

Europäische Akademie

zur Erforschung von Folgen
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Direktor:

Professor Dr. Carl Friedrich Gethmann

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Newsletter *Akademie-Brief*

Editorial

The integration of European perspectives into its research is a goal that the European Academy is pursuing by several means. Up to now the Academy has approached this goal mainly by inviting European and international scientists to participate in project groups and in interdisciplinary conferences. Our first research fellow, Professor Banse, carried out a study on the Ethics of Science and Technology Assessment in Eastern European countries. After having moved into more spacious offices in October 1999, the European Academy is enlarging its Research Fellowship Programme with the beginning of the year 2000. The purpose is to invite highly qualified foreign scholars to carry out research projects in the field of the consequences of scientific and technological advance at the European Academy in Bad Neuenahr-Ahrweiler. Research fellowships for a stay of between 3 and 6 months are offered on a European-wide, competitive basis. The main criterion for selection – besides quality and feasibility – is the relatedness of the proposed projects to the scientific work of the European Academy. Approximately 3 to 5 research fellowships are available per year. We are looking forward to receive qualified applications which can be submitted as of today. Further information are available on our Homepage: <http://www.europaeische-akademie-aw.de>.

ENH

Focus

Drug effects in combination

Gerald Pöch

Das Thema der Kombinationseffekte von Pharmaka hat stets viele Wissenschaftler in seinen Bann gezogen; so etwa Forscher auf dem Gebiet der Chemotherapie, wo hohe Wirksamkeit und Nebeneffekte eine wichtige Rolle spielen. Erste Beschreibungen lassen sich Ende des letzten Jahrhunderts finden, als die Kenntnisse über die Wirkungsweisen sehr begrenzt und bestenfalls hypothetisch waren. In den ersten Jahrzehnten dieses Jahrhunderts wurden derartige Beschreibungen intuitiv formuliert und resultierten in Modellen „ähnlicher“ Wirkung: *Dosis-Additivität*, *Unabhängigkeit* und *Effekt-Additivität*. Wir kennen heute die Wirkungsweisen vieler Pharmaka und beginnen, die Prozesse hinter den alten Modellen zu verstehen. Bei den pharmakodynamischen Mechanismen der Arzneimittel-Wirkungen in Kombination verdient das Modell der *Unabhängigkeit* das größte Augenmerk.

In real life we widely observe effects in combination, although we rarely use the expression „combination“, except when drugs and toxic chemicals act „together“. „Co-operations“ can generally be described as processes acting in the same or in the opposite direction, in politics or business, for example, as well as in biology and medicine. Special attention has always been paid to the effects of drugs in combination. It is not surprising, therefore, that attempts at *describing* or *predicting* the effects of drugs in combination date back more than 100 years, yielding rules and rather intuitive models in the first decades of this century. These models were probably derived from everyday experience in other fields and formalized what was understood as „working together“ (synergism) or „working against each other“ (antagonism). These models still play a role in describing combined effects, e.g., of environmental agents. Today we have a number of mechanistic *explanations* for the effects of certain combinations, which make these models still attractive. This article is confined to drugs and therapy rather than attempting to describe and discuss all aspects of all

kinds of combination effects in all fields of interest.

We first have to know how drugs produce effects in order to understand how they could act when present together. Today, we already have reliable and profound knowledge about many drugs and groups of drugs, as can be seen from textbooks on pharmacology. This knowledge not only tells us how the molecules of drugs act on certain cells or cell systems but also tells us which processes generally precede the action of drugs. Therefore, pharmacology deals not only with the dynamic actions and processes (pharmacodynamics) but also with the processes by which drugs are absorbed by the body, distributed within the body, metabolized and eliminated from the body (pharmacokinetics).

