSATURATED FATTY ACIDS 4.3

The importance of various polyunsaturated fatty acids for the brain is undisputed. For example, docosahexaenoic acid (DHA) is present at particularly high concentrations in the active zones of synapses and photoreceptors and is important for normal development of vision and cognition. The omega-3 fatty acid eicosapentaenoic acid (EPA) and the omega-6 fatty acids gamma-linolenic acid (GLA) and arachidonic acid (AA) are important for brain function (Rempe 2008, p. 22). These fatty acids are believed to play roles in, among other things, changes in dopaminergic functions, intracellular signal transmission, and the growth of nerve cells and the development of synapses.

Unsaturated fatty acids are said to possess a multitude of health-promoting properties (e.g. in relation to the cardiovascular system and in rheumatoid diseases). The existence of such effects is suggested by findings obtained in a large number of studies which, however, are based partly on consumption of fish rather than on consumption of individual substances in capsule form. Despite these findings, many questions about the actual benefits of these fatty acids remain unanswered (Rempe 2008, p. 19). According to the EFSA (2010, p. 3) omega-3 fatty acids support normal brain functions. Consumption of omega-3 fatty acids appears to have beneficial effects in a number of illnesses, however no definite proof of this is available as yet.

18 www.klosterfrau.de/index~uuid~8F3CC613B926E9AEEF473EF5B4CAB162~prod_ids~100~p_group_id~-1003~s_group_ids~-1003.htm, 05/10/2010
19 www.biovital.de/index.php?page=biovital_dynamic, 05/10/2010

Blood levels of omega-3 fatty acids have sometimes been found to be lower in individuals with ADHD than in normal individuals (Antalis et al. 2006). A number of meta-analyses of the effectiveness of unsaturated fatty acid supplementation in individuals with ADHD have concluded that the results obtained to date are unconvincing and representative of the great heterogeneity of results of studies on this subject in general. Thus, the available data do not support the use of such supplementation as first-line therapy, nor do they support routine supplementation with unsaturated fatty acids except in cases in which an actual deficit of unsaturated fatty acids has been diagnosed (Grosse 2006; Hässler et al. 2007; Richardson/Montgomery 2005). The German Medical Association (*Bundesärztekammer*) and the *Arbeitsgemeinschaft ADHS der Kinder- und Jugendärzte e.V.* (ADHD working group of physicians in child and adolescent medicine) have issued extensive statements concurring with these conclusions and have incorporated them into their ADHD treatment guidelines (Table 11, Section III.3.5). Similarly, the EFSA considers the presently available data on possible links between long-chain unsaturated fatty acids on the one hand and the development of the infantile brain, other cognitive abilities, concentration, and vision on the other hand as heterogeneous and inadequate overall. The advertising of foods on the basis that such links exist therefore seems questionable (EFSA 2008; Rempe 2008, p. 20).

There is evidence to suggest that supplementation with omega-3 fatty acids can delay disease progression in individuals with cognitive impairment and Alzheimer's disease (Morris et al. 2005), however no definite proof of efficacy has been demonstrated.

TYROSINE 4.4

In a study performed in 2008 that was commissioned by the US Defense Department, 86 food supplements were tested and assessed from a military perspective for their potential as performance enhancers (Williams et al. 2008). Of these substances, only tyrosine was found to be of interest for further analysis, as evidence was found that in stress situations cognitive abilities can be improved by increased tyrosine consumption.

Tyrosine is formed from the essential amino acid L-phenylalanine, which is ingested with food. It is a starting substance for the biosynthesis of other amino acids such as levodopa, which in turn can be converted into dopamine and thence into epinephrine and norepinephrine.

Williams et al. (2008, pp. 33ff.) conjecture that as an intermediate product in the synthesis of dopamine and norepinephrine, tyrosine can exert a weakly positive influence on cognitive performance parameters by improving resistance to acute

stress situations, however they doubt whether it can improve cognitive abilities to any significant extent, since the effects observed in the study were very small.

5. COGNITIVE TRAINING AND OTHER METHODS

5.1 PSYCHOLOGICALLY BASED TRAINING TECHNIQUES

The following is a brief presentation highlighting the effects of training and learning on cognitive abilities and performance. It is largely undisputed that individual mental ability dimensions can be augmented and made more efficient through training and learning. However, the question as to whether mental abilities as a whole can be improved remains a matter of controversy (Schumacher/Stern 2008, p. 10). This means that it is unknown whether targeted training can improve information processing in general or »intelligence« or »working memory«. Outside science it is taken for granted that it is possible to improve the mental processing of information as a whole. Terms such as »mental gymnastics« and »brain jogging« are regularly used in promotional material and suggest that the brain basically functions like a muscle and can therefore be trained and conditioned like the skeletal musculature through stamina exercises. But it is not scientifically proven that brain jogging really makes people more intelligent (Schumacher/Stern 2008, S. 11). Numerous studies have merely shown that by solving mental-gymnastic or intelligence-test tasks one can become an expert in that specific area (Salomon/Perkins 1989). Various studies have investigated the effects of brain jogging on cognitive abilities (Mac Donald et al. 2007; Papp et al. 2009). Probably the most extensive study to date, in which 11,430 healthy participants aged 18 to 60 years engaged in brain jogging for six weeks, showed that regular training enabled the subjects to solve the tasks more quickly. However, no transfer effects were empirically demonstrated, not even on very similar cognitive tasks (Owen et al. 2010). Brain jogging appears to be a way for the elderly to keep mentally fit (Deary et al. 2007). However, to date there is no proof that these methods are any more efficient than other mental activities, for example reading. Jaeggi et al. (2008) claim to have demonstrated the effects of training on working memory. However, there are many doubts concerning the methodology of this study (Sternberg 2008).

Irrespective of the initial state of the working memory or intelligence, diverse cultural techniques have been devised to help people use their existing mental resources efficiently. And there are certainly way to compensate for low intelligence through targeted exercises and the acquisition of knowledge. An especially efficient domain-specific cognitive training method is thought to be the learning of automatic behaviors, which reduces the capacity of working memory needed

to perform individual tasks. Studies have shown that knowledge previously acquired through training and learning facilitates the efficient assimilation and rapid recall of knowledge. This relieves the working memory and can compensate for intelligence differences (Grabner et al. 2003 and 2006). However, such automatic behaviors remain domain-specific: automating driving skills, for example, does not mean that one has automated mental mathematics (Schumacher/Stern 2008, p. 34).

Schumacher/Stern (2008, pp. 31ff.) believe that knowledge is a prerequisite for ability; that the acquisition of such knowledge universally presupposes targeted and often lengthy exercise, particularly in the case of complex skills such as abstract mathematical thinking, which only emerged in the course of cultural development; and that this applies as much to intelligent as to less intelligent individuals, i.e. intelligence is not a *carte blanche* for ability.

Schumacher/Stern (2008, p. 32) contend that it is a myth that intelligence is more important than knowledge for cognitive performance and academic and occupational success. Without denying the advantages of intelligence for acquiring knowledge, they point out that acquired domain-specific knowledge is the best factor for explaining and predicting *performance* differences. Intelligence, they say, is neither a necessary nor a sufficient condition for high performance. Rather, knowledge/expertise and intelligence are two factors that independently influence performance. Hence, their effects are additive in that lower intelligence can be compensated by greater expertise.

However, there is evidence that specific training methods can improve even complex cognitive abilities. Schumacher/Stern (2008, pp. 36ff.) regard these measures as approaches to the domain-spanning promotion of cognitive abilities that specifically target »cognitive learning«, which is regarded as being far more complex than simple »associative learning«. Although motivational training as a means of strengthening emotional ability dimensions and a factor influencing domain-specific learning processes appears to have effects on the efficiency of the working memory, it is not clear if this can be generalized (Schumacher/Stern 2008, p. 11).

NONINVASIVE TECHNICAL METHODS 5.2

DIRECT CURRENT

An method of modulating brain functions that is neither pharmacological nor substance-related is stimulation of the cerebral cortex with direct current applied from outside to the cranium (Schumacher/Stern 2008, pp. 23ff.). The mechanism underlying this form of neuromodulation is still largely unknown. It is suspected

that the direct current affects activation of the cerebral cortex by altering the resting membrane potential and therefore the stimulability of neurons.

In a manner similar to the study of the effects of levodopa, Münster University Hospital investigated the extent to which the application of direct current can facilitate the vocabulary learning (Flöel et al. 2008a). Following random assignment, 19 subjects took part in 30-minute sessions under three different conditions: stimulation with anodic direct current, stimulation with cathodic direct current, or no stimulation. In each session the participants were asked to commit a set of nonsense words to memory. In the tests following the leaning phase the group exposed to anodic direct current performed better than the group exposed to cathodic direct current and the control group. The authors conclude that this type of electrical intervention may serve as a means to support language training in stroke patients. Direct current was also used in an experimental study at Lübeck University with the aim of consolidating newly learned information during sleep (Marshall et al. 2006). Thirteen subjects learned word pairs before going to bed. While they slept, direct current was applied (experimental group) or was not applied (control group). In the test given to the subjects the following morning those in the experimental group remembered about twice as many word pairs (approx. 45 %) than the control group (approx. 20 %). The authors conclude that direct current has a positive effect on the consolidation of associatively learned information.

MAGNETIC FIELDS

Apart from direct current, there have been experimental attempts to either stimulate or inhibit areas of the brain with magnetic fields. This likewise noninvasive technique is referred to as transcranial magnetic stimulation (TMS) or repetitive TMS (rTMS: series of more than three individual stimuli at the same frequency). A magnetic field above a certain strength threshold is able to induce a sufficiently strong electrical field in small areas of the superficial cerebral cortex and exert effects (Barker et al. 1985). For example, there have been attempts in connection with the experimental treatment of depressive states to derive a benefit from the targeted manipulation of prefrontal cortex activity. However, it cannot be determined on the basis of preliminary studies on the treatment of neurological diseases whether the use of TMS or rTMS achieves therapeutically relevant effects (Ridding/Rothwell 2007). Potential side effects of TMS/rTMS have been reported to be epileptic attacks, painful local muscular contractions, and transient headache and tinnitus (Völkel 2007, p. 13).

Interference – albeit negative – between rTMS and learning and memory functions via the associative cortex were observed in experimental studies. rTMS administered to the same area five seconds before a visual working-memory task

resulted in a significant increase in wrong answers (Pascual-Leone et al. 1994). And rTMS applied via the prefrontal cortex also significantly impaired the short-term recall of word lists and the generation of random numbers (Grafman et al 1994). Although rTMS has occasionally been shown to improve symptoms in depressive patients, healthy subjects have reported an increase in sadness (Pascual-Leone et al. 1991).

In view of the negative effects of TMS/rTMS on various brain functions, its use for enhancement purposes appears unlikely.

ULTRASOUND

Research methods that use ultrasound waves (low-intensity, low-frequency ultrasound [LILFU]) to specifically influence brain functions also fall into the category of noninvasive technologies. Unlike the use of direct current and magnetic fields, which »only« reach the surface of the brain, ultrasonic stimulation can at least theoretically reach lower-lying brain regions. Stimulation has so far been achieved in animal experiments. Advocates see a great potential for ultrasound, e.g. for improving attention and perception, reducing stress, and relieving pain.

DARPA (Defense Advanced Research Projects Agency), a research and development department of the US Department of Defense, funds outside research into the targeted use of ultrasound.[20] A patent is pending for an ultrasonic helmet, and a company has been set up to market the technology.[21]

CONCLUSION 6.

A large part of the enhancement debate proceeds from the assumption that substances exist or will exist that can exert performance-enhancing effects in healthy individuals without causing serious side effects. Enhancement of *physical* performance dimensions by drugs is regarded as an established fact, as is the fact that consumption of substances for this purpose is associated with many (short-, medium-, and long-term) side effects. This forms the conceptual basis for the prohibition of doping in sport. Whether the situation of mental performance dimensions is analogous to this is an open question in a number of respects.

20 http://medgadget.com/archives/2010/09/darpa_funding_transcranial_pulsed_ultrasound_to_stimulate_soldiers_brains.html, 13.10.2010

21 http://pages.synsonix.com/home, 13.10.2010

ENHANCEMENT OF MENTAL PERFORMANCE DIMENSIONS IN HEALTHY INDIVIDUALS

The range of *mental* performance dimensions is broad. To date there is no generally accepted definition of human performance, either physical or mental (emotional, cognitive, or social), and consequently no standard method of recording and measuring human performance. Unlike in sport, in which a few individual dimensions of physical performance are clearly defined, human performance dimensions in everyday, and especially in occupational, settings remain qualitative items that are difficult to quantify. Despite the difficulties that lie in the way of finding generally valid definitions of human performance, there is a consensus that certain, in particular cognitive, abilities and brain functions are of central importance for mental performance.

Pharmacological substances can be used with the intention of improving or prolonging specific individual abilities or organ functions (e.g. the ability to concentrate). Even if they succeed in this regard, it is only when the improved ability is used that it becomes apparent whether use of the substances has actually resulted in improved performance. In particular, experiments with medicines that increase wakefulness have shown that a longer period in the waking state is not synonymous with improved performance.

Our knowledge of specific effects of individual substances on various brain functions and associated metabolic processes is still extremely limited. Despite intensive research efforts, scarcely any effective drug therapy is available for the various mental illnesses that are accompanied by a decline in cognitive abilities. The few cases in which efficacy has been demonstrated in patients cannot be extrapolated to the situation of healthy individuals; instead, they can at best be regarded as evidence of possible effects.

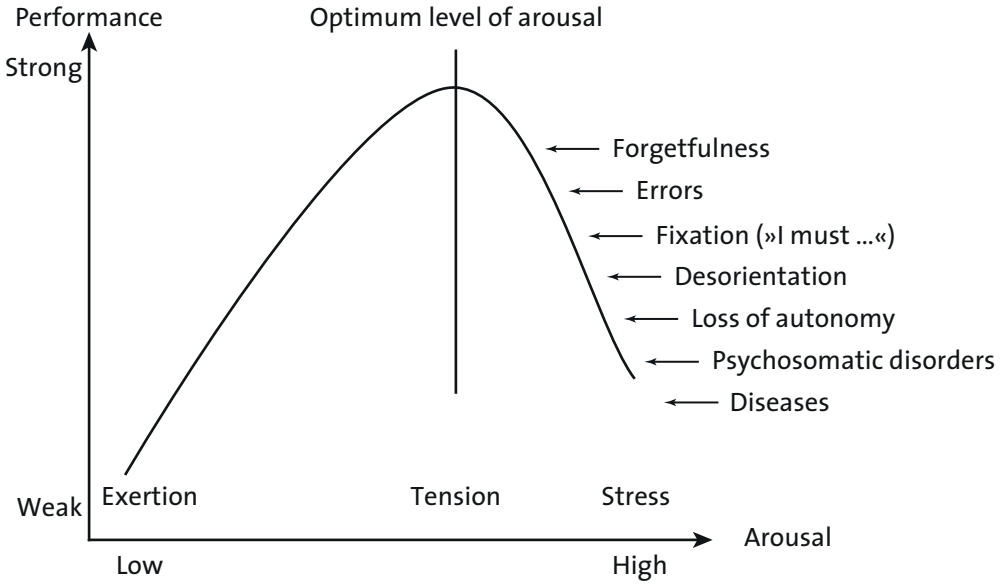
Because of the present legal situation, very few studies on the efficacy of medicines that could potentially enhance mental performance have been conducted in healthy subjects. For methodological reasons the results of the few such studies that have been conducted are scarcely comparable with each other, therefore no reliable conclusions can be drawn about, for example, the relative potencies of different substances.

The results obtained in various studies on the efficacy of pharmacological substances in healthy subjects have been contradictory overall. There is much evidence to suggest that the physical and mental state of healthy study participants is an important determinant of results. There is also some evidence to suggest that in the studies performed to date pharmacological substances had performance-relevant effects only in individuals with a baseline deficit, even one that was not explicitly defined as pathological. Thus, in the case of all psychostimulants (Section II.3.1) an activating effect was observed not in healthy subjects but only in subjects in whom certain abilities were substantially impaired by in some

cases extreme sleep deprivation and in subjects with a relatively poor working memory or a lower IQ (which in turn suggests that dopamine concentrations were at least slightly reduced in these individuals). Conversely, there is some evidence to suggest that in individuals with high baseline levels of neurotransmitters any additional rise in neurotransmitter levels or activation of general wakefulness may even have negative effects on various brain functions. In subjects with higher IQ or very good working memory, consumption of psychostimulants tended to impair performance.

These observations are consistent with the Yerkes-Dodson model (Fig. 4), which assumes the existence of an inverted U-shaped relationship between individual level of physical arousal and performance level. As long ago as 1908 Robert Yerkes and John Dodson concluded from experiments with mice that brain functions can be stimulated up to a certain level by physical activation but that with further activation, e.g. by stress, anxiety, nervousness, or even psychostimulants, performance level starts to fall (error rates rise, memory skills diminish, etc.) (Yerkes/Dodson 1908).

FIG. 4 PERFORMANCE LEVEL AND PHYSICAL AROUSAL LEVEL (YERKES-DODSON MODEL)



Source: mentalmed© 2007 (www.mentalmed.de/blog/uploads/Stress-modell/Yerkes-Dodson.jpg, 03/03/2011)

This suggests the overall conclusion that pharmacological interventions in the body's highly complex neurotransmitter systems are useful for treating brain diseases which because of impaired or reduced activation of neurotransmitters are accompanied by impairment of brain functions and abilities, but not for improving processes that do not arise as a result of any baseline deficit. Like psychost-

imulants, neither anti-dementia agents – a class of substances whose therapeutic action is in any case weak – nor antidepressants have been shown to have any effect on mental abilities or performance in healthy individuals.

Substances with lower levels of bioactivity – e.g. vitamins and individual nutrients, which fall into the legal category of foods because consumption of limited amounts of them is physiologically necessary and because the consequences of overdosage of them are considered to be less problematic because their toxicity is relatively low – are by definition scarcely able to exert any relevant effects on specific abilities, since if they were they would be classified as medicines. Manufacturers' claims that suggest otherwise can be seen as forming part of an advertising strategy aimed at increasing consumer demand for these products or even creating such a demand in the first place (for details, see Section III below).

By contrast, various cognitive training techniques that do not explicitly interfere with the self-regulatory mechanisms of neurotransmitters are regarded as being both effective, relatively free of side effects, and able to bring about a sustained improvement in mental performance in healthy individuals.

SIDE EFFECTS

Most substances that are thought to have a potential to improve mental abilities interfere with the metabolic processes of neurotransmitters. In view of the diverse interactions and complex control and regulatory processes of neurotransmitters, it seems extremely unlikely that any such substances can selectively improve specific abilities in healthy individuals without at the same time causing side effects. All of the presently licensed medicines that are thought to have a potential to improve cognitive abilities and/or general level of arousal (wakefulness) in healthy individuals have a broad range of side effects, some of which are serious (Section II.3).

OVERALL BENEFIT-RISK ASSESSMENTS

Despite this proven and obvious potential for side effects, very disparate overall assessments of the relationship between the benefits and risks of individual pharmacological substances continue to be made. For example, as recently as 2008 Repantis/Heuser (2008, p. 13) described modafinil as being effective and relatively free of side effects overall, whereas in 2010 the EMA drastically revised its assessment of this drug, concluding that the benefit-risk relationship was negative except in a single indication (narcolepsy in adults) and revoking marketing authorization for use of the drug in all other indications.

In the case of licensed psychotropic substances Repantis/Heuser (2008, p. 18) found an overall shortage of empirical and experimental data on neuroenhancing effects. Against this backdrop it can be concluded that the existence of the

material object of the enhancement debate – effective, relatively side-effect-free performance-enhancing drugs for use by healthy individuals – cannot be inferred from a benefit-risk assessment of available substances based on present knowledge.

A targeted study could yield more reliable data both on potential effects and on potential side effects. At present, however, this is prevented by various obstacles that have arisen over the past few decades as a result of the use of pharmacological substances not only in science but also in everyday life including in humans (Section III). The possible and necessary preconditions for future targeted research and development of »genuine« enhancement agents are discussed in Section V of the present report.

ENHANCEMENT SUBSTANCES: FOODS OR MEDICINES? LEGAL DEFINITION, REGULATORY TREATMENT, AND ROUTES OF DIFFUSION III.

In the debate about enhancement it is often argued that the existing regulatory framework for the use of medicines does not form a suitable basis for dealing with substances with specifically performance-enhancing effects and relatively few side effects that may be developed in the future. Given that in recent years enormous scientific, economic, and political resources have already been deployed at the national, European, and international levels in efforts to place the licensing, marketing, and diffusion of medicines (and medical devices) on a more transparent and rational basis and to harmonize the applicable procedures, any more than marginal change to existing regulations would require further enormous efforts.

Compelling reasons would therefore be required in order to justify the reasonableness of any political move in such a direction. The question of what changes in terms of data and opinion forming would be necessary for this purpose is dealt with in Section V of the present report in connection with a »scenario of expansion«. Nevertheless, the developments that have occurred to date in this field are set to evolve – in all likelihood not only in the short term but also in the foreseeable future – via the existing regulatory system, the precepts and organizational structures of which will therefore exert a decisive influence on the future diffusion and use of potentially performance-enhancing substances.

The focus of the present report is on pharmacological interventions to improve performance. This might suggest that the report is limited to medicines – to the exclusion of substance categories that do not possess explicitly pharmacological properties, for example foods. However, in order to understand the issue of enhancement in all its complexity it is necessary also to consider the interface between performance-enhancing substances and foods, since this interface, at which demand is created and the market base is thereby consolidated, appears to function as a pathway and wish intensifier (Section III.2.4). A consideration of food legislation also appears to be important because in the present debate about how society should deal with purportedly performance-enhancing substances a mixing of categories is often to be observed. For example, arguments in favor of a more liberal approach to the use of medicines mostly refer to consumption of foods such as coffee.

In the present debate about the phenomenon of enhancement there is also a broad consensus that future enhancement substances should in principle be assigned to existing substance categories. Still to be answered is the question of

which of the existing regulations and norms can and should be applied to possible enhancement substances. Against this backdrop, the present regulatory approach to the various substance classes is outlined and reference is then made to structures and environmental factors that are very likely to prove relevant to the phenomenon of enhancement.

The following section compares the present legal regulations governing the licensing and placing on the market of foods with those that govern the licensing and placing on the market of medicines (with particular reference to provision of information and advertising) and discusses the role of »gatekeepers« such as doctors and pharmacists. To this end the distinguishing criteria, and the resulting legal definitions, of foods and medicines are firstly discussed in detail (Section III.1). This discussion is followed by an overview of the regulatory treatment of foods (Section III.2) and medicines (Section III.3). In Section III.4 attention is turned to consumer behavior. In Section III.5 the legal and economic factors that influence the diffusion of enhancement substances are summarized.

1. SUBSTANCE DEFINITIONS AND DISTINCTIONS

In order to maintain their vital functions, organisms require a number of substances that are either obtained via food and then transformed or else produced by the organism itself. A basic distinction must be made between substances that supply materials and/or energy for a variety of processes in the human body and substances that play a role in the control and regulation of these processes without themselves supplying substances or energy. The former group are referred to as nutrients, since their essential feature is their physiological role in nutrition (as sources of energy and/or substances). Mixtures of substances that consist mostly of nutrients are classified as foods. A distinction is made between nutrients and specific active substances which when present even in very small amounts can bring about functional changes by participating in control and regulatory processes. Such specific agents are described as medicinal substances if they can produce a therapeutic effect on functional impairments or illnesses, that is to say if they have pharmacological properties. Mixtures of substances that contain medicinal substances are classified as medicines. By contrast, specific active substances with no pharmacological properties are described as hazardous substances.

In legal parlance the terms »foods«, »medicines«, and »hazardous substances« are used in complementary fashion and distinguished from one another as follows:

- *Foods* are covered by food law[22] and are defined as substances or products, whether processed, partially processed, or unprocessed, which are intended to be, or reasonably expected to be, ingested by humans and which among other things are not medicines, tobacco products, or addictive substances (narcotics and psychotropic substances) (Art. 2, Regulation [EC] no. 178/2002). A number of legally defined subgroups (e.g. food supplements, food additives) exist, as do other subgroups, some of which – e.g. *Genussmittel* (a German term that refers to foods or substances that are consumed primarily because of their taste or stimulant effect) – are historically rooted and not clearly defined (see box, Section III.2.2).
- *Medicines* arc covered by medicinal products law[23] and are defined as all substances or combinations of substances with properties for curing, alleviating, or preventing illnesses and substances which by means of a pharmacological, immunological, or metabolic action influence physiological functions of human beings or are used for medical diagnosis and which among other things are not foods, cosmetic agents, or tobacco products (§ 2 AMG). The term »medicine« is normatively narrow but not linked exclusively to a therapeutic property. A subgroup is formed by *narcotics* (medicines that are assumed to be especially liable to improper use and the consumption of which can be particularly hazardous to health; § 1 no. 3 BtMG[24]).
- *Hazardous* or *dangerous substances* are covered by chemicals law[25] and are substances which among other things are harmful to health, toxic, carcinogenic, toxic for reproduction, or mutagenic but which are not foods, tobacco products, or medicines (§§ 2 and 3a ChemG).

An important criterion for classifying substances is the effects that they exert. A substance that exerts a nutritional effect on the organism is classified as a food. Foods serve the purpose of human nutrition by meeting the body's requirement for a continuous supply of nutrients. From the normative point of view, when consumed at the usual doses foods should not exert any specific effect on the organism other than their nutritional effect (Rempe 2008, pp. 5ff.).

Substances that exert a specific effect on the organism are classified as either medicines or dangerous substances on the basis of their degree of dangerousness in conjunction with any medicinal, i.e. therapeutic, value that they have, i.e.

22 Germany: *Lebensmittel-, Bedarfsgegenstände- und Futtermittelgesetzbuch* (Food and Feed Code, LFGB); EU: Regulation (EC) no. 178/2002

23 Germany: *Arzneimittelgesetz* (Medicines Act, AMG); EU: Directive 2001/83/EC (Community code relating to medicinal products for human use, most recently amended by Directive 2008/29/EC)

24 *Betäubungsmittelgesetz* (Narcotics Act)

25 Germany: *Chemikaliengesetz* (Chemicals Act, ChemG); EU: Regulation (EC) no. 1907/2006 (REACH Regulation); Directive 67/548/EEC amended by Directive 2006/121/EC

their pharmacological action. Since dangerous substances are assumed by definition to have no favorable effect on the organism, they are not considered further in this report.

By contrast with foods, medicines are assumed to possess no nutritional properties, but instead to possess pharmacological properties of considerably greater potency in terms of effect on the organism. Nonetheless, both medicines and foods are mixtures of substances, and the most relevant criterion for deciding which of these two mutually exclusive regulatory categories they should be assigned to, and thus what regulatory treatment they will receive, is the amounts of individual substances that they contain. Thanks to a multitude of technical developments, however, these amounts can now be varied to an ever-increasing extent, with the result that the boundaries between these two categories are becoming increasingly blurred. For this reason new substances are now often assigned to one or the other of these two categories on a case-by-case basis (Rempe 2008, p. 10). In 2007, in response to this development, the German Federal Administrative Court (*Bundesverwaltungsgericht*, BVerwG) made the assignment criterion more specific by decreeing that a medicinal property is present only if robust scientific findings prove that the agent in question exerts a substantial influence on the functional conditions of the human body (BVerwG 2007). So far, however, there are no accepted values or indices by means of which a *substantial* effect, or the lack of effect, of a substance can be quantified. In the field of medicinal product licensing these decisions are made on a case-by-case basis. Useful guidance in this regard is provided by medical classifications of diseases and their signs and symptoms. The importance of a close connection between the effects of a substance and an illness-related purpose as a criterion for classifying a substance as a medicine has also been emphasized by the European Court of Justice. According to that court, the fact that a product generally promotes health is not sufficient for classification of the substance concerned as a medicine; rather, it must genuinely possess the property of preventing or curing (an illness). On this basis garlic capsules were not accorded the status of a medicinal product (European Court of Justice, judgment of November 15, 2007, Case C-319/05) (Rempe 2008, pp. 10–11).

At odds with this already difficult system of classification is the existence of some historically derived sociocultural anomalies in the classification of individual substances (e.g. caffeine, alcohol). Requirements in terms of purity and minimum and maximum amounts are certainly applied to specific food additives, but not to more potent generic constituents, the action of which is typically described and advertised as being »natural« or »purely herbal«. As a result of longstanding and widespread use, certain substances (e.g. alcohol- or caffeine-containing substances used as foods) have acquired the status almost of protected species, however the assignment of such a status cannot be used as a basis for

the licensing of newly developed products. Instead, these must be made subject to the presently agreed procedures.

REGULATORY TREATMENT OF FOODS 2.

The most important constituents of foods are nutrients, which provide for the growth and sustenance of the organism (nutritional function). These are classified as either

- *macronutrients* (e.g. proteins, carbohydrates), which are metabolized in relatively large amounts and which provide substances and energy for the growth and specific functions and abilities (e.g. physical, cognitive) of organs (e.g. skeletal muscle, brain), or
- *micronutrients* (e.g. vitamins, minerals), which are required in far smaller amounts and which participate in a variety of control and regulatory processes in the organism.

A variety of other substances can also be present in foods. These are classified as »natural constituents« if they arise in the course of the biological formation of the food, or as »additives«[26] if they are added, e.g. as preservatives or antioxidants, in the course of processing of the food for a technical purpose. Such substances can have many dimensions of action, however in general they do not possess nutritional properties.

THE PRINCIPLE OF ABUSE 2.1

The fundamental regulatory requirement of foods is that they should not pose any risk to health. At the same time, consumers are expected to exercise discretion in their use. In general, therefore, foods may be manufactured and placed on the market unless a specific form of behavior is expressly prohibited. This approach is referred to as the »principle of abuse« in food legislation. A prohibition applies to

- foods that are harmful to health or unsuitable for consumption,
- specific additives not naturally present in a food, which require official approval, and
- foods derived from animals insofar as they contain pharmacologically active substances in excess of stipulated maximum amounts (Section 2, German Food and Feed Code [*Lebensmittel- und Futtermittelgesetzbuch*, LFGB]).

26 Approximately 300 additives are licensed throughout the EU and identified by means of a unique number. They can serve a variety of purposes (e.g. flavor enhancers, preservatives) and therefore have different potential uses.

People are therefore basically free to produce and market safe foodstuffs. However, in order to safeguard health, prohibitions on manufacture, handling, and marketing and restrictions on marketing may be imposed (§ 5 LFGB), e.g. the prohibition on the supply of alcohol-containing drinks to minors (*Jugendschutzgesetz*) (Youth Protection Law) or the EU regulation on novel foods (Regulation [EC] no. 258/97) and its update (Regulation [EC] no. 1882/2003).

SUBCATEGORIES, MARKETABILITY 2.2

The marketing of foods is basically unrestricted. Based on their natural biological occurrence, foods may be placed on the market without having to pass through any licensing procedure. Manufacturers' product ranges are therefore orientated directly towards consumers and their perceptions and preferences. Decisions on what to consume in what amount are taken by consumers alone at their own responsibility.

As more and more individual substances can now be extracted from foods and/or produced synthetically, it is becoming possible both to add individual substances to (or remove them from) foods and to supply them in highly concentrated form. As a result, the amount of such substances generally consumed as part of a balanced diet can be greatly exceeded and the possibility that they may exert specific effects on the organism can no longer be excluded. Mixtures of such substances are thus increasingly liable not only to possess nutritional properties, but also to exert specific (beneficial or harmful) effects on health.

Most such mixtures of substances are still covered by food legislation. Nevertheless, subcategories (food supplements and dietary foods; see box) are being created for them and more and more risk analyses are being performed in order to ensure that individual substances and mixtures of substances are harmless to health. Based on these analyses, positive lists that are a prerequisite for marketing and that establish trade limits und regulations on provision of information are being drawn up. The marketability of these food categories is thus being restricted and the regulatory treatment of them is shifting in the direction of medicinal products legislation. Assignment to the various categories is determined largely by content of nutrients and exclusion of certain substances as compared with »traditional« foods to which no substances have been added and from which no substances have been removed.

To date, regulations on food supplements and dietary foods have only been partly harmonized internationally. Differences exist especially with regard to the assignment of individual agents to the various categories. A number of products that are available in the USA, for example, as food supplements are classified in Germany as medicines because of their effects on the organism.

LEGALLY DEFINED SUBCATEGORIES OF FOODS

Food supplements are foods that consist mostly of micronutrient concentrates (vitamins and minerals) or other substances with a specifically nutritional or a physiological action (e.g. probiotics, enzymes, dietary fiber, fatty acids) and that supplement the general diet (§ 1, no. 1 NemV[27]). Whereas nutrient concentrates and the dosing limits of these are explicitly named by means of positive lists (Annexes 1 and 2 of NemV), the question of which substances fall within the category of »other substances« with a specifically nutritional or with a physiological action has yet to be fully clarified either in Germany or in Europe as a whole. In practice this leads regularly to legal disputes. German regulatory authorities attempt to fill this legal vacuum by referring to the *Zusatzstoffverordnung* (Additives Ordinance). Since unrestricted availability means that dosing limits are easy to circumvent, the exercise of discretion with regard to intake by consumers assumes particular importance.

Dietary foods are intended for a particular diet and are directed at consumer groups with specific dietary requirements (e.g. people with impaired metabolism or in particular physiological situations; § 1 DiätV[28]). The target group consists primarily of consumers with health problems. It can also include athletes, but not the elderly, since a type of food designed specifically for elderly people does not qualify as a dietary food. Dietary foods are subject to expanded labeling requirements, in particular with regard to specific nutritional values. Ostensibly this is to ensure optimal nutrient supply rather than to achieve therapeutic success, which is considered to be a mere side effect, not the primary purpose, of use. Dietary foods are generally not visually distinguishable from other foods. A subgroup of dietary foods is formed by *supplementary balanced diets* that pursue particular medical objectives. These are intended exclusively for patients, not for »normal consumers«, must be labeled, and must be used under medical supervision (§ 21 DiätV).

Source: Rempe 2008, pp. 5 ff.

In addition to the legally defined categories of foods, other designations are used in a variety of contexts, e.g. *Genussmittel* and »functional food« (see box). These are mostly mixtures of foods from different substance categories with different constituents and properties. They make the drawing of boundaries between substance categories more difficult, if not impossible.

27 *Nahrungsergänzungsmittel-Verordnung* (Food Supplement Ordinance)
28 *Diätverordnung* (Diet Ordinance)

FOOD CATEGORIES OUTSIDE OF THE LEGAL DEFINITION

The German word *Genussmittel* refers to foods or substances that are consumed primarily because of their taste or stimulant effect. The classical *Genussmittel* are coffee, tea, and alcohol, though sugar, chocolate, and spices were formerly included in this category. Tobacco products were likewise long regarded as *Genussmittel*, but are now explicitly excluded from the definition of food. The English language has no equivalent term, the substances in question being referred to instead as »luxury goods« or »natural stimulants«, whereby the latter description explicitly highlights their specific action on the human organism. In the past, assignment of foods or substances to the category of *Genussmittel* was not based on biochemical properties, but rather evolved on the basis of sociocultural factors and the collective perception of these. It forms no basis for the licensing of new substances or products.

The term *functional food* (Rempe 2008, pp. 8–9.) has been used since the mid-1990s to refer to foods which, along with their nutritional properties, are promoted on the basis that they exert a specific influence on the health, physical capacity, or frame of mind of consumers (e.g. improvement of the body's defenses, reduction of the risk of developing diet-related illnesses, or slowing of aging processes). In most cases these are foods in which the concentration of individual nutritional constituents has been increased or decreased. As a result of the present lack of clarity regarding the definition and boundaries of this category, many products of extremely doubtful value are marketed as functional foods (TAB 1999).

The Federation of German Food and Drink Industries (*Bundesvereinigung der Deutschen Ernährungsindustrie*, BVE) uses the generic term *Gesundheits- und Wellnessprodukte* (health and wellness products) to refer to foods and drinks that have added health-promoting value (BVE 2007, p. 11). It does not define any more specific food categories.

In the English-speaking world combined terms such as »nutriceuticals« (formed from »nutrition« and »pharmaceutical«) and »nutricosmetics« (formed from »nutrition« and »cosmetics«) have been concocted to describe products that contain both foods and pharmaceuticals.

PROOF OF EFFICACY AND OBLIGATIONS TO PROVIDE INFORMATION 2.3

Since foods are assumed to possess nutritional properties and not to exert any negative effects or pose any risk to health, no proof of effect of food constituents on the human body is required by food legislation.

In order to avoid risks to health, i.e. ensure food safety, and inform the consumer appropriately, regulations governing hygiene and labeling apply. The obligatory information for packaged foods includes in particular a list of ingredients (in decreasing order of quantity, without disclosure of the recipe, including known allergens even if present only in minute quantities) as well as the »best-before« date and details of the manufacturer (LMKV[29]). Rule-compliant production, provision of information, and distribution are the responsibility of the manufacturer or merchant and in Germany are subject to spot checks by the Federal Office of Consumer Protection and Food Safety (*Bundesamt für Verbraucherschutz und Lebensmittelsicherheit,* BVL).

With the help of this information consumers are supposed to be able to make rational decisions about consumption at their own responsibility. The extent to which consumers are informed is becoming a focus of increasing attention and is seen as an important factor for improving consumer protection. Manufacturers, and also regulatory bodies, have a certain responsibility to provide information. In the Single European Market, as a result of the principle of abuse, this responsibility to provide information also implies a prohibition of deception. No explicit distinction is made between information and advertising.

For all foods,

- product advertising must not deceive the consumer (§ 11 LFGB; *Gesetz gegen unlauteren Wettbewerb* [Law against Unfair Competition]),
- illness-related claims are not permissible (§ 12 no. 1 LFGB), and
- claims that relate in general terms to effects or to health must be substantiated by sufficiently solid scientific data (§ 12 no. 3 LFGB; HCR[30]).

Due to the more stringent product liability that applies in the USA, manufacturers in that country have a more extensive responsibility to provide information. They must also inform consumers about possible risks associated with consumption (Pfeiffer et al. 2010, p. 50). In Europe there is no obligation to provide this information.

Information provided by the manufacturer must be clearly categorized in terms of whether it

- relates only to the constituent nutrients (obligatory information),
- refers also to resulting nutritional values, or
- also makes claims regarding the effect of the food on the organism.

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29 *Verordnung über die Kennzeichnung von Lebensmitteln* (Food Labeling Ordinance)

30 HCR (Health Claims Regulation): Regulation (EC) no. 1924/2006 of the European Parliament and of the Council of 20 December 2006 on nutrition and health claims made on foods

To an increasing extent, recommended daily allowances are being specified for individual nutrients (Regulation 2008/100/EC). Within the EU, a legal requirement to indicate nutritional values exists only in the case of legally defined subcategories of food or where claims relating to effects or to health – e.g. »Calcium is good for the bones« – or nutritional claims – e.g. »fat-reduced« – are made. For such claims (not for the substances themselves), the coming into effect of the Health Claims Regulation (HCR) in 2007 introduced the »principle of prohibition subject to exemptions« throughout the EU. The HCR stipulates that in order not to mislead consumers who are striving for a balanced diet and a healthy lifestyle, henceforth only foods with a »favorable nutritional profile« may bear nutritional or health claims (justification no. 11, HCR). The principal objective of the HCR is to put an end to the dubious advertising claims seen for many years that are intended specifically to create a demand.

According to Art. 4 no. 1 HCR, by January 19, 2009 the European Commission was to have established binding nutritional profiles. To date, however, this has not happened.

Though the specific mechanisms of action of individual foods and food constituents are becoming an increasing focus of research, knowledge of these mechanisms of action and interactions remains limited (Domke et al. 2004). After the HCR came into effect manufacturers were asked, in a first (national) step towards establishing a scientific basis for claims about the mechanisms of action of individual food constituents and in an attempt to gradually expand knowledge in this area, to draw up lists of claims about nutritional function, i.e. about health (Article 13 HCR), and to submit these lists for initial (national) consideration. In 2007 the Federal Association of the German Food Trade (*Bundesverband des deutschen Lebensmittelhandels*, BVL) submitted more than 2000 health claims to the Federal Institute for Risk Assessment (*Bundesinstitut für Risikobewertung*, BfR) for consideration. Of the items of evidence submitted by the manufacturers as scientific justification for health claims, the BfR adjudged only 20% to be adequate, 43% to require more detailed consideration, and 37% to be inadequate (BfR 2008, p. 4). It is generally assumed that as the HCR is progressively implemented this ratio will shift in the direction of qualitatively adequate justifications.

Certain health claims made for foods fall within the area of responsibility of the European Food Safety Authority (EFSA), and after being considered are permitted throughout Europe by the European Commission. This procedure applies to health claims relating to »general functions« (Art. 13 no. 1 HCR) such as

- growth, development, and the functions of the body,
- psychological and behavioral functions (ability to learn and to concentrate, memory), and

› body weight (weight control, weight reduction, sense of satiety).

Consideration of all 4637 health claims relating to general functions (e.g. »Protein builds up your muscles«) that were submitted was scheduled for completion by June 2011. The current processing status can be ascertained via the EFSA's web portal.[31]

A third category consists of specific product-related claims:

› reduction of the risk of illness,
› the development and health of children, or
› individual product-related claims (Art. 13 no. 5, Art. 14 HCR).

Manufacturers who wish to make such claims must submit scientific evidence and apply to the EFSA for the case to be considered on an individual basis. The EFSA then considers the case and suggests to the European Commission that the claim be accepted or rejected. In the former event the European Commission then grants permission (BfR 2007b, p. 3). To date only about 280 applications for consideration of individual claims of this kind have been submitted. Of these, about 80 have now been considered and most of these have been rejected. For example, the EFSA found no scientific evidence that Kinderschokolade® is useful for growth or that black tea improves the ability to concentrate. The few claims that have been permitted are very general in nature, e.g. the claim that omega-3 fatty acids make a contribution to optimal brain development in infants.[32] With regard to the substances described in Section II.4.2, the scientific evidence that folic acid can reduce the risks of illness by reducing the level of homocysteine is regarded as sound. The presence of a certain amount of this nutrient in a food therefore justifies advertising claims to that effect (BfR 2007a, p. 5; Domke et al. 2004, p. 169).

At present, manufacturers in Europe are not required to provide any information about possible health risks associated with consumption of foods. Only if there is evidence that risks to the health of the consumer are to be expected with usual dietary practices and correct use must safe levels be determined and taken into account. In addition, tolerable upper limits of daily consumption of vitamins and minerals based on an extensive risk assessment are increasingly being required.

As the »principle of prohibition subject to exemptions« applies also to health claims, it is to be expected that these dimensions of the action of food constituents on human beings will be investigated in more detail in the future. The remit of the EFSA to perform safety assessments explicitly covers claims relating to

31 http://registerofquestions.efsa.europa.eu/roqFrontend/questionsListLoader?panel=NDA
32 http://ec.europa.eu/food/food/labellingnutrition/claims/community_register/rejected_health_claims_en.htm#art141b, 20/12/2010

psychological and behavioral functions – dimensions that are highly relevant in the context of neuroenhancement. As long ago as 2005 the then Vice-President of the European Commission, Günter Verheugen, called for studies to provide a basis for safe use of high-dose micronutrient concentrates both for the prevention of illnesses and for optimization of organ functions in healthy people (Verheugen 2005, p. 13). Since scientific underpinning of such claims is required, there is a pressing need for research and development within the framework of the HCR.

The multiplicity of substance mixtures that can potentially be made and the complex ways in which these can interact to influence human metabolic processes form an extremely complex area of research. There is still a lack of neutral, scientifically recognized procedures for evaluating the effects of food (constituents). Up to now the benefit provided by a substance present in food has been defined on the basis of a favorable effect in terms of reduction of the probability of illnesses. The requirement for proof of health-related efficacy – in particular with regard to psychological and behavioral functions – coupled with the prohibition of claims about illness may promote the development of concepts regarding how an (additional health) benefit in the sense of enhancement can be demonstrated in the absence of a disease state. As far as food is concerned, the official entity most suited to the task of monitoring and checking R&D activities in the field of performance enhancement in healthy individuals would therefore be the EFSA.

MARKET PLAYERS: ATTITUDES AND BEHAVIOR 2.4

A particular need for certain nutrients is said to exist in certain life situations and demographic groups. The only nutritional supplements recommended by the German Nutrition Society (*Deutsche Gesellschaft für Ernährung*, DGE) are iodine (iodized table salt) for the entire population and folic acid for pregnant women. In making the latter recommendation the DGE refers to surveys conducted in Germany that show that 80 to 90% of the population (in all age groups) do not achieve the recommended intake of 200 μg folic acid per day via their diet. Against this backdrop the BfR, for example, recommends a maximum content of 200 μg folic acid per portion in fortified foods and 400 μg per daily dose in food supplements (Domke et al. 2004, p. 169).

Food industry companies regularly see a far more extensive need for special foods. They offer an expanding product range of foods for a variety of situations that are regularly advertised with claims about improvement of health and in some cases even performance enhancement and other types of additional benefit. In this regard Rempe (2008, p. 7) refers to supplementary balanced diets for the treatment of disturbances of concentration as well as stress and symptoms of exhaustion.

Wherever possible, manufacturers engaged in R&D activities aimed at developing specific foods expand these activities so as to equip the resulting foods with additional health benefits; as a result, manufacturers themselves may be playing a significant role in present market developments. Though market estimates differ to some extent due to differences in the delineation of categories, there is general agreement that the market for functional food products of this kind is extremely dynamic. Henke (2009, p. 17) estimates the sales of these products in Germany in 2007 to have been 8.1 billion euros, with annual growth rates since the turn of the millennium of about 7%. To some extent, market analyses include functional food and organic foods in the secondary healthcare market (Bundesregierung 2008), thus considerably expanding the presumed size of that market as compared with narrower definitions (Section III.3.6).

Food supplements, in particular, are generally marketed in dosed forms, especially as capsules or tablets, and increasingly are advertised on the internet and sold by mail order. As the dosage forms correspond to those of medicines, some degree of effectiveness of the ingredients is suggested, at least indirectly. Responsibility for rule-compliant production, provision of information, and distribution lies with the manufacturer. In addition to foodstuff monitoring by the German federal state concerned, independent consumer protection organizations perform spot checks on the market.

In 2008 the consumer magazine ÖKO-TEST published a report on 300 different vitamin and mineral preparations (food supplements). With the exception of folic acid preparations, the report came to somewhat negative conclusions about the dosage of the products and knowledge of their benefits and risks. Many products exceeded the maximum daily doses of food supplements recommended by the BfR. For example, many multivitamin preparations contained too much, and others too little, of the vitamin concerned (ÖKO-TEST 2008).

In a test conducted in April 2008 by the Karlsruhe Food Inspection Office (*Lebensmitteluntersuchungsamt Karlsruhe*), 22% of 79 »sports food« products advertised on the internet as being »hormonally active« were found to contain pharmacologically active substances (Löbell-Behrends et al. 2008, p. 415). In a similar test conducted in 2003, »only« 11.6% of 129 randomly selected non-hormonal food supplements advertised in Germany were found to contain undeclared pharmacological agents (anabolic-androgenic steroids) (compared with 14.8% of 634 samples internationally). Schänzer (2003) believes the main cause of this contamination to be inadequate standards in the manufacture and quality control of food supplements as compared to medicines, since not one of 201 comparable products that contained the same constituents as these food supplements but were classified as medicines was found to be contaminated with anabolic-androgenic steroids.

Despite a lack of information about their constituents and effects, use of these products has in some cases become far more widespread. According to the *Nationale Verzehrsstudie II* (National Consumption Study II), in the year 2007 a total of 27.6% of people surveyed in Germany (31% of women and 24% of men) reported that they took vitamin or mineral supplements (classified both as food supplements and as fortified medicines) at least once weekly (MRI 2008, p. 120). ÖKO-TEST concludes that about 36% of German citizens, with a slight preponderance of women over men, buy food supplements.[33] Consumption of food supplements increases with age and level of education. Only one in four people who took food supplements did so on the recommendation of a doctor. According to ÖKO-TEST, typical consumers of food supplements have a particularly healthy diet, play more sport than the average person, and consequently are less overweight than the average person. It must be assumed that these people believe that by consuming such products they are doing something for their health. A survey conducted in 2008 in North Rhine-Westphalia found that of 145 athletes questioned (members of fitness studios or sports clubs who played some kind of sport more than two hours each week), more than three-quarters took special sports food supplements to build up their muscles (70% protein-containing and almost 40% creatine-containing preparations). Most participants in the survey had nutritional, rather than pharmacological, expectations of the products and assumed the claimed effects to be scientifically unproven (Winters et al. 2008, p. 380). This situation, in which there is only a limited need for knowledge to be generated, in which knowledge is transmitted in one-sided fashion (by manufacturers or by information forums of questionable value), and in which consumer confidence in the information transmitted is limited, suggests a need for consumers to be provided with unbiased information.

