



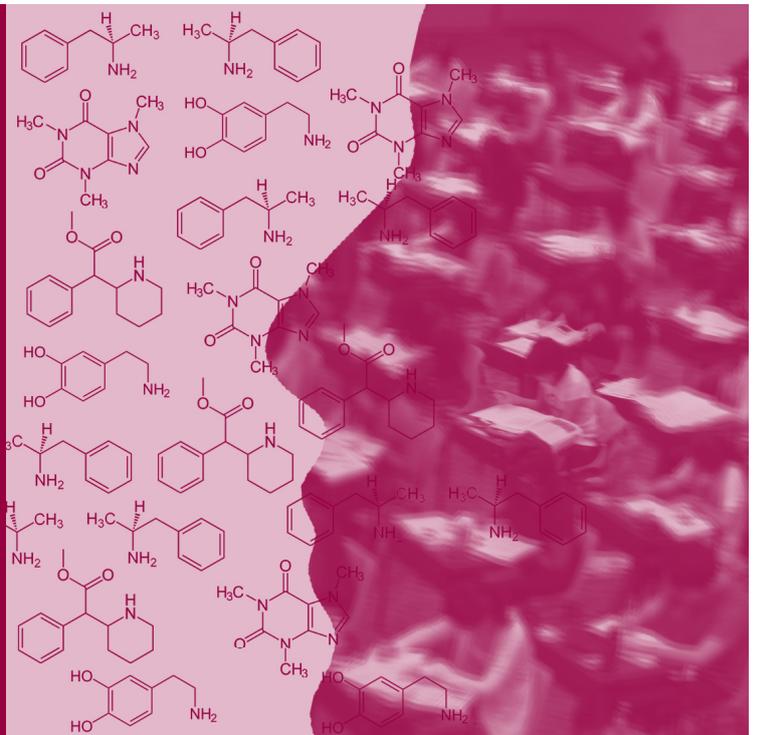
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Arnold Sauter
Katrin Gerlinger

Pharmacological interventions to improve performance as a social challenge

Summary

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»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



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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 measurement 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 influenced 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 dimensions 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 (alertness, 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.



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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-



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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 diagnosis (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 efficacy 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



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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 phar-

macological 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:



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- > 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 secu-

rity 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.

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**OFFICE OF TECHNOLOGY ASSESSMENT
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BÜRO FÜR TECHNIKFOLGEN-ABSCHÄTZUNG
BEIM DEUTSCHEN BUNDESTAG

KARLSRUHER INSTITUT FÜR TECHNOLOGIE (KIT)

Neue Schönhauser Straße 10
10178 Berlin

Fon +49 30 28491-0
Fax +49 30 28491-119

buero@tab-beim-bundestag.de
www.tab-beim-bundestag.de