The *models* describing the effects of drugs in combination, referred to above, are pharmacodynamic in nature and do not take pharmacokinetic processes into account. They are known as *dose-additivity* (*concentration addition*), *independence*, and *effect-additivity* (*effect summation*) and can be seen as special forms of



pharmacodynamic combinations. As a matter of fact, these models describe synergistic actions where the agents under study show „similar“ effects. In pharmacology we also know of antagonistic actions which can properly be described as competitive, non-competitive and functional antagonism. Antagonistic drug effects are generally not desired in therapy, except when side-effects pose a problem or when toxic reactions occur as a consequence of overdosing.

Drug effects in combination either occur at the pharmacodynamic or the pharmacokinetic level. The kinetic processes of a drug can be influenced by other drugs in various ways, leading either to increases in the drug concentration under study or to decreases compared to uninfluenced kinetics. Thus, it is clear that combination effects due to altered kinetics will either enhance or diminish the effects of drugs in accordance with the changes in the concentration of the active drug in the blood. Although it is clear today that such „blood levels“ only reflect concentrations of molecules of the active drug at their site of action, it is not possible to measure the concentrations there „directly“, with certain exceptions. The term „active drug“ emphasizes that the drug is biologically active at its site of action, i.e., it is neither a „prodrug“ nor an „inactive metabolite“. Changes in active drug concentrations in the blood caused by other drugs is a characteristic feature of a pharmacokinetic „drug interaction“. In contrast to pharmacodynamic interactions or combinations, drugs interacting at the kinetic level do not need to act either in the same direction (similar) or to act in the opposite direction. For instance, one drug inhibits the metabolism of another drug but possesses a completely different pharmacodynamic action. A well known example is the „combination“ of an anticoagulant (dicumarol) and an antiepileptic (hydantoine). It has been reported that dicumarol can prolong elimination half-life from 9 to 36 hours.

Changes in drug effects not due to kinetic interactions are by definition pharmacodynamic in nature. Both interactions lead to changes in effects, enhancement or diminution of desired drug effects or (mostly unwanted) side effects. Recent analyses of drug interactions have shown that about two thirds are caused by kinetic, one third by dynamic processes. It should be mentioned that attempts have recently

been made to model altered kinetic processes but *the* models which dominate the literature up to now are the dynamic models of „dose additivity“, „independence“ and „effect summation“.

Let us now turn to the following questions.

- 1) When will dynamic interactions (combination effects) occur?
- 2) When will they agree with one of the models?
- 3) What implications can be derived from effects in combination?
 - 1) Pharmacodynamic effects in combination are only expected when drugs act in the same or in the opposite direction, the latter mechanism is usually not desired.
 - 2) They will agree with the model of dose-additivity when the interacting drugs compete for the same molecular site, a very rare situation in therapy. Dynamic combination effects can often be approximated by model effects of independently acting drugs (acting at different sites). Less frequently, we can observe a simple summation of effects, e.g., where the sum of effects is equal to or slightly greater than effects of the independence model.
 - 3) The implications of enhanced drug effects (by employing dynamic combination effects) result in a more efficient therapy for severe illness, mostly chemotherapy of infectious diseases or tumors. AIDS, tuberculosis or eradication therapy of gastric infection with *Campylobacter pylori* are examples for this form of combination therapy. Combination therapy with three or four antitumor agents is standard in tumor chemotherapy. Clinical experience has led to several standard regimes for certain types of cancer. Nowadays, testing the effectiveness of antitumor agents using tumor cells from patients promises to achieve a great step forward towards a more specific combination therapy. This strategy, which has already become a routine analysis in certain clinics in Europe and the USA, is a similar approach to tumor therapy and anti-infectious therapy, such as in vitro testing for the best agents and best combinations of agents as the basis for individual therapeutic drug therapy.

In certain cases, kinetic interactions can also be exploited, e.g., with inhibitors of the metabolic conversion of the drug applied, e.g., in the therapy with L-DOPA (levodopa) for Parkinson's disease or in the therapy with penicilline. In the levodopa therapy, an inhibitor of DOPA-decarboxylase is employed which only acts in the body's periphery but not in the central nervous system. Thus, the concentration of dopamine derived from levodopa is increased in the brain but is decreased in other parts of the body, as desired. The result is a more effective therapy with fewer side-effects. In the therapy of infections with penicilline, some bacteria contain an enzyme, β -lactamase, which inactivates the antibiotic. This breakdown can be inhibited by an inhibitor of β -lactamase applied together with penicilline.