The range of tasks – in addition to regulatory functions – performed by public food safety and consumer protection authorities varies to some extent between countries. So far, the general trend that exists in consumer information law for public bodies to play a greater and more active role in the provision of information is apparent only to a limited extent in Germany. Though consumers in Germany have extensive rights to be provided with information, the obligation on the part of German public authorities to provide that information remains limited. Also, the level of coordination between different consumer information bodies is still considered to be in need of improvement. By contrast, Danish authorities, for example, are reported to take a more active approach to consumer information (Pfeiffer et al. 2010, pp. 49 ff.).

Manufacturers and unregulated information forums (e.g. in the internet, in fields ranging from bodybuilding through to cognitive training) have thus been allowed a great deal of scope for making claims, and so far these claims have

33 http://forum.oekotest.de/cgi-bin/YaBB.pl?num=1216150189, 27/05/2010

scarcely been qualified by information from neutral sources. Product advertising, as a communicative influencing process intended to alter its recipients' market-relevant attitudes and behavior (Meffert et al. 2007), is thus able to deliberately smooth the way for future markets by awakening wishes and creating demand while being under no obligation to refer to proof of effectiveness or risks. Often accompanied by barely substantiated factual claims and grossly oversimplified accounts of complex metabolic processes in the human body, advertising of this kind gladly accepts that consumers will draw reverse conclusions and base their consumption habits on those conclusions. Some examples of this are:

- *Causal rather than multifactorial cause-effect relationships*: A dietary deficiency can be a cause of impaired functionality. The reverse conclusion, namely that impaired functionality is attributable to a dietary deficiency and can be corrected by additional consumption of a particular dietary component, does not follow from that statement.
- *The assumption that effects can be extrapolated to other situations*: This reverse conclusion implies that effects that can be achieved when a deficiency is corrected can also be achieved in »healthy/normal« situations or even prophylactically.
- *The assumption that increased doses are not harmful to the human organism*: »A lot helps a lot, or at least it does no harm,« since metabolic processes are said to regulate themselves and the body is said to absorb only as much as it needs.

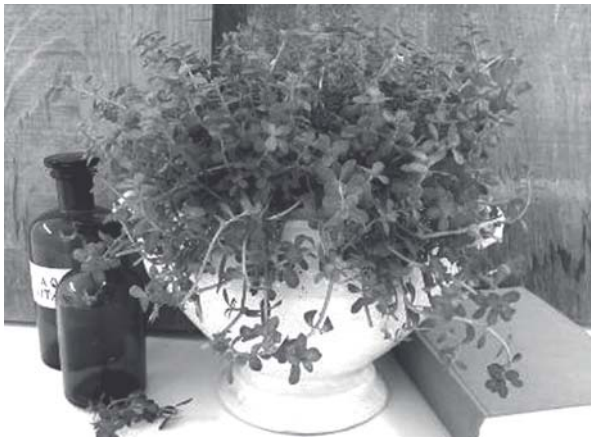
Based on such neither proven nor refuted arguments, products are often knowingly advertised – without provision of any detailed information on their mechanism of action – on the basis that they *may* exert a positive influence on consumers' performance.

In sport, with its long tradition of the use of pharmacological interventions to enhance physical performance, food supplements are regarded as door openers to doping or are described as the first step on the »stairway to doping entrapment« (Singler/Treutlein 2007, pp. 16 ff.). Step by step, people come to rely not just on their own abilities, but also on support substances that have not been proven to carry any risks, the consumption of which is not socially unacceptable, and that almost everybody consumes (and for that reason alone »must be effective«).

Based on existing structures, it is to be expected that substances that are covered by food legislation will function as pathways and wish intensifiers also in the growing field of mental performance enhancement. Coffee is regularly cited as a time-honored example of a substance that is effective, relatively free of side effects, and consumed responsibly. As such it is used to argue the case for adopting a relaxed approach to the use of such substances for enhancement purposes (Galert et al. 2009, p. 48).

FIG. 5 **TYPICAL ADVERTISEMENT FOR A PRODUCT WITH »PERFORMANCE-ENHANCING EFFECTS«**

Brahmi as an aid to memory



Under the heading »Herbs and vegetables«, the mail order company Otto made the following claims in 2010:

»Brahmi is of great value to health. It promotes long-term and short-term memory and improves the ability to think.«

Source: www.otto.de/is-bin/INTERSHOP.enfinity/WFS/Otto-OttoDe-Site/de_DE/-/EUR/OV_DisplayProductInformation-ArticleNo;sid=0iAs7i6mRzds7mKiERFsh0KsXBH9JljgNDUduOIQlyZTEh0PTm0cj4XilyZTEpK3LnzKBaC-?ArticleNo=511703&ls=0&CategoryName=&SpecialShopName=, 01/06/2010

3. REGULATORY TREATMENT OF MEDICINES

Medicines differ from foods in being defined as substances or mixtures of substances that exert a specific (pharmacological, immunological, or metabolic) action on the human organism and its health. The objective of medicinal products legislation is to permit the supply of medicines whose quality, efficacy, and safety is assured and to ensure that these medicines are used safely (§ 1 AMG). In view of the potency of such substances and in order to protect human health (from harmful effects), medicinal products legislation is based on a »principle of prohibition subject to exemptions« (Section III.3.1) that fundamentally restricts the marketability of medicinal products. In the following discussion the procedural regulations that flow from this principle are considered above all from the perspective of how they can limit or give free rein to developments in the field of enhancement. To this end reference is made firstly to existing safety and protection standards governing pharmaceutical research in human beings (Section III.3.2). These standards, which are aimed at maximizing product safety, are accompanied by a series of regulations aimed at minimizing risk in distribution and use. These regulations deal with specific marketability (Section III.3.3), provision of information and advertising (Section III.3.4), restriction of access by means of the »gatekeeper« role of doctors and pharmacists (Section III.3.5), and the various emerging pharmaceutical markets (Section III.3.6). Here too consid-

eration can be given to the question of to what extent these regulations tend to promote or prevent more widespread use of pharmacological substances for performance enhancement.

THE PRINCIPLE OF PROHIBITION SUBJECT TO EXEMPTIONS 3.1

Medicinal products contain one or more medicinal substances, whereby a single pharmacologically active substance is their smallest categorial unit. Medicinal substances and medicinal products are subject to essentially the same regulatory procedures and safety standards.

The manufacture and placing on the market of a proprietary medicinal product[34] requires authorization based on proof of efficacy of the substance concerned, whereby the burden of proof lies with the manufacturer. In the case of a new marketing authorization the manufacturer is required to investigate and demonstrate by means of scientifically recognized procedures (in most cases clinical studies) both the tolerability and safety (risk dimensions) and the medical (in most cases therapeutic) efficacy (benefit dimension, improvement of an illness-relevant state), of the product. Pursuant to § 25 AMG, both proof of a therapeutic benefit and a positive benefit-risk relationship are required for marketing authorization. The benefit-risk dimensions are represented in the marketing authorization dossier via the realms »quality«, »safety«, and »efficacy«, the relative values of which are compared and assessed by the licensing authorities. Marketing authorization of the medicinal product is then granted for treatment of the specific illness-relevant state for which the manufacturer has demonstrated a therapeutic benefit, and only for this use is the manufacturer liable for the safety of the product. Should the manufacturer wish to expand the use of the product (to other medical indications or illness-relevant states), expansion of the marketing authorization is required. The information supplied by the manufacturer on the effects and side effects of the medicinal product is likewise assessed and approved in the marketing authorization procedure.

The placing on the market of unlicensed medicinal products is prohibited. Use prior to the granting of marketing authorization or for expansion of use in the context of research and development likewise requires regulatory approval. Regulatory approval and monitoring cover, among other things, compliance with safety and protection standards both before and after the granting of mar-

34 Proprietary medicinal products are premanufactured and prepackaged medicinal products – in contradistinction to magistral/extemporaneous preparations, which are prepared individually by a pharmacist for a particular person on the basis of a doctor's prescription for licensed medicinal substances.

keting authorization. Therapeutic trials by individual doctors are exempted from this approval procedure.

PHARMACEUTICAL RESEARCH: STANDARDS FOR THE ACQUISITION OF KNOWLEDGE AND FOR MARKETING AUTHORIZATION 3.2

Research on efficacy required for obtaining marketing authorization for medicines is covered by the freedom of research enshrined in the German constitution (Art. 5 no. 3 GG[35]), though this freedom is limited by the obligation to minimize health risks to study participants (protection against threats to life and physical integrity; Art. 2 no. 2 sentence 1 GG). To this end pharmacological R&D activities both before and after the granting of marketing authorization are subject to a series of safety and protection standards aimed at minimizing health risks. R&D activities with pharmacological substances must comply with these protection standards.

ETHICAL STANDARDS

The following basic ethical standards of *good clinical practice,* which includes the voluntary and informed consent of study participants, were formulated at the international and European levels and apply to every kind of pharmaceutical research and development:

- The *Declaration of Helsinki* on the performance of medical research involving human subjects was first published by the World Medical Association (WMA) in 1964 and has been amended many times since, most recently in 2008 (World Medical Association 2008). It enjoys worldwide acceptance as a collection of principles and states, among other things, that:
  - »Every medical research study involving human subjects must be preceded by careful assessment of predictable risks and burdens to the individuals and communities involved in the research in comparison with foreseeable benefits to them and to other individuals or communities affected by the condition under investigation.« (Paragraph 18)
  - »Medical research involving human subjects may only be conducted if the importance of the objective outweighs the inherent risks and burdens to the research subjects.« (Paragraph 21)
  - In the case of vulnerable population groups there must be a reasonable likelihood that the group concerned stands to benefit from the results of the research (Paragraph 17).

35 *Grundgesetz* (Basic Law, i.e. the German constitution)

› At the level of the EU, ethical standards are governed by Directive 2001/20/EC on the implementation of good clinical practice in the conduct of clinical trials on medicinal products for human use (in Germany implemented via the GCP Ordinance of 2004):
  - »A clinical trial may be undertaken only if, in particular, the foreseeable risks and inconveniences have been weighed against the anticipated benefit for the individual trial subject and other present and future patients. A clinical trial may be initiated only if an ethics committee and the competent authority comes to the conclusion that the anticipated therapeutic and public health benefits justify the risks.« (Art. 3 no. 2a)
  - Certain groups of people, e.g. children, should be given special protection in these procedures. Medicinal products for children need to be tested scientifically before widespread use. A precondition of approval of a study is that the medicinal products concerned are likely to be of significant clinical vale for children (Recital 3).

ESTABLISHING A CRITERION OF BENEFIT

Establishing a criterion of benefit is of central importance for the granting of permission to perform a clinical trial (§ 4 Subsection 23 Sentence 1 AMG). The simplest procedure for establishing a criterion of benefit is to define an illness-relevant state, or at least a deficiency state, as a baseline from which a (therapeutic) effect, i.e. efficacy, of the substance to be studied can be demonstrated.

Various classification systems by means of which illness-relevant states can routinely be defined are already in existence. The best-known of these are the WHO's »International Classification of Diseases and Related Health Problems« (present revision: ICD-10) and the more specific »Diagnostic and Statistical Manual of Mental Disorders« (present edition: DSM-IV) (DIMDI 2010), a classification of mental disorders that is likewise relevant to the subject of mental performance enhancement. These classification systems are based to a large extent on a syndrome-based approach in which illnesses are described as syndromes on the basis of various signs and symptoms, i.e. are defined on the basis of the simultaneous presence of certain signs and symptoms at a certain level of intensity.

SYNDROME-BASED APPROACH TO DESCRIBING DISEASES, E.G. »MILD COGNITIVE DISORDER« (ICD-10: F06.7)

Mild cognitive disorders are characterized by memory disturbance, learning difficulty, and a reduced ability to concentrate on a task for an extended period. There is often a feeling of mental fatigue when attempting to solve problems. Learning that is objectively successful is experienced subjectively as

> difficult. None of these signs or symptoms is so severe as to justify a diagnosis of dementia (F00–F03) or delirium (F05). The diagnosis should be made only in association with a physical illness and should not be made in the presence of another mental or behavioral disturbance.

The number of signs and symptoms on the basis of which diseases can be defined and thus also diagnosed is constantly increasing, especially in the field of mental illness (not least because of the ever-increasing range of diagnostic possibilities). Impairments or declines in various mental ability dimensions (cognitive abilities such as intellect, memory, speech functions, and also social and emotional abilities) are recognized as symptoms of a variety of diseases (ICD-10: categories F00–99). Restlessness and agitation (R45.1), unhappiness (R45.2), and hostility (R45.5) are now also recognized in ICD-10 as symptoms that influence mood. Ever more diagnostic procedures with specific scales for measuring the severity of classified symptoms are being developed.

As a disease is defined by the simultaneous presence of a number of signs or symptoms at a given intensity, the sort of expansion of symptoms referred to above is not necessarily accompanied by an expansion of the definition of the disease concerned. However, the drawing of ever finer distinctions between individual signs and symptoms is making it possible to describe and quantify conditions that are not in themselves regarded as diseases, and any defined sign or symptom that constitutes one aspect of a disease can form the basis for the definition of a criterion of benefit. As the extent of a deficit is not yet regarded as a decision criterion, efficacy of a substance can be established even with very minor deficits.

The principle that a benefit can be established only on the basis of an initial deficit is being increasingly eroded. A benefit can also be defined as, for example, a reduction in an increased risk of developing a disease or dying (e.g. in the case of substances used for preventive purposes, such as antihypertensives, hormone replacement agents, and contraceptives). Though Directive 2001/20/EC still refers explicitly to a therapeutic benefit, even the present wording does not exclude the possibility of non-therapeutically oriented research.

The fact that medical research on human subjects and the clinical trials of pharmacologically active substances that are performed in connection with this research require approval and that independent ethics committees grant this approval on the basis of a case-specific benefit-risk analysis should constitute a certain obstacle to specific research on enhancement properties of pharmacologically active substances. However, this obstacle is by no means insurmountable, since the definition of a benefit can be construed and interpreted very broadly. Especially in the case of novel substances, assessment of risks is difficult in the absence of information derived from actual use. In the case of applications to

expand the range of indications for use of a drug, on the other hand, certain risk profiles (e.g. adverse effects including rare effects and effects that are observable only over prolonged periods) are more easily ascertained.

CLINICAL TESTING OF MEDICINES: STUDIES AND REGISTRATION OF STUDIES

Medicinal products are tested by means of clinical trials (i.e. research conducted on human beings) over a number of phases following successful completion of the preclinical phase. In each case successful completion of one phase is a precondition for progression to the next phase.

- Phase I: In a small group of study participants (generally 20 to 50 healthy volunteers or else patients for whose disease there is as yet no treatment) the tolerability and safety, in particular, along with the pharmacokinetics and pharmacodynamics (absorption, distribution, and metabolic breakdown processes) of the substance are investigated. Phase I studies generally last a few weeks to a few months.
- Phase II: In a larger group of study participants (about 50 to 200 patients) the therapeutic concept is tested (phase IIa) and an appropriate therapeutic dose is determined (phase IIb). Positive therapeutic effects should be observable at this stage. Phase II studies generally last a few months.
- Phase III: In a large group of patients (from 100 up to several thousand) statistically significant efficacy has to be demonstrated. To this end the study participants are generally divided into two groups, of which one receives the new treatment and the other receives a different drug or a placebo (sham medicine). Phase III studies generally last a few months to several years. If they are completed successfully, marketing authorization can be granted.
- Phase IIIb or IV: Even after marketing authorization is granted medicines continue to be monitored, firstly in order to further improve treatment and secondly in order to identify long-term sequelae and very rare risks about which no epidemiological assertions can be made on the basis of the marketing authorization studies. Studies in which therapeutic assertions are to be tested and treatment is therefore specified in advance are referred to as interventional studies. Studies that do not interfere with, but merely observe and document, therapeutic use of a drug in patients by doctors are referred to as noninterventional studies. These are not classified as clinical studies. They can be imposed as a condition of the granting of marketing authorization. Studies of this kind require large groups of patients (generally several thousand) and generally extend over several years.

REGISTERS OF ONGOING CLINICAL TRIALS

- *EudraCT* (European Medicines Agency, EMA): This register was set up in 2004, since which time all clinical drug trials planned to be performed in Europe must be entered in it before being initiated. The data that it contains are confidential and are accessible only to national and European regulatory authorities, i.e. not to ethics committees, scientists, doctors, or the public.
- *ClinicalTrials.gov* (US National Library of Medicine, NLM): Since 2008 all clinical trials performed in the USA have had to be registered and published. Applications for regulatory approval of medicines in the USA must be based only on studies that are listed in this register (in all clinical phases). This is one of the largest international registers of clinical trials that is accessible to the public.
- Other internet-based clinical trial registers that are accessible to the public at no cost have been established in the United Kingdom (www.controlled-trials.com) and Japan (www.clinicaltrials.jp).
- The *IFPMA Clinical Trials Portal* (www.ifpma.org/clinicaltrials) is a search portal for industry-sponsored clinical trials that was set up by an international federation of 25 pharmaceutical manufacturers and 46 national and regional associations of the pharmaceutical industry. Since 2005 it has also been available in German.

All clinical or interventional studies require official approval (obtained via a »clinical trial application«). This is granted only if the study concerned and its specific planning, including a predefined criterion of benefit and the study design, are registered and have been approved by the responsible ethics committee. Some years ago initiatives were taken at both the national and the international levels to set up clinical trial registers to provide formal information on ongoing research activities (though in most cases not on study results) (see box). Studies that were already in progress were not included.

In 2010, in addition to the obligation to register clinical trials, the members of the Association of Research-Based Pharmaceutical Companies in Germany (*Verband der forschenden Arzneimittelhersteller in Deutschland*, vfa) undertook to list their studies in the ClinicalTrials.gov register (vfa 2010). This ensures disclosure of the planning of current pharmacological research activities to be conducted in either Europe or North America in connection with a clinical trial application.

At present, disclosure and publication of study results are required only after completion of the regulatory approval process. Earlier publication is at the discretion of the study sponsor.

MEDICINAL PRODUCT LICENSING

The present requirements for the licensing of medicinal products form a major obstacle to more widespread use of pharmacologically active substances for performance enhancement in healthy individuals. The evaluation procedure that has been employed up to now demands proof of therapeutic efficacy as a basis for defining a benefit against which identifiable health risks are weighed. This rules out the possibility of licensing a substance exclusively for enhancement purposes.

A product license is not granted, for example, if the therapeutic efficacy claimed by the applicant is absent (or insufficiently substantiated) or if the benefit-risk relationship is unfavorable (§ 25 Subsection 2 Art. 4 and 5 AMG). Regulatory authorities[36] assess the submitted documentation (of clinical trials up to phase III). A license is granted for the placing on the market and use of the product in the medical indication for which efficacy of the substance has been demonstrated provided that manufacture in accordance with stipulated safety and quality standards can be ensured. The authorities have some leeway with regard to marketability, which they can determine on an individual substance basis when granting product licenses. Novel substances are generally licensed for prescription-only use in their first five years on the market (Section III.3.3).

Evaluation of a nontherapeutic and not concretely preventive benefit would require the development of new procedures. A conceptual basis for these could be provided by the requirement of food law that health-related claims be substantiated (Section III.2).

Though proof of efficacy in a single illness-relevant state is sufficient for regulatory approval of a medicine, almost all medicines can be used in more than one medical indication or clinical situation. The pharmacological profile and range of potential uses of a substance often become apparent only in clinical practice. Where appropriate, the manufacturer can selectively broaden the range of uses of a substance and thereby improve its marketing opportunities. The extension of indications that is required for this purpose likewise requires regulatory approval and brings with it a corresponding extension of liability.

PUBLICATION OF RESULTS AFTER REGULATORY APPROVAL

After regulatory approval has been granted the results of studies are published in a variety of formats.

36 Germany: Federal Institute for Drugs and Medical Devices (*Bundesinstitut für Arzneimittel und Medizinprodukte*, BfArM) and Paul Ehrlich Institute (PEI); EU: European Medicines Agency (EMA); USA: Food and Drug Administration (FDA)

REGISTERS OF CLINICAL TRIAL RESULTS

- *European Public Assessment Reports (EPARs)*: Since 1995 the EMA has published reports that summarize the results of studies performed with medicines that are approved for use throughout the EU. In the future, EudraCT entries (see previous box) made in connection with marketing authorization are to be expanded to include study results and are to be made publicly available before the granting of marketing authorization.
- *clinicaltrialresults.com (NLM)*: The study results required for regulatory approval of medicines in the USA are published and linked to the ClinicalTrials.gov study register (see above).
- *German Clinical Trials Register (Deutsches Register Klinischer Studien, DRKS)*: The DRKS is one of the ten primary registers to be recognized by the WHO. Information on ongoing or completed clinical trials in Germany can be entered in it on a voluntary basis. The register is freely accessible to the public at no cost. As well as drug trials, it includes studies on medical devices and nonpharmacological procedures.
- Another publicly accessible register exists in Japan (www.clinicaltrials.jp).

The European and international associations of pharmaceutical manufacturers have undertaken to publish online (via registers) all results of all phase III studies in accordance with the study plans concerned (vfa 2010). There is no explicit undertaking to publish the results of studies of earlier phases. The vfa suggests that publication in more than one register (e.g. European and various national registers) would be costlier and likely to lead to confusion rather than transparency; it therefore favors central international publication. The associations of pharmaceutical manufacturers have also declared their intention of taking active measures to have study results published in scientific journals (vfa 2010) (Section III.3.4).

SYSTEMATIC MONITORING OF RISKS

Even after being approved for use in a specific medical indication, medicines are subject to continuous and systematic monitoring of their benefits and risks. Where this suggests a possible change in the benefit-risk relationship of a drug, this relationship may need to be reassessed and the marketing authorization accordingly modified, made subject to restrictions, or even revoked (cf. amphetamines, modafinil; Section II.3.1).

This risk monitoring occurs via continuous documentation of all adverse drug reactions (ADRs) considered to be probably related to use of a drug. An ADR is a harmful and unintended reaction to a substance that can occur not only in association with correct use, but also as a result of interactions, overdosage, or

abuse, of the substance. This definition permits documentation of all harmful effects arising in connection with either correct or incorrect use of a substance. Manufacturers are generally required to report ADRs (Directive 2001/83/EC, § 63b AMG). In Germany reports are forwarded either directly or via a graduated pharmacovigilance plan to the responsible federal authority (BfArM), which monitors risks centrally (§§ 62 and 63 AMG) and takes measures as appropriate.

Many postmarketing observations of ADRs are made in the context of noninterventional studies such as postmarketing surveillance studies, in which medicines may be used only in their approved indication (§ 4 Subsection 23 Sentence 3 AMG). In the case of new substances the performance of such studies is often imposed as a condition of marketing authorization. Along with systematic risk monitoring, which provides empirical information especially on the frequency of ADRs, including rare ADRs, certain questions relating to substance efficacy may also be investigated. Though recommendations exist on how such studies should be performed (BfArM 2010), the specific requirements that apply to clinical trials (§§ 40 to 42 AMG) do not apply to such studies (e.g. certain requirements that the object of the investigation be approved are inapplicable, and in many cases reporting obligations extend »only« to ADRs). It is unclear to what extent postmarketing surveillance studies can, at least indirectly, provide information about enhancement properties of presently approved medicines.

Via »spontaneous« reporting systems, doctors and pharmacists are also supposed to play a role in continuous monitoring of the risks of medicines. In Germany this role (with the exception of the obligation to report reactions to vaccines) is not prescribed by law, however as part of their professional self-regulation (codes of professional conduct) German doctors and pharmacists have undertaken to report suspected ADRs via the reporting systems of their respective drug commissions.

To date, however, this spontaneous reporting system has functioned at best as a supplement to the systematic documentation of ADRs. Thus, of the 34,170 suspected ADRs that were reported to the BfArM in the period from January 1 to September 30, 2009, almost 85% were reported by pharmaceutical companies, whereas only 3.7% were reported via the Drug Commission of the German Medical Association (*Arzneimittelkommission der deutschen Ärzteschaft*) and only 3% were reported via the Drug Commission of German Pharmacists (*Arzneimittelkommission der deutschen Apotheker*) (Zagermann-Muncke et al. 2010). The causes of this unbalanced reporting situation are the subject of much conjecture but little certainty. It seems at the very least improbable that the ADRs that are required to be reported in connection with the marketing authorization procedure and postmarketing surveillance (phase I to IV studies) should occur at such a lower rate in association with everyday medical use.

Even advocates of a liberal approach to enhancement agents favor systematic monitoring or even obligatory reporting of ADRs. For example, Galert et al. (2009, p. 47) recommend that »In order for such a system to function reliably, doctors would need to document all symptoms occurring in association with the consumption of an NEP [neuroenhancement product] and forward this information to a pharmacovigilance center in standardized form. For this reason these NEPs should remain prescription products for at least a few years after being approved for use.« A precondition for the success of such a system, however, would be a willingness on the part of doctors and pharmacists to play their assigned role in it (in this regard see also Section V.2.3). Experience with the present reporting system for ADRs suggests that such willingness may be limited.

EXTENSIONS OF INDICATIONS

An extension of indications can be applied for at the manufacturer's own initiative. This sets off a new round of clinical investigation (approval and performance of studies, application for marketing authorization). Alternatively, the manufacturer can leave it to »the market« to identify new possibilities for use. The manufacturer bears no responsibility or liability for such »off-label« use, i.e. use outside of the approved indications. In the case of prescription medicines this responsibility lies with the prescribing doctor, while in the case of over-the-counter medicines it lies primarily with the user and secondarily with the pharmacist.

There are a number of ways in which doctors can extend knowledge of the effects of pharmacological substances. For one thing, they can perform studies required for regulatory approval. For another, their freedom to treat as they see fit allows them to carry out »therapeutic trials« in which they – taking into account the present state of scientific knowledge and with the informed consent of the individual patient – can prescribe medicines outside of their approved indications in cases in which no approved medicine is available for a particular disease. As the possibilities for supervising such therapeutic trials are limited, information about possible enhancement properties of medicines could be obtained in this way outside of the clinical research setting (for more detail of the role of doctors in this regard, see Section III.3.5.2).

As a result of the stricter obligations now being imposed in clinical trial applications to disclose all results of clinical trials, more information about the effects of substances is likely to be available to the public in the future. One consequence of this is that such study results will be more easily extrapolatable to other contexts. For example, the finding that a certain substance had a performance-enhancing effect in therapeutic use could potentially be extrapolated to

population groups with a smaller, or with no, baseline deficit. In such a context doctors' freedom to treat as they see fit, in combination with the near impossibility of policing observance of restrictions (e.g. in terms of off-label use), could foster developments in the field of enhancement.

EFFECTS OF THE PROHIBITION OF DOPING ON PHARMACEUTICAL RESEARCH

The AMG's prohibition of doping (§ 6a AMG) encompasses the placing on the market, prescription, or administration to others, as well as the possession of appreciable amounts, of medicinal products included in the WADA Prohibited List (WADA 2011) (as per the appendices to the AMG). The prohibition does not explicitly extend to use for research purposes. Nevertheless, it is difficult to imagine that an ethics committee or a responsible authority would recognize and approve a physical performance-enhancing action of a pharmacological substance in the absence of an illness-relevant state as a »benefit dimension«, therefore in practice any direct research of this kind would scarcely be possible within the framework of the existing standards. Any such drug research would thus be at best barely legal or else completely illegal. At present a very conservative approach is apparent even with regard to incidental conclusions arising from illness-related studies, e.g. on muscle diseases. As a result, claims of enhancement of physical performance dimensions in healthy individuals can scarcely be scientifically justified on the basis of medically recognized procedures and generally remain within the realm of neither provable nor disprovable conjecture.[37]

THE PRESENT STATUS OF RESEARCH INTO PERFORMANCE-ENHANCING EFFECTS

Most of the studies on performance-enhancing effects of medicines referred to in Section II.3 explicitly state that they were officially approved and were performed in accordance with the ethical standards of the Declaration of Helsinki. The benefit criterion was defined in the context of the treatment of disorders of the wakefulness-sleep cycle (e.g. Wesensten et al. 2005), age-related cognitive deterioration (e.g. Yesavage et al. 2002), early or even prophylactic treatment of dementia (e.g. Gron et al. 2005; Mumenthaler et al. 2003), or neurological diseases such as Parkinson's disease or stroke (e.g. Apud et al. 2007; Beglinger et al. 2005; Elliott et al. 1997; Flöel et al. 2008a and b; Knecht et al. 2004). In addition to results obtained using this definition of therapeutic benefit, a very small number of pub-

37 An exception to this was the state-sponsored doping research carried out in the German Democratic Republic in the 1970s and 1980s. Though because of the official ban on doping this always remained covert, it was practiced systematically.

lished studies have measured enhancement potential directly in healthy subjects. For example, a working group from the University of Münster reported that in addition to benefiting stroke patients, a form of direct current therapy developed by them can also help healthy individuals to learn new languages (Flöel et al. 2008a; p. 1415), and a working group from the University of Ulm published the results of a study performed explicitly in order to investigate the enhancement potential of donepezil in healthy young adults (Gron et al. 2005).

Compared to the subject of possible physical performance enhancement in healthy individuals, the subject of mental performance components shows differences in terms both of knowledge acquisition and of how this knowledge and the subject itself are dealt with. A topical example of this is a randomized, placebo-controlled, double-blind phase I study being performed in healthy volunteers at University Medical Center Mainz on the question »Is brain doping possible in competitive chess?«[38]. Similarly direct work on »physical doping« is almost inconceivable at present. The present conservative approach to knowledge about physical performance enhancement in healthy individuals is a result of decades of debate about doping (Section VI). In the event that a different approach is adopted to enhancement of mental performance dimensions in healthy individuals, relevant sociological justifications and valid proof of benefits will need to be found (Section V).

MARKETABILITY 3.3

Even after authorization for use of a drug in a particular indication in Germany has been granted, marketability of the drug is restricted. Since it cannot simply be assumed that users will – in order to obtain a therapeutic benefit at an acceptable risk – use medicinal products in accordance with instructions and since incorrect use can be harmful to health, access to medicinal products is regulated via authorized structures as part of a precautionary approach to health protection. Individual drug categories are subject to staggered safety regulations as outlined below:

› *Over-the-counter medicines* (e.g. high-dose plant extracts such as ginkgo extract that are no longer classified as foods) may be supplied also by stores other than pharmacies, since no additional guidance as to their use is required (§ 44 AMG, AMVerkRV[39]). They may be supplied by drugstores and other retail outlets provided that the sales staff of these possess an appropriate certificate of competence (Bless et al. 2010, p. 34). There are no specific re-

38 www.schachbund.de/news/data/files/Schachstudie_Hirndoping.pdf, 20/12/2010

39 *Verordnung über apothekenpflichtige und freiverkäufliche Arzneimittel* (ordinance on pharmacy-only and over-the-counter medicines)

strictions on advertising. The risk of partial use beyond the authorized therapeutic purposes does not constitute a criterion for exclusion from marketing clearance (§ 5 AMVerkRV).

- *Pharmacy-only medicines*: Sale of this category of medicines is restricted to pharmacies (§ 43 AMG):
  - *Nonprescription medicines* (e.g. mild analgesics) may be sold freely to end-users only in pharmacies. Advertising is permitted.
  - *Prescription medicines* may be dispensed only in pharmacies and only on the basis of a medical prescription (§ 48 AMG, AMVV[40]). Product advertising may not be directed at consumers, but may be directed at doctors and pharmacists.

Trade in narcotics is subject to additional safety and regulatory structures intended to ensure correct use and to exclude the possibility of manufacture for the purpose of abuse and the development or continuation of addiction (§ 5 Subsection 6 BtMG). The marketability of narcotics is more severely restricted than that of medicines. Particular care is taken to prevent overproduction and to prevent unauthorized persons from gaining access to narcotics. Narcotics are subdivided into the following categories:

- *Narcotics that may be marketed and prescribed* (Annex III BtMG): Stocks and whereabouts must be documented and use must be justified in the medical prescription. Prescribing information is available only to health professionals and advertising is restricted to this group of people.
- *Narcotics that may be marketed but not prescribed* (Annex II BtMG, in particular intermediate products, not to be dispensed to end-users).
- *Narcotics that may not be marketed* (Annex I BtMG, in particular psychotropic substances with a high addiction potential, sometimes also referred to as illegal drugs).

Unauthorized manufacture, unauthorized trade, unauthorized prescription – all that is permitted is justified use where the objective of use cannot be achieved by other means –, and possession of narcotics are all criminal offenses.41 Where they pose a high risk to health, even medicines without any narcotic effect on the organism may be made subject to additional marketing restrictions. Specific details are given in the marketing authorization of individual medicines. Presently approved pharmacological substances that have been linked to enhanced mental performance in healthy individuals (Section II.3) are represented in all the subcategories listed above. Substances that can enhance physical performance di-

40 *Verordnung über die Verschreibungspflicht von Arzneimitteln (Arzneimittelverschreibungsverordnung)* (ordinance on prescription medicines)

41 Since 1992 prosecution has been optional if the offender's degree of guilt can be regarded as small (for example, if personal use only can be assumed on the basis of the amount) or if no public interest would be served by criminal prosecution (§ 31a BtMG).

mensions in healthy individuals are regarded as potential doping substances for the purpose of their marketability.

MARKETABILITY AND THE PROHIBITION OF DOPING

Results achieved in a variety of sports especially in the 1960s and 1970s can be taken as proof that it is possible to enhance individual dimensions of physical performance in healthy individuals by pharmacological means (in particular by use of anabolic steroids) (Singler/Treutlein 2006, pp. 149ff.). Without any detailed clinical research having been conducted beforehand and in the virtual absence of any social or regulatory obstacles, such substances rapidly found their way to those individuals who could profit most from physical performance enhancement. Both in Germany and in other countries, the ensuing public debate was lively and eventful (Section VI.1). As things stand at present, the outcome of this debate about the use of medicinal agents to enhance physical performance was a high degree of rejection on the part of society.

There is a broad social and political consensus that the use of medicines to enhance performance in sport, i.e. doping, should at the very least be kept in check by means of a variety of measures. Independently of the classification of individual pharmacological agents as prescription-only or over-the-counter, use of such substances for doping purposes is expressly prohibited in Germany as per § 6a Subsection 1 AMG: »The placing on the market, prescribing, or administering of medicinal products to others for the purpose of doping in sport is prohibited.« Similarly, possession of appreciable amounts is prohibited as per § 6a Subsection 2a AMG. Pivotal to this severe restriction of marketability is the purpose of use of a substance. In the 1998 explanatory memorandum to the AMG it is emphasized that the purpose of the prohibition is to protect health, not to ensure fairness – for which sports bodies are responsible – and that the term »sport« explicitly covers recreational sport. Also as far back as 1998 the legislator made it clear that nontherapeutic use of medicines for purposes other than sporting activity, e.g. use by school students prior to examinations, is not covered by the prohibition (Bundesregierung 1998, p. 13). The substances covered by the prohibition of doping are specified in a list of substances and methods which because of their potential for enhancing performance are prohibited as doping agents. The classification of these substances is authoritative and cannot be challenged on the basis that a particular substance or method does not have the potential to enhance performance or does not pose a risk to health (NADA 2009, pp. 9–10). The list is compiled and continuously updated by the World Anti-Doping Agency (WADA 2011) and is regularly and promptly incorporated into German law. Most of the substances included in the list have prescription-only status in Germany.

The public debate that has taken place in Germany over the past few years has centered above all on the scope of the prohibition (how the word »sport« should be interpreted), the possibilities and limits of further restrictions on marketability (e.g. classification of a substance as a narcotic), and imposition of more severe penalties for violations. At present, calls for doping to be legalized are mostly emphatically rejected for reasons of sports and medical ethics as well as on the basis of political considerations (Gerlinger et al. 2008, pp. 109–110.; TAB 2008b, pp. 106–107).

PROVISION OF INFORMATION AND ADVERTISING 3.4

Knowledge of the actions of medicines is nowadays acquired via controlled studies, in the first instance under laboratory conditions. The sponsor or director of a study bears responsibility for performing the study, documents the progress of the study, and evaluates the results. The knowledge thus obtained (primary information) is protected by copyright. On the basis of this primary information, indication-specific benefits and risks are estimated and marketing authorization may be granted (Section III.3.2). As part of the marketing authorization process, the items of information on the drug in question that are deemed to be necessary are checked for correctness and certain important items of information are published in registers of study results.

The sponsor or other person responsible for the study makes decisions about any use of the study results that goes beyond what is strictly necessary. The study results are compiled, summarized, and presented and published in target group-specific fashion in accordance with the marketing strategy being adopted for the particular drug. The information issued ranges from essential and obligatory information through publications in scientific journals to demonstrably interest-driven advertising claims.

Sometimes it can be difficult to distinguish unbiased information from interest-driven information or advertising material, since the accusation that information is interest-driven and by implication not based on disinterested analysis can be leveled at many players and is very difficult to refute. Independently of the difficulty of drawing a clear distinction between information and advertising, the imparting of knowledge about medicines is subject to two normative limitations. Firstly, the AMG stipulates minimum standards for the information considered to be necessary. It lays down the basic framework for the transmission of information in order to ensure that health professionals (doctors and pharmacists), as well as users, are provided with information that is as unbiased as possible and on the basis of which they can weigh benefits against risks in the individual case and indication (Bless et al. 2010, p. 51). Secondly, claims about medicines that go beyond what is strictly necessary are restricted by the Drug Advertising Act

(Heilmittelwerbegesetz, HWG), e.g. in general a manufacturer may provide information only on drug properties that are relevant to the approved indication (i.e. statements about off-label use are impermissible).

Within this normative framework various different categories of information recipients and transmitters are distinguished:

- *Regulatory and supervisory authorities*: In their role as expert panels, these bodies make determinations on clinical trial applications (and maintain registers of these independently of trial progress and results), make determinations on marketing authorization applications for medicinal products (i.e. they receive all marketing authorization-relevant information), and arrange for long-term surveillance studies to be performed (and maintain registers of these). They thus have access to all the data relevant to marketing authorization and, while observing data protection requirements, act as unbiased imparters of information, e.g. by approving required informational texts (patient information leaflet [PIL], summary of product characteristics [SPC], public assessment reports). They also have obligations to supply information to the public (§ 34 AMG).
- *Autonomous organs of the statutory health insurance (SHI) scheme*: These too have the status of expert panels with certain obligations to inform (e.g. the Federal Joint Committee [*Gemeinsamer Bundesausschuss*, G-BA] is the highest-ranking expert panel of this type). These bodies have no access to marketing authorization documents. Where they wish to perform benefit assessments of their own, they have to ask the manufacturers concerned to supply information. They decide whether particular forms of treatment are to be included in, or removed from, the SHI benefits catalog.
- *Doctors and pharmacists*: In accordance with their professional ethos, doctors and pharmacists are assumed to possess detailed technical knowledge and to use this knowledge to the benefit of their patients' health. They are expected to undertake continuous further training and to inform and advise their patients. To this end they have access to various publicly available sources of information. They are not subject to the HWG's prohibitions of advertising.
- *Medicinal product users/patients*: This group generally has a high expectation of benefit from consumption of medicinal products but cannot be assumed to possess any specific technical knowledge. It is assumed that they obtain individual drug-relevant information primarily from doctors and pharmacists. The German federal drug regulatory authority (BfArM) is also obliged to provide this group with certain information. Direct communication between drug manufacturers and this group is meant to be prevented, or at least restricted, by means of various barriers. Major potential areas for improvement in the information provided for patients are commonly identified, e.g. in the comprehensibility of PILs to the general public (Bahr 2010).

OBLIGATORY INFORMATION

A basic distinction must be drawn between study directors' and sponsors' obligations to provide information to regulatory and supervisory authorities during the clinical research phase and the obligation to provide information to doctors, pharmacists, and consumers after marketing authorization has been granted (Bless et al. 2010, pp. 51ff.). Supervisory and regulatory authorities also have extensive access to unpublished clinical trial data. The granting of marketing authorization for a medicinal product imposes an obligation to provide a range of information on the effects of the drug demonstrated under laboratory conditions. The obligatory information to be provided by the manufacturer consists of the PIL, i.e. user information, which is directed at the consumer (§ 11 AMG), and the SPC, which is directed at health professionals (§ 11a AMG). The wording of these texts is checked and approved as part of the marketing authorization procedure.

The PIL contains precisely defined and standardized information on, among other things, designation of active ingredients, substance characteristics, effects, side effects, interactions, contraindications, dosage, duration of administration, and approved indications for use (§ 11 AMG). Medicinal products may not be placed on the market without a PIL. This is to ensure that even untrained users are provided with essential information on the medicine that they have just acquired. The manufacturer is responsible for the wording of the PIL and for ensuring that the PIL is supplied with the medicinal product. The information provided must not be promotional in nature.

The wording of PILs always results from the attempt to strike a balance between providing a description that is short and comprehensible to the general public while at the same time being as informative as possible – and thereby reducing the manufacturer's legal liability risk. PILs are often said to be too long, difficult to read, and incomprehensible and therefore unable to fulfill their role of protecting the public (Nink/Schröder 2005, pp. 16ff.).

SPCs are intended to provide specific information to health professionals and consequently are not required to be comprehensible to the general public. Pharmaceutical manufacturers must supply SPCs to doctors and pharmacists on request (§ 11a AMG). Germany's best-known compendium of SPCs is the »Rote Liste«(see box).

DRUG INFORMATION SYSTEMS

› *Rote Liste*: This drug compendium is produced and continuously updated by the pharmaceutical industry. It has been published annually in print since 1933 and biannually online since 1990. It contains brief information drawn from PILs and SPCs on medicinal products and certain medical de-

vices for which marketing authorization exists in Germany. The 2010 edition contains 8500 product entries referring to about 10,500 individual formulations. Via the issue of data licenses, *Rote Liste* has now also been incorporated into various databases. Access is available free to health professionals and at a fee to the public.

- *PharmNet.Bund* is a cooperative project of the German regulatory authorities –namely the BfArM, the Paul Ehrlich Institute (PEI), and the Federal Office of Consumer Protection and Food Safety (*Bundesamt für Verbraucherschutz und Lebensmittelsicherheit,* BVL) – together with the Robert Koch Institute (RKI) and the German Institute of Medical Documentation and Information (*Deutsches Institut für medizinische Dokumentation und Information*, DIMDI), which is run in close cooperation with the drug regulatory authorities of the German federal states coordinated by the Central Authority of the Federal States for Health Protection with regard to Medicinal Products and Medical Devices (*Zentralstelle der Länder für Gesundheitsschutz bei Arzneimitteln und Medizinprodukten*, ZLG). This German-language system, which has been available since 2007, aims to make current versions of PILs and SPCs, as well as public assessment reports, available to the general public at no charge.
- *EudraPharm.eu* is a database operated by the EMA that provides product information texts (PILs and SPCs) on medicinal products approved in the EU via the centralized procedure. It is freely accessible to the public, though so far mostly only in English. According to the web page the database is to be made available in all EU languages.

Not only pharmaceutical companies, but also drug regulatory and supervisory authorities, are required by the AMG to provide certain information about medicines. § 34 Subsection 1a AMG requires these authorities to inform the public of the granting or modification of marketing authorization and to provide SPCs and brief assessment reports with conclusions about important study results and the authority's justification for granting marketing authorization (at least in the case of marketing authorizations granted since 2006). The assessment reports issued by these authorities in connection with the granting of marketing authorization likewise consist of a general part worded so as to be comprehensible to the general public and a more detailed scientific part. In order to facilitate the obligatory provision of information by these authorities, specific drug information systems (see box) have been developed in addition to study registers.

Most of the PIL and SPC texts for the pharmacological substances referred to in Section II.3 (other than the substance amphetamine, which may not be marketed in Germany) are freely available via the PharmNet.Bund drug information portal (www.pharmnet-bund.de). As yet, however, very few of the »öffentliche Beurteilungsberichte« (public assessment reports associated with marketing authoriza-

tion) or the »Public Assessment Reports« (reports arising from the increasingly important benefit assessment undertaken in the context of the primary healthcare market; Section III.3.6) that are likewise stated on the PharmNet.Bund user interface to be available on the website are in fact available, notwithstanding the fact that the BfArM is legally obliged to make them available (§ 34 AMG). Only one Public Assessment Report (active agent: modafinil) on any of the medicines referred to in Section II.3.1 was found to be available on the website. At present the European database EudraPharm.eu contains very little information – and that only in English – on the substances referred to in Section II.3.1. Bless et al. (2010, p. 53) point out in this regard that although unbiased information about medicines is available to the German public, the full potential of the information provided cannot be realized at present because of the still fragmentary nature of the available data (notwithstanding the legal obligation for the data to be made available in full) and a lack of public awareness.

The autonomous organs of the SHI scheme also have specific obligations to provide information to SHI-accredited doctors (§ 73 Subsection 8 SGB V[42]). This obligation applies to both medical and economic aspects of therapeutic services. The National Association of Statutory Health Insurance Physicians (*Kassenärztliche Bundesvereinigung*, KBV) claims that it meets its responsibility in this regard by publishing »Wirkstoff AKTUELL«[43]. In this way information about medicines is made available, albeit in very condensed form, also to the general public. However, the amount of information supplied is very small in relation to the number of medicinal products available on the market (Bless et al. 2010, pp. 65–66). According to Bless et al. (2010, p. 66) the range of information provided at present by the autonomous organs of the SHI scheme is insufficient to act as an effective counterweight, especially in relation to the informational and promotional material published by the pharmaceutical industry.

The obligatory information on medicinal products referred to above is limited to scientifically proven effects in an approved medical indication. It therefore does not include claims about performance-enhancing properties of pharmacological substances in healthy individuals. Since 2007 medicinal products that contain substances included in the WADA Prohibited List have had to be explicitly labeled as such. This obligation to label or inform had long been a subject of debate in Germany, firstly because this dimension of drug action is not scientifically investigated whereas only scientifically substantiated information may be included in the obligatory informational texts (§ 11 AMG), and secondly on the basis of the principle that doping should not be encouraged in any way.

42 *Sozialgesetzbuch V* (German Social Code)
43 www.kbv.de/ais/12905.html, retrieved on 10/05/2010

Doctors and pharmacists also have extensive obligations to provide consumers with advice and information (Section III.3.5). They can supplement their existing scientific knowledge by obtaining additional information about the dimensions of action of medicines from the obligatory informational texts referred to above and from a multiplicity of scientific bodies and other secondary sources.

OTHER SOURCES OF INFORMATION ON THE EFFECTS OF MEDICINES

In addition to the information prescribed by law, other information on the dimensions of action of medicines can be imparted and obtained via a variety of publications and special events, each of which has its own quality control procedures. To cite just a few examples, information can arise from marketing authorization studies, be based on other types of research (e.g. publicly funded or third-party-funded research), be obtained via postmarketing surveillance studies, contain meta-analyses of a number of studies, or consist of opinions expressed in surveys. In contrast to the full disclosure of study results to the responsible authorities that is required for the granting of marketing authorization, in scientific journals and at specialist conferences study results are published in highly condensed form.

The vast majority of medical journals apply their own quality assurance procedure (known as »peer review«) to individual contributions. The primary purpose of this is to ensure compliance with scientific standards (e.g. ethical standards in clinical research, replicability of results, unbiased presentation of results, correct citation of sources). Scientific journals decide for themselves whether individual articles submitted to them are suitable for publication. It is unclear to what extent these decisions are governed by explicit rules to the effect that articles dealing with certain topics (e.g. the doping potential of pharmacological substances in healthy individuals) should be rejected on ethical grounds.

Because of the great diversity of scientific publications, a number of different bibliographic database systems have been set up to facilitate searches for specific topics in medical publications (see box).

For their systematic review of the literature on possible neuroenhancement properties of pharmacological substances, Repantis/Heuser (2008, p. 5) used both EMBASE and MEDLINE. This means that the articles cited in Section II.3 underwent the peer review process of the journals in which they were published. Findings on the possible enhancement potential of pharmacological substances, including in healthy individuals, can be published in scientific journals and consequently can be accessed via various scientific databases (e.g. Repantis et al. 2009, 2010a and b).

WELL-KNOWN DATABASES OF BIOMEDICAL LITERATURE (SELECTION)

- *EMBASE (Excerpta Medica Database)*: A bibliographic database produced by the scientific publishing company Elsevier that covers human medicine and related subjects and has a European focus. It contains records to more than 25 million articles published since 1947 in about 7000 biomedical journals (including those also included in MEDLINE, see below) from 70 countries. Bibliographic data and abstracts are searchable (in about 80% of cases), whereas full articles are not searchable but can be accessed to some extent via links.
- *MEDLINE (Medical Literature Analysis and Retrieval System Online)*: The first bibliographic database to be produced by the US National Library of Medicine (NLM). It contains records to about 18 million articles published since 1950 in about 5400 biomedical journals. Bibliographic data and abstracts are searchable (in about 76% of cases), as are separately indexed keywords. MEDLINE is now the largest component of PubMed, a more recently produced metadatabase.
- *PubMed*: A metadatabase with records to articles published in about 5500 biomedical journals. PubMed has broader functionality than MEDLINE, documents medical articles (e.g. citations), and includes links to fulltext journals. PubMed uses some search tools of its own.

