The Kaleidoscopic Brain

Valedictory Lecture delivered by

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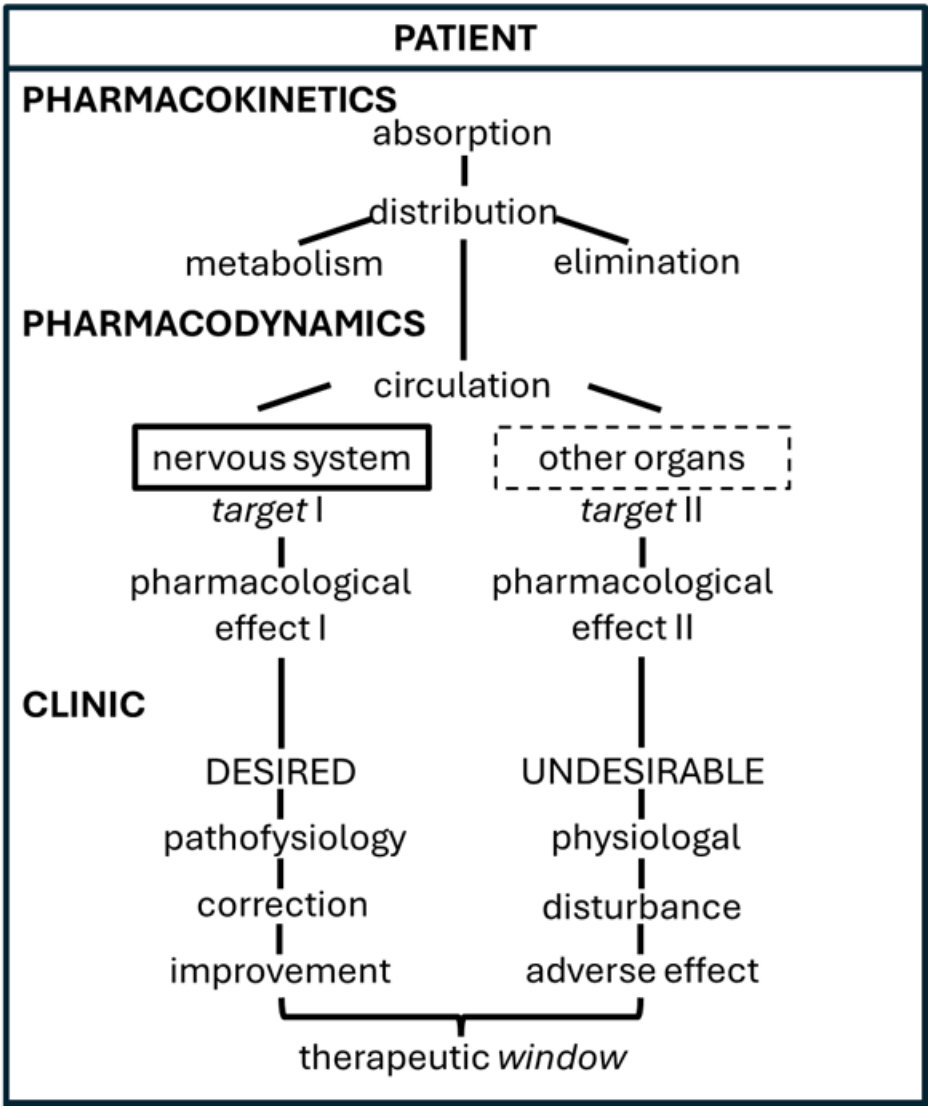
Clinical-Pharmacological Framework



Members of the Executive Board of the Leiden University Medical Center, esteemed audience –

More than twenty years ago, I stood here in this very place to deliver my inaugural lecture. I could not, at the time, share everything I have learned since, so today I would like to continue where I left off. Now, where were we again?

My inaugural lecture was about *The Befogged Brain* of Albert Hofmann, the Swiss pharmacochemist who, in April 1943, accidentally ingested LSD and experienced the first 'trip' in history while cycling home.[1] He described that experience as a kaleidoscopic vision of light and form,[2] and later wrote that it suddenly made him understand abstract art. Hofmann also realized that LSD could offer psychologists access to 'the workings of their own nervous system,' and psychiatrists to that of their patients.[3] In 1947, LSD was registered under the trade name *Delysid*® as an aid to psychotherapy – until it was withdrawn from the market in the 1960s.[4] However, I do not invoke Hofmann here to speak about psychedelics, but rather to recall what he called in his memoirs his most important insight: that there is one reality, seen from many perspectives.[5]

That *insight*, ladies and gentlemen, I share – though based on rather different experiences with psychopharmacology than Hofmann's. The question, however, remains: how do we build an *overview* from those many perspectives? That is the subject of my valedictory lecture.