Drug effects in combination are still a matter of controversy and it is certainly true that many combination schemes will become obsolete for therapy when more powerful and more selectively acting drugs are available. The rather poor reputation of combination therapy in the opinion of many researchers is due to the fact that in the past many (rather ineffective) drugs have been used in combination on an intuitive basis, backed at best by the use of „old“ models. This is especially true for the so called fixed combinations which are on the market. The better we understand the processes in disease and how drugs act in patients, the better we will understand the pharmacodynamic processes of the combined effects of drugs. This, in turn, can lead to a more scientific approach and, consequently, a better therapy where drug effects in combination are still required. The experience gained from scientific studies with drugs is already helpful in the design and the evaluation of studies with other chemicals or physical factors for human health and for the environment. One can only hope that research in the field of combined effects will become more attractive to scientists and will receive more financial support.

Dr. med. Gerald Pösch is Emeritus Professor for Toxicology at Graz University. He is member of the working group *Environmental Standards* at the European Academy.



Working groups

Umweltstandards

Am 13. Januar 2000 wurde die Studie ‚Umweltstandards. Kombinierte Expositionen und ihre Auswirkungen auf den Menschen und seine Umwelt‘ der Projektgruppe *Umweltstandards* der Europäischen Akademie in Berlin der Öffentlichkeit vorgestellt. Die Studie ist in der Schriftenreihe der Europäischen Akademie erschienen. Mit ihrer Veröffentlichung liegt erstmals eine umfassende interdisziplinäre Arbeit zu kombinierten Expositionen vor. Neben der Studie ist in der *Grauen Reihe* der Europäischen Akademie eine englischsprachige Zusammenfassung erschienen.

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Climate Prediction and Precautions

On 19th November the working group *Climate Prediction and Precautions* held its 7th project meeting, which centred on the discussion of the economic aspects of climate change. Corresponding sectoral and transsectoral perspectives were presented by Professor Dr. Dieter Schmitt (Essen) and Professor Gernot Klepper, Ph.D. (Kiel). Detlef Sprinz, Ph.D. (Potsdam) joined the project group as a new member, thus completing the group's expertise with respect to international and environmental politics. With this meeting the first section of the working plan – critical stock-taking from the relevant scientific disciplines – was completed.

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Electronic Signatures

The Project Group has held a kick-off meeting in co-operation with the Bundesamt für Sicherheit in der Informationstechnik (BSI), which took place in Boppard, Germany, on 2/3 December 1999. The Project Group had a unique opportunity to present their work and thesis to a select audience of 80 participants. Furthermore the meeting

provided the group with a valuable opportunity for networking with other actors from different disciplines. External speakers were: Dr. A. Heuser (BSI); Dipl.-Math. K. Keus (BSI); W. Bieser (Bundesbeauftragter für Kultur und Medien); Professor Dr. M. Hortmann (Universität Bremen); Dr. F. Büllingen (Wissenschaftliches Institut für Kommunikationsdienste); Dr. K. Friedrich (Brandenburgische Technische Universität Cottbus); Dr. Chr. Deußen (Deutsche UNESCO Kommission); Professor Dr. K. Kornwachs (Brandenburgische Technische Universität Cottbus); Dr. J. Rieß (TeleTrusT Deutschland e.V.); J. Tauss, Mitglied des Bundestages.