The situation with regard to advanced training and higher education resembles that with regard to publication in that in both cases information is systematically gathered and summarized. A large number of scientific congresses and specialized educational events are held. The extent to which the subject of neuroenhancement can or does form a subtext to, or can be or is deliberately brought up and pursued at, such events is extremely difficult to assess in any systematic way.

Since health and other professionals are presumed to possess subject-specific knowledge, they are not subject to any explicit prohibition of advertising. As a result, medicinal products may be directly promoted in biomedical journals and at biomedical events. This makes it possible for manufacturers to blend unbiased product information with interest-driven claims in order to create demand for a product.

ADVERTISING

European medicinal products legislation (Directive 2001/83/EC) and the German Drug Advertising Act (*Heilmittelwerbegesetz*, HWG) are aimed at limiting the extent to which demand for medicinal products can be created by advertising (Bless et al. 2010, pp. 54ff.). One important element in this regard is subdivision of recipients of advertising claims into health professionals and members of the

general public. The objective of regulations is to ensure that the decision to use a certain medicine is taken by the doctor alone on the basis of medical considerations and is uninfluenced by any advertising-induced demand on the part of the patient. This type of regulation aims to protect people whose condition makes them especially susceptible to commercially motivated promises of cure. For this reason deception by supplying informational material or proffering is expressly prohibited, as are, among other things, statements that create a false impression that success is certain or that no harmful effects will occur in association with correct or prolonged use (*Irreführung* [deception], § 3 HWG). Other advertising practices that are regarded as dubious and that are expressly prohibited include before-after comparisons and pictorial representation of health professionals in working clothes (§ 11 HWG).

In the case of prescription-only and other pharmacy-only medicines with certain indications (for use against insomnia or mental disturbances, or to influence mood), advertising aimed directly at the public is completely prohibited (§ 10 and Annex HWG). This prohibition of direct advertising does not extend to material directed at health professionals, though these groups too may not be deceived or misled.

ADVERTISING DIRECTED AT HEALTH PROFESSIONALS

Advertising is directed at health professionals via avenues that are not generally available in other contexts. The pharmaceutical industry employs a large number of pharmaceutical representatives who are specifically responsible for marketing medicinal products to doctors and pharmacists. The informational material that they supply ranges from scientific publications to direct advertising material and from conference invitations to offers of further training. It has been estimated that pharmaceutical representatives make 20 to 25 million personal contacts with doctors each year in Germany (Glaeske/Janhsen 2005). According to Bless et al. (2010, p. 64), this results in product advertising that turns a blind eye to actions by doctors that go beyond what is medically necessary.

A systematic review of medicinal product advertising in biomedical journals between 1950 and 2006 found the overall quality of the statements made in these advertisements directed exclusively at health professionals to be rather poor (Othman et al. 2009). This has led to calls for action ranging from better control of the quality of these advertisements through to a complete ban on medicinal product advertising.

Certainly, doctors find themselves bombarded with unsolicited, advertisement-laden secondary information about medicines, whereas if they require unbiased or critical information they generally have to obtain it at their own initiative.

WAYS OF CIRCUMVENTING BANS ON ADVERTISING TO CONSUMERS

Faced with the existing restrictions on advertising, drug manufacturers have found a number of ways of approaching consumers directly. One such stratagem for circumventing advertising restrictions is to draw a lot of attention to deficiency states without mentioning any particular drug (Fig. 6). In this way disparate individual circumstances are described in detail from the perspective of a certain deficiency state and people are encouraged to see themselves as suffering from that deficiency state – which is an important precondition for the use of medicines.

FIG. 6 EXAMPLE OF A PRODUCT ADVERTISEMENT THAT DOES NOT VIOLATE THE PROHIBITION OF ADVERTISING OF DRUGS

Source: www.mann-info.de/downloads/80/infomaterial.htm, from Bless et al. 2010, p. 59

Other stratagems for circumventing bans on advertising include provision of support to self-help groups of patients with particular diseases, e.g. via internet-based patient forums that can publicize specific forms of treatment from the perspective of people suffering from a particular disease without having to provide only unbiased information and without being subject to regulations governing advertising.

What is certain is that the prohibition of advertising can be circumvented in various ways, with the result that effective consumer protection cannot always be ensured. Purely interest-driven provision of information and advertising are nevertheless restricted to some extent in Europe compared to other parts of the world. For example, the prohibition of direct advertising of prescription medicines that exists in Europe does not exist in the USA or New Zealand. Even in those countries, however, voluntary agreements exist to the effect that advertising must be honest, must not be ambiguous, and must strike a balance between the benefits and risks of the medicinal product to which it refers. The US drug regulatory authority (FDA) monitors the activities of drug manufacturers and has rebuked some of these for advertising violations relating to the drugs described in Section II.3.

The influence of the possibilities for advertising that exist in the USA has been investigated in a number of studies. These have revealed, for example, that American patients spend 100 times as much time watching drug advertisements on the television as they spend with their doctor (Brownfield et al. 2004), that diagnoses that constitute indications for the use of advertised products are made significantly more commonly than other diagnoses, that the sales and market shares of advertised products have increased (Wasem/Gress 2006), and that 94% of new antidepressant use due to direct-to-consumer advertising is by non-depressed individuals (Block 2007).

THE DEBATE ABOUT DRUG INFORMATION AND ADVERTISING

Given that direct-to-consumer drug advertising is permitted in some countries, e.g. the USA and New Zealand, and that it is becoming increasingly easy to disseminate information globally, national restrictions on drug advertising are easily circumvented. The existing restrictions on advertising and informational material have therefore become a subject of considerable debate. Late in 2008 a »pharmaceutical package« was approved by the European Commission and submitted to the European Parliament. Among other things, this is intended to make it possible – without removing the ban on advertising – for pharmaceutical manufacturers to address information about prescription medicines directly to consumers.

Proponents of this package, e.g. the vfa, see it as a step towards making consumers more informed, i.e. giving patients specialized knowledge so that they can make their own decisions. Nevertheless, achievement of this undoubtedly accepted objective of creating informed patients whom this information would help to act in a more health-conscious manner would at the same time make it possible to draw (even) more attention to purported deficiency states and their treatability. Doctors and pharmacists would thus be at risk of losing their role as

the primary communicators of information between pharmaceutical manufacturers and consumers (Section III.3.5), and instead would play an essentially secondary role as correctors of information.

Critics of the package, who in Germany include the medical and pharmaceutical professions and the health insurance funds, complain that it fails to make a clear distinction between information and advertising. They fear that as a result, the existing prohibition of advertising of prescription medicines other than to health professionals could be circumvented (Bless et al. 2010, p. 55). The German *Bundestag* eventually added its voice to these misgivings. In subsequent discussions it was agreed that PILs, SPCs, and the public part of assessment reports from marketing authorization procedures are classified as information, not as advertising, and that pharmaceutical manufacturers are permitted to pass these documents on to consumers only in response to an active request on the part of the latter (»pull principle«) (Ausschuss für Gesundheit 2009). In any case, the public authorities are already subject to certain obligations to provide information about these documents.

As a result of the existence of different sources of information, restrictions on access to information, information structures, and ways of regulating and influencing information, it is sometimes difficult or impossible – and not just for the general public – to distinguish between high-quality substantiated information, information of questionable value, and simply false claims about the effects of medicines. This is because in addition to the abovementioned information systems, which are all subject to certain verification procedures but not (required to be) comprehensible to the general public, the internet provides a medium for an abundance of assertions the content of which is not subject to any quality control and the source of the information for which is not clear. Though some initial efforts are now being made to establish a quality logo procedure for internet-based information on medicines, these efforts are not yet widespread or well known (examples include the DISCERN project and the Health Information System Action Forum)[44].

In short, the information supplied ranges from unbiased, scientifically substantiated, and tested information (which is sometimes scarcely comprehensible to the general public) through to claims about performance-enhancing effects of substances, e.g. from sources that advocate doping or neuroenhancement (which have no difficulty issuing individual »doping prescriptions« over the internet). These purveyors of information allow no space for contrary opinions. At present, drug regulatory authorities are scarcely able to put claims arising from such questionable sources into perspective, since »authorized« information is limited to information for which there is scientific proof.

44 www.discern.de, www.afgis.de, 16/04/2011

PHARMACISTS AND DOCTORS: KEY PLAYERS FOR PLACING ON THE MARKET AND USE OF MEDICINES 3.5

Pharmacists and doctors play a key role in the placing on the market and the correct use of medicines and thereby also in the protection of health. They are jointly responsible for providing consumers with unbiased information on the use of medicines and they make possible and monitor access to and use of medicines (»gatekeeper« role). In Germany these two professions are classified as »liberal« professions, meaning that the exercise of them is deemed to constitute independent provision of a specialized service of a higher order in the public interest (§ 1 Subsection 2 PartGG[45]). In exercising their profession, doctors and pharmacists are expected to combine specialist knowledge with ethical values. The exercise of these professions therefore requires a license to practice and membership of a professional association (medical or pharmaceutical associations centralized at the level of the German federal states). Above and beyond general criminal and medicinal products law, the codes of professional conduct of the respective professional associations stipulate required activities (e.g. reporting of adverse drug reactions; Section III.3.2). Responsibility for compliance with and development of these stipulations lies with the state or federal tiers of the respective professional association.

Because social insurance is obligatory in Germany, most patients in Germany are covered by healthcare insurance such that adequate, appropriate, and necessary medical intervention is publicly financed (§ 12 SGB V). Doctors who wish to provide and charge for services under this scheme also have to obtain an SHI license and are then regarded as SHI-accredited doctors. Federal framework agreements govern the modalities of the interaction between SHI-accredited doctors and SHI funds in their role as providers of SHI, while billing for services is via associations of SHI-accredited doctors. The situation with regard to the scope of services is similar in the case of private health insurance (PHI); in this case billing is via fee ordinances.

Medical services (including the use of medicines) that are provided within the framework of SHI/PHI form the »primary healthcare market« in Germany. Services that fall outside of the scope of SHI/PHI have to be financed by patients themselves and form the »secondary healthcare market« (in some cases covered by additional privately financed insurance) (Section III.3.6). Within this overall healthcare market doctors and pharmacists are also described as service providers and the various insurance funds (bearers of healthcare insurance) as funding agencies or cost bearers. The actions of doctors and pharmacists, together with the separation of the processes of »access« and »prescription«, are meant to en-

45 *Partnerschaftsgesellschaftsgesetz* (Partnership Act)

sure that as far as possible medicines are used only in accordance with regulations and that any use not in accordance with regulations (including incorrect use and abuse) is not encouraged.

RESPONSIBILITIES OF PHARMACISTS 3.5.1

The professional responsibility of pharmacists is to supply the public with medicines in accordance with regulations. In this way they serve the health both of the individual and of the entire population (§ 1 ApoG[46], § 1 BApO[47]). In principle this permits only issue to authorized persons subject to compliance with specific obligations to document and supply information (especially in the case of narcotics). This also means taking appropriate action against identifiable abuse of medicines and refusing to issue a medicine where there is a well-founded suspicion of abuse (§ 17 Subsection 8 ApBetrO[48]). There are various, mostly vague, definitions of precisely what is meant by the term »abuse«, as the codes of professional conduct of the pharmaceutical associations of the various German federal states (*Landesberufsordnungen der Apothekenkammern*, BO-A) refer to abuse of medicines in different ways, e.g. reference to the taking of measures against abuse as a special activity-related obligation (§ 6 Sentence 1 BO-A Bavaria), restriction of the term »abuse« to the issuing of medicines to children (§ 9 BO-A Rhineland-Palatinate, otherwise as »incorrect use«; § 15), and no reference to the subject (e.g BO-A Hesse).

Pharmacists can control access to medicines as per the defined marketability of the medicine in question and prevent wrongdoing in this regard, however they cannot ensure use in accordance with regulations.

In the case of prescription medicines pharmacists play an important supervisory role. The doctor's prescription provides access to the drug and specifies the manner in which it is to be used. The pharmacist must follow the doctor's instructions in this regard (but in the case of SHI billing must check for discount agreements and the cheapest alternative and where appropriate dispense this instead of the prescribed product). Pharmacists undoubtedly act as an important barrier to noncompliant prescribing and use (e.g. incorrectly written or forged prescriptions) and to uncontrolled broader access to medicines. On the other hand, they must not call into question the doctor's therapeutic decision (Bless et al. 2010, p. 20). They are therefore not in a position to detect use contrary to indications, much less use for enhancement purposes.

46 *Apothekengesetz* (Pharmacy Law)
47 *Bundes-Apothekerordnung* (Federal Pharmacy Ordinance)
48 *Apothekenbetriebsordnung* (Pharmacy Operation Ordinance)

In contrast to the situation with prescription medicines, pharmacists can advise their customers on the use of, and can dispense, over-the-counter medicines (e.g. caffeine tablets) as they see fit, i.e. access to these products is available without authorization from a doctor. These products can also be advertised. Since 2004, when price controls on over-the-counter medicines were abolished, most such products have been removed from the SHI benefits catalog and thereby transferred to the realm of consumer self-medication (secondary healthcare market; Section III.3.6). Consumers can seek advice on the use of these products from doctors and pharmacists, however responsibility for correct use lies for the most part solely with the consumer, i.e. consumers are expected to exercise discretion in the use of these products in the same way as they do with food. Users are thus at liberty to use these products for the purpose of performance enhancement with no therapeutic intent.

It is often assumed that access to medicines for enhancement purposes is obtained mostly by bypassing the German pharmacy system by purchasing medicines abroad or via the internet. The results of a survey commissioned in 2008 by the DAK entitled »Doping am Arbeitsplatz« (»Doping at work«) in which about 3000 working people aged between 20 and 50 years participated (out of about 5000 such people who were approached) suggest that pharmacies too play some role in the use of medicines without compelling reasons as an aid to coping with workloads. Thus, 21.4% of the respondents stated that medicines had been recommended to them personally as a means of improving their mental faculties in the absence of any medical need and in almost 10% of cases this recommendation came from a pharmacy (DAK 2009, pp. 53–54). The respondents were not asked whether the medicines recommended to them were over-the-counter (and therefore advertisable) or prescription products. Almost half of those who admitted to using medicines without a compelling medical reason obtained the medicines from a local pharmacy without a prescription (compared with »only« 12% from online pharmacies without a prescription and 11% from other suppliers without a prescription) (DAK 2009, pp. 58–59). No wrongdoing on the part of the pharmacies that supplied the medicines can be assumed here, since even if the respondents themselves saw no medically compelling need for use of the medicine, they believed themselves to be suffering from a deficiency state (memory impairment, disturbance of concentration or attention, or other symptoms of tiredness) and are likely to have communicated that belief accordingly. The pharmacists thus did not breach any regulation by selling products such as caffeine tablets for the purpose of self-medication, since these are explicitly indicated for combating symptoms of tiredness. In such cases there is no need (except perhaps for reasons of cost) to circumvent these structures by using unregulated access channels, nor did the DAK survey, at least, find such circumvention to be very common.

In addition to medicines, pharmacists are allowed to sell many other kinds of product. To consumers, the distinctions made between different product classes often seem unclear and arbitrary. As a result, they tend to assume that any product that is supplied and sold in pharmacies – especially in the dosage forms in which medicines are generally supplied – is likely to be particularly effective. This situation is likely to favor substances for which no specific proof of efficacy exists but which are nevertheless available from pharmacies (e.g. »traditional« medicines for »strengthening and invigorating general condition« the claims about which are based exclusively on tradition or experience obtained over many years). Since the prices of nonprescription products can be set by pharmacists in their capacity as retailers, and since pharmacists, as well as fulfilling a societal function, are also businesspeople, sales of nonprescription products can certainly be favored by economic considerations. Against this backdrop it is also possible that the supply of medicines occurs at a number of different levels. For example, freely available medicines suggest a possibility of improving general or specific mental faculties (e.g. power of concentration). In this way they create a demand for a certain pharmacological effect at the lower levels of products that can be sold in pharmacies. As it is doubtful whether freely available substances can actually satisfy this consumer demand (since in most cases there is no scientific proof of their supposed efficacy), a demand for more potent substances can arise. The pharmacist can respond to this demand either directly – by supplying pharmacy-only substances – or indirectly – by advising the patient to see a doctor. Overall, therefore, it cannot be assumed that the business and operational model of pharmacies forms an effective barrier to enhancement tendencies. Indeed, the experts who were asked about doping at work within the framework of the DAK study regard free commerce in the commodity »medicines« as the most potent driver of doping at work (DAK 2009, p. 85).

RESPONSIBILITIES OF DOCTORS 3.5.2

The exercise of the profession of medicine is linked, via membership of a professional association, to a »pledge« (formerly the Hippocratic oath) that elevates the preservation and restoration of the health of patients to a guiding principle (Bundesärztekammer 2006, p. 5). Health, which is defined by the WHO as »a state of complete physical, mental and social well-being and not merely the absence of disease or infirmity« (WHO 1946), is nowadays mostly regarded as a multidimensional phenomenon made up of subjectively different components whose complexity should not be reduced to narrow definitions of illness. This precept, which is oriented towards the concept of health rather than that of illness, undoubtedly allows doctors a wide margin of discretion in the exercise of their professional activity, and in this imprecisely defined borderline area enhancement phenomena can find a place.

Just as the market for medicines can be subdivided into a primary and a secondary market, doctors are sometimes seen as having a primary responsibility (the responsibility to cure illness) which however they sometimes go beyond, e.g. by providing contraception and cosmetic surgery. The objective of preserving and restoring health can undoubtedly be interpreted in many different ways. In this regard the margin of discretion allowed to doctors appears to be determined to a significant extent by social acceptance (in terms of which cosmetic surgery, for example, differs markedly from doping). This allows advocates of a liberal approach to neuroenhancement practices to make the assumption that the medical profession would not suffer any harm provided that measures of this kind were at least accepted, even if not actually desired, by society (Galert et al. 2009, p. 46).

Nevertheless, as long as the possibility of side effects cannot be ruled out, the precept of »serving health« undoubtedly constitutes an important obstacle to widespread involvement of doctors in enhancement practices. Since, however, it can be interpreted more or less broadly or narrowly, this precept does not provide direct guidance on action; rather, it has to be discussed and fleshed out in individual situations, e.g. in the case of performance enhancement in sport by reference to the statement by the German Medical Association on »doping and medical ethics« (Bundesärztekammer 2009). As in many other areas of medicine, there is a need for a public debate about enhancement so that the range of actions available to doctors can be precisely defined. A debate about ethical legitimacy, in particular, has now been initiated but cannot be regarded as anywhere near complete as yet (Section IV).

The range of action of doctors is generally limited »below« by the professional obligation to exercise »due diligence« (§ 276 BGB [*Bürgerliches Gesetzbuch*: German civil code], with civil and even criminal liability). In the case of billing by SHI-accredited doctors, the range of action is limited »above« by »adequate provision« (§ 12 SGB V). SHI-accredited doctors are individually liable for the economic efficiency and permissibility of their prescriptions (in cases of doubt an extrajudicial auditing procedure is initiated [§ 106 SGB V]; if this does not lead to agreement it may be followed by social court proceedings).

As part of their responsibilities doctors provide their patients with comprehensive information, determine what normal or abnormal conditions are present, and state whether these conditions require medical intervention and if so what therapeutic interventions are practicable and which of these are adequate, appropriate, and necessary. Doctors make decisions on a case-by-case basis. It is expected that for this purpose they will take account of various guidelines on individual diseases and, in their role as SHI-accredited doctors, comply with various other agreements. A particularly complex example of the exercise of medical discretion in decision-making and treatment is provided by the diagnosis (box) and treatment (Table 11) of attention deficit hyperactivity disorder (ADHD).

TABLE 11 TREATMENT OPTIONS FOR ADHD

Treatment method	Comments/evaluation
Psychoeducative measures (e.g. discussions with affected people and their guardians, behavioral therapy, self-help groups, treatment of developmental disorders)	If, after these measures have been practiced for several months, no satisfactory improvement is apparent and there is a definite impairment in performance and psychosocial function accompanied by psychological strain in the child/adolescent and parents and a risk to the further development of the child, drug therapy is indicated.
Drug therapy	Comparison of various treatment methods has shown that drug therapy tailored to individual needs has the greatest beneficial effect on the core symptoms of ADHD and also favorably influences associated disturbances. The therapeutic benefit offsets potential risks and side effects.
Methylphenidate (psychostimulant)	approved for the treatment of children and adolescents up to 18 years of age
Atomoxetine (SNRI-type antidepressant)	approved without age restriction
Interventional therapy (e.g. special training, inpatient rehabilitation)	This can be given if the therapeutic objectives cannot be satisfactorily achieved using the abovementioned therapeutic measures, especially if ambulant therapy is no longer successful due to the existence of associated disturbances and/or serious crises in the family.
Neurofeedback (special training in how to learn)	The studies performed to date suggest that neurofeedback training is costly but promising, especially with regard to the training of slow cortical DC potentials. No final conclusion as to the effectiveness of this method can be reached at present. The availability of this method is very limited as yet. The SHI funds are not obliged to reimburse costs.
Dietary measures (e.g. elimination of food additives, supplementation with essential fatty acids)	All the major studies performed to date have failed to demonstrate any benefit of dietary measures.

Source: adapted from *Arbeitsgemeinschaft ADHS* 2009

The syndrome-based approach to the diagnosis of ADHD developed by the German *Arbeitsgemeinschaft ADHS* (ADHD working group) describes precisely how the condition can arise and at the same time allows the doctor considerable discretion with regard to the diagnosis of an illness-relevant state. Notwithstanding attempts to objectify the subjective impressions of patients and doctors by means of guidelines, perceptions and psychological strain relating to particular symptoms and groups of symptoms vary between individuals. Impairments to

health and resulting wishes for treatment can therefore vary greatly between individuals both from the internal perspective of the person affected and from the external perspective of the doctor (in this regard see also Section IV.2.2.1).

As a result of this variability, the boundaries drawn between pathological and healthy states are shifting and dependent on arbitrary decisions, even at the individual level. This elasticity in medical decision-making can also be influenced by the demand behavior of the patient. Advertising strategies, for example, can deliberately pathologize conditions at the margin of illness in order to create a need for treatment of conditions that in fact may not require any treatment at all (Bless et al. 2010, pp. 46–47; Section III.3.4).

DIAGNOSIS OF ATTENTION DEFICIT HYPERACTIVITY DISORDER

ADHD is characterized by core symptoms (inattention, hyperactivity, and impulsivity), suggestive symptoms (peculiarities of behavior and performance), and associated disturbances the intensity of which varies with age. ADHD can be diagnosed if at least six out of nine specific symptoms of inattention and/or at least six out of nine symptoms of hyperactivity/impulsivity (core symptoms) have been present for at least six months at a developmentally inappropriate level. ADHD can also be diagnosed if some signs that cause impairment were present before the age of seven years or if significant impairment in social, school, or work functioning is present.

Source: Arbeitsgemeinschaft ADHS 2009

A doctor's diagnosis formally attests to the presence in a patient of a specific deficiency state or even an illness-relevant state. In accordance with specific regulations, doctors enjoy not only a monopoly on the diagnosis of deficiency states and illness-relevant states, but also a partial monopoly on the treatment of individual signs and symptoms. In addition, their designated role (to act in the interests of the health of patients) allows them a degree of freedom in their choice of treatment. Notwithstanding this, every treatment requires that the patient be provided with detailed information on possible therapeutic effects and side effects and give his or her informed consent. Treatment is also subject to a duty of medical confidentiality with regard to third parties from which only the patient can relieve the doctor. Even with the consent of the patient, a therapeutic measure may not be unethical, i.e. it must be based on the current state of knowledge. Only then does the doctor's therapeutic intervention not render him or her guilty of assault (*Körperverletzung*) as defined in the penal code (§ 223 ff. StGB[49]) (Simon et al. 2007, p. 40).

49 *Strafgesetzbuch* (German penal code)

The example of ADHD can be used to illustrate the latitude allowed to doctors and to show where borderlines (including those potentially leading to enhancement) lie. Where a doctor, based on the not merely brief occurrence of several core symptoms of ADHD, makes a diagnosis of ADHD in a patient who is legally a minor, use of methylphenidate is permissible in accordance with the ADHD guidelines (Arbeitsgemeinschaft ADHS 2009, pp. 6 ff.) and the marketing authorization of this drug (Section II.3.1). Where only individual core symptoms that do not fully justify a diagnosis of ADHD are present, an impairment to health may nevertheless be perceived on an individual basis and the person concerned may thereby become a patient. This is because doctors may derive a professional responsibility to act even from such a perceived impairment to health. Doctors are able to prescribe drug therapy for individual core symptoms on the basis of their therapeutic freedom of choice. They may prescribe a medicine outside of the illness-specific situation in which its efficacy was demonstrated in the marketing authorization process provided that they are convinced that in so doing they are acting in the interests of (preserving or restoring) the patient's health. Such use is permissible as part of a »therapeutic trial«, though some legal uncertainty exists with regard to strict liability claims (the manufacturer is not liable for off-label use and therapeutic trials should not become a routine).

Based on its benefits data for the year 2007, the DAK analyzed drug prescriptions made out to people insured with it (DAK 2009, pp. 61ff.). To take methylphenidate – which was subject to the special restrictions on use and prescribing of the Narcotics Act – as but one example, almost half (46%) of prescriptions gave no, or only a medically unclear, justification of the need for prescription and 17.4% of prescriptions were for explicitly off-label use (diagnoses in the field of depressive illnesses).[50] This DAK analysis shows that for the period in question these »therapeutic trials« in which medicines were used in off-label fashion must be regarded as something more than a mere fringe phenomenon of medical practice. On the other hand, it must be assumed that the SHI funds are making efforts to progressively exclude such borderline areas from their range of reimbursable services (primary healthcare market) by means of various regulations (Section III.3.6).

Critical voices have expressed the view that diagnoses are already being overstretched and that as a result »enhancement on prescription« is already possible. However, it is natural that any drawing of boundaries, at least in the case of constant characteristics, will enclose borderline areas with certain stretchable diagnostic possibilities. A decision not to draw boundaries would frustrate any attempt to objectify subjective decisions and appears not to be a practicable alternative.

50 In the case of modafinil, 40% of prescriptions did not mention any diagnosis corresponding to the marketing authorization and 16% mentioned diagnoses related to depression, which likewise constitutes off-label use.

Treatment ordered by doctors is directed mostly at signs and symptoms associated with diseases, including individually perceived deficits of individual dimensions of mental ability. It can exert at best only limited influence on the causes of signs and symptoms. For example, it can exert scarcely any influence on work-related causes of shift worker syndrome, which manifests itself via symptoms such as sleep disturbance. The effective treatment options for this condition comprise sleep hygiene and pharmacological measures (modafinil) to alleviate the effects of shift work. These measures correct the consequences of working conditions that are known to induce illness to the extent that the patient can put up with the working conditions, and remain functional in the working environment, for longer. It would presumably be difficult to justify the drawing of a line between this approach – which is accepted for the purpose of SHI benefits – and the situation of employees who, for example because of excessively demanding working conditions, likewise demand pharmacological substances to enhance their individual performance so that they can cope with workplace demands at all times (Bless et al. 2010, p. 46). The fact that this is more than just a theoretical consideration is shown by the responses of the experts interviewed in the DAK survey, who considered excessively demanding working conditions to be the most important causal factor for use of medicines by healthy individuals (DAK 2009, pp. 82ff.). Work-related reasons for use of medicines were likewise cited by users in the survey of UK and US scientists undertaken in the run-up to the »Nature survey« (Sahakian/Morein-Zamir 2007, p. 1159). Social service providers therefore already have a responsibility to pay more attention to the question of work-related illnesses and symptoms and prevention of these by means of occupational health and safety measures.

The public survey conducted by the DAK also showed that doctors play at least a partial role in the use of medicines without medically compelling reasons as means of coping with workloads. Thus, 21.4% of the respondents stated that medicines had been recommended to them personally as a means of improving their mental faculties in the absence of any medical need, and a fifth of the men and a third of the women who had received such a recommendation had received it from a doctor (DAK 2009, pp. 53–54.).

Of the various treatment options that are available, the SHI scheme covers only services that are deemed to be adequate, appropriate, and necessary. SHI-accredited doctors (doctors who can bill healthcare insurance funds for services) must therefore distinguish between services that form part of the primary healthcare market, i.e. services for which they issue an SHI prescription for use of a drug, and extra services that form part of the secondary healthcare market, i.e. services that they are allowed to provide as »individual health services« (Individuelle Gesundheitsleistungen, IGeL) and for which they issue a private prescription or bill the patient. The latter type of service provision also makes it

easier for demands by patients (e.g. requests for treatment in the absence of any definite illness-relevant state, requests for specific drugs) to be satisfied (Bless et al. 2010, p. 30).

The task of prescribing medicines forms part of the general responsibilities of doctors; approval cannot be given by a healthcare insurance fund. The doctor or pharmacist can be made liable for reimbursement only downstream via recourse/retaxation (Bless et al. 2010, p. 20). As the relevant social security regulations are based on many different legal and contractual provisions (caps on billing for services, budget management of individual service categories, etc.) and are correspondingly complex and not always properly intermeshed, medical decision-making is an area of potential conflicts. One way of avoiding such conflicts is to prescribe treatment outside of the SHI benefits catalog. As far as medicines are concerned, this implies the use of private prescriptions and a corresponding shift in drug provision towards the secondary healthcare market (Bless et al. 2010, pp. 28–29).

Empirical proof of the existence of such a development is provided by the surveys of SHI members about their experiences with »individual health services« (IGeL) that have been conducted over the past few years at the behest of the Scientific Institute (*Wissenschaftliches Institut*, WIdO) of the General Local Health Insurance Fund (*Allgemeine Ortskrankenkasse*, AOK). In 2005 the proportion of respondents who indicated that they had enquired about medical remedies and aids or been offered these as »individual health services« (IGeL) was 8.2%, whereas by 2010 this figure had risen to 11.5% (Zok 2010; Zok/Schuldzinski 2005; see Section III.3.6 for more detail).

The existence of »individual health services« (IGeL) makes it increasingly possible for doctors to become providers of services that are at least partly a response to patients' wishes without necessarily constituting »wish fulfillment medicine« in the narrow sense.[51] And in this context doctors have some influence in cases of doubt as to what measures should be regarded as necessary, possible, and desirable. Certainly, doctors are not obliged to order treatments in response to a patient's request; rather, they can refuse to order measures that are not in accord with their professional responsibilities.

The multilevel medical decision-making process (diagnosis, therapeutic options and needs) determines whether a medicine is or is not being used in accordance with regulations, i.e. at what point or points use of a medicine ceases to be correct and could develop into enhancement. The decision-making criteria that are

51 Explicitly wish-fulfilling medicine such as cosmetic surgery is already partly classified and billed as a VAT (value added tax)-liable business activity (Simon et al. 2008, p. 23). There have even been occasional suggestions that cosmetic surgery should be made subject to a special tax (e.g. the »Botox tax« to cofinance healthcare reform in the USA).

used in this process have evolved gradually over time, are to some extent applied in different ways, are subject to change, and are often ambiguous or in need of interpretation. The process of diagnosis and treatment proceeds at least to some extent in consultation with the patient and in most cases allows doctors some leeway (Bless et al. 2010, p. 13).

The boundaries of medical activity in terms of treatment options that are referred to above (e.g. off-label use of medicines or treatment of individual symptoms of illness in the absence of a clearly defined illness-relevant state) illustrate the various points at which a clearly defined, rule-compliant range of actions in relation to drug therapy can expand into a broader range of actions that may be seen either as misuse of medications or as enhancement. In this regard the range of benefits provided, especially those provided via the SHI scheme, is becoming progressively less useful as a demarcation criterion; rather, determination of this range contributes to conceptual difficulties (see below).

COST BEARERS AND HEALTHCARE MARKETS 3.6

Unlike foods, which consumers pay for themselves, medicines are under some circumstances subject to claims for cost reimbursement. In Germany this cost reimbursement occurs mostly via the statutory health insurance (SHI) scheme, which covers many, but not all, citizens.[52]

This obligation to take out health insurance provides insured persons, in their capacity as benefit recipients, with certain rights, including the right to be provided with medicines. From the perspective of insurers, these rights confer an obligation to provide benefits that is borne by various health insurance funds in their capacity as benefit providers and cost bearers. The code of practice of SHI is laid down in the German Social Code (*Sozialgesetzbuch V*, SGB) and its subordinate statutes. The national legislature itself thus plays an important role in determining the range of benefits to be provided by SHI and has basically determined this range to be broad. Thus, the remit of SHI is to preserve, restore, or improve the health of insured persons (§ 1 SGB V). Whether *pharmacological enhancement of the performance of healthy individuals* could be construed – or

52 People for whom health insurance is obligatory (workers and employees up to a certain level of income) are insured via statutory health insurance (SHI) funds. People for whom health insurance is not obligatory can arrange private health insurance (PHI) as an alternative to SHI. As compared with SHI funds, PHI funds operate on a different legal basis, namely the Civil Code (*Bürgerliches Gesetzbuch*), the Commercial Code (*Handelsgesetzbuch*), the Insurance Supervision Act (*Versicherungsaufsichtsgesetz*), the Insurance Contract Act (*Versicherungsvertragsgesetz*), laws governing general terms of business, the General Conditions of Insurance (*Allgemeine Versicherungsbedingungen*), and special agreements in individual insurance contracts. Loss events and claims for benefits are similar, but do not correspond in every respect, in SHI and PHI.

on the contrary is ruled out at the outset – as an improvement in a person's state of health at this high hierarchical level of the general assignment of responsibilities is an open question, not least because the public debate on this topic has so far been largely hypothetical.

In the following paragraphs attention is directed at the next levels at which various obligations to provide benefits are made concrete. Also discussed is the question of to what extent enhancement is excluded from the range of benefits that must be provided – and how a trend towards enhancement can thereby be influenced – at these levels.

ILLNESS AS AN INSURED EVENT

On occurrence of an insured event, SHI-insured persons become entitled to receive various benefits. SHI benefit categories include in particular prevention, early detection, and treatment of illnesses and also a narrowly defined area to which the concept of illness does not apply, including pregnancy and maternity benefits (»non-insurance« benefits) (§ 11 SGB V). PHI funds provide essentially similar benefits. Even this first level of definition links the range of benefits to be provided by health insurance funds to a substantial extent to the concept of illness established by social security legislation. Notwithstanding the existence of this link between benefit entitlements and the concept of illness, however, »illness« remains difficult to define and demarcate as a general state. Neither in the German Social Code (*Sozialgesetzbuch V*, SGB) nor in the standard terms and conditions of PHI is the insured event »illness« legally defined (for the purposes of SHI and PHI, respectively). As a result, the task of establishing such a definition falls to the jurisdiction of the social courts. In 1972 the German Social Court (*Bundessozialgericht*, BSG) defined illness as »an anomalous physical, mental, or emotional state that causes incapacity for work and/or requires treatment«.[53] In 2004 the BSG added the rider that »not every physical irregularity ... has the legal status of an illness«; rather, it said, »an illness is present only if the bodily functions of the insured person are impaired or if the anatomical anomaly is disfiguring«[54] (Bless et al. 2010, pp. 19–20). Even these formulations, however, are considered to be imprecise, and as a result there is disagreement as to what states should be accorded the status of illness and whether alternative formulations would be more expedient for the purpose of establishing the limits of benefits to be provided under social legislation (e.g. Werner 2004). Individually perceived deficits in capabilities (Section II.1.2) can in principle constitute an illness for which prompt or even preventive countermeasures are justified.

53 BSG judgment of May 16, 1972, 9RV 556/71
54 BSG judgment of October 19, 2004, B1 KR 9/04 R

At the next level of definition, illnesses are described in more precise terms. This is the level of various classification systems (e.g. ICD-10) and specific guidelines (DIMDI 2010) that define illness on the basis of the presence of certain symptoms of a certain intensity (Section III.3.5). The SHI funds are increasingly urging that benefits should be payable only on the basis of the applicable guidelines, i.e. that in the individual case the presence of an illness-relevant state must have been demonstrated by the presence of specific signs and symptoms and that only measures that have been shown by means of evidence-based procedures to be effective in the illness in question have been used for treatment (for example, in the case of ADHD this means the presence of six out of nine defined core symptoms).

Perceptions of the extent to which individual states are pathological are influenced by developments in society. Against this backdrop, reference is sometimes made to a pathologization of individual states whose recognition as illnesses in the public mind implies possibilities and limits of treatment. ADHD and deficits associated with the aging process are often cited as examples of this (Section IV.2.2). At present the illness-relevant status of ADHD in children is largely undisputed, the public debate instead being more concerned with the frequency (prevalence) of the condition, the most effective therapeutic strategy, and the situation in adults. Here too a link to therapeutic options is apparent in that at present methylphenidate-containing products are approved in Germany only for the treatment of 6- to 18-year-old ADHD patients.

Another example of evolving attitudes is that of age-related changes, a field in which the question of demarcation must also be considered. Case law from the time of the German Imperial Insurance Office (*Reichsversicherungsamt*, RVA) does not grant age-related conditions the status of an illness (Bless et al. 2010, p. 45). Later it was argued that the loss of faculties that occurs naturally with increasing age can be regarded as an illness on the basis that it requires treatment (Brackmann 1993). On this basis the use of hormone replacement therapy, for example, became possible. Following the introduction of sildenafil (Viagra®), public debate about the illness relevance of certain at least partly age-related states intensified. In response to claims for health insurance benefits for such conditions, German social courts originally drew a distinction between illness and physical states that were normal for the age of the person concerned. According to a ruling by the BSG, Viagra could be »prescribed at the expense of the health insurance funds until the end of 2003, not in order to improve a physical state that is usual and typical for the age of the person concerned, but certainly in cases of erectile dysfunction resulting from serious illness«.[55] This meant that the causes of certain symptoms were to be taken into account in the assessment of claims for benefits. Despite this, it is not always possible to draw a clear distinction between, on the one hand, the therapeutic approach accepted

55 BSG judgment of May 10, 2005, B1 KR 25/03 R

by society and social security law of restoring or creating capabilities that have been lost or are diminished by comparison with the average person and, on the other hand, attempts to improve lifestyle. In 2004 the legislature abandoned this distinction and ruled out benefits of this kind even in cases of illness. This exclusion of impotence remedies from health insurance benefits (§ 34 SGB V) was intended to keep so-called lifestyle medications out of the SHI benefits catalog (Bless et al. 2010, p. 45). In an effort to limit expansion of the range of benefits, social security legislation pertaining to SHI is to an increasing extent countering the trend towards a broadening of the concept of illness (Werner 2004, p. 139; Section IV.2.1) by imposing benefit specifications and even exclusions from benefits.

From the perspective of insurance legislation, the presence of an illness-relevant state or medical indication that constitutes an insured event is determined (both in the case of SHI and in that of PHI) by the doctor alone via a diagnosis. As illness-relevant states come to be more precisely delineated via specific guidelines, doctors are becoming better equipped to make correct assessments (Table 11, Section III.3.5). This drawing of distinctions can nevertheless leave gray areas of assignment and the possibility that concepts may at least be stretched towards more or less definitely false conclusions and even incorrect actions. For example, an insured person could feign an illness and doctors could use the considerable latitude that they still enjoy to legitimize a medical indication (Bless et al. 2010, p. 44).

INSURANCE BENEFITS AND THEIR CONTAINMENT – PRIMARY HEALTHCARE MARKET

Against the backdrop of the continuous expansion of the concept of illness and the existence of gray areas in terms of the diagnosis of illnesses, the law allows the SHI scheme to exclude treatment of certain signs and symptoms from its benefits catalog even when an illness-relevant state has been diagnosed. According to the BSG this applies in particular when the primary purpose of treatment is to improve quality of life beyond life-threatening states and in situations in which the boundary between a pathological and a nonpathological state depends to a significant extent on the subjective perception of the individual insured person.[56] This provides a legal basis for focusing insurance benefits on serious illnesses and life-threatening conditions.

As a result of advances in medicine, the limits of what is therapeutically possible in illness – and of what insured people generally want and doctors are under a professional obligation to do – are expanding. In order to keep the costs to the mutual societies within reasonable limits, the range of benefits provided by SHI is being increasingly restricted by the principle that medical services must be ad-

56 BSG judgment of May 10, 2005, B 1 KR 25/03 R

equate, appropriate, and cost-efficient and must not exceed what is necessary (§ 12 Subsection 1 SGB V). Since not all licensed forms of treatment satisfy these criteria and since SHI funds can impose additional exclusions from benefits (§ 34 SGB V) and restrictions on benefits (§§ 31, 35, 129 SGB V), especially in the ambulant setting, the presently existing general right of insured persons to be provided with medicines is being increasingly eroded. The SHI funds impose the following exclusions from benefits for medicines:

- *In relation to manufacturers*: uneconomic medicines. This includes, for example, medicines that contain ingredients that are not necessary for a therapeutic purpose, that contain a large number of active ingredients, or that have not been shown to provide a therapeutic benefit.[57]
- *In relation to doctors*: medicines used in off-label fashion. In 2002 the BSG ruled that in general a licensed medicinal product may not be prescribed at the expense of the SHI in an indication that is not covered by its marketing authorization. At the same time, however, it stated that this rule may exceptionally be broken in cases of serious illness where no therapeutic alternative exists and where the current state of scientific knowledge indicates a reasonable prospect that therapeutic success can be achieved with the medicine in question.[58] In the case of medicinal products that are not licensed in Germany or throughout the EU, off-label use at the expense of the SHI is permissible only in emergencies and under strict conditions (Bless et al. 2010, pp. 22–23).[59]
- *In relation to the insured*: since 2004, all medicines that are officially classified as nonprescription medicines (but with various exceptions, e.g. as standard treatment in serious diseases, in children under 12 years of age) and services provided for illnesses with certain indications (e.g. trivial illnesses such as colds, lifestyle indications such as cessation of smoking, impotence). According to Bless et al. (2010, p. 22) these exclusions from benefits are intended firstly to give expression to the legal precept of § 2 SGB V that services provided for trivial disturbances of health may be charged to the insured, and secondly to mark out the boundary of the concept of illness in relation to medicines that are being used primarily not to treat an illness but rather to improve quality of life.

This results in a division of the healthcare market into a »primary healthcare market« made up of adequate services financed by cost bearers (both SHI and

57 Initially, these exclusions could be imposed and communicated to doctors by means of a negative list (Bless et al. 2010 p. 22). Among the substances referred to in Section II.3, ginkgo preparations (in a small number of dosage forms), for example, were included in the negative list (KBV 2002, pp. 7 & 13). In January 2011, however, when the Pharmaceutical Market Reorganization Act (*Arzneimittelmarkt-Neuordnungsgesetz*, AMNOG) came into effect, the negative list became inoperative.

58 BSG judgment of March 19, 2002, B1 KR 37/00 R

59 BSG judgment of April 4, 2006, B1 KR 7/05 R

PHI) and a »secondary healthcare market« made up of healthcare services that are excluded from the primary healthcare market. The prices of medicines included in the primary healthcare market are uniform throughout Germany (as they are governed by the AMPrVO[60]) (Bless et al. 2010, p. 30). Despite this, people involved in the healthcare market often find it lacking in transparency, among other reasons because of the existence of additional restrictions on benefits:

- Restrictions on SHI benefits that impact directly on manufacturers include reference price regulations and various restrictions on benefits based on post-marketing cost-benefit analyses (which are becoming increasingly important as a »fourth hurdle« in the healthcare system) (Bless et al. 2010, p. 24).
- Restrictions on SHI benefits that impact directly on doctors and pharmacists are aimed at ensuring that patients have a right to be supplied only with a prescribed pharmacological agent, not with a particular product (though exceptions are possible). To this end discount agreements between health insurance funds and manufacturers that the pharmacist has to take into account, »aut-idem« (»or the same«) regulations whereby the pharmacist dispenses the cheapest product, and import quotas have been introduced (Bless et al. 2010, p. 25).
- Restrictions on SHI benefits that impact directly on the insured include in particular less than full reimbursement of the cost of medicines. At present the copayment to be made by insured persons aged 18 years and above is 10% of the selling price but no less than 5 and no more than 10 euros (though exceptions are possible) (Bless et al. 2010, p. 24).

Pharmacies collect the data from SHI prescriptions and then store these data and forward them to the individual health insurance funds. As well as being used for accounting purposes, these data can be used for statutory tasks such as drug early warning systems and cost-efficiency analyses, strategic planning by health insurance funds to control their expenditure, and scientific purposes. As stated in Section III.3.5.2, an analysis of drug prescriptions for people insured with DAK revealed, among other things, frequent off-label use of methylphenidate and modafinil (DAK 2009, pp. 67ff.).

THE PRIMARY HEALTHCARE MARKET AS A PATHWAY TO ENHANCEMENT AGENTS

Because entitlement to benefits for provision of medicines is tied to the concept of illness, substances that are used explicitly to enhance performance are in principle not reimbursable by the SHI scheme. This principle is confirmed by the fact that medicines that are used primarily to improve quality of life (lifestyle products) are excluded from benefits (§ 34 SGB V). Furthermore, off-label use of otherwise potentially reimbursable medicines for enhancement purposes is excluded

60 *Arzneimittelpreisverordnung* (Pharmaceutical Price Ordinance)

from SHI reimbursement by BSG case rulings on the basis that use for enhancement would not fall within the narrow criteria for exceptions to the exclusion of off-label use.

Notwithstanding the apparently unambiguous reasons for exclusion from benefits, the possibility of incorrect provision of benefits must be borne in mind. This can arise on the one hand from the finding of a pathological state (a setting in which doctors have some discretion and patients can dramatize or feign illness) and on the other hand from the gray areas that still exist as a result of imprecision and overlapping of the boundaries between treatment and enhancement (Viehöver et al. 2009; Section IV.2). In borderline cases the therapeutic approach accepted by society and social security law of restoring or creating capabilities that have been lost or are diminished by comparison with the average person cannot be clearly differentiated from the approach of improving performance parameters. With regard to anti-aging preparations it should be noted that a basic right to pharmacological reversal of aging processes – assuming this to be possible – could probably not be inferred from the social security legislation governing the SHI scheme.

THE SECONDARY HEALTHCARE MARKET

The secondary healthcare market includes those healthcare services for which SHI funds are not obliged to provide benefits and the cost of which consumers themselves therefore have to bear. This market has yet to be clearly defined, nor have uniform boundaries for it been drawn, especially in relation to products used in everyday life (a category that includes services defined as being not therapeutically »necessary« and health-promoting products and services).

As part of the secondary healthcare market, the secondary pharmaceutical market consists of all over-the-counter medicines and of prescription medicines prescribed by doctors as »individual health services« (IGeL) by means of a private prescription. Because it is excluded from benefits, the secondary pharmaceutical market is not subject to the provisions of SGB V, whereas regulations pertaining to marketing authorization, manufacture, and marketing are fully applicable to it. This is true in particular of the AMG, in which marketing authorization and distribution routes are defined, and includes the AMG's subordinate regulations on prescription-only status (AMVV)[61] and the special provisions of the BtMG and the HWG.

Via these regulations pharmacists and doctors working in the secondary pharmaceutical market too are assigned staggered gatekeeper roles the purpose of which is to ensure that as far as possible pharmaceuticals are used in ways that promote health and prevent harm:

61 *Arzneimittelverschreibungsverordnung* (Pharmaceutical Prescription Ordinance)

- In the over-the-counter sector the gatekeeper roles played by doctors and pharmacists do not exert any substantial regulatory influence, as this category of medicines can also be sold in supermarkets and drugstores provided that the sales staff of these possess an appropriate certificate of competence (which they can obtain via a two- to three-day workshop). Once marketing authorization has been obtained, competitive structures similar to those of the food and cosmetics industries apply. According to health expenditure accounts, 5.6% of medicines sold in Germany in 2008 were sold via retail outlets (Statistisches Bundesamt 2010a).
- In the pharmacy-only nonprescription sector pharmacists can exert a regulatory influence, as they recommend medicines and give advice on an independent basis. Doctors too can exert a regulatory influence, as their treatment recommendations can include nonprescription medicines. One of the objectives of the Act to Strengthen Competition in the SHI system (*GKV-Wettbewerbsstärkungsgesetz*) that formed part of the German healthcare reform of 2004 was to allow market and competitive structures to become increasingly effective in this market sector. One element of competitive structures is freedom of pricing, however the price competition desired by the legislator still occurs only to a limited extent in the secondary healthcare market, as most pharmacies still follow manufacturers' nonbinding retail price recommendations (Bless et al. 2010, pp. 30ff.). Another element of market and competitive structures is advertising, which the HWG permits to a limited extent in this sector even at the level of the consumer and which is therefore able to exert an influence.
- In the prescription sector doctors have the actual gatekeeper role, as they make medicines of this category available to consumers as »individual health services« (IGeL) by means of private prescriptions. The main role assigned to pharmacists is that of checking. The prices of medicines in this category are fixed, and product advertising may be directed only at health professionals.

As it is financed by consumers, the secondary healthcare market is shaped above all by consumers' wishes and ability and willingness to pay. Critics of this situation argue that this orientation towards consumers' wishes and willingness to pay makes it possible for pharmacists and doctors to link their own economic interests to their assigned roles, with the result that the gatekeeper role of both these professional groups is put under strain when consumer wishes are not conducive to health but nonetheless help finance the gatekeeper's business (Bless et al. 2010, p. 30). At the same time, third parties have considerably less incentive to check, or possibility of checking, for correct performance of this role than in the case of provision of services at the expense of the SHI system. Moreover, the restrictions on off-label use of medicines imposed by social security legislation are of course inapplicable to the self-paying sector. In the light of the increasing restrictions being placed on the primary healthcare market, pharmaceu-

tical manufacturers also have an incentive to take active steps to tap into the self-paying market. According to Bless et al. (2010, p. 31) the advertising possibilities are exploited with corresponding creativity and expenditure, with the result that manufacturers, pharmacists, and doctors find themselves in competition for clients in a way that is in conflict with their regulatory roles and the restrictions to which they are subject.

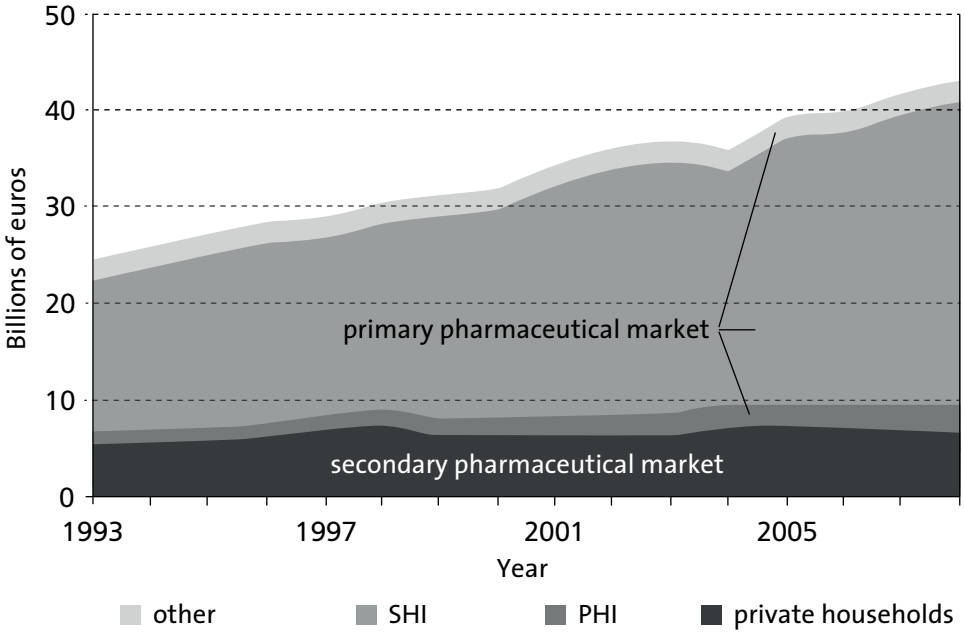
Because of the lack of definition and demarcation, the fuzziness of the borderlines between the secondary healthcare market and the food and fitness/wellness markets, and the consequent near-arbitrariness of boundaries, estimates of the size and dynamism of the secondary healthcare market vary greatly. For example, the German federal government estimated the value of the entire secondary healthcare market for the year 2007 to be 60 billion euros and in this regard referred to a study that included even functional food and organic food in this market. For the purpose of comparison it pointed out that in 2003 the market value had been estimated at 49 billion euros, suggesting a mean annual growth rate of 5.2% over the period from 2003 to 2007 (Bundesregierung 2008). The Scientific Institute (*Wissenschaftliches Institut*, WIdO) of the AOK estimated the market volume of individual health services (IGeL) provided as part of the secondary healthcare market in 2010 to be 1.5 billion euros (cf. 0.95 billion euros in 2005) and the mean annual growth rate over the period from 2005 to 2010 to be 10% (Zok 2010, p. 1; Zok/Schuldzinski 2005, p. 32).

In a survey commissioned by WIdO, a representative nationwide sample (2000 to 3000 people) of SHI members have over the past few years been asked about their experiences with individual health services (IGeL). It was found that the proportion of respondents who over the previous year had been offered private health services by doctors or who had asked for such services has risen continuously (over the period from 2005 to 2010 the mean annual growth rate was 5.5%) and that these additional services were offered above all to patients of higher income and higher educational level in private medical practices. A breakdown by type of service showed that between 2005 and 2010 medical remedies and aids, in particular, were requested and supplied with increasing frequency (mean annual growth rate from 2005 to 2010: 7%). That means that this category has become the third most requested type of individual health service (IGeL), after ultrasonography and glaucoma screening (whereas in 2005 it was in fifth place). The WIdO estimates that three out of every four such requests or offers led to provision of the service concerned. The proportion of respondents who stated that they had either asked for or been offered dietary supplements was 0.9%.

However, statements about the dynamism of the secondary health services (IGeL) market sector based on consumer surveys must be considered in relation to findings obtained via explicit analyses of the secondary pharmaceutical mar-

ket and the annual health expenditure accounts of the Federal Statistical Office (Statistisches Bundesamt 2010a). Such analyses provide information on both the primary and the secondary pharmaceutical markets. According to this type of analysis a total of 43.2 billion euros (approximately a sixth of total healthcare expenditure) was spent on medicines in Germany in 2008. Of this amount, 73% (31.6 billion euros) was borne by the SHI scheme and 6.7% (2.9 billion euros) by the PHI scheme, these being the two major cost bearers of the primary pharmaceutical market, while 5% was spent by other cost bearers. According to the annual health expenditure accounts, private households bore 15.2% of pharmaceutical costs themselves in 2008, spending a total of 6.59 billion euros. An analysis of pharmaceutical expenditure over the past 15 years shows a continuous rise (apart from a deviation in 2004 in 2005), with a mean annual growth rate of 4.7% for SHI and 6.3% for PHI (primary pharmaceutical market). At 2.4%, the mean annual growth rate of pharmaceutical expenditure by private households (secondary pharmaceutical market) between 1993 and 2005 was substantially less than that of the primary pharmaceutical market. Since 2005 the secondary pharmaceutical market has even diminished, the mean annual growth rate over this period being -3.4% (Statistisches Bundesamt 2010b, p. 13) (Fig. 7).

FIG. 7 DEVELOPMENT OF PHARMACEUTICAL EXPENDITURE IN GERMANY



Source: German Federal Health Monitoring (Gesundheitsberichterstattung des Bundes) (www.gbe-bund.de)

Of all pharmaceuticals sold, 85% were sold via public pharmacies and 5.6% via retail outlets (the remainder being obtained through hospitals for inpatient use

or from outside of Germany). Pharmaceutical expenditure by private households includes in particular spending on self-medication and private prescriptions, which are not covered by PHI (from 1995 to 2008 on average 60% of private pharmaceutical expenditure), and copayments (on average 30%). According to the Federal Statistical Office, spending on self-medication and private prescriptions rose by an average of 1.8% per year until 2005 and has fallen since then. In the period from 2005 to 2008 the mean annual growth rate of the self-medication and private prescription market was -2.7%.[62]

These findings are supported by sales figures of over-the-counter medicines obtained for the Federal Union of German Associations of Pharmacists (*Bundesvereinigung Deutscher Apothekerverbände*, ABDA). Given that prices remained essentially stable over the period from 2005 to 2009, the reduction in spending on over-the-counter medicines that occurred over this period is attributable mostly to declining sales. In the self-medication sector the mean annual growth rate over this period was -1.3%, while the corresponding figure for private prescriptions was as low as -4.1%.

So far, therefore, the dynamism of the secondary healthcare market that is sometimes assumed to exist, especially in the self-medication sector, as a result of aggressive advertising by manufacturers, factors that intensify competition, and increasing orientation of manufacturers, pharmacists, and doctors towards customer wishes together with an increasing tendency of these groups to follow their own economic interests cannot, at least on the basis of health expenditure and sales figures for over-the-counter medicines, be shown to exist in the pharmaceutical sector. At most, only random surveys of SHI-insured people could provide evidence of this supposed dynamism.

An analysis of the secondary pharmaceutical market as a whole provides no evidence that consumers do not make reasoned decisions in this market sector or would not apply limits to this market. However, whether this overall judgment can be extrapolated to the consumption of individual substances that could potentially be used for enhancement purposes, e.g. caffeine tablets, is an open question that can be answered only by market analyses of individual substances. So far, however, systematic analyses of this type are not available.

62 The many changes to relevant laws that were made in the years 1997, 1999, 2004, and 2006 led to substantial rises and falls in copayment amounts. Over this period annual growth rates fluctuated between -27.5% and 47.2%. As a result, mean annual growth rate is not a suitable reference parameter.

THE SECONDARY PHARMACEUTICAL MARKET AS A PATHWAY TO ENHANCEMENT AGENTS

As compared to the primary pharmaceutical market, the secondary pharmaceutical market provides enhancement agents that are covered by medicinal products legislation with a similarly regulated but – depending on the pharmaceutical category (over-the-counter, pharmacy-only, prescription-only) – more structurally porous point of entry (Bless et al. 2010, pp. 47–48).

The fundamental obligation of doctors and pharmacists to serve the purpose of health stands in conflict with economic considerations. Depending on the side effect potential of a drug, the conceivable – and from the regulatory perspective foreseen – likelihood that a doctor will refuse to issue a prescription in response to a patient's wishes or that a pharmacist will refuse to provide a medicine that a patient has asked for can be considered to diminish in proportion to the likelihood that another doctor or pharmacist will accede to these wishes. The lower the side effect potential of a substance, the lower is the refusal rate likely to be. Since doctors can charge more for issuing such prescriptions to private individuals as individual health services (IGeL) – since the medical fees ordinance governing private health services permits application of incremental factors to scheduled fees, in some cases without need for justification – than they can via the SHI billing system and since SHI funds are increasingly monitoring compliance with the precept of economic efficiency, the secondary pharmaceutical market can be assumed to provide more »enhancement-friendly« access structures.

Given the economic orientation of manufacturers and the increasing restrictions being placed on the primary pharmaceutical market, it is natural that manufacturers should strive to tap into the secondary pharmaceutical market. In this regard it should however be noted that newly licensed drugs are automatically given prescription-only status for five years so that the risk they pose can be more reliably assessed.

In the secondary pharmaceutical market consumers bear a greater responsibility for their actions, while the decisions they make are influenced both by reason and by emotion. As a result, there is also a demand for medicines that have yet to be shown by evidence-based methods to provide a benefit. This situation allows enhancement agents to gain a foothold. Nevertheless, developments over the past few years, in particular the downturn in market volume, suggest that consumers in this secondary pharmaceutical market are more circumspect than they are often assumed to be. This is because notwithstanding the fact that a substantial proportion of medicines have been displaced from the primary to the secondary pharmaceutical market, the dynamic development of the primary pharmaceutical market and of the expanded healthcare market in general cannot be transferred to the secondary pharmaceutical market. Over the past few years

consumers have in fact become less willing to pay for medicines in the secondary market. At present, therefore, this reluctance of consumers to pay must be regarded as an obstacle to the use of medicines for enhancement purposes.

Particular obstacles to use for enhancement purposes exist in the case of medicines that are classified as narcotics or doping agents or that are not approved for use in Germany. The severe restrictions to which medicines in these categories are subject, including requirements for detailed documentation and control mechanisms; the potential risk to the patient/customer from incorrect use; the risk, especially in the case of doping, of overstepping professional ethical guidelines; and societal disapproval: all these factors combine to make it very likely that doctors and pharmacists will observe these regulations even in the face of explicit »customer wishes« (Bless et al. 2010, p. 48).

THE INTERNET MARKET AS A SECTOR OF THE PHARMACEUTICAL MARKET

Since 2004, pharmacists who operate a retail pharmacy have been allowed to apply for permission to operate a mail order pharmacy as well (Bless et al. 2010, pp. 31ff.). German medicinal products legislation, including regulations on the licensing, manufacture, marketability, and advertising of medicines, is also applicable to the internet trade in medicines. German law applies also to the mailing of medicines from other countries to Germany (the Pharmaceutical Price Ordinance [*Arzneimittelpreisverordnung*]) applies; medicines that are not licensed for use in Germany may not be mailed). The legal mail order trade in medicines is governed by essentially the same regulations as those that govern the primary and secondary pharmaceutical markets, however customer contact with the pharmacist is more anonymised than in the case of a retail pharmacy and the gatekeeper role of the pharmacist in terms of providing advice is correspondingly diminished (Bless et al. 2010, p. 49).

However, compliance with these legal regulations is difficult to enforce. In addition to the legal mail order trade, there are many illegal ways in which medicines can be acquired over the internet. The following methods of circumventing regulations are especially common (Bless et al. 2010, pp. 32–33.):

- Taking advantage of drug regulations of other countries that differ from those that apply in Germany, e.g. mailing from countries such as the USA in which the categorization of medicines is less restrictive (this method extends to illegal activities and is extremely difficult to monitor by means of control systems that assume the existence of a retail pharmacy,);
- Issue of prescriptions by an »online doctor« who is supposed to review questionnaires and authorize prescriptions;
- Opaque offers permeated with counterfeit medicines.

In international trade the customer, who as a private individual is actually not authorized to import medicines and who generally lacks any specific knowledge of what can or cannot legally be purchased, also runs the risk of suffering adverse effects. These are scarcely calculable, since the internet market is largely out of reach of the AMG, even the process of manufacture being largely uncontrolled. Consumers find it difficult or impossible to distinguish between genuine and counterfeit drugs, especially as the primary pharmaceutical market has already led them to accept and have confidence in reimports and repackaged products. In addition, price competition plays a greater role in mail order purchases than in purchases from a retail pharmacy and tends to direct demand towards the cheapest offers, which in turn are less likely to meet all the requirements of medicinal products legislation. Bless et al. (2010, p. 40) describe the internet market in products that are claimed to enhance cognitive performance as a market characterized by opaque offers of substances, permeated by off-label use of prescription medicines some of which are subject to the stringent requirements of the BtMG and associated regulations governing prescription, and supported by illegal procurement channels and areas of overlap to illegal drug consumption. As compared with the conventional trade in medicines, it requires separate control measures such as involvement of Federal Customs. The amounts of medicines seized by Customs have risen continuously over the past few years, e.g. the amount of amphetamines seized has risen from 212 kg in 2007 to 668 kg in 2009 (BMF 2010, p. 10). The impenetrable structure of the internet market is considered to be a major reason for this.

Were a strong consumer demand for enhancement substances to arise, very little in the way of inhibitory influences could be expected in this market sector. The internet market thus represents a potentially important point of entry for enhancement agents that eludes any genuine transparency (Bless et al. 2010, p. 49).

THE CONSUMPTION SIDE: FINDINGS ON USE OF MEDICINES FOR PERFORMANCE ENHANCEMENT 4.

Both food law and pharmaceutical law specify what constitutes correct use of substances that fall within their respective remit and impose individual prohibitions aimed at protecting (public) health.

Because of the general personal rights – including the right to harm oneself – that are enshrined in the German constitution (Art. 2 Subsection 1 GG), individual actions such as improper use of foods or medicines are at present regarded as nonpunishable actions in German criminal law. Measures taken by third parties at a person's request to improve that person's body in the absence of a need for treatment are regarded as an expression of that person's constitutionally en-

shrined right to self-determination. This right is, however, limited by the constitutional order, the rights of others, and moral laws (Art. 2 Subsection 1 GG; Simon et al. 2008, pp. 20–21). Any restriction of personal rights could be justified only on the basis of a protected good of similar standing, e.g. the personal rights of third parties or public health (e.g. the prohibition of driving after consumption of alcohol contained in road traffic regulations).

On this basis the consumption of particular substances, even substances that are harmful to health (e.g. doping agents and illegal drugs), is not prohibited by law in Germany; instead, only the handling of such substances and actions by third parties that could encourage such handling are prohibited (Section III.3.3).

As a consequence of freedom of association (Art. 9 Subsection 1 GG), organizations (e.g. sports clubs, professional associations) may, as part of their autonomous self-regulation, determine the rights and obligations of their members in accordance with their own criteria and values and in so doing restrict the personal rights of their members (Simon et al. 2007, pp. 16–17). On this basis sports organizations can, for example, prevent their members from taking part in competitions if the members concerned have ingested potentially performance-enhancing substances and can monitor compliance with such an organization-internal prohibition of consumption.

On this basis it is at present basically not against the law in Germany to consume substances either for the purpose of enhancing performance (except in organized sport) or for other purposes if access to such substances is available. However, in order to prevent possible harm to health such access is restricted, above all in the case of medicines. Despite this restriction, the German Medical Association (*Bundesärztekammer*) notes the following epidemiologic findings on problematic use of medicines (Bühren et al. 2007, pp. 10–11):

- Approximately 1.4 to 1.9 million people in Germany are dependent on medically prescribed psychotropic medicines. Another 1.7 million people are regarded as being at moderate to high risk of developing substance dependence of this type. To these must be added people who abuse nonprescription medicines and whose abuse of medicines is therefore difficult to detect.
- About 5% of adult citizens in Germany have problems associated with the use of psychotropic medicines (i.e. they abuse or have become dependent on potentially addictive medicines).
- About twice as many women as men suffer from dependence on medicines.
- Prevalence increases from the age of 40 years, while from the age of 60 years use of psychotropic medicines not in accordance with a prescription is a widespread problem.

It may be assumed that a proportion of these people develop this behavior despite having »only« wanted to maintain, or perhaps also improve, their performance in occupational settings.

EMPIRICAL FINDINGS ON PHARMACOLOGICAL PERFORMANCE ENHANCEMENT 4.1

A very small number of empirical studies provide evidence of the extent to which pharmacological substances have been used for the purpose of performance enhancement up to now. The situation in the occupational and work settings in Germany is described in the DAK health report (DAK 2009). Under the heading »Doping am Arbeitsplatz« (»Doping at work«) this report attempts to provide empirical evidence of the extent to which pharmacological substances are taken for the purpose of performance enhancement at workplaces in Germany. To this end a sample of working people aged between 20 and 50 years from all parts of Germany were asked about their use of »potent medicines« to improve their mental capacity or psychological wellbeing in the absence of any medical need. Of the approximately 5000 such people approached, about 3000 responded. As in the questionnaires on doping used in elite sport, the respondents were first asked whether they were aware of anybody who took medicines to improve their performance or brighten their mood in the absence of any medically compelling reason. About a fifth of respondents answered this question in the affirmative. A similar number of respondents reported that they themselves had been offered potent medicines in the absence of any medical need (DAK 2009, pp. 52–53).

Five percent of respondents stated that they themselves had taken potent medicines in the absence of any medical need and 2.2% said that they did this often to regularly. Women used such substances more often to improve their psychological wellbeing, men more often to improve their cognitive abilities (DAK 2009, pp. 56–57).

Assuming the sample to have been representative of the approximately 40 million working people in Germany, this means that about two million working people were taking or had taken potent medicines to improve their performance or brighten their mood at work in the absence of any medically compelling reason for doing so and that about 900,000 of those people did this often to regularly. The purpose of the DAK survey was to gather evidence on the extent of doping at work in the general working population. In this regard this survey differed from most other surveys on doping and enhancement behavior in that these have focused on potential risk groups assumed to be exposed to particularly high performance requirements, in some cases in particularly competitive environments.

For example, an online survey undertaken by the science journal »Nature« (Maher 2008) extended only to the journal's own readership, which can be assumed to consist primarily of professionals in scientific and related fields from whom a high level of cognitive performance is expected. Of the 1400 people

from 60 countries who responded to this survey, 20% stated that they had taken medicines to improve their mental performance in the absence of any medical need. Maher (2008) states explicitly that this sample is not representative of the general population.

School and tertiary students are likewise regarded as a segment of the population that is regularly exposed to demands for high cognitive performance. Between 2009 and 2010 Franke et al. (2011) asked 1035 school students (mean age 19.3 years) and 512 tertiary students (mean age 24 years) in Germany to provide anonymous written information on their consumption of various substances. The students were asked whether they took stimulants when not ill to improve their cognitive abilities (e.g. alertness, concentration, memory), whereby the substances taken were classified as either prescription medicines (e.g. methylphenidate, modafinil, anti-dementia agents) or illegal drugs (e.g. amphetamines, cocaine, ecstasy). In response, 1.5% of the school students and 0.8% of the tertiary students stated that they had taken prescription medicines for enhancement purposes, while 2.4% of the school students and 2.9% of the tertiary students stated that they had consumed illegal drugs for this purpose. Approximately 50% of the consumers stated that they had taken both medicines and illegal drugs.

Schermer et al. (2009, p. 79) refer to similar pilot surveys, namely a survey of Dutch schoolchildren aged between 12 and 18 years (prevalence: 2.4% for consumption of non-indicated psychostimulants, 1.2% for consumption of Ritalin in particular) and a survey of 1500 Belgian tertiary students (prevalence: 3% for consumption of non-indicated psychostimulants during the study period). In the USA students have long been asked about their consumption of various substances. Best known are the surveys conducted as part of the regularly performed US »College Alcohol Study« (CAS), which in recent years has also dealt with consumption of medicines. In 2003 a total of 10,904 students from 119 colleges and universities were questioned. Of the 52% who responded, 6.9% stated that they had taken prescription-only stimulants without a medical indication on at least one occasion (McCabe et al. 2005, pp. 98ff.). Similar prevalence rates were found in a survey of students of the University of Michigan. In this survey 8.1% of the 9161 students who participated (47% of the student population) admitted to consumption of this type on at least one occasion, men being significantly over-represented compared to women in this regard (Teter et al. 2005, pp. 256–257).

A number of empirical studies have also been conducted on doping behavior in sport, however these too relate mostly to specific risk groups rather than to all athletes. These risk groups include on the one hand competitive and elite athletes (at present there are about 8500 »squad athletes« in Germany who are subject to the doping control system of the National Anti-Doping Agency) and on the other hand fitness club members (of whom there are 5 to 6 million in Germany). Based on an anonymous internet-based survey of German squad athletes, Pitsch

et al. (2005) found a doping frequency of about 26% (however the authors estimate that 20% of the »non-dopers« may have given incorrect answers). In 1998 Boos/Wulff (2001) performed an anonymous questionnaire-based survey of the members of 58 fitness clubs. Based on the responses obtained they calculated that approximately 19% (men 22%, women 8%) of the fitness club members had used doping substances (specifically anabolic steroids) on at least one occasion. Assuming that the samples used in these surveys are representative of the population groups concerned and that the size of these groups is known, these figures can be extrapolated to provide estimates of the extent of doping in these groups in terms of absolute user numbers (Table 12).

TABLE 12 FREQUENCIES OF USE OF MEDICINESFOR PERFORMANCE ENHANCEMENT

	Workplace		School/university		Sport	
Literature reference	DAK 2009	Maher 2008	Franke et al. 2011	McCabe et al. 2005	Boos/Wulff 2001	Pitsch et al. 2005
Sample	3017 workers (20–50 years)	1400 scientists	1547 school and tertiary students	10,904 tertiary students	454 fitness club members	448 squad athletes
Region	Germany	worldwide	Germany	USA	Germany	Germany
Total population	approx. 40 million workers	unknown	unknown	unknown	approx. 5–6 million fitness club members	approx. 8500 squad athletes
Prevalence						
at least once to occasionally	5% (~2 million)*	20%	1%	7%	19% (~ 1 million)*	26% (~ 2200)*
frequently to very frequently	2.2% (~ 0.9 million)*					

* extrapolated to total population

Table drawn up by the present authors on the basis of the cited literature references

Unlike in the DAK survey, in which no real sociodemographic analysis was attempted, in the other surveys of cognitive performance enhancement efforts were made to identify more precisely the population groups that used pharmacological substances for performance enhancement and the setting in which they did this. In the »Nature« survey (Maher 2008) people in all age groups admitted to using neuroenhancers (with prevalence highest, at 25%, in the under-25-year age group; lowest, at 10%, in the 45 to 55-year age group; and with a second peak in the over-55-year age group).

The US College Alcohol Study (CAS) (McCabe et al. 2005) found that people who used Ritalin without a medical indication tended to be male, white, and members of a student union and to achieve slightly below-average academic results. Relatively more of them also admitted to other forms of risky behavior (e.g. consumption of illegal drugs). The proportion of students who admitted to using Ritalin without a medical indication ranged between 0 and 25% at different colleges. Colleges with particularly competitive admission procedures showed the highest rates (McCabe et al. 2005, p. 96). The prevalence of non-medically indicated use of prescription-only stimulants was found to be significantly higher in specific surveys of school and tertiary students than in similar surveys of young Americans as a whole (in whom the prevalence was less than 1%) (Teter et al. 2005, p. 259).

In the German study significantly more school students from *Berufsschulen* (vocational schools) than from *Gymnasien* (academic high schools), and more students with poorer grades, admitted to using medicines. More male than female school students admitted to using illegal drugs for enhancement purposes. Significantly more students who were members of student fraternities stated that they used stimulants (both medicines and illegal drugs) (Franke et al. 2011).

The surveys by Pitsch et. al. (2005) found doping behavior to be more common in types of sport in which specific parameters of physical performance are compared (»CGS« sports, in which performance is measured in centimeters, grams, or seconds) than in types of sport that call for more complex parameters of sporting performance (game-type sports). Athletes who competed only at national level were less likely to admit to doping than athletes who competed at international level. However, a more detailed analysis showed that the prevalence of doping fell again at the very highest performance levels, which are most subject to the system of doping control in organized sport. Pitsch et al. (2009, p. 19) consider doping to be a problem mostly of the »second tier«, since the already high level of performance and success of athletes in the »first tier« means that for them doping is scarcely likely to bring any additional benefit, whereas it could cause considerable harm (see also Section VI).

In view firstly of the difficulty of determining precisely what constitutes use of medicines for performance enhancement in occupational settings and secondly of the considerable inclination on the part of respondents to give incorrect answers that must be assumed to exist given the high degree of moral disapproval of doping that exists and the prohibitions imposed by sports authorities and medicinal products legislation, surveys on this topic can provide only general information on the societal dimension of pharmacological performance enhancement in educational, occupational, and sports settings. Analysis of this information is based mostly on extrapolated absolute frequencies. For example, in the analysis of the DAK survey the number of people who use potent medicines often or very

often for performance enhancement is further reduced to include only those people who are assumed to obtain the medicines concerned by irregular means. The figure of 1 to 1.9% that then remains is described as not indicating the existence of a widespread phenomenon. Instead, the authors conclude that the picture presented in the public debate about this topic is distorted (DAK 2009, p. 60).

Nevertheless, an extrapolation of the results of the DAK survey to the totality of working people in Germany suggests that approximately two million working people have taken medicines for the purpose of performance enhancement at work on at least one occasion but do so no more than occasionally and that as many as a million working people do so frequently to very frequently (Table 12). And this extrapolation does not even take account of the fact that problematic patterns of consumption of medicines are observed more commonly with increasing age whereas working people over the age of 50 were excluded from participation in this survey, as a result of which these figures may even be underestimates. An assessment of the situation should therefore take account of the absolute figures. Boos (2007) refers not only to prevalence rates derived from the results of the survey, but also explicitly to extrapolations to all fitness club members in Germany (a total of one million fitness club users, of whom more than 700,000 males and almost 300,000 females were said to be dopers, i.e. people who had taken doping substances on at least one occasion) and describes the doping situation in fitness clubs in Germany as horrendous.

It must also be borne in mind that highly aggregated observations can paint a distorted picture of the specifics of the problem. For example, as doping behavior is expected above all in competitive athletes engaged in certain types of sport and in members of fitness clubs, but not in people who engage in sport in general (e.g. the approximately 27 million people who are presently members of sports clubs in Germany), it must also be conjectured that specific questioning of occupational groups subject to different levels of pressure to perform would reveal differences in the frequency with which medicines are used for performance enhancement at work. This should be taken into account in the planning of future studies (Section VII).

REJECTION VS. ACCEPTANCE

The use of potentially performance-enhancing substances in everyday and occupational settings seems to meet with less social rejection than does doping in sport, which is subject to a high degree of social rejection in large segments of public life.

The level of acceptance was highest in the participants in the »Nature« survey. Whereas »only« 20% of respondents stated that they themselves had taken neuroenhancers, 80% felt that healthy adults should be allowed use such substances at their own volition. Potential side effects were scarcely seen as a compelling

reason for rejection, 69% of respondents stating that they would be prepared to risk the possibility of moderately severe side effects if the substances did actually improve their performance (Maher 2008).

The DAK survey yielded the following findings: Most respondents (63% of men and 56% of women) fundamentally rejected the idea of using medicines to improve *intellectual ability*. The idea of using medicines to improve *psychological wellbeing* was rejected by a slightly higher proportion of respondents (70% of men, 60% of women) (DAK 2009, pp. 78–79). The most commonly stated reason for rejection was the absence of medical need (cited by two thirds of the respondents who generally rejected such behavior). A third of the respondents did not consider that such use of medicines would bring any benefit in terms of occupational activities, and a third rejected the use of medicines for this purpose in principle. By contrast, only 2.7% of women and 3.4% of men saw undeserved advantages as a reason for rejecting enhancement in principle.

Those respondents who did not in principle reject the use, including by healthy people, of medicines to *improve intellectual ability* were asked to state what reasons they would consider to justify such behavior. The most important such reason cited was a general improvement in attention, memory, and ability to concentrate (28% of women, 25% of men), followed by a wish to reduce tiredness during working hours and to extend working hours when under pressure of deadlines. Those respondents who did not in principle reject the use, including by healthy people, of medicines to *improve mood* considered the most important justifications to be an improved ability to cope with stress, a reduction in nervousness and jitters, and better mood in the private realm (DAK 2009, pp. 79ff.).

If a proportion of the population considers the use of medicines to improve individual abilities or to brighten mood in the absence of a medical indication to be acceptable und if a proportion of the population is even prepared to accept side effects as a price worth paying for these benefits, it is necessary to ask how the potential consequences of such behavior should be dealt with and who should bear the cost of any treatment that may be necessitated by such behavior.

DEALING WITH POTENTIAL COSTS ARISING FROM USE OF (ENHANCEMENT) SUBSTANCES 4.2

Despite the existence of regulations and procedures intended to ensure that insofar as possible medicines are used only in ways that are conducive to health, problematic use develops in a proportion of users, and this is by no means a new phenomenon. The WHO's International Statistical Classification of Diseases and Related Health Problems (ICD-10) defines various illness-relevant states that can arise as a result of consumption of psychotropic substances (categories F10 to

F19) and distinguishes them from consequences of consumption of non-dependence-producing substances (category F55, which is subdivided into subcategories [»diagnosis codes«] such as vitamins [F55.4], specific herbal or folk remedies [F55.6], and various others). The substances discussed in Section II can be assigned to individual categories of this classification. These categories are further differentiated into various forms of damage that can arise as a result of substance consumption. These range from acute intoxication (F1x.0) through harmful use (F1x.1) to impairment of short- and long-term memory, also known as amnesic syndrome (F1x.6).

When an illness-relevant state arises as a result of inappropriate consumption of medicines, treatment falls within the direct area of responsibility of doctors (Section III.3.5). Depending on the particular situation, both acute treatment and withdrawal treatment may be required. Some doctors and hospitals have already made themselves specialists in the follow-up treatment of incorrect use of certain substance groups (e.g. hypnotics and tranquilizers, analgesics) or of certain categories of patient. Medical help for health problems resulting from incorrect use or abuse of medicines is thus provided independently of the possible causes or purpose of the use of a substance in the individual case and at present falls within the benefits catalogs of various different cost bearers.

Nevertheless, the state makes people who are liable for social security contributions partly responsible for their own health by requiring them to contribute to the maintenance of their health by acting in a health-conscious way (§ 1 SGB V). Until 2008 no restriction on the provision of benefits was applicable in cases in which a person who was liable for social security contributions failed to comply with this demand and as a result developed an illness-relevant state, since in this situation the person was deemed to be only partly responsible for the illness. Since 2008, however, health insurance funds have been entitled to require people insured with them who have intentionally made themselves ill to contribute to the costs arising from their illness (§ 52 Subsection 1 SGB V). In the case of damage to health resulting from non-medically indicated esthetic operations or from tattooing or piercing, the health insurance fund is not just entitled, but actually obliged, to do this (§ 52 Subsection 2 SGB V). Moreover, in such cases the insured person has no claim to sickness benefit for the duration of the illness. A similar ruling applies in private health insurance (§ 178b VVG [*Vertragsverich-erungsgesetz,* Insurance Contract Act]; Simon et al. 2008, p. 25).

Simon et al. (2008, p. 26) point out that this change in the law represents the first application of sanctions for self-inflicted illness in order to relieve the burden on the insured community. Also introduced in 2008 was a ruling that obliges the treating doctor to inform the health insurance fund of any evidence of damage to health caused by third parties (§ 294a Subsection 2 SGB V).

It remains to be seen to what extent this restriction on benefits (§ 52 SGB V) and this obligation to inform (§ 294a SGB V) might also apply to the potential consequences of enhancement measures. It seems likely that premeditation and a cause-effect relationship between substance ingestion and illness would need to be proven. In this event a treatment plan for dependence on medicines would probably have to be provided, since the disparity between the treatment of the consequences of simple incorrect use and that of the consequences of intentional misuse would need to be justified. In this regard it must also be noted that both these rulings (§ 52 Subsection 2 and § 294a Subsection 2 SGB V) are presently regarded in the legal literature as being constitutionally contentious, since in addition to a violation of the right to self-determination, a violation of the principle of equality as enshrined in Art. 3 GG can be inferred insofar as only the consequences of the named medical procedures, but not, for example, the consequences of high-risk types of sport, are subject to restriction of benefits (Simon et al. 2008, pp. 26–27).

5. CONCLUSION

Foods and medicines are normatively separate categories (Section III.1) that are distinguished from one another by their effects on the human organism. Depending on which of these two categories it is assigned to, a substance is subject to very different procedures in relation to proof of efficacy, user information, accessibility, and surveillance and control structures. Table 13 summarizes the procedures of this kind that are described in detail in Sections III.2 and III.3.

Due to the increasing number of ways in which individual substances can be extracted and added to processed foods, food products are becoming increasingly difficult to categorize as possessing either exclusively nutritional or specifically pharmacological properties and in some cases can be categorized only on the basis of an individual juridical decision.

The consumer, who may be assumed to be able to exercise »reasonable discretion« but cannot be assumed to possess detailed knowledge, sometimes finds it difficult to distinguish between different substance categories and their subgroups. This is made all the more difficult by the fact that products that are assumed to have some potential for performance enhancement (Section II.3) may belong to either of these two substance categories or their subgroups. Along with specific marketing strategies by manufacturers (e.g. giving food supplements the appearance of medicines and advertising to the point of deception), easy availability (many products can be sold both via ordinary retail outlets and in pharmacies) helps to make it at least difficult for consumers to deal with, i.e. evaluate and consume, individual products in a discriminating and competent manner.

TABLE 13 **FOODS AND MEDICINES: SUMMARY OF DIFFERENCES AND REGULATORY TREATMENT**

	Foods	Medicines
Defining properties	Nutritional actions (in Germany foods may not exert any pharmacological action or have any therapeutic value)	Pharmacological, immunological, or metabolic action (prevention or cure of illness)
Intended function	Nutrition, preservation of health	Prevention and cure of illnesses
Essential ingredients	Nutrients	Medicinal substances
Legal basis	Food legislation (German Food and Feed Code [*Lebensmittel-, Bedarfsgegenstände- und Futtermittelgesetzbuch*, LFGB])	Medicinal products legislation (Medicines Act [*Arzneimittelgesetz*, AMG]; Narcotics Act [*Betäubungsmittel-gesetz*, BtMG])
Legal principle	Principle of abuse: Safe foods may be manufactured and placed on the market unless a specific form of behavior is expressly prohibited Nutrients do not require approval; additives (added for technical purposes) require approval	Principle of prohibition subject to exemptions: Production and distribution require prior approval
Basis of assessment	For restrictions: risk analysis	For approval: benefit-risk analysis
Benefit assessment/ approval	No general proof of efficacy Positive list of additives based on risk analyses Claims of a health-promoting action must be scientifically proven (testing by the Federal Institute for Risk Assessment [*Bundesinstitut für Risikobewertung*, BfR] [Germany] or the European Food Safety Authority [EFSA] [EU]) Few scientifically recognized procedures for establishing efficacy and safety are available at present	Manufacturer must provide evidence-based proof of pharmacological efficacy via an illness-specific benefit-risk assessment (burden of proof lies with manufacturer) National/international regulatory authorities (BfArM [Germany], EMA [EU], FDA [USA]) check evidence and where appropriate grant permission for manufacture and sale
Substance protection	No disclosure of recipe	Temporally limited patent protection for new substances Temporally limited protection of marketing authorization documents

TABLE 13 **CONTINUATION**

	Foods	Medicines
Legally defined subgroups	Additives and equivalent substances Food supplements Dietary foods	Nonprescription/prescription medicines Marketable/nonmarketable narcotics
Provision of information, labeling, advertising	Naming of ingredients Nutritional information must be correct Health-related claims and statements about reduction of risks of illness must be verifiable (principle of prohibition subject to exemptions [HCR]) Prohibition of illness-related claims and indications (exceptions as per Diet Ordinance [*Diätverordnung*, DiätV])	Statements about composition and illness-related claims about proprietary medicinal products may be made in the form of standardized informational texts (package leaflets) for consumers, doctors, and pharmacists More detailed technical information is often available only to health professionals Prescription medicines: advertising of products to consumers is prohibited, only advertising to health professionals is permitted
Accessibility	Marketability unrestricted, open market Sale via retail outlets, internet, in some cases also pharmacies	Marketability restricted Sale only via authorized structures (pharmacies, in some cases only with a doctor's prescription)
Monitoring of safety	Responsibility lies with the manufacturer Control: food regulatory authorities (BVL [Germany], EFSA [EU]); burden of proof in the case of infractions lies with the regulatory authorities BfR can make recommendations Use: responsibility lies with the consumer	Manufacturer bears responsibility for R&D, production, and long-term monitoring of substances Control: regulatory authorities Use: consumer bears degrees of responsibility; pharmacists and doctors also bear considerable responsibility (undertaking in accordance with medical and pharmaceutical licensing acts) Control: professional associations
Financing	Consumers	*Primary healthcare market:* SHI: Federal Joint Committee (G-BA) can restrict benefits (legal basis: SGB V) PHI has its own contractual agreements *Secondary healthcare market*: Consumers (in some cases via supplementary insurance)

Table compiled by authors

The fact that market analyses of the secondary healthcare market classify some medicines together with functional food products, and in some cases even with organic foods, shows that this mixing up of categories is still going on. The great dynamism that the secondary healthcare market is generally assumed to possess obscures the fact that the situation in the food sector may be quite different from that in the pharmaceutical sector. In the past, the market for foods that could be advertised as providing an additional health benefit was regularly said to be growing rapidly.

To date there has been scarcely any need to provide factual evidence in support of claims that foods provide additional health benefits, since neither German nor European food law contains any general requirement that food components be shown to have any effect – either favorable or unfavorable – on the human organism. As a result, knowledge of the possible effects of individual components of foods remains limited. Due on the one hand to the paucity of obligations to provide information and on the other hand to a lack of restrictions on advertising, food manufacturers have for years been able to suggest that their products have performance-enhancing properties and even make scientifically unfounded advertising promises to that effect. Such foods were therefore able to become door openers and presumably also wish intensifiers that create a demand for more potent performance-enhancing substances in the absence of any discussion of possible risks.

However, the introduction of the Health Claims Regulation has made it increasingly difficult to make unsubstantiated advertising claims about the supposedly beneficial effects of foods on the human organism. Whether this will have a critical impact on overall demand and market development in this sector remains to be seen. There is a basic expectation that consumers should exercise reasonable discretion in relation to all foods. Further improvements in the provision of information to consumers are considered to be crucially important in this regard. Information provided by unbiased public sources should put interest-driven claims by manufacturers and unregulated information forums into perspective. In many European countries, e.g. Denmark, official requirements that consumer information about foods be unbiased are more stringent than they are in Germany.

As in future all health-related claims will need to be scientifically substantiated, it is to be expected that concepts will be developed to explain, for example, how a non-illness-related additional health benefit of an individual food can be defined and demonstrated to exist. At a conceptual level this could pave the way for pharmaceutical research for enhancement purposes. The definition of benefit that is presently accepted in pharmacological research – and on the basis of which clinical research with pharmacological substances is legitimized, marketing authorization is granted, and reimbursement of costs via the public health system is determined – assumes the existence of an illness-relevant state, or at

least a deficiency state, as a basis for demonstrating a (therapeutic) benefit in the form of an improvement (alleviation, cure). At present, therefore, clinical studies do not provide a basis, at least in the context of medicinal product licensing, for any claims of performance-enhancing effects in healthy individuals and no such effects are referred to in the obligatory product information texts.

The regulations that govern marketing authorization, marketability, and financing via the public health system appear to act as obstacles to public adoption of enhancement practices. Over the past few years restrictions on access have if anything been tightened and made more specific, especially in the pharmaceutical market. The first hurdles that clinical R&D has to overcome (the need for research projects to be approved by an independent ethics committee and in some cases also by a regulatory authority) impose limits on direct research on enhancement but cannot prevent it entirely, as a therapeutic objective is very easy to define. The next hurdle, namely the marketing authorization procedure, demands *proof of therapeutic efficacy* and thereby explicitly rules out marketing authorization for enhancement purposes. Over the past few years both German and European judicial decisions have underscored this approach (medicines must exert a therapeutic effect of a certain strength). On this basis medicines can be used for enhancement purposes only outside of the medical indication for which marketing authorization for their use was granted, i.e. in off-label fashion. And the public health system, at least, is, via SGB V, placing more and more obstacles in the way of such use. For example, the scope of benefits to be provided by SHI funds must not exceed that which is necessary, adequate, and economically efficient. More and more restrictions are being imposed on off-label use of medicines, and exclusions from benefits are already being imposed in cases in which, notwithstanding the existence of an illness, the use of medicines can be linked above all to a gain in terms of quality of life.

Even though these obstacles cannot completely prevent enhancement practices, the extent to which such practices are rejected, at least at the regulatory level, has if anything increased, as is apparent from judicial decisions made over the past few years. At present no trend towards a more liberal approach is evident at that level. And use of medicines to enhance physical performance, i.e. doping, is rejected even more emphatically. Indeed, over the past few years the legislature has tightened restrictions in this area (prohibition of possession, increased penalties). In order for the present approach to the use of medicines to enhance mental performance dimensions under everyday conditions to be changed, socially relevant reasons would first need to be found (for details, see Section V).

The secondary healthcare market that arises above all because of the existence of restrictions on SHI benefits is often said to be the most fertile ground for enhancement services to become established. Evidence such as the increase in prescriptions for medicines in the framework of individual health services (IGeL)

points in this direction, as do advertising strategies developed explicitly for this market (Section III.3.4). Other factors that favor this development include a lower level of scrutiny than in the primary healthcare market and the fact that doctors are becoming increasingly obliged to take account of economic factors in the exercise of their profession.

Despite all this, the trend towards provision of enhancement services in the secondary healthcare market appears to be far less pronounced than is commonly supposed. Notwithstanding the factors that favor an expansion of the secondary healthcare market, spending on medicines by self-paying patients has risen more slowly than has spending on medicines by health insurance funds at all times since the 1990s. Since 2005 private spending on medicines has even fallen. This situation could change, however, if the performance-enhancing substances with few side effects that presently exist only in theory were to become available in this market, since it can be assumed that a significant proportion of the population would accept the use of such substances (Section III.4.1). The ever more common advertising strategies by means of which consumers are encouraged to see themselves as suffering from deficiency states can likewise be understood as door openers and pathways to the use of pharmacological measures to combat such supposed deficiencies. Precisely in this area, provision of unbiased user information is important as a basis for competent individual decision-making, since technical supervision by health insurance funds is absent and the unbiased position of doctors and pharmacists in their role as gatekeepers is to some extent compromised by economic considerations. Attempts to provide unbiased sources of information that are accessible to all consumers and that satisfy the requirement of being comprehensible to the general public are now being made, however considerable scope for improvement remains in this regard.

Any discussion of the topic of enhancement should deal with more than just the hypothetical scenario of the use of performance-enhancing substances with few side effects. Rather, in both the short and the medium term there is also a need for, among other things, a discussion of the social and political dimensions of the question of what approach should be adopted in the event that increased use of medicines for the purpose of performance enhancement at work and in everyday life leads to damage to health or to illness. Answers are required to, among other things, the question of whether the approach to be adopted in such circumstances should differ from the treatment as per the SHI benefits catalog of »normal« abuse of medicines, dependence resulting from excessive consumption of alcohol, or other forms of unhealthy behavior.

THE DEBATE ABOUT ENHANCEMENT IN ETHICS AND THE SOCIAL SCIENCES IV.

This report focuses on urgent research and health-policy issues regarding pharmacological interventions whose aim is to enhance performance at work and in everyday life. It does not delve deeply into the ethical debate about enhancement – if only because many, if not most, relevant analyses are based less on empirical observations or plausible assumptions than on examination of hypothetical »enhancement agents« (Schöne-Seifert/Talbot 2009; Schöne-Seifert et al. 2009). In the majority of cases this approach leads to individual and socioethical considerations that shed little light on the regulatory darkness of the real and expected future use of pharmacological substances, whether in the form of foods, *Genussmittel* (a German term that refers to foods or substances that are consumed primarily because of their taste or stimulant effect), medicines, or narcotics. This is shown below on the basis of the expert report by Ach/Bisol (2009) (Section IV.1).

Drawing on empirical findings, the social sciences can be expected to provide a closer look at the social conditions, backgrounds, personal and social motives, institutional dynamics, driving forces and possible consequences of enhancement-related developments. Section IV.2 discusses key points of the report by Viehöver et al. (2009), who carried out a social-science classification of enhancement in the context of larger societal processes and developments in the field of »biopolitics«. They proceed on the assumption that »enhancement tendencies are part of a historically new medicalization process that is shifting the categorial boundaries of medicine and changing the way modern medicine perceives itself (key phrase: mandate to heal)« (Viehöver et al. 2009, p. 2).

Section IV.3 summarizes the most important conclusions of the ethical and social-science debate about enhancement and the findings of Sections II and III of this report concerning the need for research and clarification, which is particularly relevant in the context of politics and society. Thus, the conclusion serves as a link to the two subsequent main Sections V (the scenario of expansion) and VI (possible lessons to be drawn from doping in sports).

THE ETHICAL DEBATE ABOUT ENHANCEMENT 1.

The expert report by Ach/Bisol (2009) gives a concise summary of the intensive (bio)ethical debate about enhancement that has taken place in recent years, mainly in the USA at first but for some time now also in Europe and Germany (Ach

2009; Coenen et al. 2010; Gesang 2007; Miller/Wilsdon 2006; Parens 1998; Savulecu/Bostrom 2008; Schöne-Seifert/Talbot 2009; Schöne-Seifert et al. 2009). The debate is closely linked to and overlaps extensively with the debate about analogous visions of the use of nanotechnology (Grunwald 2008) and so-called converging technologies, i.e. the postulated future merging of nanotechnology, biotechnology, information technology and cogno(= neuro)technologies, or NBIC for short (discussed in detail in TAB 2008a). These essentially visionary scenarios are of little relevance to the perspective of this report and are therefore only briefly dealt with below in the context of the debate about »naturalness«. Nor does the report discuss the technicophilosophical debate about the function and value of »speculative« or »explorative« ethics in the scientific debate about the use of technologies such as nanotechnology in (very) early stages (Grunwald 2010; Nordmann 2007).

Generally speaking, the (bio)ethical debate about enhancement concentrates on three principal questions:

- What is enhancement? What agents are used and what objectives are pursued? How does enhancement differ from other behaviors and the pursuit of other objectives?
- Where does enhancement stand in relation to the four »classical« principles of medical bioethics: beneficence, nonmaleficence, autonomy, and justice (Beauchamp/Childress 2001)?
- What are the potential consequences of enhancement on our understanding of human nature and our notions of humanity and society and how can they be evaluated?

DEFINITION AND DEMARCATION PROBLEMS 1.1

If we wish to examine and evaluate an action, its means, and its purposes as stringently as possible from an ethical point of view, the object of the examination must be defined as unambiguously as possible: who wishes to do what with what means and to what purpose?