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News in Brief

Workshop "Konstruktive Logik"

The European Academy organised a workshop on "Konstruktive Logik" in Bad Neuenahr-Ahrweiler on 18/19 November 1999. The aim was to re-initiate a debate on the justification of constructive logic as an instrument for controllable reasoning. Professor Dr. P. Janich (Marburg), Priv.-Doz. Dr. D. Hartmann (Erlangen-Nürnberg), Professor Dr. C. F. Gethmann (Bad Neuenahr-Ahrweiler), Professor Dr. Ch. Thiel (Erlangen-Nürnberg), Professor Dr. P. Schröder-Heister (Tübingen), Dr. R. Inhetveen (Erlangen-Nürnberg), Priv.-Doz. Dr. Sh. Rahman (Saarbrücken), Dr. G. Kamp (Bad Neuenahr-Ahrweiler) held lectures on developments in constructive logic and its application in computer programming, argumentation theory and language philosophy. It appeared that in logic programming constructive logic seems to be the adequate instrument.

The discussion will be documented in an omnibus volume. A sequel on the main topic of the philosophy of action and language philosophy is projected.

Membership

Professor Dr. Carl Friedrich Gethman was elected for a second election period (2000-2002) as a member of the „Ausschuss für die Vergabe von

Forschungsstipendien an deutsche Wissenschaftler für Forschungsaufenthalte im Ausland“ of the Alexander von Humboldt-Stiftung. This Committee decides among other things about the awarding of the Feodor-Lylen-Forschungsstipendien.

Gesundheitsstandards

Für das Projekt *Gesundheitsstandards* der Berlin-Brandenburgischen Akademie der Wissenschaften (BBAW), das von Professor Dr. Carl Friedrich Gethmann geleitet wird, wurde als Projektleiter Dr. Thomas Krause durch die BBAW eingestellt. Dienort ist die Europäische Akademie.

Welcome

Dr. Kathrin Prieß (since 01/11/99) and Minou Bernadette Friele, M. A. (since 01/10/99) are new members of the scientific staff of the European Academy. Since 01/10/99 Maria Icking is responsible for the accounting.

Organs

Gesellschafterversammlung

Am 07.12.99 fand die 8. ordentliche Sitzung des *Geschäftsführenden Ausschusses* und der *Gesellschafterversammlung* der Europäischen Akademie GmbH statt. In dieser Sitzung wurde u. a. der Haushaltplan 2000 genehmigt.

Council

Several new members were appointed in the *Council* of the European Academy: Professor Dr. Gerhard Banse (Universität Potsdam), Dr. Helmut Bäuml (Datenschutzbeauftragter Schleswig-Holstein), Professor Dr. Jos Dumortier (Universität Leuven), Notar Dr. Riccardo Genghini (Mailand), Professor Dr. Armin Grunwald (Institut für Technikfolgenabschätzung und Systemanalyse, Karlsruhe), Professor Dr. Andrzej Kiepas (Universität Kattowice), Professor Dr. Bernd Lutterbeck (Technische Universität Prag), Dr. Petr Machleidt (Universität Prag), Professor Dr. Andreas Pfitzmann (Universität Dresden), Professor Dr. Georg Rudinger (Universität Bonn), Detlef Sprinz, Ph.D. (Potsdam) Dr. Otto Ulrich (Bundesamt für Sicherheit in der Informationstechnik, Bonn), Professor Dr. Reinhard Voßbein (UIMC Wuppertal).

Lectures

Carl Friedrich Gethmann:

„Wissenschaftsimmanentes Ethos“: Internationale und Interdisziplinäre Ringberg-Konferenz „Ethos der Forschung“ (Schloß Ringberg), 20.10.99

„Welche Fortschritte bringt die Kulturalistische Logikbegründung?“, Fachgespräch „Konstruktive Logik“ der Europäischen Akademie GmbH, 18.11.99

„Wissenschaftstheoretische und ethische Aspekte der Gentechnik“, Symposium des Arbeitskreises Gentechnologiebericht der Berlin-Brandenburgischen Akademie der Wissenschaften, 20.11.99

„Wahrheit und Beweisbarkeit. Heytings formale Regeln der intuitionistischen Logik“: Gemeinsame Sitzung der Geisteswissenschaftlichen und der Mathematisch-Naturwissenschaftlichen Klasse der Berlin-Brandenburgischen Akademie der Wissenschaften, 26.11.99

Christian J. Langenbach:

„Virtuelle Bildung in der Informationsgesellschaft“, Lehrveranstaltung „Entwicklung und Gestaltung der Informationsgesellschaft“ an der Fachhochschule Ingolstadt, 10.11.99

Eva Neumann-Held:

Kommentar zum Vortrag „Technikfolgenabschätzung und -bewertung im Forschungsprozeß“ von Professor Dr. Regine Kollek, Workshop „Perspektiven der Technikfolgenabschätzung“, Bielefeld 11./12.11.99

Felix Thiele:

„What is special about ‚genetic‘ knowledge? The scope and limits of ethics in technology assessment“, European Workshop on Legal, Regulatory and Ethical Aspects in Pharmacogenetics, Berlin 12.11.99

New Publications

C. F. Gethmann: „Zumutbarkeit und Inkaufnahme von Risiken“, in: *Jahrbuch für Wissenschaft und Ethik* 4 (1999) 283 – 291

U. Rehberg, K. Egger, H. Karrasch: „The Effects of Different Methods of Grassland-preservation“, in: *Ecosys. Beiträge zur Ökosystemforschung. Sustainable Landuse Management. The Challenge of Ecosystem Protection*. Suppl. Bd. 28, 1999 (Proceedings of the Conference 28.9.-1.10.99, Salza), S. 269-274

C. Streffer, J. Bücken, A. Cansier, D. Cansier, C. F. Gethmann, R. Guderian, G. Hanekamp, D. Henschler, G. Pösch, E. Rehlinger, O. Renn, M. Slesina, K. Wutke: *Umweltstandards. Kombinierte Expositionen und ihre Auswirkungen auf den Menschen und seine Umwelt*. Springer, Berlin 2000

Graue Reihe

The following volumes of the European Academy's documentation series *Graue Reihe* were published in 1999 and can be ordered from the European Academy:

13 Gerhard Banse, Christian J. Langenbach (Hrsg.): *Geistiges Eigentum und Copyright im multimedialen Zeitalter. Positionen, Probleme, Perspektiven*; 2/99

14 Karl-Michael Nigge: *Materials Science in Europe*; 3/99

15 Meinhard Schröder, Stephan Lingner (eds.): *Modelling Climate Change and its Economic Consequences. A review*; 6/99#

16 Michael Decker (Hrsg.): *Robotik. Einführung in eine interdisziplinäre Diskussion*; 9/99

17 Otto Ulrich: *Protection Profile. Ein industriepolitischer Ansatz zur Förderung des „neuen Datenschutzes“*; 11/99

18 Ulrich Müller-Herold und Martin Scheringer: *Zur Umweltgefährdungsbewertung von Schadstoffen und Schadstoffkombinationen durch Reichweiten- und Persistenzanalyse*; 12/99

19 Christian Streffer et al.: *Environmental Standards. Combined Exposures and their Effects on Human Beings and their Environment*; 12/99

Personalities



Professor Dr. med. vet. Dr. h.c. *Gottfried Brem* studied Veterinary Medicine, Agricultural Sciences and Economic Sciences at Munich University, where he graduated in 1979. He specialized in Breeding Techniques and Molecular Genetics and finished his habilitation in Animal Breeding and Genetics 1985. In 1987 he was appointed a newly founded Chair for Molecular Animal Breeding at the Ludwig-Maximilians-University of Munich. He was offered full professorships at the Universities of Kiel, Hannover, and Vienna. From 1993 to 1997 he was the director of the Institute of Animal Breeding and Genetics at the Veterinary University of Vienna, since 1994 he has been head of the Department of Biotechnology in Animal Production at the Interuniversity Institute of Agrobiotechnology (IFA) Tulln and since 1997 he has been the director of the Ludwig-Boltzmann-Institute for Cyto-, Immuno- and Moleculargenetic Research.

Professor Brem holds several international scientific awards such as the Martin-Lerche-Forschungspreis and the Uovo d'Oro and is member of numerous advisory boards in scientific institutions such as the FWF-Kuratorium in Austria.

Professor Brem is a member of the project group *Xenotransplantation* of the European Academy.

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