Bioethical questions can relate to a range of different »examination objects« (in the sense of a specific action or objective for the application of bioscientific findings): for example the establishment of biobanks, where both the methods of collection and the objectives pursued are extremely heterogeneous; the creation of transgenic animals for the production of pharmaceuticals, where the means and objectives are narrowly defined; and the use of predictive, i.e. prognostic, genetic tests, where the means but not the objectives are quite clearly defined.

Enhancement is an extremely diffuse concept in the current bioethical debate, both with regard to the agents and methods considered and the purposes and ob-

jectives pursued. Enhancement is a multifaceted term that can mean »augmentation«, »potentiation«, »optimization«, »heightening« or »intensification« (in the sense of a perceived distortion of time), or »attaining physical fitness« (Ach/Bisol 2009, p. 11). No single German synonym exists. Many attempts to render the term in German hinge on the word *Verbesserung* (improvement), which however requires explanation, for example with regard to its comparative scale and the positive connotation it conveys (Grunwald 2008, pp. 249ff.). Even a cursory survey of the relevant literature reveals a multitude of terms in use (Ach/Bisol 2009, p. 11). A key difference is whether enhancement is interpreted merely as a quantitative increase or also as a qualitative augmentation of a specific human characteristic or function. Following on from Jotterand (2008), Grunwald (2008, p. 255) proposes the following categories for the purpose of differentiation: healing, doping, improvement, and modification:

1. »*Healing* as the elimination of deficits relative to recognized standards for an individual of average health in a manner analogous to an ophthalmologist prescribing glasses or contact lenses if a patient's visual acuity diverges from a reference value by a defined amount.
2. *Doping* as the heightening of an individual's performance in the absence of a deficit as defined in (1) but to a degree that the performance thus achieved can still appear normal within the range of human abilities.
3. *Improvement* as performance enhancement above and beyond the abilities regarded as ›normally‹ achievable by healthy individuals who can and are willing to perform under optimal conditions.
4. *Modification* of the human constitution, e.g. the creation of new organs or body functions.«

This system of differentiation and categorization therefore depends on the initial state of the individual and the final state that is aimed for and achieved. As will be shown in the following discussion, a distinction between (conventional) healing and non-medically indicated measures would be useful for an ethical assessment. However, such a distinction is in fact highly controversial and inevitably lacks sufficient discriminatory power.

A second problem area that is approached in a variety of ways concerns differentiation based on the agents used: in the majority of cases the term »enhancement« tends to be used to denote pharmacological, biomedical, and technical or even surgical methods for heightening performance that are the result of progress in medical, bio, nano, genetic, and information technologies. But bioethicists in particular tend to use very broad definitions in the context of comparative ethical assessments. John Harris for instance understands enhancement to be »all mechanisms which make possible (though not of course inevitable) better life« or »things that change the nature of the human condition« (Harris 2007, pp. 13 & 56, cited in Ach/Bisol 2009, p. 12). Thus, for Harris all human cultural

technologies – including the taming of fire, the invention of the wheel, writing, printing, computers, and smartphones – are forms of enhancement. This is the broadest interpretation possible, and of course it renders any discussion about the ethics of enhancement treatments highly problematic and arbitrary. A broad interpretation of enhancement is reflected in attenuated form in frequent references to a lack of differentiation between new pharmacological agents and traditional substances such as nicotine and caffeine on which a liberal position can and should be based (Galert et al. 2009; Schöne-Seifert 2009).

»ENHANCEMENT« AS AN ANTONYM OF »THERAPY«

The (German) *Lexikon der Bioethik* defines enhancement as »a remedial intervention in the human organism that does not treat a disease and is not medically indicated« (Fuchs 1998). This definition, which at the time of its formulation related solely to genetic interventions, explicitly invokes the definition of illness and would cover three of the above categories according to Grunwald (2008) and Jotterand (2008) , i.e. doping, improvement, and modification.

Such a definition, which is similar, for example, to that proposed in the influential report submitted to the US president: *Beyond Therapy. Biotechnology and the Pursuit of Happiness*, namely »the directed use of biotechnical power to alter, by direct intervention, not disease processes but the ›normal‹ workings of the human body and psyche, to augment or improve their native capacities and performances« (President's Council on Bioethics 2003, p. 13), sounds plausible. On closer examination however it proves highly problematic (Ach/Bisol 2009, pp. 15ff.). Essentially this is because there exists no undisputed, precise definition of illness or health but rather a plurality of more or less well-founded concepts of illness, each of which has different implications for the distinction between treatment and enhancement (Lenk 2002, from Ach/Bisol 2009, p. 18). Moreover these concepts are reviewed and refined on a continuous basis depending on the treatability of deficits (Section III.3). The problems relating to the definition of concepts such as »normal« performance are particularly clear in the booming field of anti-aging medicine – which is also interpreted in disparate ways and is viewed by many authors as a form of enhancement (Viehöver et al. 2009; Section IV.2) – because they can diverge greatly as an individual ages. Typical examples that are frequently cited to illustrate the definition and indication problems include the use of methylphenidate/Ritalin in children for the treatment of ADHD (Viehöver et al. 2009; Section II.3.1, III.3, and IV.2.2.1) and the administration of growth hormones for short stature of various causes (Fuchs et al. 2002; Nagel/Stephan 2009).

From an ethical and regulatory point of view a differentiation between therapeutic and enhancement measures is particularly important because it would help draw a distinction between the necessary medical treatment of ill patients on the

one hand and normatively unclear interventions on healthy individuals that go beyond essential treatment on the other and would therefore define that group of medical interventions which every citizen in a fair society is or should be entitled to (Juengst 1998, from Ach/Bisol 2009, p. 16).

This report does not delve into or document the medicotheoretical debate about the differentiation between treatment and enhancement (Nagel/Stephan 2009; Talbot 2009). It boils down to the fact that in many cases a sweeping differentiation is not possible. Instead, there exists a decision-making framework, on the basis of which doctors can and must decide on a case-by-case basis (Section III.3.5, Table 11). Ach/Bisol (2009, pp. 18–19) conclude: »All things considered, skepticism is justified as to whether it is possible to differentiate between ›permitted‹ and ›prohibited‹ improvements (or at least improvements regarded as problematic) in terms of whether they constitute ›therapy‹ or interventions ›above and beyond therapy‹. As Borchers also pointed out, the demarcation debate ›has not yet led to a consensus of opinion‹ (Borchers 2008, p. 49). It would appear that an exceptionalistic position with regard to pharmacological, surgical, and biotechnical enhancement methods does not appear justified. Rather, it appears more promising to examine the objectives of performance-enhancing interventions themselves – whether they be of a ›conventional‹ or pharmacological, surgical, or biotechnical nature – and subject them to an ethical analysis.«

The fact that Ach/Bisol (2009) introduce the categories »permitted« and »prohibited« in this context without first having formulated the question of a possible ban reflects a characteristic of the bioethical discourse about enhancement: from the early US debate (Whitehouse et al. 1997) to the latest publications by German researchers (Galert et al. 2009; Daele 2010) the principal proposition of liberal positions is that there are no fundamental objections either of a moral or of an anthropological nature against enhancement in general or pharmacological neuroenhancement in particular. The lack of distinction between enhancement and therapy – together with several other ethical arguments, especially with regard to people's freedom of action – is cited as a sort of pragmatic justification as to why enhancement or the use of enhancement agents cannot be summarily prohibited if their therapeutic use is allowed. This line of argument is a kind of circular reasoning, because the problem of (a lack of) differentiation is due solely to the fact that enhancement is postulated as a phenomenon but is then treated as a category. One approach to avoid this trap that is adopted by many participants in the debate about enhancement is to examine from an ethical point of view hypothetical, specifically acting, relatively side-effect-free performance-enhancing agents that are not also used as medicines. However, the resulting evaluations are not directly applicable to currently available psychopharmaceuticals or other substances with relatively nonspecific activity and/or with substantial side effects (Section II.3).

ETHICAL PRINCIPLES ACCORDING TO BEAUCHAMP AND CHILDRESS 1.2

In the predominantly Anglo-American bioethics debate, the established approach – for want of a comprehensive, specific ethical theory – is to examine bioethical interventions on the basis of four »principles of moderate abstraction level« according to Beauchamp/Childress (2001). These can be applied as guiding principles on which a consensus can be reached, as they are based on »moral everyday convictions and are reconcilable with various ethical arguments« (Marckmann 2000, p. 499, cited in Nagel/Stephan 2009, p. 34). The principles are beneficence, nonmaleficence, autonomy, and justice. Although these principles cannot be used to derive morally correct behavior, they do make it easier to identify ethical conflicts and to structure the approach to the problem. Because they tie in with the widely shared concepts of morality and traditional medical ethics, in many cases in practice ethics committees can draw upon them to reach a consensus (Marckmann 2000, p. 502). They are also frequently cited in the theoretical bioethical debate.

BENEFICENCE AND NONMALEFICENCE

According to the *principles of beneficence and nonmaleficence*, a person performing an act should refrain from causing harm, prevent or alleviate harm, and improve the situation of others insofar as this is in his power (Ach/Bisol 2009, p. 20). Ach/Bisol (2009, p. 20) point out that pharmacological, surgical, and biotechnical agents and methods already exist as a means for aiding and promoting the pursuit of happiness, though so far only to a limited extent. One requirement for this is that *there are no unacceptable health risks or adverse effects* for users and that potential users are informed about the possible risks of enhancement interventions – in the sense of consumer protection above and beyond mere health safety. Health risks and adverse effects are of particular consequence in the case of »improving« interventions, they argue, as the aim of enhancement is not to relieve or cure a disease, which usually justifies the acceptance of risks and adverse effects in a medical context (Ach/Bisol 2009, p. 21). This level of assessment and argumentation reflects the regulatory use of pharmacological agents, as enshrined in medicinal products and food legislation.

An entirely different perspective or issue is the »quality of happiness« that can be achieved through enhancement (Ach/Bisol 2009, pp. 21ff.). This relates, for example, to the different effects of »traditional forms of mental »self-transformation« or »self-formation« (Kipke 2010), such as concentration exercises, meditation, psychological coaching, etc. in comparison to (hypothetical) pharmacological enhancement. Because no effective pharmacological substances actually exist (Section II.3), such approaches cannot be underpinned by empirical results.

This report omits a presentation of the debate about whether the use of enhancement agents constitutes an (impermissible or undesirable) shortcut (where key valuable aspects of the action in question are lost) and therefore contributes to the »trivialization of life plans and the hedonization of the living environment,« because the views concerned are predominantly of a speculative nature (e.g. the consideration that enhancement interventions could also be used in an »individually productive and socially responsible way to shorten the time required for learning, assimilating, and memorizing information so as to allow more time for artistic work and/or development aid, to outline a trivial antithetical view,« Schöne-Seifert 2006, p. 287, citing Ach/Bisol 2009, p. 22). With regard to the question of »true« or »false« happiness Ach/Bisol (2009, pp. 22–23) also stress that the plausibility of objections based on the implications of neuroenhancement for the well-being of individuals or society depends on empirically determinable but hitherto nonexistent circumstances and also that the assessment is strongly characterized by an individual's attitudes and concepts and is therefore very difficult to generalize. The associated ethical considerations are closely related to the question of authenticity of persons and experiences that is discussed below in connection with the autonomy principle.

From the principles of beneficence and nonmaleficence Ach/Bisol (2009, pp. 23–24) derive an evidence-based approach for evaluating the risks and opportunities of enhancement interventions and their alternatives and an obligation to inform potential users and the public at large. If the latter is done on a sufficiently broad basis, informed individuals living in a liberal society should be able to voluntarily accept the risks and adverse effects of performance-enhancing agents or methods – including substantial risks if they exist – in pursuit of their objectives. A prohibition of neuroenhancement agents or methods would not come into consideration.

This view is evidently diametrically opposed to the hitherto usual regulation of the use of pharmacological substances, where side effects are a key consideration for determining regulatory approval and sales controls (Section III). The fact that regulatory approval and sales controls are assumed even in the case of products that are free or relatively free of adverse effects and that regulatory changes would be required for such agents to be marketed are issues that the present report discusses in Section V in connection with the scenario of expansion in respect of the research and innovation system.

AUTONOMY

The *principle of autonomy*, which relates chiefly to the right of individuals to self-realization and to make their own decisions, calls for respect of the life plans, aims, wishes, and ideals of others (Ach/Bisol 2009, p. 20). This gives rise in partic-

ular to questions regarding the authenticity and accountability of actions and the voluntary nature of the use of enhancement agents (Ach/Bisol 2009, p. 24).

Enhancement agents could give rise to untoward, ethically problematic effects if they led to major or irreversible alteration of the personality of users (Galert 2009). However, the possible impairment of *identity and authenticity* by enhancement substances in a narrow sense (enhancing substances that are relatively free of side effects and specifically improve cognition, e.g. intelligence) is – like the aforementioned question regarding the quality of happiness – highly speculative in nature, since no such agents exist as yet. The ethical debate therefore hinges on an evaluation of the effects of psychopharmaceuticals, especially SSRI-type antidepressants (Section II.3.3), specifically Prozac (Krämer 2009; Schmidt-Felzmann 2009). In the case of interventions that influence a person's emotional abilities, it appears especially difficult to predict the individual's experience. Kramer (1993), for example, report that some patients given Prozac have the feeling of finally being the person they have always seen themselves as and of finally being »themselves«. Others, by contrast, experience alienating effects, even if they otherwise feel fine under the effects of the substance (Ach/Bisol 2009, p. 23). An overarching evaluation on which a consensus can be reached hardly appears conceivable. Concluding from the »intuition that people *strive to* live authentically« that »they *should* live authentically« is certainly a fallacy (Müller 2008, pp. 200–201, cited from Ach/Bisol 2009, p. 25).

By contrast the question regarding the *voluntariness* of the use of enhancement agents can – and therefore should be – asked also in the case of performance-enhancing pharmaceuticals with less substantive effects than the alteration of personality or identity. Whereas the right to self-determination can be adduced as an argument for modifying a person's own body and functions with the help of enhancement agents, the principle of personal autonomy must be discussed at the social level mainly with a view to averting covert or insidious pressure or indeed an obligation to practice pharmacological performance enhancement (Ach/Bisol 2009, p. 28). In this context it is necessary to ask whether the individual and ostensibly autonomous use of enhancement substances can set in motion a spiral of competition where decision-making can no longer be assumed to be autonomous, similar to the effects of doping in sport (Section VI). According to a frequently expressed assumption, the act of taking or not taking advantage of enhancement measures should always be socially mediated and subject to – usually tacit – social standardization. Social pressure and social policy developments can greatly limit the individual's freedom of choice with regard to the use of enhancement measures (Ach/Bisol 2009, p. 29).

Fears that future employers or insurers of employees or clients could demand the use of enhancement agents cannot be dismissed out of hand. Such circumstances are known in the military field (the targeted use of uppers/amphetamines in the

form of so-called »go pills« for combat missions and the use of sedatives as »no go pills« for standby periods; Rötzer 2002). Surgeons, bus drivers, train drivers, pilots, and rescuers in disaster areas are often mentioned in the debate about hypothetical, specifically acting enhancement agents – individuals for whom the use of such substances in special stress situations might be seen as morally and practically justifiable and could therefore be demanded. According to Ach/Bisol (2009, p. 30), the ethically acceptable use of enhancement measures is only possible if (1) the possibility of abuse of enhancement agents by employees, educational institutions, the military, etc. is prevented or limited by effective political safeguards; (2) the social and socio-economic circumstances are such that the risk of »tacit« pressure to use enhancement methods appears acceptable; and (3) exceptions to a strict voluntariness rule, if at all justifiable, are limited to precisely defined situations (a framework of this sort can be found in the favorable review by Greely et al. 2008; Section I.5). In addition, it should be ensured that a right to use enhancement measures is counterbalanced by a right to forego such interventions or a »right to remain in a natural state« (Schöne-Seifert 2006), similar to the »right to ignorance« that has been acknowledged in the debate about genetic diagnostics (Ach/Bisol 2009, p. 30).

JUSTICE

According to Ach/Bisol (2009, p. 20) the *principle of justice* calls for the fair distribution of goods and opportunities and also that each individual receives what he or she has earned or to which he or she is entitled.

In contrast to the requirement to protect against pressure exerted by the social environment on individuals to use enhancement agents, as derived from the autonomy principle, it is sometimes argued in the ethical debate that, based on the justice principle, society has an obligation to provide and finance such agents with a view to preventing unfair, socioeconomically distorted competitive conditions, e.g. in examinations and application procedures or to equalize disadvantages and inequalities resulting from »nature's lottery« (Ach/Bisol 2009, pp. 30ff.).

These considerations also assume a scenario of specifically acting enhancement substances. Since these do not yet exist and are not expected to be developed in the foreseeable future, questions concerning ethical justice appear to be of little relevance at present. A scenario in which grossly under-average intelligence, for example, is improved by means of pharmacological enhancement (e.g. Gesang 2007; Lenk 2009; Müller 2009) remains purely theoretical for the time being. From the more »practically oriented« perspective of this report it must be assumed that substances that could conceivably improve mental impairment would in any case be classified as medicines in the narrow sense and would therefore fall under the usual care and reimbursement systems. Few people

would seriously advocate the view that the use of Ritalin and other substances by students for putative performance enhancement in examination situations (Section III.4) requires that individuals who are still nonusers should be supplied with those agents through public funding – not only because the effects on examination results are entirely unknown but also because no accepted comparable social obligation exists, e.g. to provide performance-enhancing training of other kinds to less able examination candidates.

Concrete justice and fairness issues relating to performance-enhancing substances have so far arisen mainly in competitive sport. Experience from this social subsystem is discussed in Section VI in respect of future (neuro)enhancement substances and their use at work and in everyday life.

CONCERNS ABOUT THE FUTURE OF HUMAN NATURE 1.3

Besides the above ethical considerations based on the principles formulated by Beauchamp/Childress (2001), which relate to potential specific consequences of the use of biomedical technologies for individuals and society (and are therefore particularly relevant to technology assessments), fundamental concerns about the »future of human nature« are also frequently expressed in the enhancement debate (Habermas 2001). These relate either to far-ranging visions of biotechnical manipulation (see below) or to scenarios of the wholesale »pharmacologization« of everyday life.

Thus, the authors of the report by the US President's Council on Bioethics (2003) fear that pharmacological (and technical) aids for enhancing mental and cognitive performance could fundamentally destroy the relationship between humans and their actions – especially the internal connection between their actions and the associated experience of fulfillment or happiness – thus, jeopardizing the »integrity« of the naturalness of human action (Ach/Bisol 2009, p. 35). A similar view is expressed by Sandel (2008, p. 107, from Ach/Bisol 2009, p. 35) who believes that enhancement threatens our appreciation of the character of human abilities and success as a »gift« and »key element of our moral landscape«, which he describes using the terms modesty, responsibility, and solidarity. Fukuyama (2004) even speaks of the »demise of mankind« in connection with enhancement.

Such far-reaching sociocultural and generic fears are possible consequences of projecting barely conscious concerns about the quality of individual happiness and the authenticity of individuals and experience as discussed in Section IV.1.2 onto the level of society as a whole – assuming that relevant enhancement technologies become more or less the standard. The extent to which such a development is thought to be realistic depends not only on assumptions about the potential future

efficacy of enhancement substances and methods but also crucially on the interpretation of the current diffusion and use of pharmacological self-manipulation. Empirical data on the use of such means with the aim of enhancing performance are limited (Section III.4). In the case of their use for modifying mood and coping with stress the key question is whether a quantitatively or qualitatively new medicalization trend has occurred in recent years in comparison to, say, the 1950s and 1960s (Langlitz 2010b). Thorough sociological studies are required to answer this question more precisely, (Sections IV.3 and VII).

Besides social and behavioral views of pharmacologization and medicalization trends, the bioethical debate has given rise to visions of the targeted, fundamental, and extensive modification of human nature, which form the background to many considerations and debates regarding the subject of enhancement (see Coenen et al. 2010 for a summary of the conceptual and cultural history and a literary overview). These visions relate to what is believed to be a fundamental human urge to improve human characteristics and abilities and to diverse utopian scenarios of technical manipulation of the human body for the purpose of influencing performance above and beyond medical therapy. The first half of the 20th century up to the 1960s was dominated by wide-ranging visions of human evolutionary control by means of centrally planned genetic interventions to solve humanity's major problems (Wess 1989). However, when the technical means of genetic modification became a reality in the 1970s, the targets (e.g. of gene therapy) then shifted fundamentally to far more specific medical objectives of healing diseases (e.g. the Human Genome Project and its follow-on projects).

Scenarios of pharmacological control form the basis of Aldous Huxley's famous dystopian novel *Brave New World* and his lesser known utopian novel *Island* (Langlitz 2010b). Later visions of improved humankind from the 1990s and 2000s, which were disseminated partly under the label of converging technologies, borrowed from emerging developments and technologies – especially the neurosciences and nanotechnologies but also tissue and organ cultivation based on stem-cell techniques – and combined them with the rapidly growing capacities of information technology to create far-reaching, sometimes wholly unrealistic visions of future technologically equipped man-machine hybrids that would radically prolong life or even enable an individual's mind to live eternally outside the body. The associated world view is known as transhumanism (for a detailed treatment see TAB 2008a). Such futuristic and utopian fantasies burgeon only as long as the envisioned technical interventions are imaginable but not yet concretely foreseeable and describable.

Seen objectively, the prospects of such visions – whether utopian or dystopian – being implemented are dim. No scientifically supported plausible scenarios exist for the permanent targeted manipulation of »human nature« by pharmacological means without affecting the genetic, i.e. inheritable, level. With regard to the

concept of physical performance enhancement with a view to improving athletic performance, the TAB was able to show in its report »Gene Doping« that there is no evidence of »realistic« objectives of permanent genetic manipulation, because the various parameters of physical performance cannot be assigned to isolated genetic elements – at least so far (Gerlinger et al. 2008; TAB 2008b). This is even less likely in the future with regard to mental, i.e. cognitive and emotional, abilities or performance, because their genetic basis is even less clear. All things considered, the aspect of the »future of human nature« in the sense of fundamental biotechnical manipulation appears to hold little relevance for the present study.

2. PERSPECTIVES OF THE SOCIAL SCIENCES: ENHANCEMENT AS PART OF A MEDICALIZATION PROCESS

One task of sociological analysis in the biopolitical discourse is to examine whether the assumptions about social conditions and consequences are empirically accurate or at least appear plausible on the basis of empirical social-science data (van den Daele 2005). Viehöver et al. (2009, p. 5) emphasize the significance of the role of the social sciences, which investigate the social and cultural genesis and integration of desires to achieve optimization (Wehling 2008a). The following evaluation of the expert report by Viehöver et al. (2009) concentrates on results that illustrate integration of enhancement in the broader context of medicalization – irrespective of whether performance enhancement is actually achieved in users.

TRANSITIONS, BLURRING OF BOUNDARIES, REDRAWING OF BOUNDARIES

According to Viehöver et al. (2009, pp. 3–4), enhancement is a collective term that encompasses various scientific and technical developments concerning the technicalization, transformation, and »perfectivization« of the human body and mind. They too refer to the unresolved problem of differentiating between enhancement and therapy (Section IV.1.1) and to the fact that many pharmacological and medical projects on physical and mental performance enhancement cannot be implemented at present (and it is unclear for many whether they ever can be). Nevertheless, they note, it must be assumed that our »social perceptions of mind, body, personality, autonomy, and identity are changing as a result of the ongoing debate on optimization« (Viehöver et al. 2009, p. 5). In this context key guiding differentiations, e.g. between illness and health and analogously between therapy (curing) and optimization of the human body, have been blurred and need to be redefined. In particular, they note, it is controversial *who* should draw the future boundaries, *how* they should do so, and on the basis of *what* legitimization this should be done (Viehöver et al. 2009, p. 5).

»Transitions«, »blurring of boundaries« and »redrawing of boundaries« are therefore the key analytical terms with which Viehöver et al. investigate the «(bio)political strategies and practices of enhancement and their assimilation by individuals«. Relevant developments are seen in the narrow area of medical science (its self-perception and remit for action; Section IV.2.1), at the subject level (the patients and the ways in which they adopt enhancement practices; Section IV.2.2), and in the context of socioeconomic circumstances (particularly changes in the healthcare market and social systems; Section IV.2.3) (Viehöver et al. 2009, pp. 6ff.).

Compared to earlier visions of improving humans in terms of their mental and moral abilities and their physical attributes, Viehöver et al. (2009, p. 9) believe that »a new stage has been reached … through achievements in biotechnology in recent decades.« The areas subsumed under the term enhancement, i.e. cosmetic surgery, anti-aging medicine, doping in competitive and recreational sport, and the use of psychopharmaceuticals for the treatment of non-medically indicated phenomena such as shyness (Wehling 2008b and c) or specifically to enhance performance, are seen as part of a medicalization process[63] whose driving forces are themselves in a state of flux (Viehöver et al. 2009, pp. 10ff.).

Viehöver et al. (2009, p. 6) view enhancement tendencies as »part of a *structurally* new process of medicalization … that appears to be shifting the categorial boundaries of the medical field and the way medical science sees itself.« Other authors interpret these developments in terms of a transition from curative medicine to an era of »wish-fulfilling medicine« (Kettner 2006a and b) or from »corrective medicine« to »preventive medicine« (Bamberger 2008, pp. 12ff.). Not least because of new enhancement techniques, Viehöver et al. (2009) believe that a fundamental blurring of boundaries is occurring in the medical field, making it increasingly difficult to draw clear distinctions between health and illness or between healing and improvement – distinctions that until now have explicitly or implicitly guided actions.

At the subject level it has been observed that more and more segments of society are opening up to the medicalization of everyday life by enhancement practices and techniques and to the accompanying debate. According to Viehöver et al. (2009, p. 7), »this could have unforeseeable consequences for the socialization of the individual and his/her (personal) identity, whereby boundary transgressions can occur both with regard to the *natural physical basis* and to modern *concepts*

63 The term medicalization has gained currency since the 1970s, particularly in English-language sociology (Conrad 1992). In in a broad sense it denotes the perception of social problems in medical terms. Its roots lie in Foucault's analysis of the development of modern practices and techniques for disciplining the human body (Foucault 2002; Nye 2003) and in the medical works of the 1960s and 1970s, e.g. by Szasz (1961) and Illich (1975).

and *interpretations* of personality, identity, autonomy, and self-determination.« These theoretical and conceptual considerations are supported by study results in the fields of »anti-aging« and ADHD therapy and the associated backgrounds, underlying motives, and consequences (see below).

In this context the relationship between state and market is emphasized. Given the growing markets for enhancement products and services, this relationship needs to be readjusted. The expansion of enhancement practices is viewed in the context of an emerging secondary healthcare market (Section III.3.6), which is generating a »structure of opposing processes that is blurring institutional boundaries« and giving rise to new interests and patterns of the players involved (Viehöver et al. 2009, p. 66).

BOUNDARY SHIFTS IN THE NARROW AREA OF MEDICAL SCIENCE: ILLNESS, HEALTH, HEALING, IMPROVEMENT 2.1

Medical science emerged in the 16th century as a distinct social system whose actions and practices are based on a distinction between health and illness (Bauch 1996). After undergoing semantic changes, the concepts of illness and health have become established as an asymmetrical antithetic pair (Koselleck 1989, p. 211) whose primary function is to define precise boundaries of the medical field (Viehöver et al. 2009, p. 13).

For some time now, limiting the remit of medical science to the healing of the ill no longer appears to be a valid approach in view of various developments *within* and *beyond* the medical field (Kickbusch 2006). Viehöver et al. (2009, pp. 14ff.) see a trend towards a blurring of boundaries at three levels:

- nature and culture,
- health and illness, and
- healing and improvement.

Nature – culture: Although the notion of the naturalness or nature or God-givenness of the human body has been fundamentally called into question by the natural sciences since the dawn of the Modern Era and the Enlightenment, it has until recently remained institutionally and practically useful as a legitimate concept. However, it now appears to be gradually losing its significance as a normative value and orientation aid for cultural action. The ethical and biopolitical debate about enhancement makes it clear that any recourse to the »nature« of humans is highly ambiguous and requires justification (Clausen 2006; section IV.1.3).

Health – illness: Increasingly, the common view of »illness« as a deviation from a natural, normal state of the human body is no longer taken for granted. Features

of the human body previously perceived as »natural«, e.g. aging, physical appearance, height, weight (and obesity), and common behavioral traits such as shyness, are tending to be seen as »deficits« and »disturbances« that can and should be treated (Lau/Keller 2001, p. 85; Lau et al. 2005; Wehling 2008c). »Illness« is increasingly understood as the »suboptimal« development and utilization of a fundamentally enhanceable physical potential which can be remedied by medicotechnical or pharmacological means. In some cases, e.g. in the case of »anti-aging« measures, entire phases of life appear to have been relegated to the realm of illness. One consequence of this development is that (real or supposed) everyday certainties and premises that inform people's actions are disappearing. The propagation of preventive medicine rather than »remedial medicine« (Bamberger 2008) would appear to be another way of conveying this shift in boundaries. Thus, in medical science an operative value is attributed not only to illness, as Luhmann (1990) believed, but also increasingly to health: to an increasing extent medical interventions are aimed at the healthy human body. This is particularly true of anti-aging medicine in its various guises. Earlier guidelines on maintaining health through (para)medical measures or on systematic preventive hygiene policies have a long and varied cultural tradition. By contrast, the new and future form of preventive medicine is oriented towards substance-mediated interventions, e.g. the use of medicines that allegedly have specific desirable health effects (e.g. preventing age-related »degradation processes«). This concept of preventive medicine is therefore closely related to the third dimension of the processes of boundary blurring.

Healing – improvement: As long as medicine is seen within the cultural and institutional framework of expected »healing«, it will remain linked – in the sense of an ideal *restoration* of a »natural« or »normal« state that has been altered or jeopardized by illness – to the concept of a preordained nature of the human body (Rheinberger 1996, p. 289). Nevertheless, some forms of improvement of physical abilities have long been part of medicine, e.g. immunization and measures to compensate for disabilities. For this reason an »ontological« or »essentialistic« dichotomy between therapy (in the sense of healing the unaltered natural body) on the one hand and enhancement (as the creation of a technically manipulated »artificial« body) on the other hand appears inappropriate. What is new specifically are the extended possibilities of (biotechnical, pharmacological) intervention and the individualization of the objectives of such interventions – in contradistinction to »medical«, especially »eugenic«, objectives of improvement based on state-controlled selection in the first half of the 20th century. In this context novel forms of »naturalized« discrimination can emerge, as discussed in the debate about preventive (genetic) diagnostic methods (Lemke 2006; Wehling, P. 2005).

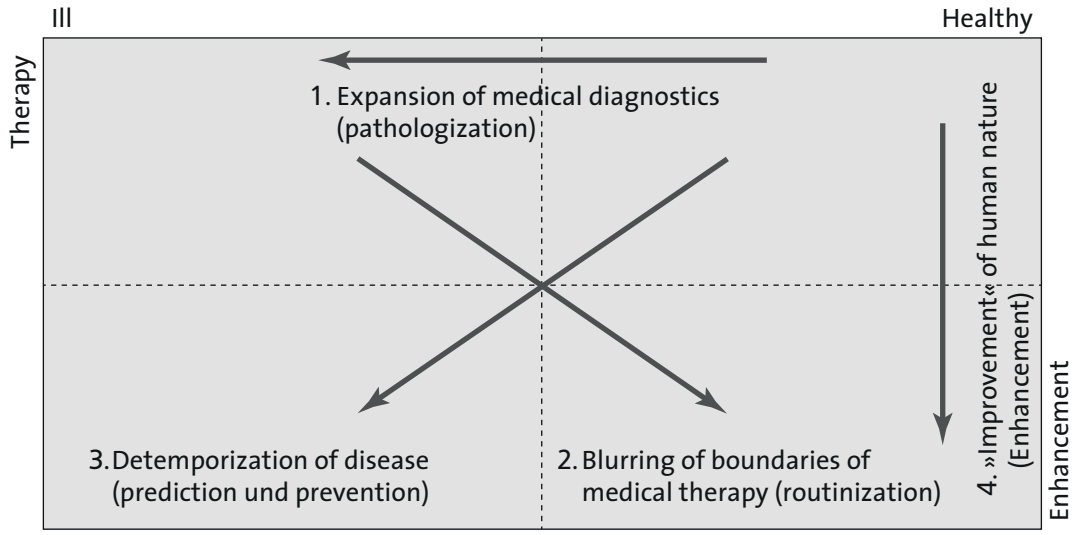
FOUR DYNAMIC PROCESSES OF BOUNDARY BLURRING

If we place the two dichotomies »health versus illness« and »healing (treatment) versus improvement (enhancement)« in a heuristic cross-table, it is possible to identify four typical forms and dynamic levels of boundary blurring and boundary transgression (Fig. 8) (with regard to this and the following discussion, see Viehöver et al. 2009, pp. 21ff.):

1. Expansion of medical diagnostic options (pathologization)
2. Expansion of medical therapy beyond its former boundaries into everyday life (routinization)
3. Detemporalization of illness (prediction and prevention)
4. »Improvement« of human nature (enhancement)

According to Viehöver et al. (2009), the »expansion of medical diagnosis« encompasses new specific definitions of physical, psychological, and/or mental phenomena (physical states, behaviors, and the like) as pathological. An outstanding example is the emergence of the diagnosis of attention deficit hyperactivity disorder (ADHD) in the 1970s (Conrad 1976a and b) and its extension to adults in the 1990s (Conrad/Potter 2000). Other examples include the pathologization of male and female libido and shyness. An shared element of many of these boundary changes is a shift of emphasis from psychosocial to somatic explanations and attributions of causality and thus an overall increasing tendency to frame social phenomena in medical terms, i.e. medicalization (see above).

FIG. 8 **BOUNDARY-BLURRING PROCESSES IN BIOMEDICINE**



Source: from Wehling et al. 2007, p. 558

However, these expansions are not occurring without resistance and are generally vigorously disputed. The outcome therefore need not necessarily be the continued acceptance of boundary shifts. Instead the result is often a blurring of boundaries, which can ultimately lead to their disappearance (Viehöver et al. 2009, p. 21).

A noteworthy observation is that the *expansion of medical diagnostic options* does not emanate predominantly from the medical profession. Other key players are gaining importance in this respect, including pharmaceutical companies, the media, and affected individuals themselves, notably in the form of patient organizations and self-help groups. This gives rise to a gray zone of ambiguity where individuals are able to interpret and define their own well-being (and that of their children) themselves. In the process they are stimulated and guided by the media, advertising by the pharmaceutical industry, self-tests on the internet, medical and popular-science advice booklets, etc.

When we examine attempts in the bioethical debate to define boundaries between enhancement and therapy, an expansion of medical diagnostics would actually appear to act against the phenomenon of enhancement. After all, the aim of diagnostics is to define behaviors and actions within the legitimate remit and responsibilities of medical science. Equating medicalization with enhancement then makes no sense. At best one would have to ask whether the pathologization of behavioral forms previously regarded as normal (melancholy, hyperactivity, hypoactivity, etc.) increasingly leads individuals to believe that it is normal to influence their own well-being by pharmaceutical means.

The *blurring of the boundaries of medical therapy* results from pathologization as well as from the second important form of medicalization, i.e. the use of medical technologies for conditions not usually regarded as pathological (routinization). The most obvious example of this is cosmetic surgery, which to all intents and purposes has become argumentatively, ethically, and economically decoupled from the healthcare system, while the anti-aging sector embodies a combination of both pathologization and routinization (Section IV.2.2.2): On the one hand falling hormone levels that can be unambiguously measured are cited as an indication for specific »therapeutic measures«. On the other hand a large number of substances with obscure and unproven effects that are claimed to slow aging processes are being sold, administered, taken, and applied to the skin. It appears plausible that the diffusion of dubious and ineffective »neuroenhancement agents« will be most rapid in this area.

Detemporalization of illness denotes an increasing decoupling of the concept of illness from actually manifest (acute or chronic) symptoms and complaints and an »anticipatory shift« of diagnoses to specific signs and »risk factors«. The result is a »healthy ill person« for whom strategies of »preventive risk manage-

ment« are increasingly being devised. This development is most strongly promoted by the results of genome research and genetic diagnostics in the form of so-called predictive genetic tests, which have been discussed more than actually used in recent years (Hennen et al. 2001; Kollek/Lemke 2008). The question regarding the impact that informing individuals about their genome has not only on society but also on behavior, developmental potentials, and life perspectives has been a central topic of the medicalization debate in recent years (Lemke 2006; Wehling 2006). In this context individual and social rights and objectives (including the right to ignorance, voluntariness, and protection against discrimination) have been discussed and elaborated as intensively as any other biomedical technology, for example by the Rights and Ethics of Modern Medicine Enquiry Committee (Enquiry Committee 2002) and, after protracted and thorough deliberation, is now regulated in Germany by the Genetic Diagnosis Act (GenDG).

However, if predictive genetic diagnostics is not pursued along these lines in the coming years due to a lack of success and prospects, as was expected until recently, this could be interpreted in retrospect as confirmation that an excessively vague and unclear medical offer cannot achieve social and socioeconomic success in the long term. If that is the case, it would probably also be due to the fact that a means of prevention or a promise of success cannot necessarily be derived from such predictions. Conversely, in the case of anti-aging measures, for example, even if they are vague and unclear they could nevertheless enjoy long-term success because they always convey a positive promise, irrespective of whether it is fulfilled (»Maybe it did help?«).

Whether the conscious targeted »improvement of human nature« really has the significance that is often attributed to it as a guiding principle of the life sciences can be called into question for a number of reasons, as argued in various places in this report. Viehöver et al. (2009, p. 30) refer to the well-known futuristic bio and techno visions of transhumanists and other technological utopists (»elimination of aging«, connection of the human brain to IT systems, technical improvement of sensory capabilities) and to doping in competitive and recreational sport. In this context the boundaries between health and illness and between diagnosis and therapy clearly play no role, as the objective is to push performance boundaries beyond the capacities previously achieved by the individual without technical or pharmacological help or to fundamentally augment the abilities of the human species.

As shown in Section II, sport (particularly cgs and endurance sports; Section II.1.1) is the only field of pharmacological performance enhancement in which measurable boundary shifts have occurred (e.g. in running and swimming records, average speeds in cycling events, etc.). All other examples (Section III.4.1) are not measured in performance parameters and have either only been observed and interpreted (e.g. in the case of the use of Ritalin in examination situations,

whose effect cannot in any way be investigated, let alone proven, on the basis of examination results) or are not amenable to a concrete description as performance-enhancing (e.g. the use of antidepressants by healthy individuals or stimulants in creative professions – phenomena that can hardly be regarded as new).

Viehöver et al. (2009, p. 30) rightly emphasize that this fourth dynamic process of boundary blurring has so far occurred chiefly at the discursive level in the form of strategies and research programs whose aim is to describe and legitimize the aims and possible motives of relevant enhancement measures by means of specific rhetorical strategies. Unlike in the USA, extreme visions outside the historical context of ideas and culture play almost no role (Coenen et al. 2010), and isolated uses in scientific communication (Coenen 2009) and even modest enhancement objectives tend to be conveyed as an element of overarching research programs or fields, e.g. in the context of anti-aging measures (Section IV.2.2.2). However, voices are increasingly being heard in the biopolitical and bioethical debate in Germany and other European countries that regard hypothetical enhancement practices as acceptable in principle or even see fundamentally positive aspects in them (e.g. Galert et al. 2009; Gesang 2007; Schöne-Seifert 2006).

COMMONALITIES AND DIFFERENCES

All four dynamic processes (Fig. 8) point – in each case in a specific form – towards the erosion and blurring of distinctions between illness and health and/or treatment and enhancement. Each dynamic process opens up new scopes of action for individual or professional players. At the same time ambiguities arise in the everyday and institutional/professional sphere with the possible consequences for self-perception and acceptance already alluded to (with regard to this and the following discussion, see Viehöver et al. 2009, pp. 32ff.).

The most important differences between the four types of boundary shift and medicalization referred to above relate to the social roles, legitimation, and makeup of the various players involved (from medicine, business, media, science, politics, and not least individual patients or »customers«). »The blurring of the boundaries of medical therapy« is particularly marked in the case of cosmetic surgery, which is driven to a considerable extent by self-help literature, media reports, and clients themselves – at a certain remove from a »conservative« segment of the medical profession (»Coalition against Beauty Mania; German Medical Association 2004). In the case of predictive genetic diagnostics, by contrast, the process of boundary blurring between illness and health is clearly different: the driving force in this case tends to be basic research in the biosciences, which is linking more and more diseases to genetic risk factors, while affected patients (especially those from so-called »high-risk groups«) are responding at least to some degree with considerable constraint. The case of ADHD as an example of

the »expansion of medical diagnostics« is characterized by quite different constellations of players and patterns of acquisition (Section IV.2.2.1).

The typology of boundary-blurring processes shows that it is futile to assume the existence of a homogeneous trend towards »medicalization«. Rather, a differentiation must be drawn within the field. Whether, and if so to what extent, enhancement technologies and practices will gain currency; whether they are perceived individually, socially, or professionally as such; whether counter-trends are socially effective and successful – these are all questions that require empirical answers (Section VII). With regard to the ethical debate one should therefore ask whether and under what conditions in everyday and working life decisions are actually made on the basis of ethical criteria (Nassehi 2006).

THE SUBJECT LEVEL: ACQUISITION FORMS BETWEEN SOCIAL PRESSURE AND SELF-DETERMINATION 2.2

On the basis of two case examples – ADHD and »anti-aging« – Viehöver et al. (2009, p. 34) show that the typology of boundary shifts can plausibly be applied to individual cases and that it is appropriate to consider the point of view of the »user« and his/her forms of acquisition. This concerns far more than just the changing relationship between doctors and patients, which in the age of »individual health services« (IGeL) is increasingly taking on the characteristics of a doctor-client relationship (Kettner 2006a and b; National Ethics Council 2004).

ADHD: AN OPPORTUNITY FOR NEUROENHANCEMENT? 2.2.1

The example of attention deficit hyperactivity disorder (ADHD) illustrates how predominantly social phenomena – in this case abnormal behavior (hyperactivity) or variants of cognitive abilities (attention deficits) – can be interpreted as pathological symptoms and how the boundaries between restorative and optimization measures are being blurred in the minds of those affected (with regard to this and the following discussion, see Viehöver et al. 2009, pp. 36ff.).

With a prevalence of 2 to 6 percent, ADHD ranks among the most common psychiatric clinical pictures in children and adolescents. Only 1 % of boys and 0.3 % of girls receive pharmacological treatment with methylphenidate (Steer/Strassmann 2008, p. 682). In recent years ADHD has also been diagnosed in adults. It is currently estimated that one to two thirds of affected children will have pronounced impairments as adults, resulting in an adult prevalence of 2 to 4% (Philipsen et al. 2008).

A striking feature of ADHD is the historical development of the diagnosis and the term itself (e.g. Hennen et al. 2008, pp. 153ff.). The stage was set by Hoff-

mann's »Fidgety Philip« in the mid-19th century, whose behavior was presented as a morally judged deviation. In the 1930s a seemingly paradoxical calming effect of amphetamine on hyperactive children was observed serendipitously, and it was then assumed that something that can be treated must be a pathological condition. Competing terms such as »minimal brain dysfunction«, »hyperkinesis«, and »hyperkinetic reaction of childhood« were still being used in the literature to describe the symptoms into the 1980s. Since the American Psychiatric Association published the fourth edition of the *Diagnostic and Statistical Manual of Mental Disorders* in 1994, ADHD has been listed as a polymorphic disease with three chief forms: predominantly inattentive, predominantly hyperactive, and combined. This covers a broad range of behavioral and performance deficits, placing indicated medical therapy in a gray zone between the treatment of disease and everyday enhancement. Which ADHD-related behavioral and performance deficits are pathological symptoms or nonpathological variants from the norm remains a matter of some controversy. Although there can be no serious doubt as to the medical significance of severe forms, some observers regard ADHD as an example of the medicalization of deviant cognitive performance and social behavior.

Ritalin is the drug of first choice for the treatment of ADHD in adolescents (Section III.3.5, Table 11).[64] As Döpfner et al. (2000, p. 29) note, »the medication can reduce oppositional behaviors … and at the same time increase desirable behaviors.« (Short-term) effects of the pharmacological treatment are reported to include a reduction in aggressive behavior and an improvement in concentration and attention span with specific effects such as improved handwriting. The medication can therefore bring about an (at least temporary) restoration of conformant behavior and an improvement in individual cognitive abilities, enabling the affected individual to achieve an expected level of performance more easily. In many cases the answer to the question as to which behaviors are »still healthy« and which are »already abnormal« is unclear because it depends on the judgments of others and on a person's self-perception.

Particularly in the case of adults diagnosed with ADHD, some understand and exploit the disorder as an »opportunity« because the diagnosis facilitates access to medical means of self-optimization (Conrad/Potter 2000). In group discussions with affected individuals (diagnosed adults [some from self-help groups], their partners, and parents of diagnosed children) Viehöver et al. (2009) identified four attitudes to Ritalin therapy and use (Table 14). They showed that

64 However, it has recently been decided that products containing the active substance methylphenidate can no longer be prescribed in Germany for the treatment of ADHD in children but only as part of a broader multimodal strategy. This was decreed by the Federal Joint Committee (G-BA) on September 16, 2010 (Federal Psychotherapist Chamber 2010a).

many patients see an opportunity in the medical reinterpretation of their own personal history in order to rid themselves of the fateful burden of performance deficits, leading at least in some cases to self-perpetuating medicalization.

TABLE 14 **ATTITUDES TO RITALIN THERAPY**

	Accepts **Ritalin therapy**	***Rejects*** **Ritalin therapy**
Accepts the diagnosis	Type 1: Sees ADHD as a pathological deficit: treatment in the sense of restoration of the »natural« normal state	Type 3: Accepts the medical significance while at the same time rejecting pharmacological treatments
Rejects the diagnosis	Type 2: Diagnosis is largely irrelevant: uses medicines for targeted performance enhancement *= explicit enhancement*	Type 4: Critic of medicalization: rejects medical interpretation of symptoms and their treatment

Source: From Viehöver et al. 2009, p. 43

When first diagnosed, most affected individuals – regardless of their later »patient career« – struggle to come to terms with the personality characteristics that are perceived as a deficiency or indeed as a disorder or disease. Often they read information on the internet and in self-help literature before consulting a doctor, so that their entire case history writes itself, as it were – in the internet age a common phenomenon with other (suspected) diseases. Intense preoccupation with the symptoms brings about a medical reinterpretation of the individual's self. Sometimes the individual's own behavior is not interpreted in a pathological context until other family members have been diagnosed, e.g. parents of children with diagnosed ADHD, when they retrospectively draw parallels to their own childhood experiences (with regard to this and the following discussion, see Viehöver et al. 2009, pp. 41ff.).

Reactions to the later medical diagnosis vary widely. One type of individual often encountered in group discussions is convinced that he suffers from a biological impairment and sees the use of medicines largely as a cure for a pathological deficit (type 1 in Table 14). From this point of view the medicines are essential in order to lead a »normal« (natural) life. Compliance with doctors' instructions is strong, so that this type most closely corresponds to the action orientation of the classical patient role.

Type 2 individuals, who are prominent in discussion groups, take the medications explicitly for their performance-enhancing effects and largely independent-

ly of medical recommendations. Their own identity is not decisively defined by the diagnosis or the diagnosed deficit. Some ignore medical assessments, favoring a pragmatic, targeted, and proactive use of the medicine, chiefly in situations where enhanced performance and attention are required. This behavior is probably one of the few plausible examples of targeted and effective neuroenhancement – but by individuals who have been medically diagnosed with a psychological or neurological deficit, even if it is contentious.

Type 3 looks askance at the use of medicines. Although such individuals acknowledge the effect of the medication, they nevertheless regard it as »unnatural«. Accordingly, metaphors from the non-human realm (»robots«, »zombies«) abound in descriptions. Quite differently from type 1, who sees his »own ego« restored by the medication, these individuals see their identity threatened or supplanted by the medicines. It is worth noting that this type of rejection of medication observed in the discussion group, whose participants were members of self-help groups, was scarcely observed by Viehöver et al. (2009). On the contrary, their group almost universally accepted the use of psychopharmaceuticals for coping with everyday life.

Type 4 embodies the »antipode«, as it were: the convinced »medicalization critic« who fundamentally rejects the medical interpretation of his ADHD symptoms and who regards characteristics associated with ADHD as a normal behavioral variant.

Viehöver et al. (2009, p. 44) conclude from their studies that individual and social concepts and expectations of authenticity and autonomy can change if individuals perceive themselves as »authentic« and »self-determined« only after taking substances that interfere with the brain's metabolism (Karsch 2007). This could also be understood as a first step towards a more advanced scenario of the bioethical and biopolitical debates of recent years, according to which the treatability of negatively perceived behaviors and performance limitations leads to new demands on the way individuals understand and relate to each other; these demands are first socially formulated and then internalized (Ach/Pollmann 2006; Fuchs et al. 2002; Gesang 2007; Roco/Bainbridge 2002; Wehling 2008a, b, and c). A new characteristic compared to earlier methods for altering cognitive or emotional states (meditation, illicit drug use, etc.), say the authors, is an orientation towards optimized social »functioning« of the individual and the promise of more targeted medical and technical intervention (Viehöver et al. 2009, p. 44).

It can be observed that the medicalization of behaviors and deficient abilities has led to social pressure for individuals to take advantage of such options. Thus, according to some affected individuals, teachers are demanding that behaviorally disruptive children be put on drug therapy by their parents, thus assuming the role of active medicalization agents. Moreover, it has been found that »biosocial

generalization« processes (Rose 2005) and new dynamics of self-control have become important factors contributing to medicalization (Viehöver et al. 2009, p. 44–45). Both personal responsibility (self-diagnosis, self-treatment, and self-medication) and biosocial shaping of identity (e.g. in the form of shared acquisition of knowledge and coping with problems in everyday life) are promoted by self-help groups and lead to a gain in autonomy compared to the professional medical-care landscape. All things considered, Viehöver et al. (2009) say, ADHD is a multifaceted example of medicalization. Similarly multilayered but quite different in many respects is the second example discussed by Viehöver et al. (2009): »anti-aging«.

»ANTI-AGING« AS THE MEDICALIZATION OF THE AGING PROCESS 2.2.2

The term »anti-aging« covers a variety of phenomena and processes in research, medicine, and everyday life (Stuckelberger 2008). Essentially, its objective is to prevent or counteract age-related symptoms and performance losses. Demographic change with its already apparent and above all predicted social and economic consequences as well as new – supposed or real – scientific approaches to pharmacological and/or biotechnical interventions have a strong influence on people's perception of the social and medical significance of anti-aging measures. The manipulation of human metabolism in such a way as to slow down the aging process and not only enhance the quality of life (»healthy aging«) but also (significantly) increase the human lifespan is a typical utopian vision of transhumanists (Heil 2009) and as such forms part of the basic orchestration of the enhancement debate.

Given an assumed steady age-related decline in performance, expectations regarding the effects of anti-aging measures are probably lower than the expectations younger people place in performance-enhancing agents (although the suppliers of anti-aging products emphasize the early onset of the aging process). This may be one reason why the range of options on offer is bewildering, heterogeneous and rarely supported by robust evidence of efficacy: in some cases it is evidently sufficient evidence for the individuals concerned to assume that their decline in performance would have been even greater without the agents. »Anti-aging« is probably the most significant and varied aspect of the medicalization of a growing segment of the population.[65]

65 A similarly broad process of medicalization is otherwise observed only with regard to pregnancy, although in this area autonomous decisions and choices are becoming increasingly more difficult because health insurers define clearcut requirements for monitoring and care.

In accordance with the contradictory nature or the contrary trends of the dynamic boundary-shifting processes (Fig. 8, Section IV.2.1), aspects of both pathologization and routinization are present (with regard to this and the following discussion, see Viehöver et al. 2009, pp. 47ff.). Thus, typical anti-aging proponents emphasize, in contradistinction to classical geriatrics, that the aging process should be seen not as a pathological state and a target for therapeutic measures but as an object for predictive and optimizing biomedical interventions and educational programs derived from an ethos of personal responsibility (e.g. Bamberger 2008; Klentze 2003; Markert 2008). At the same time, the »health society« (Kickbusch 2006) is increasingly making aging, as well as physical beauty and genetic dispositions, a medical topic – probably also because the »performance society« is as little prepared for the growing numbers of those who »no longer serve productivity« as for the mental and physical problems that accompany aging (Gandolfi 2006). Demographic aging is increasingly developing into a social and institutional problem for healthcare and social security systems (Birg 2003), which are responding with strategies to individualize healthcare and the care of the elderly (Conrad 2005). Pensioners lose their »passive status« and are addressed as autonomous, active, and responsible individuals. This can be interpreted as a subtle form of social pressure to take advantage of available anti-aging measures.

This situation is compounded by the economic motives of suppliers: aging generations control an increasing share of the purchasing power of modern societies. Moreover the market for anti-aging products can be expanded rapidly if it can be successfully suggested that aging basically starts at birth and therefore that aging well and successfully while maintaining performance requires relentless strategies and lifestyle practices.

Generally speaking, all four of the aforementioned boundary-blurring dynamic processes are observed in this field (Fig. 8, Section IV.2.1):

- Aging processes (e.g. falling hormone levels) are pathologized and are essentially explained as *requiring* treatment (expansion of medical diagnostics).
- Alternatively, the treatment *option* is emphasized: this is specifically selected to actively enhance quality of life but relies on the same or similar medical or pharmacological agents (blurring of the boundaries of medical therapy).
- Preventive therapy is initiated as early as possible (detemporalization of illness).
- At least as a utopian vision, aging is completely »banished« and/or life expectancy is (greatly) prolonged (improvement of human nature; Gray/Rae 2010).

The analysis of relevant advisory literature and group discussions by Viehöver et al. (2009) produced much evidence of the first three processes. In addition, there are »weaker« variants at the boundary of lifestyle, cosmetics, and wellness medicine (anti-aging creams, Botox) as well as explicit opposition to pathologization (»Aging [menopause, etc.] is not a disease!«).

Consistent with the lack of proof of efficacy for most substances (Section II.3), it can also be said specifically in relation to anti-aging medicine that no examples of effective pharmacological *cognitive* performance enhancement exist, notwithstanding the widespread use of *Ginkgo biloba* products. Specific physical effects have been demonstrated for sildenafil (Viagra), whereby, as described in Section III.3.6, the costs were reimbursed for a while not for age-related waning libido but for erectile dysfunction as a specific disease symptom (and meanwhile not even for that). As typical anti-aging substances, hormones – including melatonin, growth hormone, and various steroidal hormones and their biochemical precursors – are »traded« (in an extended and literal sense). Yet no »performance-enhancing« effects in persons with hormone levels commensurate with their age have been demonstrated (Stuckelberger 2008). Most of these substances are not freely available in Germany (unlike the situation in the USA, for example) and, moreover, are subject to special restrictions as doping substances.

Thus, even if – despite the efforts of many players – anti-aging medicine offers few examples of »genuine« enhancement, the medicalization of an increasingly longer life phase means that it is probably one of the major drivers of a growing willingness on the part of young, healthy individuals and others to consciously engage in pharmacological performance enhancement. This relationship should be explored more closely in a future survey of the attitudes and behaviors of the population (Section VII).

SOCIOECONOMIC BOUNDARY SHIFTS: FROM HEALTHCARE TO HEALTH MARKET 2.3

Until now the health market, at least in Germany, was very tightly regulated. Only recently has it changed as a result of liberalization processes (with regard to this and the following discussion, see Viehöver et al. 2009, pp. 65–66 and Section III.3.6). This liberalization, which was largely a result of cost pressure, has opened up new market opportunities. The introduction of individual health services (IGeL) by the National Association of Statutory Health Insurance Physicians is seen as an engine for the transformation of »medicine as a service sector« towards a »wish« or preference medicine (Maio 2006, p. 340). This form of medical care includes services that border on enhancement in the broader sense. The secondary healthcare market is taking shape in opposition to a primary market that remains pivotal to healthcare (Section III.3.6). Viehöver et al. (2009) believe that the establishment of enhancement practices is related to the establishment of the secondary healthcare market and the underlying institutional and (socio)economic boundary-blurring processes (see Viehöver et al. 2009, pp. 68ff. with regard to the following).

MARKETING AS A STRUCTURAL FEATURE OF MEDICALIZATION

The healthcare system is an important economic sector, accounting on average for 10% of gross domestic product in central European countries (in Germany in 2008: 10.5 %; OECD 2010). The enormous expansion of medical options for the diagnosis and treatment of diseases and increasing life expectancy of citizens has caused financial difficulties – especially for healthcare systems hitherto organized along welfare-state lines.

In addition to rationalization measures and the early forms of rationing (for example by imposing higher deductibles on insured patients to cover real costs), which have been practiced for years in Great Britain's National Health Service, an additional reaction is that preventive and health-promoting measures are increasingly being propagated to »strengthen the personal responsibility of the insured« and to »overcome the prevailing corrective mentality« – commonly used catchphrases in the debate. To some extent the insured are directly supported by the health insurance funds in acquiring and exercising health-promoting behaviors (e.g. by assuming the costs for back training or granting discounts for participation in preventive programs). By and large though an appeal is made to the individual's own sense of responsibility. Programs in the gray area between health promotion and performance enhancement (as in the case of »anti-aging«, see above) are also promoted in this way.

Together the four boundary-blurring processes of medicalization (Fig. 8, Section IV.2.1) lead to an expansion of medical options, which traditional healthcare systems finance only to a limited degree, if at all, for financial reasons but also with reference to an absence of medical necessity (Section. III.3.6). Because health insurance funds and healthcare policymakers no longer evaluate necessity and efficacy – though decision-making in this area has always been the subject of vigorous criticism from various quarters – a field has opened up for suppliers that is limited only by the regulatory requirements of food and medicinal products legislation (Section III). In the absence of major regulatory changes, the (growing) requirements for proof of efficacy will probably result in largely unspecific, poorly effective and often dubiously advertised »performance enhancing« agents (»wonder pills«) still being sold, while more potent substances will be obtained through illegal distribution channels, or charged as individual health services (IGeL), or disseminated via the primary healthcare market in the gray zone of off-label or »favor« prescriptions (Section III.3.6; cf. also the scenario of expansion in Section V).

CONSTITUTION OF ENHANCEMENT MARKETS

All these developments could promote the establishment of markets for enhancement as part of a wish-fulfilling medical offer. The growing importance of elective services is changing the relationship between doctor and patient, the lat-

ter being increasingly seen as a »customer« who can be (and wants to be) courted. In addition, there is the enormous importance of the internet as a cross-border source of information and goods, so that the field of healthcare services, which used to be relatively tightly organized by national governments, has been thrown wide open (Section III.3.6).

Often it is not the technical options themselves but their media-driven and market-like diffusion that opens the gateway to the routinization of enhancement practices. Thus, falling costs and depictions in the media – of cosmetic surgery for example – contribute decisively to the erosion of hitherto culturally established concepts of naturalness and related standards of normality (Schäfer/Gross 2008; Villa 2008). In this respect the marketing strategies of pharmaceutical companies and other suppliers of health services play a key role. The American medical sociologist Peter Conrad (2005, p. 6) describes the pharmaceutical industry's strategy as »marketing diseases and then selling drugs to treat those diseases.« This ploy, known as »disease mongering«, is particularly evident in the USA, where advertising for prescription medicines aimed at end-customers and consumers has been allowed since 1997. The marketing strategies for Prozac (Section II.3.3) and Viagra are the best-known and probably most illustrative examples of the targeted pathologization of behavioral and well-being problems that used to be regarded as »normal« in the area bordering pathological states that require treatment.

The extent to which products with the specific aim of enhancing performance have materialized in the secondary healthcare market in Germany cannot be determined on the basis of the available data. As shown in Section III.3.6, pharmaceutical expenditures in the self-financed secondary market have remained relatively stable for years, whereas health-insurance-fund expenditures have soared. Nevertheless, it is widely assumed that cosmetic treatments, dietary consultations, and lifestyle drugs are increasingly becoming significant elements of individual medical practice – particularly in the context of anti-aging products.

The uncoupling of medical options from the professional setting and its quality criteria has opened up the field to a flood of suppliers, who need not necessarily possess medical expertise (e.g. in the similarly booming field of alternative or paramedicine). However, this uncoupling also leads to pressure for medical practices to present themselves as companies: »They have to be – not demigods in white coats – but brand articles in white coats« (Bartens 2006). In this sense the doctor becomes a »health and lifestyle advisor« or a »purveyor of healthcare services«. In addition to the »commercialization« of medical practices, a diverse range of new suppliers are emerging, for example in the rapidly growing direct-to-consumer market. They range from shops offering Botox treatments in a »coffee-to-go« style to marketing via internet pharmacies and special to product and service gateways (Section III.3.6). The overall equalization of medicine with

other demand-driven forms of commerce clearly stands in stark contrast to professional self-imposed ethical restrictions (Kettner 2006a). For this reason quality standards are increasingly being mooted (Gerst 2005), and certifications, for example in the form of a seal (Rieser 2005), are being considered.

3. CONCLUSION

As shown in Section II.3, there exist at present no pharmacological substances that have been shown to bring about a relevant enhancement of cognitive performance in healthy individuals. Moreover, every substance specifically aimed at enhancing physical performance exhibits severe side effects (albeit not to the same degree in all users). The difficulties in defining and measuring »abilities« and »performances« at a multidisciplinary level are now clear (Section II.1). Hence, enhancement *agents in the narrow sense* (specifically active and free of, or at least relatively free of, side effects) have so far tended to be merely a construct of the debate or a research vision.

It was then shown in Section III.4.1 that scant robust data are available on the conscious and intentional use of (at least putatively) performance-enhancing substances – both medicines and illegal drugs – by people in everyday life. Little is therefore known *de facto* about the extent or characteristics of pharmacological performance enhancement as a social phenomenon. As this chapter has shown, philosophers/ethicists and social scientists/sociologists have reacted differently: in exaggerated terms ethicists by discussing hypothetical enhancement agents, social scientists by embedding enhancement within the higher-level context of a trend towards the medicalization of psychosocial problems.

Many participants in the debate conclude from the ethical assessment of hypothetical enhancement substances that neither the agents nor the related research and development work should be banned. Some authors, for example the authors of a memorandum entitled »The Optimized Brain« (Galert et al. 2009), even conclude that there is an obligation to carry out research (with roles divided between the public and private sectors), arguing that both the objectives (or the potentially achievable effects, e.g. the ability to learn foreign languages or musical instruments more easily but especially the ability to cope with stress situations at school and work) and the agents to be developed are comparable (in terms of their potential side effects) to conventional methods and strategies (learning training, mental methods of self-improvement, consumption of tea and coffee). Detractors, on the other hand, deny that the objectives or agents are comparable or similar. They doubt whether effects of a pharmacologically and technically specific and complex nature could ever be achieved that are comparable to those attained with the aforementioned »conventional« learning train-

ing and techniques of mental and emotional self-improvement. They also emphasize the adverse effects of substance use. Ultimately, however, both views must remain hypothetical until the advent of enhancement agents of proven potency.

In view of the weak empirical underpinnings and the often hypothetical character of the ethical debate, we will forgo a discussion of possible effects and side effects of future performance-enhancing substances. Instead, we will address and examine a question which – although obvious – has been left out of the far-ranging enhancement debate: how could the targeted research and development of enhancement agents in the narrow sense proceed against the backdrop of existing research and regulatory structures? This question forms the subject of the extended scenario in Section V.

The results of the social scientific view of enhancement within the higher-level context of a trend towards medicalization points to a need for further multifaceted research and elucidation (Section VII). In addition, Chapter VI addresses an aspect that has so far received little attention: the question regarding specific aspects of the objective of performance enhancement under the perceived conditions of growing competition in education and the workplace. This leads us to look at those social subsystems in which measurable performance is a key yardstick for evaluation and in which targeted performance improvement through training, technology, and substance use is more widespread than anywhere else: competitive and, at least in some areas, ambitious recreational sport. Often during the enhancement debate the link to doping issues has only been drawn in attention-grabbing headlines or introductory paragraphs (Section I.5). Following up on TAB's consideration of the sports system in the Gene Doping Project (Gerlinger et al. 2008; TAB 2008b), Section VI looks at the commonalities and differences between the use of performance-enhancing substances in sports on the one hand and working life on the other.

PERFORMANCE-ENHANCING AGENTS OF THE FUTURE – A SCENARIO OF EXPANSION V.

As was clearly shown in the preceding sections, although the topic of (neuro)enhancement has received a great deal of scientific and public attention, at the same time there is still little scientifically sound evidence of effective pharmacological performance enhancement in healthy individuals. This view was shared by most of the participants in the debate. Nevertheless, most commentators assume that the debate will grow in importance and pace, because the driving forces and promoting factors leading to the use of performance-enhancing agents (performance demands in education and working life, personal responsibility for maintaining performance, budgetary changes to the healthcare system, information, and accessibility via new sales channels) are more likely to become stronger, not weaker, in the future.

The available empirical data suggest that despite the lack of a comprehensive, knowledge-based survey of effects and side effects, the use of medicines to enhance performance is already being practiced to some extent (Section III.4.1) and is set to increase because there is a general trend towards medicalization in connection with psychosocial problems (Section IV.2).

For policymakers the question arises as to whether it is necessary and possible to exert a guiding influence on this development. On the one hand, at the level of the individual the consumption of even highly harmful substances falls under the right to personal development (Art. 2 of the German Constitution [GG]). On the other hand, at the supraindividual level, substances with specific effects – particularly those with a high potential to cause harm, such as chemicals, medicines, and narcotics – are subject to specific regulations to protect humans, animals, and the environment.

As shown in Section III, medicinal products legislation, not food legislation or chemistry legislation, is applicable to substances with specific performance-enhancing effects in humans. Currently known substances that are used non-therapeutically and for which performance-enhancing effects in healthy users is at least suspected to some degree are essentially all medicines, and all of them have a significant side-effect potential (Section II). In view of the tightly regulated and well established procedures for handling pharmacological substances, a decoupling from existing structures due to new expectations of benefits in healthy individuals is scarcely conceivable without a profound societal and political change. It is therefore expected that, without such a change, access to, diffusion of, and use of these substances will continue to develop along current lines – within medical border areas via prescriptions that will be influenced by chang-

es, extensions, and refinements of indications (Sections III and IV.2) as well as outside existing healthcare structures and therefore at least in part illegally.

However, a different situation could arise in the future if new, specifically active, and relatively side-effect-free substances are serendipitously discovered or are intentionally sought and developed. Many bioethical analyses and stances on the topic of (neuro)enhancement assume that comprehensive marketing restrictions on such substances cannot be legitimized, even if the substances are regarded as medicinal products by law (Section IV.1). Although current knowledge about performance-enhancing effects and side effects of pharmacological substances in healthy individuals makes it unlikely that substances will be found that have potent and specific effects on relevant abilities without at the same time adversely or at least undesirably affecting other physical or mental processes (Lieb 2010; Quednow 2010), this remains merely an assumption – albeit a scientifically plausible one – not a certainty. It would therefore appear sensible to examine a »scenario of expansion« of highly effective substances that are free or relatively free of side effects (hereinafter referred to as HPED for hypothetical performance-enhancing substances). The question arises as to what scientific and regulatory conditions, driving forces, and obstacles would influence such a development and what possible ramifications need to be considered.

The following exposition does *not* deal with the conceivable effects of hypothetical future substances, because that could only take the form of pure speculation. Rather, it discusses the changes that would be necessary in Germany's (and Europe's) research and innovation system to render possible or even promote the targeted research and development of performance-enhancing substances for healthy individuals compared to the situation today. This question has not been dealt with in depth, even though – given the extensive and detailed regulatory approach and limits of pharmacological research and development at the European and national levels – it may well be of key importance with regard to the social significance of enhancement agents in the future.

In many respects the following analysis of a »scenario of expansion« – the result of specific scientific efforts and political decisions – is therefore breaking new ground. It proceeds from the expert report of Eckhardt et al. (2010), which was prepared in close cooperation with TAB staff. Section V.1 describes the players who come into question and the possibilities they have to develop performance-enhancement drugs within the current research and innovation system. Section V.2 looks at elements and implications of the scenario of expansion: necessary changes to the legislative framework for premarketing research and development, possible requirements for long-term monitoring, conceivable consequences for the healthcare system, and repercussions for the innovation system.

1. DEVELOPMENT OF PERFORMANCE-ENHANCING AGENTS IN THE CURRENT RESEARCH AND INNOVATION SYSTEM

The dissemination and use of HPED – like all other medicinal products and so-called individual healthcare services – would be driven by supply and demand in the increasingly bewildering hodgepodge of the »healthcare market« (Section III.3.6).

Demand for performance-enhancing substances comes initially from users, who act primarily as individuals (e.g. athletes or students). At the same time, users must be understood as elements of groups, group dynamics, and group structures that exert strong influence on individual members (e.g. in sport or in the military). The military in particular is ascribed a special role as a potential purchaser and user of both physical and mental enhancement substances (Williams et al. 2008). Factors that increase demand include marketing by the pharmaceutical industry, advertising or at least mediation by doctors and pharmacists (Section III.3.5) and not least the creation of public awareness and expectation behaviors by the media and the socioethical debate.

The *available range* of existing medicines used for performance enhancement are chiefly characterized by the regulatory procedures enshrined in law, the distribution structures of the healthcare market (Section III), and the resulting consequences for investment and marketing decisions.

Given the safety standards of regulatory procedures, distribution structures and reimbursement conditions of the healthcare system, the development, regulatory approval, and marketing of new drugs is a protracted, and – because of refinancing pressure in the case of privately funded research – a financially risky proposition (see below).

Given that the boundaries between foods and pharmaceutical products have become blurred in recent years (Sections II and III) and the food processing industry is increasingly being required to provide scientific substantiation of efficacy claims, this industrial sector could in principle also play an active role in the development of performance-enhancing substances. Large companies in this sector are most likely to have the necessary resources. However, if claimed and/or real effects of food products cross the line to become actual pharmacological effects, in case of doubt the more stringent medicinal products legislation applies (Art 2 (2) of Directive 2001/83/EEC). Consequently, food manufacturers would have to act like pharmaceutical manufacturers. For this reason food manufacturers are not explicitly singled out as players in the following discussion.

PLAYERS IN PHARMACOLOGICAL RESEARCHAND DEVELOPMENT 1.1

Both in Germany and internationally there is a trend towards a multistage model of pharmacological research for medical purposes with

- mainly publicly financed basic research, healthcare research, and research in other specific areas (by independent or university-affiliated public research institutions);
- establishment of small, innovative, and often highly specialized companies (spin-offs), who undertake the first development step leading from a research finding to a product; and
- increasingly major pharmaceutical companies, who can provide the necessary resources for product development leading to regulatory approval.

The individual players in research are interconnected by diverse links. The R&D players orient their activities largely along the lines of the requirements of research sponsors (especially in the noncommercial area) and/or criteria for regulatory approval (in the case of commercial clinical trials), compliance with which is ensured by national and international regulatory and supervisory authorities.

Besides legal structures, there are also illegal structures within which performance-enhancing substances could be developed and produced.

PUBLICLY FINANCED RESEARCH INSTITUTIONS

The field of publicly financed biomedical research is broadly ramified and is coupled with diverse mandates: research, teaching, and the treatment of patients are pursued in parallel. Economic concerns about publicly financed institutions have grown in recent years. Since institutional funding was rolled back, many scientists at public institutions can pursue their research effectively only with the help of third-party funding. These third-party funds, in turn, can come from public or private-sector sources (especially the pharmaceutical industry). At the same time, third-party funding is gaining importance as a quality parameter in the allocation of institutional funding and in the evaluation of scientific work (in addition to student numbers, publications, etc.), against which institutional funding is measured (Minssen/Wilkesmann 2003, p. 123). A high proportion of third-party funding in publicly financed research institutions therefore pays off twice.

In addition, a declared aim of German research sponsorship is to support cooperation between clinicians and researchers on the one hand and industry and the healthcare system on the other. To this end, since 1996 the German Ministry for Education and Research (BMBF) has contributed approximately 82 million euros to the establishment of model centers for interdisciplinary clinical research (ICR) at eight German universities (BMBF, no year). The aim of ICR is to create a ba-

sis for the rapid translation of innovations from clinical research into marketable products through industrial involvement. In addition, from 1999 to 2009 the BMBF funded coordination centers for clinical trials as an infrastructure measure. The aim of the coordination centers is to improve practical clinical research in Germany and also to cooperate closely with university institutions, health centers, and the pharmaceutical and medical technical industries (http://kks-netzwerk.de/).

Various types of clinical trials, i.e. studies on humans, are conducted at public clinical research institutions. They include so-called commercial clinical trials that are required for regulatory approval and are initiated by research-based pharmaceutical companies, which, as a legal entity, assume responsibility and funding and are referred to as »sponsors« (Art. 4 Subsection 24 AMG). A doctor, referred to as the »investigator« or, if several study sites are involved, the »principal investigator«, is responsible for carrying out the trial (Art. 4 Subsection 25 AMG). For all commercial clinical trials used for regulatory approval a review by an ethics committee as well as official approval must be obtained. In addition, the study protocol, investigators, and sponsors must be disclosed (Section III.3.2).

Doctors can initiate trials themselves (»investigator-initiated trials«, IITs). These are then referred to as »noncommercial clinical trials«, because their primary purpose is not to obtain regulatory approval. The logical fallacy that noncommercial studies should be funded and carried out without industrial involvement should be avoided, because often such trials are only made possible by mixed forms of funding or partial industrial sponsorship (TAB 2010, p. 6). Other mainstream sources of funding besides the pharmaceutical industry are national and international research programs supported by public funding or foundations. For trials conducted outside the regulatory procedure, no financial disclosure statement has to be submitted. In these investigator-initiated trials doctors can freely define research questions. They can refine existing treatments and therapeutic concepts, undertake experimental treatments, carry out observational studies (Section III.3.2), or address basic pharmacological questions and in so doing use medicines off-label within their professional remit. However, the systematic investigation of performance-enhancing effects of pharmaceutical substances in healthy volunteers would overstep the bounds even of this research framework.

IITs enable pharmaceutical manufacturers to have certain research questions addressed without themselves being associated with this activity. In noncommercial clinical trials too public research institutions often rely on industrial or private funding.

At present the neurosciences are particularly attractive to researchers at public institutions thanks to their wide-ranging publicly financed sponsorship pro-

grams, their strong research dynamics, their future prospects, and their social recognition. At least in the area of basic research, the investigation of aspects of cognitive performance or emotional constitution is already seen as a scientifically intriguing and potentially worthwhile pursuit. Thanks to new techniques, i.e. imaging techniques, it is becoming easier to observe processes in the brain and shed light on them. Publication prospects are good owing to the large number of journals and are also supported by broad public interest, especially in the media. A case in point in Germany are the publications that have emerged from a research cooperation dealing with the »potentials and risks of pharmacological enhancement of mental characteristics«, which was sponsored by the BMBF in connection with the sponsorship program entitled »Ethical, Legal and Social Aspects (ELSA) of the Modern Life Sciences and Biotechnology«. Both the systematic evaluation of available study results on the enhancement potential of approved medicinal products (Repantis et al. 2009, 2010a and b), whose results also formed the basis of the expert report by Repantis/Heuser (Section II.3), and the final memorandum of the scientists at public research institutions involved in this project were published in renowned journals and generated a fair amount of media interest (Section I.5).

Other German trials identified in the TAB project that produced evidence of an enhancement potential in healthy individuals (regarding levodopa: Flöel et al. 2008; Knecht et al. 2004 [Section II.3.2]; regarding the use of direct current: Flöel et al. 2008 [Section II.5.2]) were approved by competent ethics committees and conducted at university institutions in compliance with the Declaration of Helsinki (Section III.3.2). The trials focused primarily on therapeutic questions. However, it was explicitly pointed out in some of the publications that the results could also be relevant to healthy individuals (Flöel et al. 2008, p. 1415): »We wanted to test the potential to enhance associated verbal learning, a skill crucial for both acquiring new languages in healthy individuals and for language reacquisition after stroke-induced aphasia.« As far as was documented, the authors were employed at university-affiliated institutions. No information was provided on the funding of the trials.

Application-oriented approaches, e.g. the specific analysis of the performance-enhancing effects of pharmacological substances in healthy individuals or the direct development of active substances – and thus possible cooperation with the pharmaceutical industry – are unlikely to become attractive to public research institutions unless the regulatory conditions for the approval of neuroenhancers are relaxed. Because there are still substantial barriers to this at present (see below), the pharmaceutical industry can act at best as a basic sponsor of research that addresses questions relating to performance enhancement but not as a direct sponsor of trials.

SPIN-OFFS

The step from basic research to application orientation is taken on the basis of a positively evaluated cause-effect correlation (proof of principle), often via corporate spin-offs devoted to further research and development. A prerequisite is to secure the necessary financial resources, often referred to as venture capital because it is usually highly uncertain whether the positive research result can be translated into a product that covers the R&D costs. At present only around one in 10,000 candidate substances is developed into a marketable product (Gassmann et al. 2008, pp. 10ff.).

Spin-offs that have so far been set up with the aim of developing substances to enhance mental performance paint a sobering picture (see box). Their lack of success can be seen as proof that the development of cognitive performance enhancement is still in its infancy. Because of the considerable and growing importance of therapeutic and preventive strategies to tackle dementia and, for example, to boost learning performance after a stroke or myocardial infarction, products of this nature have such a huge market potential, particularly in an aging society, that – notwithstanding the failures to date – venture capital is relatively easy to secure as soon as basic research produces new findings indicating that a substance can at least halt waning performance.

In 2004 the magazine *Science* presented four new companies conducting research in the field of potential cognition enhancers for dementia. Six years later the situation is as follows (Stix 2010, pp. 52ff.):

- *Memory Pharmaceuticals*: One of the cofounders of the company, which develops drugs known as phosphodiesterase inhibitors (e.g. MEM1414), is E. Kandel, who shared the Nobel Prize for Physiology or Medicine with two other researchers for his work on signal transduction in the nervous system. In 2008 Roche purchased the company after several clinical trials failed and staff were dismissed.[66]
- *Cortex Pharmaceuticals*: Originally a financially strong partner was sought. In the end, the rights to ampakine components, including CX-717 (Section II.3.6), were sold off in March 2010.[67]
- *Helicon Therapeutics*: Despite substantial investment funds, the company has not been able to develop any substance to a late testing stage.[68]
- *Sention*: The company has meanwhile been dissolved.

66 www.roche.com/de/media/media_releases/med-cor-2008-11-25.htm, October 14, 2010
67 www.cortexpharm.com/corporate/index.html, 14/10/2010
68 www.helicontherapeutics.com, 14/10/2010

RESEARCH-BASED PHARMACEUTICAL MANUFACTURERS

Research-based pharmaceutical companies are strongly dependent upon innovations, as their products are patent-protected only for a short period, and during this time the innovation costs must be recouped before generics manufacturers are also allowed to produce and market those products. Since the mid-1990s, however, innovation efficiency has declined, and fewer novel pharmaceuticals with truly new active substances are reaching the market. Many costly development projects with new substances fail only in late phases of clinical testing (Section III.3.2; Gassmann et al. 2008, pp. 3ff.), so that the development of new drugs is associated with considerable economic risks for pharmaceutical companies.

In total, the development of an innovative active substance requiring approval (»new chemical entity«, NCE) now costs around 1.5 billion US dollars on average. Only three in ten approved drugs generate income that covers or exceeds their R&D costs (Gassmann et al. 2008, pp. 1ff.). The high costs are due to, among other things, the stringent rules governing clinical trials and the fact that new technologies needed to discover and develop promising substances are expensive. R&D costs account for approximately 20% to 40% of the expenditures of research-based pharmaceutical manufacturers. Nevertheless, profit margins in the pharmaceutical industry remain substantial, i.e. approximately 20% in 2003 (Gassmann et al. 2008, p. 23). In view of high growth rates in the past, expectations of continuously rising profits are relatively high in comparison to other sectors. Between 1970 and 2002 sales of pharmaceuticals worldwide increased on average by 11% per year (Gassmann et al. 2008, p. 3). This growth was probably based mainly on product improvements and extended indications. By contrast, substances that are genuine pharmaceutical innovations play a diminishing role, at least on a *pro rata* basis (Gassmann et al. 2008, p. 12).

Innovation decisions in the pharmaceutical industry are influenced largely by the available funding and the expected return. The decisive scope for action is defined by the regulatory procedures of the pharmaceutical market at home and abroad. Other factors that determine the expected return and available funding are intellectual property rights, the size of the sales market, the price level, nearness to the financial market, and research opportunities.

Decision-makers at major pharmaceutical companies see the greatest future economic risks in regulatory procedures in the USA and in pricing levels and long-term cost reimbursement in the EU (Deck 2008). Because the pharmaceutical market is becoming increasingly globalized, pharmaceutical companies in Europe and the USA must adjust to strong competition from emerging markets (China, India, Brazil) (Gassmann et al. 2008, p. 19). Because of rising costs in the healthcare system, increased pressure on prices is also likely. In this respect growing price consciousness on the part of users, e.g. in response to a trend for patients to share the costs of prescription drugs, as well as the formation of

strong special-interest groups by patients, and government regulation are all important factors (Gassmann et al. 2008, p. 25).

Anti-dementia drugs that counteract ebbing mental performance in the elderly are highly attractive owing to the large user group and therefore constitute a very important product group for the pharmaceutical industry. Intensive R&D activity is expected in the coming years – also in areas bordering pathological states, because great hopes are also being pinned on preventive strategies (which apply to healthy individuals). Regulatory approval is probably possible even in the case of substances with little efficacy, as few therapeutic alternatives exist. Pharmaceuticals that are effective this indication constitute potential neuroenhancers – whether they have or, as has been the case so far, lack proven efficacy in healthy individuals (Section II.3.4).

As shown in Sections II, III, and IV, other relevant indications for the development of potential enhancing substances are mental disturbances (of well-being), whose definitions and symptom catalogs are in flux (from ADHD to shift worker syndrome), and preventive strategies to slow aging processes. This is already opening up a certain market potential in border areas between health and illness (Section IV.2). A distinct market for performance-enhancing drugs as such does not yet exist in the major sales markets (North America, Europe, Japan). However, especially in the USA some of the advertising for antidepressants that are approved as therapeutic agents blatantly encourage off-label use (Section III.3.4).

Without a change in regulatory conditions, the pharmaceutical industry will continue to research performance-enhancing drugs for borderline pathological states and try to bring them to market, similar to the situation with Viagra. New fields of use beyond those approved might then also be opened up in areas bordering legal structures, as is the case now, with the help of opaque and sometimes subtle advertising strategies (Section III.3.4). On the other hand, the »hijacking« of such substances by illegal market players and structures would hardly be in the interest of the pharmaceutical industry.

REGULATORY AUTHORITIES AS A CONTROL AND SAFETY INSTANCE

Drug regulatory authorities exercise important functions in averting health dangers and continuously improving drug safety. Pharmaceuticals are primarily approved at the national level – in the case of Germany, for example, by the Federal Institute for Drugs and Medical Devices (BfArM) and by other federal institutions[69] for specific indications. Alternatives to national approval at the EU level

69 The Paul Ehrlich Institute acts as – and is also called – The Federal Institute for Vaccines and Biomedicines (e.g. monoclonal antibodies and gene therapies); the Robert Koch Institute as the federal institution for infectious diseases and non-transmissible diseases (especially those that pose a grave danger, are widespread, or are of significant public or public-health significance).

are the procedure of mutual recognition by the EU member states and centralized regulatory procedures (and procedures to restrict or withdraw approval), which are either coordinated by a national regulatory agency and carried out in consultation with other national authorities or coordinated directly by the European Medicines Agency (EMA).

In the context of drug research the main areas of activity of the BfArM are the approval of clinical trials, the assessment and analysis of drug risks, drug licensing and registration, monitoring of the trade in narcotics, involvement in the development of regulatory and scientific standards and normal specifications, and the provision of advice and information to health professionals and the public (www.bfarm.de).

For the German pharmaceutical market the BfArM and its subsidiary regional offices (and special institutes) constitute the most important control instance for maintaining legal regulations regarding research, development, and regulatory affairs and for continuous postmarketing risk monitoring. To fulfill these functions, the BfArM is vested with wide-ranging powers (Art. 28 AMG). In justified cases the federal authority can impose additional safety standards in advance or deny or subsequently limit regulatory approvals. In the case of substances that are suspected of having a high misuse potential, it can demand that the manufacturers set up a substance-specific risk-management system (Art. 28.3a ff. AMG) to prevent unapproved use as far as possible. At any time it can also retrospectively limit or withdraw regulatory approval if new findings require a revision of the benefit-risk assessment. In the past this has repeatedly happened in the case of pharmaceuticals alleged to have an enhancement potential. Examples from Germany and Europe include the stepwise regulatory restrictions imposed on amphetamines and the tight restrictions placed on indications for methylphenidate (Ritalin) in November 2010 and modafinil in February 2011 (Section II.3).

EXCURSUS: ILLEGAL MARKET PLAYERS AND STRUCTURES

All activities not covered by medicinal products law or by the mandates of doctors and pharmacists (Section III.3) must be understood as illegal acts (or even explicit drug crimes). Public awareness of the topic has grown in recent years. In 2007 the Bundeskriminalamt (Federal Criminal Police Office, BKA) considered relevant aspects of the phenomenon of »drug criminality« to paint an overall picture (Sürmann 2007). The following are the most frequent offenses based on the criminal acts defined by the AMG (Sürmann 2007, pp. 12ff.)

- *Manufacture of counterfeit substances and packaging*
  - General imitation of a licensed product
  - Imitation products with identical packaging
  - Visually identical products containing no active substance
  - Products containing harmful or toxic substances

- *Sales of these substances*: Mainly via the internet (offers, ordering, marketing including advertising, provision of instructions for consumers, and even chatrooms to exchange information), but scarcely via the distribution chain of the conventional pharmaceutical market
- *Specific doping offenses*

Pharmaceutical crime is usually only discovered through policing activities, and much of it presumably goes undetected and unreported. Given the ease with which forgers can produce counterfeits, often with little investment in time and money, the straightforward distribution channels, and the possibility of uncomplicated, fast contact via the internet, structures that create opportunities for crime are growing, especially since the online trade in medicinal products was sanctioned in 2004 (Sürmann 2007, p. 48).

At the same time, the number of offenses discovered by the police has been rising steadily in recent years. Lifestyle agents (to enhance potency or lose weight) and a whole range of performance-enhancing substances in the bodybuilding world are available on the internet. The latter are the products that are most often discovered by customs. They have been identified as coming mainly from Asia. Extensive networks that are becoming increasingly well-established facilitate the illegal trade and international marketing of these products (Sürmann 2007, pp. 25ff.).

The resulting threat is seen mainly in the danger the trade poses to the health of consumers. Affected pharmaceutical companies also point to collateral damage in the form of flagging sales and tarnished product images. The first counterfeiting cases were discovered by companies in the 1990s. The leading countries and regions of origin of pharmaceutical counterfeits are reported to be China, India, Russia, and increasingly Latin America and the Middle East (Sürmann 2007, pp. 30ff.).

Failure to comply with research-and-development guidelines for medicinal products (e.g. the performance of unapproved drug trials) is also a punishable offense under the AMG (Art. 96 Subsections 10 and 11 AMG). However, the publication by the Public Prosecutor's Office does not look into this aspect in detail (Sürmann 2007).

CURRENT DEVELOPMENT AND DIFFUSION ROUTES 1.2

If we consider the substances used to date that are consumed with a view towards enhancing performance, the following points stand out:

Stimulants in particular have seen relevant diffusion as performance-enhancing substances in everyday life (Section II.3.1). First and foremost, the consumption

of caffeine and nicotine is widespread – substances that occur as natural chemicals in various plants and have been consumed for a long time, either as beverages in traditional form (coffee, tea) or synthetic form (caffeine-containing soft drinks) or as so-called legal drugs (tobacco). Beverages are classified as foods. Tobacco is now uniquely classified in Germany. For many years it has been undergoing a social shift in the way it is viewed and evaluated – away from an emphasis on enjoyment towards greater stress on its danger to health. Highly concentrated dosage forms (e.g. caffeine tablets, nicotine patches) fall under medicinal products law, which dictates how they are handled (regulatory approval procedures, restricted distribution), as described in Section III.3.

If we look at those pharmacological agents with an alleged performance-enhancing potential (Section II.3), it is clear that such substances have so far rarely been specifically sought and discovered. Rather, most had been approved for years for the treatment of various pathological symptoms before their (supposed) performance-enhancing effect in healthy individuals was serendipitously discovered during use. For example, amphetamines were first synthesized over 120 years ago (Section II.3.1). Their industrial-scale manufacture around 80 years ago led to a rapid spread in medical science (as medicines for the treatment of colds, obesity, and various psychological and neurological diseases). Only through frequent use was their stimulating effect discovered. This then led to their use in working life and everyday life and notably to their systematic use in the military. At the time the use of bioactive substances was still viewed uncritically. Their side effects and risks were poorly researched and seldom discussed. Not until the thalidomide scandal in the early 1960s did national and international attention begin to focus on the risks and safety aspects of pharmaceuticals, culminating in a fundamental reform and tightening of the regulatory approval and supervision of pharmaceuticals. This also ushered in a new attitude towards the use of amphetamines for therapeutic purposes, because their side effects were increasingly coming to the fore. Having meanwhile been replaced by alternatives with better benefit-risk profiles, amphetamines are now scarcely used for therapeutic purposes – at least in Germany. No finished pharmaceutical products containing amphetamines are currently available in Germany.

Unless clinical testing and approval procedures, which have so far prevented a targeted search for performance-enhancing effects of pharmacological substances in healthy individuals, are changed, one can plausibly assume that enhancement will continue to be driven more strongly by this route of development and diffusion, i.e. via »incidental expansion of use«, than by the results of targeted medical (basic) research and development (Section V.2.1).

The existing regulatory system can hardly be directly blamed for the nontherapeutic use of pharmacological substances for enhancement purposes. There is

little evidence of a »lax« benefit-risk assessment by regulatory authorities.[70] The off-label use of a pharmaceutical product for performance enhancement in healthy individuals may be suspected during the approval procedure, and authorities may demand countermeasures to at least limit such use, but they cannot entirely prevent it.

Likewise, the trend for doctors and patients to agree on the off-label use of pharmacological substances and charge such use »privately« (as individual health services [IGeL]) can be countered only to a limited extent by measures such as risk-management systems and risk liability. Empirical findings about this route of diffusion are currently based on consumer surveys (Zok 2010), not on a systematic examination. Specific substance-related analyses would only be possible at great expense, if at all (Section III.3.6).

POSSIBILITY OF RESEARCH AND DEVELOPMENT IN THE AREAS BORDERING EXISTING LEGAL STRUCTURES AND BEYOND

Specific research and development of performance-enhancing pharmaceuticals could follow several routes in the areas bordering existing legal structures, whereby the groups of those involved and informed differ markedly in each:

- The performance-enhancing potential of a new substance is discovered and developed by illegal market players directly for the illegal market in connection with basic research, i.e. before the clinical research phase and before regulatory and/or supervisory authorities become involved. The only knowledge that the research institution with its internal control structures might have or notice of the research and its findings is that the results are only partly published, if at all. Regulatory and/or supervisory authorities are unable to gather information about such activities, as they are not subject to the usual registration obligations for regulatory research. Reputable pharmaceutical manufacturers are not involved (route 1).
- The performance-enhancing potential of a substance is discovered at an early stage. A pathological symptom is construed, as it were (e.g. in areas bordering psychological disorders of well-being or abnormal social behaviors) in order to obtain regulatory approval. In parallel with the official publication of the results in study registers, the performance-enhancing effect in healthy individuals is also reported in biomedical journals. Patterns of use in border areas between health and illness become established. Information is largely public, so that it is not »necessary« to resort to illegal structures (route 2).

70 A rather rare counterexample is the latest pharmaceutical scandal in France, where the appetite-suppressing, amphetamine-containing product Mediator could still be sold until the end of 2010, despite the fact that studies had shown the danger of the product as early as 1999. As a result it is currently being debated whether to further tighten the French regulatory system for pharmaceuticals and focus more strongly on risks.

- A substance is developed with a view to marketing it as a medicinal product, or development work is carried out with a view to expanding the medical indication of a known substance. During the development process the performance-enhancing effect is discovered. However, the substance fails in the regulatory process, e.g. because unacceptable serious side effects occur and/or the therapeutic benefit is marginal. The substance and the knowledge gained about it fall into the hands of illegal market players, who distribute the substance on illegal markets. All the study results are known to manufacturers and regulatory authorities, who can inform law-enforcement agencies to enable them to observe and prosecute illegal market structures (route 3).
- The research and development of an enhancement substance and its regulatory approval occur in a country that does not strictly adhere to international standards (Section III.3.2) but has the necessary scientific capacities (e.g. China, India, Brazil). The substance is licensed in that country and from there it is distributed internationally via online suppliers and/or illegal market players. In this context national differences in substance classification may also be relevant, e.g. if a substance that is classified as a pharmaceutical in Germany is deemed to be a food supplement in the country in which it is produced and is therefore freely available there (route 4).
- The substance is manufactured from the outset specifically for illegal use. Research and development *per se* are not performed; at the most a simple chemical modification of known molecular structures is carried out, as is the case, for example, with today's designer drugs (route 5).

It is conceivable that research work in Germany, e.g. at universities or in the pharmaceutical industry, could be diverted into illegal developmental routes as an »incidental result«. Routes 2 and 4 are legal. Route 5 clearly implies – both nationally and internationally – a criminal act which, however, also cannot be ruled out.

2. ELEMENTS AND IMPLICATIONS OF A SCENARIO OF EXPANSION

The aim of the »scenario of expansion« is to assess prospective prerequisites for and obstacles to a possible intensification of the enhancement phenomenon which could emerge from targeted scientific developments and regulatory changes. It is assumed that there must be an interplay between scientific developments, public debate, and decisions about the direction of policies for a relevant acceleration of the R&D work on performance-enhancing substances to occur, because – at least in most industrialized countries – current conditions prohibit the approval and legitimate marketing of »true« enhancement substances that are not primarily developed and used as therapeutic agents.

Based on route 4, a process of change could proceed, for example, as follows: Various interest groups in Europe and North America could make the discovery of new performance-enhancing substances that evidently have few side effects – and possibly the start of product development in emerging high-tech countries such as China, India, or Brazil – the subject of intense debate so that they are increasingly perceived by scientists and policymakers as a socially important option, especially in order to maintain economic competitiveness. Consequently, preventive regulatory regulations could be relaxed, public and/or private resources could be obtained and invested, and the quest for specific performance-enhancing substances and the development of relevant products in Europe and other industrialized countries could gather pace.

It is impossible to predict if new performance-enhancing substances that are more specific than those currently known will be discovered in the foreseeable future. The possibility cannot be ruled out that existing substances might be reassessed if they are tested more extensively for performance-enhancing effects under normal conditions, which has not previously been done for the reasons outlined above.

The preparation of the expert report by Eckhardt et al. (2010) showed that in view of the limited research carried out to date and the rather restrictive legal regulations, it is not easy to elaborate a scenario of expansion that is not entirely unrealistic. It became clear that *if the current legal framework* governing the handling of foods and medicines is maintained, the marketing of effective performance-enhancing drugs that are relatively free of side effects (HPED) as an independent product group can be virtually ruled out. In view of the scientific and financial resources required and the uncertain marketing possibilities, the intensified and targeted development of performance-enhancing drugs for healthy individuals is extremely unlikely within the reputable public and industrial research and innovation system (except possibly through military research).

Following up on Section III.3, we will first describe the existing basic legal restrictions and relevant regulatory changes that would be necessary for targeted research, development, and marketing (Section V.2.1). We will then flesh out the scenario by discussing the challenges and difficulties of developing »true« innovative enhancement agents in the R&D process prior to regulatory approval (Section V.2.2), addressing possible requirements for long-term supervision (Section V.2.3), and shedding light on consequences of the assumed necessary regulatory changes (Section V.2.4). Potential repercussions on the innovation system are then discussed (Section V.2.5), and the possible triggers of the scenario are reviewed (Section V.2.6).

Thus, the scenario of expansion illustrates the option of a »reasoned pro-enhancement approach«[71] as formulated by the European Technology Assessment Group (ETAG) (Coenen et al. 2009, p. 144). We do not discuss possible reasons why HPED could or should be regarded as socially beneficial and its research as a politically relevant goal. This debate must be conducted far more extensively and concretely than has previously been the case before any decision is made about a change of policy direction. Ethics and the social sciences provide the initial arguments and orientations but in many respects must remain unspecific (Section IV). It would have to be examined what kinds of performance enhancement with HPED actually appear feasible and whether they represent socially desirable and worthwhile objectives (see also Section VI).

CURRENT LEGAL RESTRICTIONS – NECESSARY CHANGES 2.1

The framework conditions of regulatory approval procedures, which have been harmonized particularly in Europe but to some extent also internationally, as well as access to substances and funding (regulated in Germany by the Social Security Code V (SGB V) for the statutory health insurance funds) are key to the diffusion of pharmacologically active substances and are therefore important in respect of the research and innovation system. This is especially true of the manner in which the potential approval of HPED is regulated. It remains fundamentally unknown whether the scenario of expansion will take hold only in Germany or – more probably – at the level of the European Union or within an even larger group of countries. Although the strongly globally oriented pharmacological innovation system tends to be subject to internationally valid requirements, divergent national positions are also possible on specific issues (Art. 13, Regulation (EC) 726/2004). The following observations relate to Germany as well as to the framework European legislation and is based on the expert report by Eckhardt et al. (2010).

Current legal requirements oppose the regulatory approval of nontherapeutic performance-enhancing substances: neither medicinal products law nor food law provides a suitable framework (Section III). Access via an expansion of food categories appears unlikely, because HPED (by definition) have biological effects above and beyond the effects permitted under food law. From today's point of

71 »In a reasoned pro-enhancement approach, EU policy would explicitly fund R&D on (nontherapeutic) human enhancement technologies, while preserving all applicable elements of existing ethical frameworks and, as a matter of course, respecting fundamental European values. In such a strategy, EU policy would try to stimulate a societal dialogue about how risk-averse we can be, and how open to innovations, which might run counter to traditional value systems. Initiatives to stimulate discussion of deregulation in such areas as drug and doping policies or reproductive technologies could be elements of this strategy.« (Coenen et al. 2009, S. 145)

view, it therefore appears most likely that HPED will be subject to regulation based strongly on medicinal products law. Moreover, according to experience gained to date, substances that have high biological activity usually have the potential to cause nontrivial side effects. Virtually all substances currently used for performance enhancement, e.g. amphetamines and methylphenidate, are unapproved for use or are approved only for use under medical supervision due to their serious side effects or potential for abuse.

Under German law the term »medicinal product« denotes a substance that serves to influence physiological functions (Art. 2 Subsection 1 No. 2 AMG; see Section III.1 for details). It does not necessarily presuppose the existence of a disease to be treated. Drugs that enhance performance in healthy individuals and have no relation to a disease therefore meet the definition of a medicinal product. The concept of illness therefore has no significance at the definition or product-classification level but it does have significance in the context of marketing authorization (regulatory procedures) and questions relating to distribution.

According to Art. 21 Subsection 1 Sentence 1 AMG, proprietary medicinal products that are medicinal products as defined by Art. 2 Subsection 1 or Subsection 2 No. 1 AMG can only be marketed if they have been authorized by the competent authority.[72] Provided that the requirements set out in Art. 21ff. AMG are met, authorization is granted. The applicant has a right to authorization if none of the grounds for denial pursuant to Art. 25 AMG applies. Two reasons for denial relevant to enhancement are an unfavorable benefit-risk relationship (Art. 25 Subsection 2 No. 5 AMG) and the absence of therapeutic efficacy or insufficient substantiation of therapeutic efficacy by the applicant in accordance with the established state of scientific knowledge (Art. 25 Subsection 2 No. 4 AMG). However, the term »therapeutic efficacy« is not in itself defined by the AMG. According to rulings by the Federal Administrative Court, a medicinal product possesses therapeutic efficacy if its use is responsible for successful healing.[73] Thus, both the legislature and the courts proceed from the assumption of therapeutic success which the medicinal product must demonstrate in order to be granted authorization. The possible authorization of a »genuine« enhancement agent would therefore not fail on the definition of a medicinal product but probably on the more stringent requirements of authorization law. This applies analogously to European authorization law, as here too therapeutic efficacy is a criterion for authorization (Art. 26 Subsection 1 let. b of Directive 2001/83/EC).

In the European Union innovative pharmaceuticals are authorized mainly via the centralized procedure based on Regulation (EC) 726/2004. Art. 13 of the regula-

72 Non-proprietary medicinal products, e.g. formulations prepared in a pharmacy (§ 7f. Pharmacy Operating Ordinance) are not considered in the present context.

73 BVerwG, PharmaR 1994, 77/80

tion defines the general assessment criteria for authorization as follows: »In the interest of public health, authorisation decisions under the centralized procedure should be taken on the basis of the objective scientific criteria of quality, safety, and efficacy of the medicinal product concerned, to the exclusion of economic and other considerations. However, Member States should be able exceptionally to prohibit the use in their territory of medicinal products for human use which infringe objectively defined concepts of public policy and public morality.« These aspects will probably be more important in the case of performance-enhancing pharmaceuticals, as reflected by the current ethical debate on enhancement (Section IV.1). It would then have to be discussed what role »economic and other considerations« that are currently categorically excluded should or can play. Even if performance enhancement were deemed to be beneficial to the individual and society in the broad sense, the requirements for safety testing and the overall benefit-risk assessment would probably be more stringent than in the case of authorization for therapeutic use. One requirement for authorization would presumably be the exclusion of direct health damage. At the same time, attention would focus on rare and long-term but probably also indirect side effects and consequences of both an individual and societal nature (Section V.2.3). Inevitably these are very difficult to determine, and a lengthy and complicated scientific, public, and political dispute about how they should be handled would be foreseeable (see also TAB 2000 for the long-term and indirect effects of transgenic plants and their consequences for the authorization procedure).

A gatekeeper model is an obvious candidate for determining consequential damage, i.e. where the dispensing of HPED would be prohibited except by legitimate persons charged with notification and documentation obligations to whom user feedback can be directed. Restricting the gatekeeper function to doctors, whether in parallel with their therapeutic activity or as a specialist function, appears realistic (Section V.2.3). Their psychosocial training must be specifically augmented. The concept of medical action in the code of professional conduct for doctors would have to be reconsidered and probably expanded (Simon et al. 2008).

From the point of view of administrative law, the question would arise as to whether enhancement should be subject to special supervision, regulatory obligations and quality-assurance procedures (Simon et al. 2008, p. 27). More stringent requirements are imposed by the courts in respect of interventions that aim to improve, e.g. cosmetic surgery, than on interventions carried out for therapeutic purposes. This concerns, for example, information provided to the patient. Accordingly, more stringent requirements would also be placed on providing information to the users of performance-enhancing drugs.

OVERALL ASSESSMENT

Enhancement as a possible field of application of the law could in principle be dealt with by applying existing regulations of medicinal products law, provided one is prepared to modify the authorization regulations and possibly the regulations on procurement and use, supervision, information, and advertising or to pass explicit »enhancement regulations« within medicinal products law. Special authorization would be necessary owing to the linking of the current regulatory procedure to the therapeutic success of medicinal products, which does not apply to enhancement agents. The formulation of specific regulatory requirements for enhancement agents as an extension of existing authorization regulations, i.e. a separate authorization procedure within medicinal products law, would come into consideration.

By contrast, the creation of a new and separate product category of enhancement substances under pharmaceutical and food law (e.g. from rather unspecifically acting functional foods to true HPED) is very difficult to imagine, because – given the current concepts of foods and pharmaceuticals – demarcation problems would arise that would be very difficult to resolve. The concept of a medicinal product would probably have to be fundamentally modified or limited. A new product category would create another uncertainty factor with regard to the already difficult demarcation of foods, medicines, and chemicals (Section III.1).

PREMARKETING RESEARCH AND DEVELOPMENT 2.2

Compared to the development of therapeutic pharmaceuticals, HPED pose new challenges and problems with regard both to proof of efficacy and the assessment of risks – as the basis for a robust benefit-risk assessment in the context of later authorization. As explained in Section II, there are substantial uncertainties and differences in the interpretation and conceptualization of the nature and influenceability of human performance. This would come to the fore in connection with the targeted research and development of HPED.

BIOMEDICAL RESEARCH ON HUMANS IN GENERAL

When is research on humans legitimate? When can medical interventions be performed and their effects investigated on humans? Key considerations for answering these questions are the relationship between benefits and risks or burdens for the trial participants on the one hand and their voluntary informed consent on the other (Section III.3.2). The Declaration of Helsinki of the World Medical Association states that »the well-being of the individual research subject must take precedence over all other interests« (WMA 2008, Art. 6). The importance of the objective of the research must »outweigh the inherent risks and burdens

to the research subjects« (WMA 2008, Art. 21). Similarly, the European Council stipulates that the interests and well-being of the research subjects must take precedence over the interests of society or science (European Council 2005, Art. 3).

The Council for International Organizations of Medical Sciences (CIOMS) also requires that the risks for the subjects be minimized. In addition, a balanced relationship of risks and benefits must be aimed for (CIOMS 2002, p. 31): »Risks of interventions that do not hold out the prospect of direct diagnostic, therapeutic or preventive benefit for the individual must be justified in relation to the expected benefits to society (generalizable knowledge). The risks presented by such interventions must be reasonable in relation to the importance of the knowledge to be gained.« This requirement is reiterated by the European Council (2005, Art. 6). Overall, the international biomedical and medicoethical agreements are in accord that, to be ethically acceptable, clinical research, i.e. research on humans, must have a societal value (SAMW 2009, p. 27). Any assessment must also be based on a discussion of possible societal risks associated with a clinical research project (SAMW 2009, p. 51).[74]

In the case of studies whose direct objective is to relieve or heal a pathological state – also known as therapeutic trials – the question regarding the societal value is usually deemed to be positive. In pharmaceutical research, phase II and III clinical trials (Section III.3.2) serve to investigate the therapeutic efficacy of a substance and are therefore therapeutic trials. Pharmaceutical studies in earlier phases are not regarded as therapeutic trials.

Nevertheless, EU Directive 2001/20/EC on the implementation of good clinical practice in the conduct of clinical trials on medicinal products for human use applies to all trials (therapeutic and nontherapeutic) in which medicinal products are used. It was implemented in German law in 2004 by the GCP Ordinance, which stipulates specific procedures for conducting studies, e.g. approval by an independent ethics committee and the competent authority. Both must come to the conclusion that the expected benefit outweighs the risks (see Section III.3.2 for details).

In addition to pharmaceutical research, there are many other medical research issues that can be addressed only if trials are carried out on humans. These studies, referred to as nontherapeutic trials in basic research, usually involve investigations with a small number of healthy volunteers to whom the research project has been explained and who have consented to participate in it (»informed consent«). This research is generally regarded as being justified by the fact that it

74 The Declaration of Helsinki also addresses environmental risks: »Appropriate caution must be exercised in the conduct of medical research that may harm the environment.« (WMA 2008, Art. 13)

serves the further development of medical science and therefore can also yield therapeutic benefits in the future (Merkel 2005, p. 138). The extent to which performance enhancement in healthy individuals and an associated benefit can justify nontherapeutic trials in basic research has yet to be evaluated in detail or debated extensively.

PHARMACOLOGICAL RESEARCH

In contradistinction to other areas of the life sciences, pharmacology is concerned with interactions between substances and organisms. Over the years various internationally recognized research phases have been established. Approval of a clinical trial or study usually presupposes that the previous research phases have been completed (Section III.3.2). Before efficacy trials can be commenced, important safety issues must be investigated. However, in practice the two research aspects of *efficacy* (as a benefit dimension) and *safety* (as a risk dimension) cannot be handled entirely separately. Rather, trials in which safety questions are addressed also provide initial evidence of the effects of a substance, and efficacy studies always also consider safety aspects.

PRECLINICAL RESEARCH

Before a novel substance can be tested on humans in clinical research, certain effect dimensions must be investigated in animals. This relates primarily to safety and risk questions (e.g. toxic or genotoxic effects). Animal experiments are therefore also referred to as preclinical research.

In animal experiments, too, the welfare of the experimental animals must be respected (WMA 2008, Art. 12). There must be a reasonable relationship between the anticipated benefit from the research and the risks and burdens to the animals. This ethical demand underscores the requirement regarding the potential benefit of pharmacological performance enhancement and at the same time raises the barriers for the investigation of such substances. Animal experiments are also subject to official approval (Art. 7 to Art. 9 of the Animal Protection Act). In the approval procedure, the societal benefit must be weighed against potential damage to the animals.

Because toxic or genotoxic effects of substances are often similar in animals and humans, a certain risk assessment in humans can be undertaken on the basis of data from animal experiments (Greaves et al. 2004). Health damage in mammals raises the suspicion of similar effects in humans, though the converse does not hold true: the safety of a substance cannot be concluded from the absence of health damage, as some effects are species-specific. This is particularly true of the desired therapeutic effect, because physiological, genetic, and biochemical differences play a substantial role. The history of pharmaceutical development is

replete with examples where substance effects that had been observed in animal disease models did not manifest themselves in the same way in humans and where entirely different effects occurred (Ferrari et al. 2010, pp. 35ff.). Especially where more complex forms of specific human abilities are concerned – notably operative brain functions such as learning, memory, and cognition, as is the case in the search for and development of HPED – the predictive value of animal models is extremely limited.

All things considered, it appears plausible that, in view of the assumed greater safety requirements, preclinical investigations of safety and risk aspects would be expanded in a scenario of expansion of future HPED, whereas efficacy investigations would probably play only a very small role.

CLINICAL RESEARCH: SAFETY AND EFFICACY

Preclinical investigations are followed by phase I clinical testing of tolerance, safety, pharmacokinetics, and pharmacodynamics in humans (usually on 20 to 50 healthy volunteers; Section III.3.2). Phase I clinical trials would probably differ little from those carried out with drugs for therapeutic purposes. In both cases emphasis would be placed on safety questions. Because therapeutic effects cannot be substantiated in healthy subjects, efficacy aspects are not very relevant to phase I drug trials. However, since the efficacy of HPED must be demonstrated in healthy subjects, both safety aspects and initial efficacy aspects could be investigated in phase I. Consequently, study planning, approval procedures, and the conduct of phase I studies would be more elaborate and extensive than is the case for therapeutic drug studies.

The actual proof of efficacy for the therapeutic use of pharmaceuticals is established in phase II and III trials. In the case of HPED, the *concept* of efficacy would be different. Hence, *proof* of efficacy would have to be adduced in a different manner than is currently the case for the regulatory approval of medicines.

Even if performance enhancement were deemed to be beneficial to the individual and society (the initial hypothesis of the scenario of expansion), not only the requirements for safety and risk testing and evaluation would be more stringent than in the case of therapeutic pharmaceuticals, so too would be those pertaining to proof of efficacy – both from an empirical and causal point of view. The Health Claims Regulation could provide a conceptual framework for defining and demonstrating the efficacy of substances without reference to a disease or treatment. The directive calls for all health-related claims on the efficacy of individual food items (or food constituents) to be scientifically substantiated while at the same time prohibiting disease-related claims (Section III.2.3). Even if there is currently no consensus as to how claims such as »fortifies health« or »promotes well-being« can be regarded as being scientifically substantiated, it is expected that this will be discussed more intensively in the future and that appropriate

procedures will gradually be established. Because greater potency is generally attributed to HPED than to foods, the requirements for proof of efficacy will probably be very similar to those applied in pharmacological research. Hence, important aspects of current therapeutic study planning would be applied (determination of parameters, dosage, subject recruitment, data recording and analysis, etc.).

PROOF OF PERFORMANCE ENHANCEMENT: PARAMETERS AND MEASUREMENT CONCEPTS

As a prerequisite for specific proof of efficacy it would first have to be clarified which specific effects are to be investigated. In the case of HPED that would be certain brain functions or individual dimensions of mental abilities (Section II.1). In the debate about the performance-enhancing potential of substances that are already available, specific parameters such as attention, concentration, perception, and memory are mentioned (Section II.3). These parameters are investigated and recorded as symptoms of various diseases (mental and behavioral disorders F00–F99 ICD-10; e.g. ADHD, Table 11, Section III.3.5) in medical diagnostics or as attributes in the estimates of personal potential (e.g. the identification of highly gifted individuals). Various tests, e.g. to measure individuals' intelligence or its various dimensions, and procedures for measuring working memory performance are available (Section II.1.3). The existing tests would probably have to be modified or refined to investigate the clinical efficacy of HPED in healthy individuals.

Studies that have so far demonstrated the effects of a pharmaceutical on individual cognitive ability dimensions in healthy individuals (e.g. by means of flight-simulator exercises [Yesavage et al. 2002, pp. 123ff.] or simple associative learning tasks [Knecht et al. 2004]) are very unlikely to be sufficient as proof of efficacy, as they model individual situations very specifically. Moreover, particularly in the case of mental and cognitive performance, it cannot be assumed that they can be transferred to other environments. In this case the multitude of interactions, e.g. of cognitive abilities and emotional states, play an important role. This includes the observation that a particularly strong expression of individual mental abilities may be accompanied by a reduction of other abilities (an extreme case being the »savant syndrome«). Proof of effective performance enhancement must therefore be obtained on the basis of multiple, easily measured parameters in informative experimental setups that cannot be defined on the basis of the current state of scientific knowledge and have not yet been developed. Because there is no scientific consensus regarding the internal structure of mental performance and abilities and a wide variety of measurement concepts therefore exist (Section II.1), it is foreseeable that controversial debates on the definition of parameters and the selection of measurement concepts will ensue.

SUBJECT GROUPS

Depending on the selection of parameters and the measurement method used, a study design and a protocol must be developed. Lengthy tests with various subject groups under performance conditions that are as realistic as possible would probably be necessary. In principle, the heterogeneity of the potential users would complicate the proof of efficacy. An HPED that improves mental concentration, for example, could theoretically be used by schoolchildren as well as by elderly people whose performance in everyday life has diminished; by individuals who do strenuous physical exercise and by those who spend the day sitting in an office; by student mothers with young children; by doctors who suffer from chronic lack of sleep and excessive workloads; and by healthy pensioners who would like to take up the challenge of academic study in old age. Certainly, the requirements for the recruitment and selection of subjects for clinical trials to demonstrate the efficacy of performance enhancement in healthy individuals are far greater than those that apply to current drug trials.

Investigations into the performance-enhancing effects of pharmaceuticals so far conducted do not rule out the possibility that they occur only in subjects who are suffering from a transient state of deficiency, where individual brain functions or abilities are temporarily reduced (e.g. because sufficient time has not passed for regeneration, because of a »deficiency« of certain transmitter substances, or because of a poorer working memory or lower IQ than the average population; Section II.1.3). These circumstances must be taken into account. In addition, what constitutes a healthy subject needs to be defined more precisely than is currently the case.

In light of the high level of acceptance of the use of pharmacological substances for cognitive performance enhancement – at least by some segments of the population – on which a scenario of expansion is based (Section III.4.1), it will presumably be possible to recruit a sufficient number of volunteers.

EFFECT STRENGTHS

If only mild performance-enhancing effects occur during the testing of HPED candidates and only in a (small) proportion of users, from today's point of view this hardly constitutes a convincing »additional benefit« – unlike in the case of medicines – that could outweigh the inevitable risk associated with the use of pharmacologically effective substances. The more clearly a performance enhancement in healthy individuals is recognized as a benefit dimension, the more opportunities there will be to obtain marketing authorization for substances with only moderate effects, especially in the early phase of targeted research and development, since no alternative substances are available that could serve as comparators in the benefit-risk assessment.

REQUIREMENTS OF LONG-TERM MONITORING 2.3

Besides efficacy, the safety and tolerance of a substance are also continuously and simultaneously investigated in phase II and III clinical trials. To this end *adverse effects*, among other things, are systematically recorded, checked, reported, and analyzed. This is done on the one hand by the investigator/sponsor of a clinical trial and on the other hand by the competent ethics committee and the regulatory authority, who are responsible for independent risk monitoring in parallel with the investigator/sponsor.

If we assume that HPED can have adverse psychosocial consequences owing to their action on central functions of the brain, these too must be especially intensively investigated during clinical testing, which would thus, develop into a form of *clinicosocial test regimen*. In this context entirely new assessment standards and methods would probably have to be developed. The following requirements for HPED appear plausible (Eckhardt et al. 2010, p. 88–89):

- The probability of adverse biomedical and psychosocial side effects for users must be low, that of severe and long-term effects very low.
- There must be no evidence of a physical dependence potential. The mental dependence potential, which cannot be ruled out specifically in the case of neuroenhancers, must be low.
- The desired enhancement of abilities must not produce a one-dimensional stereotypical performance profile and must not be achieved to the detriment of other abilities.
- The product must consolidate the user's performance without contributing to growing fluctuations in performance and if used according to instructions must not lead to individuals exhausting their resources beyond their personal tolerance limit.
- The HPED must not cause any irreversible fundamental changes in the performance profile of an individual or otherwise in his or her personal identity.

Compared to the current risk assessment of new pharmaceuticals in connection with regulatory approval, this – probably far from exhaustive – list includes qualitatively new parameters, particularly with respect to effects on performance, performance profiles, and personal identity, whose testability can hardly be seriously evaluated at present. But the assessment of dependence potential is anything but trivial. Plus, there is broad scope for interpreting the question regarding what probabilities of adverse side effects should be classified as low or very low. All things considered, it appears obvious that systematic long-term monitoring will figure prominently. However, appropriate structures and methods would first have to be created.

PHASE IV CLINICAL TRIALS/LONG-TERM MONITORING

In most cases today the regulatory approval of a new pharmaceutical is followed by a product observation phase – phase IV clinical testing, also known as post-marketing surveillance. This phase includes a large number of users and investigates the safety and efficacy of a medicinal product under everyday conditions.

This phase would be particularly important for HPED, which represent a novel product group for which there is very little experience with regard to their long-term effects. In accordance with the anticipated effects, it would be expedient to focus not only on possible individual but also on societal dimensions, e.g. reduced sleep requirements resulting from the use of HPED. Do adverse effects on memory, mental health, or the immune system perhaps manifest themselves only after a certain time? Are average working times prolonged? Does leisure behavior change? Can young men and women arrange work and childcare more easily among themselves than is currently the case? In the context of clinicosocial regulatory testing such potential long-term side effects can hardly be clarified but at best anticipated in a way that makes it possible to derive appropriate observational parameters and procedures.

However, it remains entirely unclear who is to do this and how. Until now therapeutic effects as well as health-related and mental side effects have been recorded and passed on by doctors in phase IV clinical trials under conditions of use. The gain in knowledge pertains mainly to rare and long-term side effects, about which *a priori* conclusions can hardly be drawn. Although the systematic observation of individual psychosocial effects in users would be virgin territory for most doctors, it is possible with the help of additional qualifications and the prospects of remuneration. By contrast, neither doctors nor epidemiological study centers would be suitable for carrying out the systematic observation of consequences at the general societal level. Observational parameters and concepts, assessment criteria, responsibilities, funding, and much more besides would all have to be clarified.

POSSIBLE CONSEQUENCES FOR THE HEALTHCARE SYSTEM 2.4

A number of potential consequences of a scenario of expansion for the healthcare system are outline below.

Whether HPED would alter the problem of borderline cases between health and illness to a relevant extent (Eckhardt et al. 2010, p. 100) is unclear and could conceivably be a societal effect that would have to be assessed and monitored on a continuous basis.

It is conceivable that HPED will raise an existing collective performance standard, as has been observed in some sports as a result of widespread doping. Consequently, more and more individuals would no longer be able to meet that standard, and their lesser performance might then be regarded as pathological. In this case demands could be voiced to use HPED therapeutically if they alone are able to specifically eliminate the new »deficiency state« that they themselves created.

As shown in Sections III and IV, the boundaries between health and illness are constantly being renegotiated socially, politically, and legally. In Section V.2.1 it was argued that the creation of an HPED regulatory category or indication would necessitate a legal demarcation or redefinition of the concepts of »illness«, »impairment«, »therapy«, and »medical necessity« from a legal point of view. The definition of a medical act under medical law would have to be reconsidered. Many experts, including the expert reviewers Simon et al., believe that this is already necessary irrespective of the further course of development (Beck 2006; Eberbach 2008; Simon et al. 2008, p. 4).

COST REIMBURSEMENT, PRICES, ILLEGAL MARKET

In the debate about hypothetical enhancement agents the assumption is repeatedly made that new uncertainties could arise as to whether these agents fall under the obligatory services of health insurance funds. This appears highly unlikely. The scenario of expansion presented here – like the majority of bioethical considerations (Section IV.1) – assumes that HPED form a definable group of substances that are used by healthy individuals to enhance performance. The existing social security system in Germany, in particular the statutory health insurance system (based on SGB V), provides no examples where potential performance enhancement is accepted as grounds for funding a service in the absence of an initial deficiency state, disease, or impairment. The current trend toward limitations of the statutory health insurance fund to sufficient, expedient, and cost-efficient services that must not exceed the scope of what is necessary (Art. 12 SGV V) as well as the service restrictions (Art. 31, 35 and 129 SGB V) and service exclusions (Art. 34 SGB V) clearly militate against the possible reimbursability of HPED in healthy individuals (Section III.3.6).

If research, development, and market-introduction costs for HPED were high, this would be reflected in high product prices – at least until possible protective rights have expired. Because HPED users would probably have to pay additional fees for highly qualified gatekeepers, only high earners would presumably be able to afford such enhancement. The more straightforward the actual manufacturing process of an HPED is, the greater is the danger that illegal market players will counterfeit the substance and that an illegal market will emerge (e.g. as in the case of Viagra) (Section V.1). Possible consequences for consumers (health

risks), manufacturers (loss of earnings and refinancing problems as well as damage to their image), social security systems (due to follow-on treatments) and law-enforcement agencies (customs, the German Federal Criminal Police Office responsible for drug offenses) would be likely.

INFORMATION FOR USERS

Since HPED would be subject to medicinal products law in the scenario of expansion, information for users would also have to be regulated. This concerns mandatory information (contents of package leaflets and summaries of product characteristics must be defined). In addition, given the current stringent requirements with regard to informing patients, e.g. in the case of cosmetic surgery, the information and advisory obligations of gatekeepers would probably also be set high – particular in light of the potential psychosocial risks posed by HPED. Special labelling regulations would have to be discussed, and demarcation problems concerning the obligatory labeling of doping substances would be likely.

It would therefore be likely that the internet would spawn myriad purveyors of poorly substantiated information, which must be countered by information that can easily and reliably be identified as sound. This also poses a hitherto largely unsolved problem in the area of therapeutic interventions (Section III.3.4). For laypeople it remains very difficult to distinguish reliable information from advertising, empty promises, and false claims.

ADVERTISING

Guidelines on the advertising of HPED in Germany would probably be accommodated within the legal regulations for food advertising by the Health Claims Regulation and the provisions of the *Heilmittelwerbegesetz* (Medicinal Product Advertising Law). A complete ban on the advertising of approved HPED to consumers would certainly be out of the question, because the health risks must already have been deemed to be low during the regulatory procedure. If, as is assumed in the scenario of expansion, the legislature and subsequently the supervisory authority were well disposed towards HPED, direct advertising aimed at consumers would actually suit users, as it means that the current dominant indirect and therefore difficult-to-control marketing strategies for pharmacological substances would be supplanted.

DEALING WITH PROBLEMATIC CONSUMPTION

It must be assumed that some users of HPED will develop problematic patterns of use. Dependence tendencies, a decline in other abilities, states of exhaustion and the like that might result from problematic use would become evident at least to some extent as adverse side effects during normal patterns of use and

should already be tracked attentively – and not just by manufacturers. Regulatory authorities have important supervisory obligations and far-reaching powers to avert health dangers (Section V.1.1). Because it must be assumed that the provisions of medicinal products law would also apply for the most part to HPED, regulatory authorities could require a substance-specific risk-management system (Art. 28 AMG) in the case of substances suspected of having a high potential for abuse (albeit not to the extent that regulatory approval is denied) in order to prevent noncompliant use as far as possible. This situation would probably apply to most HPED, so that corresponding risk-management procedures would usually have to be submitted at the time of marketing authorization or would be demanded if problems occur. Abuse could lead at any time to a reassessment of the benefit-risk relationship, culminating in revocation of approval.

Thus, there would be a tendency towards more extensive possibilities to counter the problematic use of HPED than is the case with medicinal products (e.g. analgesics which, despite problematic patterns of use, cannot be entirely removed from the market due to their therapeutic benefit) or foods (where at best false claims can be prohibited but marketing restrictions are rarely implemented). In addition, it would be possible, as with medicinal products and foods, to prevent such patterns of use with the help of support from gatekeepers and user information – through health education or preventive campaigns – even if these measures probably cannot entirely prevent such consumer behavior. It must be clarified who would bear the costs for such measures.

In the case of individual health damage due to substance misuse or abuse, procedures similar to those for current substance use would probably come into play. Follow-up measures would be carried out either in connection with acute treatment (e.g. for poisoning cases) or the treatment of addictions (in cases of substance dependence). Detoxification, withdrawal, and rehabilitation programs, which already exist for various drug dependencies, would also have to be adapted for HPED. Potential service providers are therefore likely to be special clinics for drug dependencies and/or burn-out patients, which could expand their services appropriately. However, it is questionable whether it would be possible to require consumers to share the costs of follow-up measures for the improper use of HPED (see Section III.4.2 for details).

REPERCUSSIONS ON THE SYSTEM OF INNOVATION 2.5

There are close and multifaceted interactions between scientific progress, political promotion, and regulatory changes. These interactions are complex and dynamic, making precise predictions about long-term effects in the context of a scenario of expansion highly speculative. However, bearing this limitation in mind, we can consider what changes to strategies and activities of the players in the research

and innovation system would be plausible if the development of HPED were accelerated by a relevant change at some level (e.g. in the form of a scientific breakthrough or recognition of performance enhancement as a relevant benefit dimension in pharmacological research) (see Eckhardt et al. 2010, p. 105 f.):

- Once the granting of marketing authorization for HPEDs has become a realistic possibility, especially in the European Union or the USA but perhaps also in the growing markets of emerging economies, pharmaceutical companies would be likely to embark on an intensive R&D program aimed at gaining access to new markets. Such expansion would require the sort of major investment that tends to be possible only for large, globally active companies.
- The search for substances would be pursued both by big companies and by public research institutions and specialized smaller companies or spin-offs. In the long term, companies – either independent entities or subsidiaries of pharmaceutical companies – could emerge that specialize in the HPED business.
- The opening up of these new markets would lead to at least a temporary slowdown in R&D activity in the core area of medical pharmacology, since some of the limited resources (both personnel and financing) available to this industrial sector would be drawn from the therapeutic field and redirected into the field of enhancement. The competent regulatory authorities would also have to reallocate human resources.
- For public research institutions there would be improved possibilities for third-party funding of HPED-related projects, especially by the industry. The effect would automatically strengthen current structures of institutional funding (Section V.1.1), even if no explicit additional promotion of public research were planned. If this proved successful in the long term, new educational pathways and continuing-education programs could emerge for developers and gatekeepers.
- For regulatory authorities it would be necessary to establish an independent risk monitoring system for effects on individuals and society.
- Some areas of the food industry could enter the HPED market. Large companies are most likely to have the necessary resources and might try to market new mixed products (e.g. highly effective energy drinks). Legal disputes about substance classification would be likely. Promotional claims would have to be examined on a case-by-case basis and would occupy the attention of food surveillance agencies.
- Healthcare providers would find new opportunities for growth. Specially trained doctors could care for users of HPEDs. Closer cooperation could develop between medical practices and pharmaceutical companies that distribute HPED – even if only in health packages. This could give rise to HPED networks.
- Given that HPED-related services would have to be financed privately and that doctors' fees are lower for services provided via the statutory health in-

surance scheme and these would therefore become even less attractive, medical care could change in some ways. The shortage of doctors that has already become apparent in some areas of treatment would be exacerbated.

- Social security systems would incur treatment costs arising from improper use – or at the very least would find themselves embroiled in expensive legal disputes about liability in respect of the reimbursement of the cost of HPEDs. Pressure to establish more precise procedures for limiting and excluding cost reimbursement would mount.
- The development of the illegal market for enhancement substances is difficult to predict. The illegal market could initially lose customers following the approval of HPED. It might then concentrate more on »hard« substances, including byproducts of HPED research (especially potent substances with nontrivial side effects) that would still not be approvable. The widespread use of HPED could raise the inhibition threshold of the population to use illegal drugs.

CONCLUSION: POSSIBLE TRIGGERS OF THE SCENARIO OF EXPANSION 2.6

The above reflections on a possible scenario of expansion were intended to shed light on key questions that are implicitly referred to in the ethical debate but are not usually explicitly asked and therefore not answered: How can hypothetical side-effect-free or relatively side-effect-free but highly effective performance-enhancing agents, whose (future) use has been the subject of such intense bioethical and neuroethical debate in recent years, come into the world? How can the current logic and procedures of pharmaceutical research and development be made consistent with the objective of enhancing performance in healthy individuals? And what consequential dimensions and open questions arise and need to be considered.

The scenario of expansion discussed here proceeds from the assumption that an interplay between scientific development and political decisions must exist for a relevant acceleration of R&D of performance-enhancing substances to occur as a prerequisite for widespread diffusion and use. The normative basis for any legal facilitation must be the recognition of performance enhancement in healthy individuals as a benefit dimension for pharmacological R&D both in the framework of regulatory approval of medicinal products and in the framework of existing medicoethical evaluation procedures. One outcome of this development would be numerous regulatory changes. These presuppose a dedicated political will as well as the acceptance of large medical scientific organizations such as the World Medical Association and the Council for International Organization of Medical Sciences as issuers of globally valid declarations.

Two developments are conceivable as triggers: firstly, the proactive advocacy and promotion of pharmacological performance enhancement as a socially beneficial and desirable phenomenon and, secondly, a reaction to »external« (competitive and economic) pressure resulting from »serendipitous« discoveries of HPED, possibly intensified by prior targeted development in countries with increasing economical, technological, and scientific capabilities that have less restrictive regulations, e.g. Brazil, China, and India.

In terms of the principal political mandate for action, the second possibility calls for the continuous monitoring of international R&D work on pharmaceuticals and the economic and public debate in those countries. The first possibility – the recognition of pharmacological performance enhancement as being explicitly beneficial to society and a resulting advocacy of systematic research into human performance and its biochemical manipulation in the absence of an initial deficiency state – is, by contrast, difficult to imagine. It would presuppose a corresponding shift in attitude on the part of numerous social players and committees with relevant decision-making powers – not just on the part of the healthcare system in the narrow sense. In this context the potential benefits of enhancement agents for individuals and their expected effects on society and the economy would have to be overwhelmingly positively evaluated by the majority of those concerned. An important existing base of knowledge for such an evaluation are the findings of doping research regarding the possible implications of the targeted and widespread use of performance-enhancing substances, whose impact on working life is the subject of Section VI.

DOPING AND ENHANCEMENT: SIMILARITIES AND DIFFERENCES BETWEEN SPORT AND WORKING LIFE VI.

The parallels between (neuro)enhancement and doping in sport are strikingly obvious: in both cases individuals take pharmacological agents in order to improve their performance. It is therefore expedient to analyze information derived from the scientific study of doping in competitive and recreational sport in connection with an assessment of the possible implications of pharmacological performance enhancement within competitive structures, which are also increasingly becoming part of educational and working life. Relevant questions are, for example: What prompts people to resort to pharmacological substances with putative performance-enhancing effects? What consequences does this have for the individuals and social groups concerned? What social processes might this unleash? However, because competitive sport constitutes a very special subsystem of society – Franke (2004 and 2007) refers to the »special world of sports« – one cannot assume that the observations and explanations relating to doping can be applied unreservedly to enhancement in everyday and working life.

The following section is based on the expert report by A. Singler (2010) entitled »Doping and Drug Abuse in Sport and Working Life: Sociological and Psychological Aspects of Doping and their Potential Extrapolation to the Enhancement Problem«. The report portrays the doping debate in Germany over the past 100 years as an argument about the necessity and ethical acceptability of pharmacological performance enhancement (key results are summarized in Section VI.1). It explains the pervasive tendencies to escalate doses despite higher risks and decreasing benefits and the withdrawal or rejection of athletes and trainers who are unwilling to engage in doping practices (Section VI.2). It shows how doping in sport is learned within social settings as an essentially noncompliant, deviant behavior and how the way in which the doping problem has been dealt with so far has resulted in systemic influences being ignored, while individual causes of doping activities are only partly perceived (Section VI.3). Research results are then analyzed which indicate the existence of a strong correlation with the addictive use of substances in sport pursued to extremes and suggest links to body-perception and behavioral disturbances (Section VI.4). Preventive approaches are discussed with regard to medicalization beyond the field of sport (Section VI.5). Findings obtained in competitive sport are extrapolated to high-level performance in working life (Section VI.6).

Complementing the introductory discussion of the term »enhancement« (Sections I.2. and I.5), the following discussion of the term as understood by Singler (2010, pp. 8ff.) is important. Singler defines *doping* from a theoretical normative

point of view *as* a violation of the prohibition of doping in organized competitive sport. It is currently defined as the use of agents or methods that are deemed to constitute doping according to the code of the World Anti-Doping Agency. Within sport and its regulatory structures doping is usually described as misconduct on the part of an individual, by means of which the individual seeks advantages over fellow athletes in anticipation of an economic or ideal benefit. By contrast, psychology and the social sciences tend to regard doping mainly as deviant behavior of individuals and as an expression and consequence of social structures and processes.

According to Singler (2010), *medicine abuse* is committed when medicines are taken in the absence of a medical indication. Thus, doping is a special case of medicine abuse in the context of organized competitive sport. The use of agents suitable for doping in leisure sport, which is now no less performance-oriented, would therefore fall under medicine abuse. In the everyday debate, however, the term doping is applied to both activities. (Even the AMG fails to distinguish between competitive sport and other sports (Section III.3.3).

Galert et al. (2009, p. 41), for example, define *neuroenhancement* as any »improvement in cognitive performance or mental well-being where no therapeutic or preventive intentions are being pursued and where pharmacological or neurotechnical agents are used.« As described in Section IV, neuroenhancement is often viewed, particularly in the bioethical debate, not as a process but in terms of this objective. However, a comparison with the doping phenomenon is sensible only if neuroenhancement is understood as a social act irrespective of its success.

1. DISCUSSION OF DOPING: ARGUMENTS AND PATTERNS OF JUSTIFICATION

A review of the doping debate in Germany since the early 20th century (Singler 2010, pp. 10ff.) documents several strategies and activities whose aim is to achieve acceptance of doping or to create a mood in which *de facto* acceptance can be established through tacit tolerance. For example, »discursive subversion« is continuously casting new doubts on the sense of the prohibition of doping, even if acceptance is not explicitly advocated. The aim of this strategy is not to achieve a concrete political measure (change in doping regulations, modification of medicinal product and narcotics laws) but to create a climate in which the deviation is perceived as a »trivial offense« or a peccadillo. This is accompanied by emphasis on the expected benefit, which at the societal level finds expression mainly in the possibility of national representation through international sport-

ing successes. Typical arguments for a liberal attitude towards doping, which despite knowledge to the contrary can be based on conviction, include:[75]

- Medicines primarily have a therapeutic, not a doping effect. Labeling them as doping agents is therefore rejected as long as possible.
- Doping relates to an improvement in physical constitution, not the enhancement of performance. The agents only help to realize one's true potential personal performance. The pharmacological manipulation serves only to activate, not create performance.
- New doping agents can help maintain the health of athletes by replacing known agents with greater potential to cause harm.
- Competitive pressure within the system is seen as justification or a compelling argument for the use of medicines. Doing without them implies forgoing international competitiveness in (elite) competitive sport and all its political and economic advantages.
- Along the lines of »damning the damning« (Sykes/Matza 1968), it is not doping behavior or the effects and side effects of pharmaceuticals that are problematic but society's negative reactions to them. It is implied that the criticism of detractors constitutes the main problem[76] and that objective harm, insofar as it can be demonstrated beyond a doubt, is negligible.
- A frequent accusation against critics of doping, even if they are former outstanding elite athletes with a medical education, is that they lack competence, objectivity, or scientific expertise. These same attributes are repeatedly intoned (»inexpert«, »emotional«, »unscientific«, »subjective«). Such accusations are almost never leveled against advocates of manipulation measures. Their use as a discursive exclusion strategy is therefore obvious.
- An attitude that appears defensive but is effective and far-reaching is that of »pragmatic fatalism«: once such agents have come into the world, there is no turning back the clock. New agents will inevitably be taken. Doctors, scientists and politicians are therefore tasked with controlling their use, which at any rate cannot be prevented, along moderating lines (»practical tolerance«).

The analysis by Singler (2010) shows how individuals in key social positions – scientists, doctors, media representatives, politicians – have been able to shape

75 The highly interesting details of the sometimes amusingly, sometimes shockingly subjective, trivializing or desperate-sounding debate on doping cannot be discussed here at length due to space constraints (a more extensive treatment can be found in Singler 2010).

76 In several cases in Germany medical associations, for example, have admonished critics after intervention by those being criticized but have never demanded a statement by a member known to advocate doping. According to information given to A. Singler, in March 2010 the German Medical Association had no data on »the number of cases in which medical associations were actively involved in doping accusations«. Singler (2010) assumes that no medical doping case has yet been punished by revocation of a medical license or, indeed, by less serious sanctions.

and dominate the public debate on doping. Stances have changed, attitudes modified, priorities readjusted with a certain regularity. Although in the course of time very clear antidoping regulations have been passed and competent institutions have been established, they are confronted with numerous problems in terms of implementation and monitoring (Gerlinger et al. 2008; TAB 2008b). Existing inadequacies in the perception and conveyance of the problem remains of fundamental importance, especially with respect to the topic of the present report. Environmental and systemic relationships and responsibilities as well as suprainindividual pathological abnormalities and causes of »misconduct« on the part of individuals are – consciously or unconsciously – suppressed. This then is the subject of the next section.

2. DOPING SPIRAL: THE QUANTITY LAW AND DROP-OUTS

Singler (2010) argues that elite sport acts upon its protagonists in a similar way as aspects of the working environment on workers. Two prevailing dynamic processes of the doping phenomenon in competitive sport shed light on enhancement: the compulsion to increase the dose despite increasing risks and decreasing benefit (the »quantity law of doping«) and the withdrawal or exclusion of athletes and trainers who are unwilling to engage in doping (drop-outs) as well as doctors, functionaries and other players within and outside sport.

The »quantity law of doping« (Singler 2010, pp. 80 ff.) argues against the realistic prospect of a moderate, »civilized« or »controlled« form of human pharmacological optimization. Even if one assumes that something akin to harmless doping is possible at low »therapeutic« doses, evidently in the course of their careers athletes inevitably move into the »nontherapeutic« dosage range that is increasingly harmful to health and at the same time promises diminishing returns in the way of a gain in performance. This has been confirmed by athletes from various disciplines and environments. It is not only athletes whose bodies respond to doping substances particularly strongly in the intended way and/or tolerate the deleterious side effects of doping substances especially well, at least for a while, who increase the dose to a significant degree; so too do »nonresponders«, for whom the risk-benefit relationship is particularly poor.

But irrespective of an individual's physiological response, in the long term the fact that doping is almost inevitably practiced at increasingly higher doses and is therefore associated with increasingly high risks sets in train individual and social downward spirals. This poses a general threat to the social system (in this case the social subsystem of sport). A systemic consequence that has received little public attention is the withdrawal of both athletes and staff at the coaching and functionary levels who are critical of doping, referred to by Singler/Treutlein

as drop-outs (2001, pp. 16ff.). As a result, sport loses highly critical, self-confident, and consistent actors in the form of young up-and-coming athletes and intelligent and creative trainers, who elect not to engage in pharmacological performance enhancement.

Besides such individuals who consciously drop out of their own free will, some athletes are excluded because they cannot meet doping-based requirements. The higher performance levels achievable through doping are due at least in some sports to one-dimensional effects, e.g. extreme muscle building in sprinters with the help of anabolics. This, in turn, affects the nature of training, which then becomes oriented to the doped body type. Nondoping athletes who have adapted to the new training schemes favored by doping then often train incorrectly and are exposed to a greater risk of injury (Singler/Treutlein 2001, p. 22).

Assessment of the benefit associated with the use of performance-enhancing agents is fundamentally reduced to individual quantifiable parameters. Doping limits essential elements of the complex development of performance to well-defined, easily manageable and controllable factors. If one reduces the physical and mental complexity of individuals to a manageable scope and trivializes this originally difficult-to-regulate complex system due to doping, it is highly likely that performance characteristics can be planned relatively precisely at specific desired times, while long-term qualitative aspects of performance are disregarded, e.g. by systematically ignoring known expected physical harm or mental and social consequences.

3. PHARMACOLOGICAL PERFORMANCE ENHANCEMENT: DEVIANT BUT ADAPTED BEHAVIOR?

The parallels between doping and enhancement are strikingly obvious. In both cases individuals take pharmacological agents to improve their performance. This raises social and political questions about how this phenomenon is dealt with: Is enhancement socially desirable and should it therefore be promoted? Or is it at least acceptable and unworthy of a ban? Or is it risky and should therefore be (strictly) regulated. Especially in the case of potential novel enhancement agents, it is not merely a matter of the possible effects on health but also, as presented in the scenario of expansion, a question of potential psychosocial consequences (Section V.2.3). Sociological and psychological research provides a number of findings that are discussed by Singler (2010, pp. 86 ff.) and summarized below.

PERFORMANCE AS A VALUE IN SPORT AND WORKING LIFE

In the tradition of modern Western industrialized countries, performance and ethics form a *value complex*. This system of performance ethics, which Max Weber traces to the influence of Protestantism, occurs in particularly conspicuous form in competitive sport. Demands such as fairness and equal opportunities form the ethical regulatory of an unconditional performance principle. Taking the example of doping, there has been at least a partial decoupling of performance and ethical principles, and performance *per se* is ascribed a high level of importance irrespective of how it is acquired and delivered.

This observation can probably be extrapolated unconditionally to the working environment: here too performance has positive connotations, regardless of the conditions under which it is delivered. Against this backdrop, the view that the use of non-medically indicated drugs constitutes performance enhancement in the sense of an »improvement« is understandable. It cannot be ignored that arguments exchanged by opponents and advocates of doping in the past century are cropping up in similar or identical form today in the debate about neuroenhancement, e.g. the right to self-determination, the right to harm oneself, equality of opportunity, and fairness (Section IV.1). Given the positive connotation of (enhanced) performance, the question as to whether pharmacological intervention actually brings about an improvement in performance is often not even discussed in any substantive way. What counts is the »laudable« attempt at self-optimization.

A certain willingness can be assumed on the part of sections of society to view additional pharmacological self-optimization of »performers« as understandable and possibly even as an »innovative maneuver« – unlike substance abuse by overtaxed workers faced with less demanding tasks (or to cope with personal crises), where one is likely to speak of an (addictive) pathology. The »performers« are usually »brain workers« who have to work through complex procedures in their minds and are generally under considerable time pressure. Their income is above average, and the taxes they pay are important to society. It therefore comes as no surprise that enhancement tends to be discussed and perceived in highly-qualified professions as a positive innovation in the sense of a »useful illegitimate act« (Bette 1989, p. 200, with reference to Luhmann 1984) rather than as a reprehensible way of influencing performance. The assessment must also consider that in cases of »doping at the workplace«, in contrast to doping in sport, competitors are not usually barred from competing as a result of pharmacological manipulation.[77] Rather, enhancement is rationalized by argu-

77 It therefore appears consistent that ethical arguments for rejecting non-medically indicated medicines play only a marginal role in the DAK Health Report (2009, 81–82). The insurees simply do not perceive the work setting as a competition, though this does not necessarily rule out exposure to considerable stress and pressure.

ing that individuals acting in this way contribute to the attainment of corporate goals. They therefore ensure the survival of the organization and continued economic prosperity in economically difficult times.

A comparison between the sporting and working environments, however, reveals not only similarities but also differences, for example in the regulatory framework, which exerts a strong influence on individual and social attitudes.

Doping in sport is also a multifaceted topic because it is explicitly prohibited (and is also defined in those terms). This is not the case in working life, where a formal violation is committed only if illegally acquired substances or medicines are taken. Use of the substances is not in itself a punishable act, only dispensing or trafficking in them. However, the aforementioned performance ethics and other value-based attitudes towards one's own body and the use of pharmaceuticals to influence it result in the fact that a relevant section of the population nevertheless views the targeted use of (putatively) performance-enhancing substances as aberrant behavior that deviates from the (ethical) norm. This is reflected by the journalistic use of the terms »routine doping« or »brain doping« and the results of the survey conducted by the DAK health-insurance scheme (DAK 2009), which found rejection rates (for use by the respondent him/herself) of 55 to 70 % (Section III.4.1). However, a detailed study of the attitudes of users and nonusers, which would be of great value for the future debate about enhancement, is not available (Section VII). Interesting questions are, for example, whether the aforementioned assumed positive and »sympathetic« assessment is based on the view that pharmacological performance enhancement serves not only egoistic purposes but also important corporate goals, and whether this changes as soon as an effect that raises performance requirements is assumed or feared, as has happened in sport.

DOPING AS AN INDIVIDUAL ADAPTATION TO SYSTEM REQUIREMENTS

Sports sociology has shown how misleading it is to interpret doping behavior as no more than a form of misconduct for which the individual concerned bears sole responsibility, as still often occurs in the public debate. Singler (2010, p. 89) stresses that doping always represents an act committed against the backdrop of the values and norms of the cultural reference system in which it takes place. Deviations from permissible measures (physical and mental training, food supplements) occur when these means are no longer sufficient to meet the demands of the system (Singler 2010, p. 141). They represent an illegitimate attempt to adapt to objectives that are widely accepted by society. Rule violators can then rationalize their infractions as an expression of conformity and a willingness to integrate.

Doping occurs when athletes are exposed to excessive demands that are typical of the escalation process (with regard to this and the following discussion, see

Singler 2010, p. 142). Deviant behavior is also facilitated when official norms that prohibit doping coexist with informal norms that countenance doping or relativize its moral reprehensibility. Attitudes that favor doping are formed not by individuals but by society, i.e. they are taught and learned in the context of social processes. A key factor for the emergence of such deviant learning processes is contact and identification with individuals who condone or even explicitly demand deviant behavior. Subcultural groups exist who hold special values that favor rule infractions. This does not necessarily imply an attack on the rule itself. Cognitive dissonances that arise from the coexistence of contradictory values can be dealt with by neutralization techniques and rationalization. For example, doping is facilitated when it is not called doping or perceived as doping. The use of terms such as »therapy«, »constitutional enhancement« or »avoidance of disadvantages« makes it appear to be a morally legitimate, acceptable, or even compelling act.

In any system in which success and the methods by which it is achieved are not resolutely scrutinized, the nondoping athlete assumes a social risk (with regard to this and the following discussion, see Singler 2010, p. 102). It is not the honest athlete who is publicly praised, financially sponsored, and held up to young athletes as a role model but rather a victorious rival, even if his or her performance suddenly improved for no plausible reason and doping might be suspected. Athletes who reject doping and who publicize manipulative practices of their sport are not rewarded for their whistleblowing efforts. Quite the contrary, they are threatened with defamation and repression. They are often maligned as sore losers and find themselves the subject of disciplinary proceedings. In the history of sports, doping accusations have almost always been sanctioned more severely than doping itself. If organizations react to criticism in this way, their members will assume almost perforce that doping is desired – at least as long as it remains unproven.

Neuroenhancement can also be seen as a deviant, »innovative« form of behavior, an attempt by individuals to adapt to excessively demanding social structures (with regard to this and the following discussion, see Singler 2010, pp. 103–104). Increasingly excessive demands in working life and education are an expression of such processes, and a substantial percentage of people evidently respond by taking performance-enhancing agents. Lüschen's observation (1981, p. 204) with regard to sport – namely that the more uncertain the outcome of a competition is, the greater is the likelihood of deception – can be formulated analogously with regard to the working and educational environments: the more uncertain individuals are of being able to perform as required and the greater the perceived risk of losing their job or failing to achieve important training objectives is, the more likely those individuals are to respond by resorting to drug abuse.

The argument that everybody could decide for themselves whether to use enhancement products for the purpose of improving well-being or work performance if they were freely available is unconvincing (with regard to this and the following discussion, see Singler 2010, pp. 93–94). Pressure to use such substances would not diminish but rather increase, because it is likely that pressure to perform would mount further. Given the binding rules of sport and the severe penalties for repeated offenses, including banishment from professional sports, one might assume that relatively few individuals in elite sports engage in doping. In reality, such a high prevalence is assumed that doping is actually viewed as the *informal norm,* e.g. in competitive cycling.

At the same time, a willingness to take medicines or other substances to enhance performance appears to be a sign of lack of confidence in one's own abilities, as described by Hurrelmann (2006, p. 99), by which he meant an »individual's confidence to engage in a given behavior and in so doing to overcome obstacles or difficulties« (with regard to this and the following discussion, see Singler 2010, p. 130). This can be regarded as a fundamental argument against the use of neuroenhancement products. Labeling them as mental »optimization« measures in no way makes it plausible that a person whose high intellect is documented by his educational qualifications and career path would experience a pharmacologically induced improvement in performance as a gain in personal sovereignty or autonomy (Section VI.6).

WHICH SOCIAL GROUP IS PREDESTINED FOR NEUROENHANCEMENT?

The College of Alcohol Study points out that an individual's willingness to engage in pharmacological performance enhancement correlates to a large degree with the socioeconomic status of his or her parents (McCabe et al. 2005; Section III.4.1). The higher the educational level of the parents, the more likely it is that students will use non-medically indicated prescription drugs. Two reasons or pieces of evidence indicate that this was not an isolated finding (for the USA) and that enhancement is fundamentally more likely to occur in members of higher social strata (Singler 2010, pp. 104–105): first, they have strong performance orientation and, second, they evidently have a greater willingness to engage in medicalization, especially with preventive intentions, as shown by a study commissioned by the Federal Association of German Pharmacists (ABDA 2009). It found that 11% of parents in the general population give their children food supplements and that this is »twice as common in the highest income group than in the others« – even though at the same time they are more likely than parents in other groups to regard their children as healthy. Overall, 20% of parents who believe that their children's health is »very good« or »good« nevertheless give them vitamins or food supplements, a practice discouraged by both the German Society for Nutrition and the German Society for Sports Medicine and Prevention (DGSP) unless specifically indicated (Hipp/Niess 2008).

A list of the risk factors for social medicalization and its attendant adverse effects on health would have to include high educational level and more generally high socioeconomic status. For that reason alone it is naive to believe that neuroenhancement agents could contribute to greater social fairness. It is far more logical to conclude that individuals of low socioeconomic status resort less often to performance-enhancing agents, especially since the potential occupational and financial gain is usually substantially smaller in lower income groups.

PATHOLOGICAL ASPECTS OF PERFORMANCE 4.

A surprising observation in recent years is that many individuals take doping substances even though they are not competitive athletes (with regard to this and the following discussion, see Singler 2010, pp. 142ff.): although they participate in fun runs and marathons or do strength exercises several times a week, they do not pit themselves against others for competitive or occupational purposes. Their opponent is their own inner clock or their personal performance yardstick. In recreational sport, where the human desire for self-optimization finds expression in many forms, whether in the form of measurable performance or physique in strength sports, there are probably one million people in Germany who take doping substances (Table 12, Section III.4.1). Technically, they are engaging in drug abuse and not doping, the latter denoting the behavior of organized competitive athletes in violation of the rules of their sport. Nevertheless, the label attached to the behavior says little about the individual's psychological aspects or about the social and cultural dimensions of this phenomenon.

There are good reasons to assume that the same cultural conditions underlie doping in competitive sport, where participants vie with each other according to the rules of organized sport, and medicine abuse in recreational sport, which is pursued for the most part without special rules or regulations. The view that doping, like medicine abuse, could be an expression of a problematic, sometimes pathological aspect of society's performance orientation has so far received little attention in Germany. In France and the USA, by contrast, sport and its societal evolution and manifestation have long been scientifically examined from this perspective.[78]

Like cosmetic interventions, psychiatrists and sociologists view body-oriented activities – notably diets and various forms of intensive, organized or unor-

78 Especially after the 1998 Festina scandal surrounding the Tour de France, a critical school of thought has emerged in France among doctors, psychiatrists, and sociologists, who view the extreme pursuit of competitive sport with great scepticism. However, relevant evidence had already been presented earlier (e.g. Carrier 1993 and Carrier/Violette 1990).

ganized sport to improve stamina, increase strength or beautify the body – as an expression of a desire of individuals to at least exercise control over their own body as far as possible in the face of excessive demands placed on them by the complexity of modern societies (Bette 1989 and 1999; Yates 1991). These self-modeling attempts are undertaken with extreme perseverance by strongly performance-oriented individuals and evidently tend to spiral out of control. This is evidenced by increasing numbers of cases of eating disorders, the phenomenon of sport addiction, which Singler (2010) believes has received too little attention, and the suspected growing prevalence of doping and medicine abuse in recreational sport (Boos et al. 1998; Kläber 2009; Striegel et al. 2006).

However, there is little scientific clarity with regard to the determinants of these conditions or the factors that intensify them. An important question in the present context is what interactions exist between performance orientation, substance use, and addiction problems and what other health and social consequences can occur. Worrying evidence comes mainly from studies by French experts on addiction, who found (elite) competitive athletes to be at substantially greater risk for drug addiction than individuals who do not engage in sport or do so only occasionally. The extent to which this is primarily due to the pre-existing personality structure of the persons concerned, which leads them both to competitive sport and to substance addiction, and the contributions made by substance use *per se*, the structure of competitive sport, and effects on the work and life prospects of individuals who concentrate for many years on sport are questions that need to be further examined (Peretti-Watel 2009; with regard to this and the following discussion, see Singler 2010, pp. 121ff.).

In the French studies the majority of drug addicts among former athletes said that they saw no connection between their addiction and doping. Most of them only became addicts after their sporting career had ended, and it was irrelevant whether the end of their sporting career had been ushered in by an injury or was age-related (Lowenstein 2005, p. 181). In any case, this suggests that the intensive pursuit of sport does not have a protective effect, as is often surmised, and may even increase the risk of addiction (Lowenstein et al. 2000, from INSERM 2007, p. 553). Evidence of a causal relationship between the intensive pursuit of sport and addiction has so far come from animal experiments (Larson/Carroll 2005; Ferreira et al. 2006) in which hyperactive rats showed marked withdrawal symptoms and an increased affinity for amphetamines or morphine following prolonged exercise abstinence (INSERM 2007, pp. 551–552). It is suspected that, by inducing the release of endogenous opioid peptides, extreme exercise can lead to dependence in a manner similar to the exogenous administration of opiates. An athlete, says Lowenstein (2005, p. 187), becomes dependent on »inner drugs« that are produced during intensive sport« (adrenalin, dopamine, endorphin, etc.). Even a long pause in a sporting career marked by a permanent state

of hyperactivity is sufficient to break the neurobiological reward circle. This increases the risk that an athlete will resort to the exogenous administration of drugs to satisfy an unmet need. According to Lowenstein (2005, p. 183), the risk is particularly high if daily training exceeds four to five hours. Above and beyond that threshold, he says, the danger increases that exercise will be regarded as the sole acceptable form of a life-affirming feeling. Sport then develops into a compulsion. The thought of stopping evokes a feeling of foreboding. Injuries may be perceived not merely as a physical impairment but as a full-blown psychological catastrophe (Lowenstein 2005, p. 188).

Social setting appears to be one of the key factors that can exert a moderating or intensifying influence on athletes, given the growing danger of addiction and dependence behavior in intensive elite sport. It is not substances or modes of behavior *per se* that cause addiction, but rather the manner in which a particular personality deals with substances in a sociocultural setting (Hautefeuille 2009, p. 83). It is therefore not possible to solve this complex problem through simple preventive strategies (Section VI.5).

In connection with hyperactivity in sport and working life, it is remarkable how little attention society has paid to this very obvious problem. The suspicion expressed by the psychiatrist Alayne Yates (1991) appears plausible, namely that the high value society places on performance distorts our perception of its pathological aspects. According to Singler (2010, p. 126), assessments of doping and medicine abuse should assume more than has been the case to date that a pathological process is at least *also* involved. The type of person cast as a rationally acting innovator who purposefully and prudently doses himself with a performance-enhancing substance for a limited time and who can stop taking it again without any problems may exist. But – at least in the case of doping – another type usually dominates – one who must be understood as the victim of a pathological social development.

The College Alcohol Study showed that the use of non-medically indicated prescription drugs is accompanied by other risky behaviors: »Non-medical prescription stimulants users were more likely to report use of alcohol, cigarettes, marijuana, ecstasy, cocaine and other risky behaviors« (McCabe et al. 2005, p. 96). Users of non-medically indicated prescription drugs were also more than twice as likely as non-users to drive under the influence of alcohol and more than three times as likely to ride in a car with a drunk driver. They were four times as likely as nonusers of non-medically indicated prescription drugs to drive after indulging in binge drinking (McCabe et al. 2005, p. 103).

With regard to neuroenhancement, the question arises as to the extent to which observations of pathological aspects of competition sport also apply to the working environment. Relevant research is clearly needed. The extent to which

extreme work affects the brain, for example, should be the subject of neurobiological research. Researchers should also look at whether mental work can produce untoward effects similar to those that appear to be caused by physical hyperactivity. Specifically, it should be examined whether or not the use of neuroenhancement products or other forms of medicine abuse constitutes an additional risk.

5. PREVENTION: STRATEGIES AGAINST FURTHER MEDICALIZATION?

What conclusions can be drawn from the results presented with regard to the future prevention of doping? In this context Singler (2010, p. 127) quotes the brain researcher Manfred Spitzer (2003, pp. 313–314): »It is up to us to shape the conditions of our social behavior in such a way that we enable individuals to behave according to the ›rules of the game‹ and in this way learn cooperative behavior. Preaching ›love one another‹ in the face of open early-capitalist attitudes in many social areas (catchphrase: the market will regulate it), tough but anonymous (because global) competition, and stock market news broadcast every half hour will not help make cooperative adults out of egocentric children (who cannot be anything else).«

We will not delve into the individual problems and inadequacies that those seeking to prevent dosing in competition and recreational sport have to contend with, because in many respects the inherent nature of sport compared to that of the working environment and everyday life creates an entirely different initial situation for specific measures. Singler (2010, p. 127) takes an extremely negative view of the success of prevention in sport and sees it as a warning and therefore instructive for this reason only. It can be held up as an example of how not to approach prevention in any circumstances. From a sociological point of view, he says, it is remarkable that little use is made of scientific knowledge that has been tested in many areas. It seems reasonable to suspect that where there is no prevention worthy of the name, the underlying problem is not being tackled with the required consistency.

As far as the abuse of medicines beyond sport is concerned, there is little doubt that behaviorally oriented approaches to prevention should be directed not toward prohibition and punishment but rather towards general education about health (Singler 2010, p. 145). Traditional concepts of (behaviorally oriented) prevention – deterring and educating – are usually aimed one-sidedly at the individual (Singler 2010, p. 133). These measures are largely outdated, at least unless they are integrated in comprehensive strategies. Especially in adolescents, efforts at prevention based on warnings about possible harm to health have proved to

be of little benefit. This is because »risky behavior in adolescents is firmly integrated in the performance of developmental tasks« (Hurrelmann 2006, p. 207). Although the conveyance of knowledge through the dissemination of information and education remains an important element of preventive strategies, it is not in itself enough.

In recent years a paradigm shift in general preventive theory has led many to abandon attempts to combat undesirable forms of behavior directly. Instead, more and more emphasis is placed on facilitating healthy or rule-conscious, compliant behavior through positive prevention. The aim is to promote *protective factors* and *skills*. The most important structures that provide opportunities for undesirable behavior should be shaped in such a way as to make undesirable behaviors less likely and desired behaviors more likely (situational prevention). This precludes the liberalization of drugs, an approach that is still often discussed seriously by addiction experts. Hurrelmann (2006, p. 177) calls for the following, for example:

- Developing economic incentive systems for healthy behaviors or sanctions against unhealthy behaviors (e.g. by means of tax-influenced pricing).
- Protecting individuals against risks by making access to medicines more difficult and tightening the conditions for the marketing of substances with a potential to cause harm or gaining better control of key determinants of the distribution of medicines (e.g. medical prescribing practices by health insurance funds)
- Controlling available information, imposing conditions or advertising restrictions on risky products and products of dubious benefit while developing advertising campaigns to promote healthy behavior and the prudent use of medicines.

With a view to developing a common strategy, Singler (2010, p. 136) pleads for an understanding of doping, medicine abuse, and drug abuse as diverse manifestations of the same set of problems. The »skill of deviancy« required for doping (extensive knowledge is often required) should, he believes, be countered by a »skill of compliance«. The individual background and social milieu of children and adolescents should be considered, so that the parental home and school environment are taken into account when formulating preventive strategies. The misguided view should be abandoned that information *per se* is the key to health education. As the example of food supplements shows (Section VI.4), high socioeconomic status can actually be a risk factor for substance use and abuse.

6. CONCLUSION

The use of enhancement products in the working environment is discussed as a quasi valid option in the sense of a response to the widely reported escalation of psychological demands in working life (with regard to this and the following discussion, see Singler 2010, pp. 145–146). It appears to be a means to reduce unmanageable complexity and cope with situations where excessive demands are being made. From a short-term perspective such expectations of a benefit may seem realistic. However, the historical development of doping suggests that the pharmacological manipulation of human beings holds out little prospect of success in the long term.

PERFORMANCE-RELATED STRESS AS A PRINCIPLE? EXCESSIVE DEMANDS IN EDUCATION

The College Alcohol Study shows that it is not mainly the best but rather the less able students who resort to enhancement (McCabe et al. 2005). The researchers noted the following predictive attributes: male, white, high socioeconomic status, academic education of the parents, middling or weak academic performance, member of a fraternity or sorority, resident in a fraternity or sorority house. With regard to the general setting, it was found – not surprisingly – that tough competitive conditions at universities and high acceptance requirements increase students' willingness to take prescription medicines with a view to enhancing performance (McCabe et al. 2005, p. 99). The high socioeconomic status of the parents then facilitates access. Thus, the nonmedical use of prescription drugs is viewed as a result of high social expectations arising from a performance-oriented family background in conjunction with subcultural milieus that provide both motivational and logistic opportunities (Singler 2010, pp. 146–147). Accordingly, neuroenhancement must be seen as an attempt to cope with overtaxing situations.

The study by Franke et al. (2010) suggests a similar pattern in Germany (where use is higher among less academic students in high schools and vocational schools; Section III.4.1). It is widely believed that the introduction of bachelor and masters courses will increase the pressure to perform and the learning requirements of students in Germany as a consequence of more frequent examinations. Advisory offices and health insurance funds have reported a rise in psychological disorders among university students (Central Study Guidance Office at Münster University; ntv 2009). However, the problem of rising performance demands and the risk of medicalization do not begin with admission to university. Other increasingly demanding educational pathways, the entire schooling phase, and even preschool childhood are all increasingly characterized by cognitive and

behavioral patterns that are shaped by the performance and efficiency concepts of a globalized and commercialized competitive society.

CONSTANT PRESSURE TO IMPROVE IN WORKING LIFE

The term »performance enhancement society« (Coenen 2008) appears less suitable to describe a future vision than the development of occupational demands in recent decades (with regard to this and the following discussion, see Singler 2010, pp. 148ff.).

The German Employees Insurance Fund (DAK) (2009, p. 46) refers to the obvious view that neuroenhancement is or can appeal especially to »groups faced with demanding cognitive tasks who have a will to perform«. They include managers, brokers, journalists, doctors, etc. A shared characteristic of these professional groups is that work and employment conditions have changed radically: social security and obligations on the part of employers have been reduced, while the demands and responsibilities imposed on individuals have grown. Radical rationalization of social areas in times of scarce resources and the constant evaluation pressure that results overwhelms the physical and mental ability of many employees to cope. According to the Good Work Index of the German Trade Union Confederation (DGB) (2009, p. 10), 12% of employees say that they have a »good job«. 25 % of those surveyed report that they had had medicines prescribed in the previous twelve months in order to remain fit for work (DGB-Index Gute Arbeit 2009, p. 19).

The IT sector has undergone especially dramatic changes in the past decade. The establishment of regions that are globally accessible via the internet has transformed the industry: positive basic attitudes and a strong tendency for employees to identify with their company have been virtually eliminated as a result of rationalization and a fundamental realignment of corporate culture (Boes/Kämpf 2009, p. 25). To an ever greater extent employees no longer perceive themselves as »whole individuals«; instead they feel reduced to their function as workers (Boes/Kämpf 2009, pp. 31–32). The sector has seen an enormous escalation of performance demands that pose a danger to the health of large sections of the workforce. This development is backfiring on the companies themselves. According to Boes et al. (2009, p. 58), increasing reliance on so-called key performance indicators (KPI) has resulted in the earlier culture of trust being supplanted by a culture of monitoring. Only phenomena that can be monitored are in fact monitored, and anything that falls outside this highly rational framework is less likely to be taken seriously as an economic factor.

The compulsions and risks that are apparent in the world of doping now appear to be gaining ground in the working world, especially among highly qualified individuals. Rising stress puts the health of individuals at risk. In addition, rising pressure and expectations calls the further development of companies and indi-

viduals increasingly into question. According to the »law of diminishing returns« in sports science, ever greater efforts are required to achieve ever smaller increments in performance. Further escalation, whether by doping, by medicine abuse, or perhaps in the future by means of effective neuroenhancement, neither reverses this process nor makes it more bearable. It must therefore be in companies' own interest to monitor, and where appropriate take countermeasures against, the rampant growth of pharmacological enhancement.

In the light of the realities of the working environment and the pathological side of the *hypertrophy of performance orientation* that has been revealed in connection with doping, it does not appear very convincing to discuss neuroenhancement in working life in terms of self-determination and self-optimization or as a cool, calculated, rational choice (Singler 2010, p. 152). Putative future enhancement substances are likely to be used mainly by students and trainees who are highly educated and are keen to perform but nevertheless feel overtaxed. The socioeconomic benefit they hope to gain would be particularly large in comparison to those who are less qualified.

If the view held by several (but not all!) brain researchers and psychopharmacologists is true, namely that pharmacological manipulation can only impair the performance of a brain that is well endowed by nature and shaped by the environment, because it is already operating essentially at an optimum level, then the conclusion to be drawn from the considerations in this section is that especially »susceptible« high-flying professionals can only incur disadvantages in every respect from enhancement. At best, the substances would have no effect at the physiological level. However, they would probably not alleviate feelings of being unable to cope (or at best only temporarily as a placebo effect) but rather augment them, because individuals would feel compelled to take such substances only to discover that they are of no benefit in the long term.

RÉSUMÉ AND POTENTIAL AREAS OF ACTIVITY VII.

This report deals with »pharmacological interventions to enhance performance as a social challenge« and focuses on the goal of boosting cognitive abilities that are seen as key skills in modern working life. For some years the pharmacological manipulation of such skills has been pursued and communicated as a vision or ambition as a result of intensive brain research and the accelerated search for anti-dementia drugs (Hennen et al. 2008). »Cognitive enhancement« or »neuroenhancement« also lies at the heart of many other studies on and debates about the »improvement of mankind« (Sections I.5 and IV.1). However, it must be assumed that a clear demarcation of cognitive from other psychological abilities of an emotional and social nature, whose interactions are essential for mental performance, particularly in working life, is not possible (Section II.1.2). Moreover, often psychological processes cannot be considered separately from physical processes in any meaningful way. Thus, physical constitution affects emotional mood and mental performance, and many hormones act both on the autonomous nervous system, which directly controls body functions, and the central nervous system including the brain and its activities.

MEAGER EVIDENCE OF SPECIFIC PERFORMANCE-ENHANCING EFFECTS

The survey and analysis of the current state of knowledge about substances believed to enhance (cognitive) performance showed that there is little evidence to substantiate a boost in relevant performance parameters – neither for prescription drugs to which a specific potential activity is attributed nor for over-the-counter substances (Section II).[79] There is, however, ample evidence that the physical and mental constitution of the – basically healthy – study subjects is a key determinant of the efficacy of various substances. Some findings suggest that the few observed effects of the pharmacological substances investigated occur only if the initial situation is characterized by a deficiency state (sleep deprivation, neurotransmitter deficiency without explicit pathology). By contrast, if the initial level of mental performance is already high, additional activation appears to induce a counterproductive overstimulation and consequently a deterioration of mental performance.

It must be borne in mind that possible performance-enhancing effects of substances in healthy individuals are not an explicit subject of scientific research, i.e.

79 Many assumptions and conjectures about the performance-enhancing effects of illegal substances are circulating that are based on numerous nonscientific, partly journalistic, partly artistic experience reports (about greater creativity/inventiveness or heightened consciousness) but not on robust data about their effects and side effects, without which a specific and substantive evaluation (beyond vague conjectures) is hardly possible.

the findings obtained to date are based on more or less unsystematic studies with a small number of subjects.

USE DESPITE LACK OF PROOF OF EFFICACY AND THE THREAT OF SIDE EFFECTS

There is no question that, even without scientific evidence of efficacy, a wide range of substances for maintaining and enhancing performance are available and that these substances are demanded and used in more than just a few isolated cases. In the food sector, food supplements are advertised with claims that they are able to enhance performance. Together with some over-the-counter pharmaceuticals they probably act as door openers and wish intensifiers leading to a demand for specifically active performance-enhancing substances with relatively few side effects (Sections II.4 and III.2.4).

Prescription drugs are also used to a certain extent in areas bordering therapeutic indications. This is suggested by preliminary studies on sales figures and prescription analyses (Section III.4), which show a significant number of off-label prescriptions of such drugs. This can be interpreted as a means of maintaining an ability to cope with particularly demanding situations in working life and education. However, detailed data are not available on the scope of use of putative performance-enhancing substances. This is an important research area for gaining a better picture of the phenomenon as a whole (see below).

Surveys suggest that a – presumably growing – number of people perceive the demands placed on them, particularly in educational and working environments, as so taxing that they can only meet them with the help of performance-enhancing substances. Since the substances currently used for this purpose (e.g. Ritalin, Modafinil) have a considerable side-effect potential (Section II.3), their use poses a basic threat to health. This problem relates to the field of general health promotion as envisioned by the Ottawa Charter of the World Health Organisation (1986) and workplace health promotion as called for by the Luxembourg Declaration of the European Network for Workplace Health Promotion (2007) and the EU Directive on Health and Safety at Work (89/391/EEC), according to which health promotion should be integrated and pursued at the individual, collective (e.g. corporate or academic), and overall social levels.

EXPANSION OF PHARMACEUTICAL FIELDS OF USE – MEDICALIZATION PROCESSES

The nontherapeutic use of various pharmacological substances by individuals in everyday situations – in addition to performance enhancement in education and work, e.g. to enhance sexual performance or to promote muscle growth in bodybuilding – is reflected by a trend in pharmacological R&D efforts to develop and provide pharmacological substances in areas bordering therapeutic use or for nonpathological states. These medicalization processes are manifested in

two trends (Section IV.2): first in the form of the pathologization of individual conditions that used to be regarded as »normal« (melancholy, hyperactivity, hypoactivity, etc.) or as life phases (»deterioration« in old age) and secondly as the »routinization« of medical technologies that are increasingly directed at explicitly nonpathological states in response to the wishes of customers – who are no longer patients – for example in the areas of cosmetics and wellness, where performance aspects in the broad sense also play a role). Thus, the original remit of medicine to treat disease or impairments and to maintain health through preventive measures is gradually being expanded.

Decisions about drawing boundaries must be constantly made both at the level of pharmaceutical development and regulatory approval (regarding the legitimacy of clinical trials as well as benefit-risk assessments) and at the level of social security systems (regarding treatability and the assumption of costs). In a work- and competition-oriented society it is logical for pharmacological substances that cannot explicitly redress pathological states of lowered work capacity to be classified as reimbursable agents if their prescribed use can reduce absenteeism and – at least temporarily – its associated costs. However, analysis of the current legal and economic situation (Section III) shows that there are a number of obstacles to the liberal use of available pharmaceuticals especially in the primary healthcare market.

LIBERALIZATION OF ENHANCEMENT SUBSTANCES – A REALISTIC OPTION?

The bioethical and public debate on (pharmacological) enhancement was analyzed in the TAB project specifically with respect to its current and mid-term social and political relevance. The most important consequences could result from demands for a liberal approach to existing and future performance-enhancing substance and systematic research into the long-term effects of their use. These demands have fueled the public debate both on the international (Greely et al. 2008) and the national stage (Galert et al. 2009) and have led to discussions about possible regulatory options (Coenen et al. 2009).[80]

This report presents two analyses relating to the options of promotion and regulation that are unprecedented in form and detail and are central to political decisions regarding the future legal and research approaches to questions concerning performance-enhancing substances: in Section III a classification in respect of pharmaceutical, food, and healthcare law, showing that a »liberal« approach to pharmacologically active substances for healthy individuals is not possible with-

80 However, the different areas of emphasis should not be overlooked: whereas Greely et al. (2008) and Galert et al. (2009) specifically focused on pharmacological neuroenhancement, the ETAG study, which was commissioned by the European Parliament (Coenen et al. 2009), focused on enhancement as a collective category of diverse biomedical technologies.

in the existing regulatory system, and in Section V considerations as to what scientific developments and political decisions would be necessary to enable a liberal scenario of the future use of pharmaceuticals to enhance performance.

REGULATORY PREREQUISITES FOR THE LIBERALIZATION OF ENHANCEMENT

Given the existing restrictions on the investigation and marketing of pharmaceuticals for nontherapeutic performance-enhancement, the scenario of expansion (Section V) argues that fundamental changes would be necessary, especially in terms of the criteria for the regulatory approval of pharmaceuticals. In this context the recognition of performance enhancement in healthy individuals would be a key benefit dimension, thus creating a new regulatory category or indication for nontherapeutic pharmaceuticals. By contrast, the establishment of a separate product group outside medicinal products legislation appears to be legally and politically unrealistic in the extreme, because the definition of medicinal product as such would have to be altered. This would have unpredictable consequences for the already difficult demarcation of these substances from foods and chemicals.

But the establishment of a (nontherapeutic, performance-enhancing) effect in healthy individuals as a benefit criterion would in itself require a resolute political will because of the associated change in the logic upon which the approval of medicinal products is based. This political will, in turn, would presuppose convincing, strong arguments in favor of the societal value of pharmacological performance enhancement. Certainly, before a favorable opinion can be formed by the relevant societal players, more robust information must be available about (future) potent substances with relatively few side effects. This information can be gained either through hitherto limited legal and semilegal research conducted under current conditions in Europe, the USA, and Japan or through intensified activities in states with increasing economic and scientific capabilities and less restrictive regulations (China, Brazil, India).

Acknowledgement that pharmacological substances can in fact bring about a relevant enhancement of cognitive performance in healthy individuals would be a necessary but by no means sufficient reason for society to recognize the benefit and desirability of their diffusion – and only such an assessment could serve as the starting point and an incentive for changing medicinal product regulations and stimulating the specific research and development of enhancement agents. A clearly positive benefit-risk assessment by society as a whole would therefore be necessary.

MEDICALIZATION OF PERFORMANCE: LESSONS FROM SPORT

Until effective cognitive enhancers are discovered, one can only resort to available information on the pharmacological manipulation of other types of performance.

The greatest fund of information has emerged from research into doping in sport as a social subsystem in which measurable performance serves as an evaluation criterion and in which targeted improvement is achieved through training, technology, and pharmaceutical substances. Even though competitive and especially elite sport is characterized by a large number of specific features of a social, legal, and ethical nature, its analysis is nevertheless an obvious approach for shedding light on the question regarding the relationship between (high-)performance drive, performance (enhancement) demands, and system influences. It is in any case surprising that possible lessons from the history and practice of doping have so far played only a subsidiary role in the enhancement debate.

The analysis in the present report (Section VI) shows that close examination of the causes, manifestations, and social consequences of doping in sport can certainly further our understanding of the potential functions of enhancement in the »performance society«. Two dynamic processes of the doping phenomenon in competitive sport appear to be of special relevance: that of dropouts, i.e. the withdrawal or exclusion of athletes and trainers unwilling to engage in doping, and that of a compulsion to increase the dosage despite increasing risks and diminishing benefits for the individual. Both favor the (self-)destruction or fundamental disruption of the competitive sport system, whose inner logic and objectives produced and promoted them in the first place.

In particular, evidence of physiological and psychological relationships between high performance and dependent substance use should be investigated and analyzed more thoroughly than has been the case. Many questions pertaining to cause-and-effect relationships and relationships to other body-perception and behavioral disorders are unanswered and define an important research area concerning high performance outside the field of sport. The debate on possible pathological aspects of extreme performance orientation appears insufficient overall, possibly due to the high social value attached to performance.

The example of doping also provides a wealth of evidence that individualization of the causes of, responsibility for, consequences of, and possible preventive measures for the phenomenon fails to address the underlying problem and is ethically dubious. This is an important insight regarding the use of potential cognitive enhancement agents in the competitive society.

Overall, the analysis of doping problems provides little evidence for the plausibility of a rationally acting, innovative user who purposefully and prudently doses himself with a performance-enhancing substance for a limited time and who can stop taking it again without any problems – i.e. the type of individual characterized as an independent enhancement user. Rather, experience in sport indicates that most users of pharmacological substances are attempting to adapt to demands that they believe they are unable to meet without the help of such agents.

CHALLENGES FOR THE FUTURE BIOPOLITICAL DEBATE

The reviewing experts Viehöver et al. (2009, pp. 78ff.) criticize the fact that the largely pragmatic, solution-oriented biopolitical debate has looked mainly at the potential risks and ethical acceptability of technical interventions in human nature. Although the social conditions under which new biomedical technologies are used are considered, the main objective, they say, is to form and shape opinion with a view to making collectively binding decisions on the approach to new biotechnical options. In the opinion of Viehöver et al. (2009), such an essentially *reactive* understanding of biopolitics falls short with regard to enhancement techniques and discussions about enhancement because it distorts the view of the societal nature of enhancement wishes and the emergence of enhancement techniques. The task and aim of »anticipatory governance«, they argue, is to recognize and discuss relevant developments as early as possible in order to identify problems which can and should be addressed more appropriately with social measures instead of technological means before the consequences of scientific, technical, and social development have created a body of hard facts.

This approach appears commensurate with the problem and convincing, at least in the context of an understanding of enhancement as a pharmacological improvement of performance in working and everyday life as considered here. Given that performance-enhancing agents do not actually exist as yet but must first be created through targeted research and development efforts, there is a real opportunity for an early (bio)political debate and social control of future developments.

AREAS OF ACTIVITY

As this report shows, the topic of enhancement relates to highly diverse activities of various individual and collective players in science, economics, and the healthcare system. Generally speaking, fields of activity pertain to the areas of research, regulation, consumer health protection, prevention, and public debates:

- With regard to research the question arises as to what investigational questions and objections are significant enough to be supported by public funding.
- With regard to regulation, it must be investigated whether the available statutory regulations and their procedural and institutional implementation appear appropriate.
- With regard to the current use of putative performance-enhancing agents, there is a need for unbiased consumer information, public healthcare, and workplace health and safety measures.
- With regard to the future debate, it must be asked whether and how social debate and opinion formation can be actively promoted.

RESEARCH

A key question concerning the enhancement debate is (Coenen et al. 2009; Galert et al. 2009): Should research and development of potentially performance-enhancing substances without therapeutic efficacy – whether for cognitive, other mental or physical enhancement – be allowed or, indeed promoted in a targeted manner? Given the current state of knowledge, targeted pharmacological performance enhancement appears to be neither particularly promising nor socially desirable. In contrast to behavior-based learning strategies, there is so far no convincing evidence that the use of pharmacological substances can actually influence complex human abilities or performance whose enhancement may be socially beneficial in a targeted and specific way without causing appreciable side effects. By contrast, in the context of a tendency to medicalize psychosocial problems there is a need for wide-ranging research into the existing social forms of the deliberate use of medicines with the aim of maintaining – and presumably in some cases with the wishful aim of enhancing – performance. A reliable survey of the status quo is required as a basis for assessing future developments. The empirical analyses that have been published to date for Germany (generally with regard to the use and misuse of pharmaceuticals and specifically the enhancement of performance in working and sport environments) (e.g. DAK 2009; Franke et al. 2011) provide a starting point that could be expanded by studies on the following specific aspects:

- What proportion of individuals who do not feel ill – broken down by social group, occupation, and life situation – deliberately take medicines (or illegal substances) in order to improve their performance, and what substances do they take?
- How is this influenced by educational status and working environment? Do the persons concerned feel under pressure to take substances and, if so, by whom or what? Are those concerned satisfied with their situation, or would they prefer alternative treatment options that do not involve consumption of substances?
- What economic and social players and developments motivate and characterize patterns of use and acceptance of the use of substances?
- How closely related is the field of anti-aging medicine as a driver of the growing medicalization of a life phase that is becoming increasingly long for many people?
- What effects does the use of other body intervention techniques such as cosmetic surgery, tattooing, and piercing have on patterns of use?
- What health effects and psychosocial consequences can be observed?

As the present report shows, the available body of data is far from adequate. To improve the empirical basis, different »risk groups« (e.g. employees in science and research, musicians, managers) could be specifically surveyed. Such analyses

could be undertaken in connection with the New Quality of Work Initiative. It would be helpful if the current body of knowledge on observed and conceivable effects of supposedly performance-enhancing substances could be evaluated – insofar as is permitted by existing regulations governing research and medical ethics – more thoroughly than has been the case. In order to systematize survey results and observational findings, specific investigations into the effects of frequently used substances on the performance of healthy individuals would probably be justifiable and acceptable within a limited scope.

Since pharmaceutical research and development is distinctly global in orientation and performance-enhancing drugs could easily gain an initial foothold outside Europe, there is a need for periodic monitoring of international developments in this field.

The analysis of doping in sport has clearly shown a need for research: firstly, into the question of the comparability and transferability of social-science and psychological findings from sport to the working environment and, secondly, into the pathological aspects of extreme performance and body orientation and its causative factors. Neurobiological approaches, for example, could be used to study the effects of extreme work on the brain. It would also be necessary to investigate the extent to which mental work can have similar adverse effects, as appears to be the case for physical hyperactivity. Specifically, it must be asked whether the use of neuroenhancement products or other forms of pharmaceutical misuse pose an additional risk.

REGULATION

No pressing need for regulation of, or modification of the laws pertaining to, pharmacological (neuro)enhancement is apparent at present. All the purportedly enhancing substances known to date are covered by pharmaceutical, narcotics, or food legislation (Sections II and III). Accessibility and marketability are decided on a case-by-case basis. Therefore, the question of a prohibition of substances or substance consumption, which characterizes not only the ethical but also the related legal debate, does not arise at present (Gärditz 2010; Merkel et al. 2007; Simon et al. 2008).

Nevertheless, it seems reasonable to request some clarification of the prohibition of doping enshrined in the German Medicines Act (AMG). In order to protect health (Art. 6 AMG), the AMG prohibits the marketing, prescription, or administration of medicinal products to others for the purpose of doping in sport (Art. 6a AMG). Were it to become apparent on the basis of detailed empirical surveys that abuse of medicines for the purpose of enhancing intellectual/cognitive performance constitutes a problem of similar magnitude to that of physical performance enhancement, it would be appropriate – given the side-effect potential of these substances – to consider putting these two practices on an equal footing in

the context of the AMG. This could lead to an extension of the doping prohibition set out in the Act. Representatives of organized sport point out that a debate appears appropriate in order to clarify the equal or unequal handling of these two practices.

Some regulatory fuzziness also exists with regard to evoking the concept of therapeutic benefit as a justification for clinical research and subsequent licensing of medicinal products on the one hand and funding by the health insurance funds, particularly in the face of constant pressure to save, on the other. For example, a substance can be licensed but at the same time excluded from the outset from the list of services that are eligible for cost reimbursement, specifically by the statutory health insurance funds. As a result, an increasing number of substances seem likely to be sold mostly in the secondary (private) healthcare market, the documentation and control mechanisms of which are less stringent than those of the primary healthcare market. For the assessment of possible trends in enhancement as well as general pharmaceutical use and misuse, a systematic, transparent, and detailed survey of prescriptions and sales would be desirable and necessary. In addition, the independent benefit-risk assessment would need to be strengthened and the provision of reliable, easily accessible, and comprehensible information for patients/clients receiving individual health services (IGeL) or off-label prescriptions would need to be ensured. The present practice by doctors – a practice which is opaque and of unknown scope – of providing off-label prescriptions or prescriptions of convenience at the borderline between treatment and performance enhancement requires careful consideration by medical associations and society as a whole rather than more stringent regulation. Professional medical organizations and associations should define their positions and examine whether their codes of conduct need to be modified. The statement on doping and medical ethics by the German Medical Association (2009) could serve as a starting point.

With regard to food legislation it would be useful to assess the extent of goal attainment that has resulted from implementation of the German Health Claims Regulation and if appropriate to review the regulations governing the advertising of purportedly performance-enhancing foods in order to restrict practices that create or reinforce a desire for performance enhancement.

CONSUMER HEALTH PROTECTION AND PREVENTION

There are many reasons for believing that the use of pharmacologically active sub-stances is not an appropriate or socially desirable option for coping with highly or even excessively demanding performance expectations and objectives. The observation that this form of behavior is of relevance to medical practice despite the threat of myriad nontrivial side effects suggests the need for the broad-based promotion of health-conscious individual lifestyles, among other

means by the provision and dissemination of reliable information and by establishing a health-promoting environment as envisaged in the WHO's Ottawa Charter for Health Promotion (1986).

An array of novel information and advertising strategies, particularly on the internet, regularly lead to new and often dishonest business practices. There are good reasons to doubt that consumer information measures (Sections III.2.3 and III.3.4) ensure appropriate and effective consumer protection. An important challenge for the various players in the healthcare system and consumer protection is therefore to create a counterweight to interest-driven advertising claims and confusing internet information and to provide clear, unbiased, comprehensive, and reliable information to consumers on claims about effects, lack of effects, and side effects both of foods and of medicines.

When working to establish health-promoting educational and working environments we must distinguish between the general question of the formulation and enforcement of demands for performance – which is discussed as a basic question for society as a whole in the next section – and the approach to specific health consequences in the workplace environment, e.g. the growing number of diagnoses of mental disorders and work disability (German Association of Psychotherapists, 2010b; Bundesregierung 2010). Promoting health at work is in employers' own interest and must be comprehensively formulated in order to be effective despite the growing complexity of work environments (European Network for Workplace Health Promotion 2007). Mental disorders among the unemployed constitute a major problem that underscores the significance of a successful employment policy and the need for comprehensive and integrated support of the unemployed.

The priorities defined by the German Federal Institute for Occupational Safety and Health with regard to research into »mental stress against the backdrop of new forms of work« (BAuA 2010) therefore appear necessary, and it would be logical to consider the problems associated with pharmacological performance enhancement. To this end cooperations could be set up with other relevant research departments and scientific institutions.

SOCIAL AND POLITICAL DEBATE

This report argues that the principal social and political relevance of the topic of enhancement arises not because enhancement is perceived as contributing towards a scientifically and technically based »improvement of human beings«, but rather because pharmacological interventions to improve performance form part of the »medicalization of a performance (enhancement)-oriented society«. Answers to the question as to whether a fundamental characteristics of the human race is to strive for »self-optimization« are doubtlessly of interest in a cultural and philosophical context but do not shed much light on the social ac-

ceptance and desirability of the use of (psychoactive) drugs to enhance performance in working and everyday life. Rather, it appears more important to discuss the impact of such medicalization on working life, education, and the healthcare system as well as on individuals' psychosocial capacities and problem-coping skills.

The social and political debate about this issue must therefore focus firstly on the likely future status of pharmacological and other (bio)medical strategies and measures for coping with performance targets and demands in a globalized educational and working environment, and secondly on the consequences of demographic change. To this end, rather than assuming at the outset that the adoption of strategies designed to maximize individual and collective performance is inevitable in the face of global competition, we need to look into conditions in secondary and tertiary education and at the workplace, and adjust performance indicators accordingly. Commercial and social considerations also favor such an approach, at least in the medium and long term. In this respect the example of doping in sport shows how a system of competition could potentially self-destruct as a result of unlimited expectations of ever-improving performance.

It is indisputable that performance is a key factor and benchmark in modern societies, and, given the future global problems and challenges, the notion of renunciation of the performance society appears neither realistic nor capable of achieving majority support. However, questions about performance (expectations) and how to deal with unequally distributed performance levels in society would be reasonable and appropriate: What kind of performance – economic, social, cultural – is socially valued and by whom and how is it rewarded? How strictly should performance requirements be standardized, and how much room is there for interindividual differences? Where do the perceptible boundaries of acceptable performance enhancement lie, and how can their transgression be avoided? Are there alternatives to the continuous ratcheting up of performance requirements for individuals, for example in the field of work organization? To what extent is the compression and shortening of academic and occupational education reasonable and necessary, e.g. in the context of continuously rising life expectancy?

The psychologist and (neuro)philosopher Stephan Schleim (2010) fundamentally calls into question the view that mental performance is in itself an asset and doubts that striving to achieve performance and improvement is an inherent element of all human actions. He points out that, irrespective of who enhances his performance or how, »only the best five percent can be the best five percent«. It is therefore time »for the rest of society to participate in the debate about enhancement and not just those who occupy the top positions in our performance-oriented institutions«. What is required, he says, is a »discussion about how much performance can be demanded of us and at what point essential elements

of a fulfilled life fall by the wayside when too much emphasis is placed on mental performance« (Schleim 2010).

One substantial argument for pharmacological enhancement that is cited in many bio-ethical submissions is that it is of particular benefit to less highly achieving individuals, especially in working life, and thereby provides greater equality of opportunity and fairness. An analysis of the effects of currently available substances also suggests that individuals who suffer from some kind of deficit at baseline may be more likely to benefit. Confirmation of this hypothesis would intensify discussion of the vexed question of boundaries that has arisen as a result of the increasing pathologization of normal conditions, a trend to which social security systems too must constantly adapt. At the same time, surveys conducted to date suggest that performance-enhancing substances are most likely to be used by very well educated and highly motivated individuals who nevertheless feel unable to cope with the demands placed upon them. All in all, therefore, occupational »enhancement« seems unlikely to be experienced as an autonomous action with beneficial consequences.

If, at some time in the distant future, more solid evidence than is presently available should emerge of performance-enhancing effects unaccompanied by significant side effects, there are likely to be pressing calls for more systematic research into enhancement agents. Given the paradigm shift in medical research that this would entail, a public opinion-forming process would need to be initiated by that time at the latest in order to give the public the opportunity to decide whether it really wishes to allocate public funds to such research.

However, the findings of the present report do not suggest that performance-enhancing substances are likely to exert a beneficial influence on public wellbeing, the social fabric, or individual happiness in the long term.

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LIST OF ABBREVIATIONS 3.

BtMG	Betäubungsmittelgesetz (German Narcotics Act)
BVL	Bundesamt für Verbraucherschutz und Lebensmittelsicherheit (German Federal Office of Consumer Protection and Food Safety)
BVL	Bundesverband des deutschen Lebensmittelhandels (Federal Association of the German Food Trade)
CGS	Abbreviation of the units centimeters (cm), grams (g), seconds
CIAA	Confédération des Industries Agro-Alimentaires (Confederation of the Food and Drink Industries of the EU)
CNS	Central Nervous System
COMT	Catechol-O-methyltransferase
DAK	Deutsche Angestellten Krankenkasse (German Employees' Health Insurance Fund)
DGB	Deutscher Gewerkschaftsbund (German Trade Union Confederation)
DGE	Deutsche Gesellschaft für Ernährung (German Nutrition Society)
DGSP	Deutsche Gesellschaft für Sportmedizin und Prävention (German Society for Sports Medicine and Prevention)
DIMDI	Institut für medizinische Dokumantation und Information (Institute for Medical Documentation and Information)
EFSA	European Food Safety Authority
EMA	European Medicines Agency
EVM	European Expert Group on Vitamins and Minerals
FDA	US Food and Drug Administration
FSA	British Food Standards Agency
G-BA	Gemeinsamer Bundesausschuss (Joint Federal Committee)
GCP	Good Clinical Practice
GG	Grundgesetz (German Constitution)
HCR	Health Claims Regulation
HPED	Hypothetical Performance-Enhancing Drug(s)
HWG	Heilmittelwerbegesetz (Drug Advertising Act)

ICD	International Statistical Classification of Diseases and Related Health Problems
ICR	Interdisciplinary Clinical Research
IGeL	Individuelle Gesundheitsleistung (Individual health service)
IIT	Investigator-Initiated Trial
INSERM	Institut National de la Santé et de la Recherche Médicale (National Institute of Health and Medical Research)
IQ	Intelligence Quotient
IQWiG	Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen (Institute for Quality and Efficiency in Health Care)
KBV	Kassenärztliche Bundesvereinigung (National Association of Statutory Health Insurance Physicians)
LFGB	Lebensmittel- und Futtermittelgesetzbuch (German Food and Feed Code)
MPH	Methylphenidate
NCE	New Chemical Entity
PEI	Paul Ehrlich Institute
PHI	Private Health Insurance
PIL	Patient Information Leaflet
R&D	Research and Development
RKI	Robert Koch Institute
RVA	Reichsversicherungsamt (German Imperial Insurance Office)
SGB	Sozialgesetzbuch German Social Code
SHI	Statutory Health Insurance
SPC	Summary of Product Characteristics
WADA	World Anti-Doping Agency
WHO	World Health Organization
WIdO	Wissenschaftliches Institut der AOK Scientific Institute of the AOK
ZLG	Zentralstelle der Länder für Gesundheitsschutz bei Arzneimitteln und Medizinprodukten (Central Authority of the German Federal States for Health Protection with regard to Medicinal Products and Medical Devices)

For some time now there has been a vigorous debate about whether the »improvement« of human performance by pharmacological means – usually referred to as »enhancement« – is a desirable goal of the modern life sciences. At the same time, there is evidence of changes in the use of »lifestyle drugs« and a growing demand for »wish-fulfilling medicine«. This book gives the most detailed account to date of the current possibilities for influencing mental performance by pharmacological means and examines the drug, food, and health regulations pertaining to such substances. Based on a systematic analysis of findings from the social sciences on the doping problem in competitive and recreational sport, the authors outline possible future trends of drug use in professional and everyday life. They do not view the »pharmacologically enhanced human« as an inevitable vision of the future. Instead, they discuss the potential impact of the growing medicalization of society on healthcare systems and on the ability of individuals to cope with problems in their professional and private lives.

TAB

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