I will begin with a brief modern history of how our understanding of the brain and mind has evolved. This will show how

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[1] Joop M. A. van Gerven, *Het Benevelde Brein* (*The Befogged Brain*) (Leiden: Leiden University, 2005).
[2] Albert Hofmann, *LSD: Mein Sorgenkind: Die Entdeckung einer "Wunderdroge"* (München: Deutscher Taschenbuch Verlag, 1979); Engelse vertaling door Jonathan Ott, *LSD: My Problem Child* (Los Angeles: J. P. Tarcher, 1979), hoofdstuk 1 "*How LSD Originated*," p. 12 van 137.
[3] *Ibid.*, 50/137.
[4] A. Hintzen en T. Passie, *The Pharmacology of LSD: A Critical Review* (Oxford: Oxford University Press, 2010), 4.
[5] Hofmann, *LSD: Mein Sorgenkind.*, 130/137: "Of greatest significance to me has been the insight that I attained as a fundamental understanding from all of my LSD experiments: what one commonly takes as "the reality," […] that there is not only one, but that there are many realities, each comprising also a different consciousness of the ego."

different, sometimes even opposing, approaches by scientists and thinkers have led to fruitful insights – but also to conflict. After that, I will turn to the central theme of this lecture – and, in a sense, of my entire career. Drugs can not only, as Hofmann himself experienced, evoke a kaleidoscopic image of our many-coloured brain; they can also help neuroscientists discern coherent patterns in the functioning of the brain, in diseases, and in treatments – and even tune their own brains to different wavelengths.

When Hofmann was born in 1906, there was no sharp boundary yet between neurology, psychiatry, psychology, and philosophy. What we now call 'neuroscience' was then a broad intellectual field in which medicine, physiology, and philosophy were closely intertwined.

At the end of the nineteenth century, psychology still stood close to philosophy. Thinkers such as Schopenhauer and Brentano sought to understand consciousness from within, while Frege, as the founder of modern logic, pursued a mathematical approach to thought and language. Wilhelm Wundt tried to build a bridge between physiology and psychology when, in 1879, he founded the first laboratory for *Physiological Psychology* in Leipzig. His approach, through the American behaviourism of Watson and Skinner, gave rise to the experimental models that still form the foundation of much neuropharmacological research today.

At the same time, another, more philosophical and phenomenological approach was taking shape on the European continent. In the nineteenth century, Wilhelm Dilthey drew a distinction between *Erklären* and *Verstehen* – explanation and understanding – to clarify the difference between the natural and the human sciences. Around 1900, Edmund Husserl laid the foundations for phenomenology, which offered psychologists and psychiatrists a systematic method for describing subjective experience. The physician–philosopher Karl Jaspers applied that distinction in his *General Psychopathology* of 1913, showing that psychiatry is concerned not only with explaining mental disorders, but also with understanding the patient as a person.

Meanwhile, within medicine, the field of *Geistes-und Nervenheilkunde* developed, in which neurological and psychiatric conditions were still regarded as belonging to a single domain. Psychiatrists such as Emil

Kraepelin sought systematic classifications, while neuropathologists such as Alois Alzheimer pursued biological explanations. And in Paris, the clinical demonstrations of Jean-Martin Charcot on hysteria and neurological disorders made a deep impression on young physicians such as Sigmund Freud, who through his psychoanalysis would leave a lasting mark not only on psychiatry, but also on psychology and philosophy.

After the horrors of the Second World War, several critical lines of thought converged in a broader reflection on the human being, the mind, and society. Paul Ricœur counted Freud among the 'masters of suspicion,' alongside Marx and Nietzsche – thinkers who looked straight through the façades of rationality and propriety.[6] In his *History of Madness* (1961), Michel Foucault showed that reason and madness are historically constructed categories, and that psychiatry is also a structure of power.[7] That insight gave the pendulum of discourse in the 1960s a strong push toward anti-psychiatry. Thomas Szasz and Ronald Laing opposed medical labelling, while Timothy Leary elevated LSD to the status of a socio-critical sacrament. The great geopolitical tensions of the Cold War were mirrored in clashes between divergent neuroscientific positions.

This intellectual struggle over the relations between brain and mind, nature and nurture, and individual and society also reached the Netherlands. When I began my studies in 1976, several controversies were playing out in the media that made a deep impression on me. There had been public outrage over unethical and completely derailed obedience experiments – by Stanley Milgram, with simulated electric shocks at Yale, and by Philip Zimbardo, with his prison experiments at Stanford. As a result, sociobiological research fell into disrepute, including that of the criminologist Wouter Buikhuisen in Leiden and the psychiatrist Herman van Praag in Groningen. Van Praag's research on neurotransmitters in the blood and cerebrospinal fluid of psychiatric patients provoked such resistance that he required

[6] Paul Ricoeur, *De l'Interprétation: Essai sur Freud* (Paris: Éditions du Seuil, 1965).

[7] Michel Foucault, *History of Madness* (J. Murphy & J. Khalfa, Trans.; original work *Histoire de la folie à l'âge classique*, 1961) (London: Routledge, 2006).

police protection.

I became indirectly involved in all this when Van Praag was appointed head of department in Utrecht in 1978. During almost my entire period of study, his colleagues literally barred him from entering the clinic on Nicolaas Beetsstraat. When, in the early 1980s, I finally attended his lectures, I discovered that Van Praag actually held remarkably nuanced views. Heredity, development, and environment together shaped mental state. This multifactorial perspective would only much later become widely accepted – just as that of Buikhuisen, who was formally rehabilitated by our university in 2009. For me, these researchers became early examples of intellectual courage – people who tried to bridge the gap between neurobiology and psychosociology long before that became common practice.

In the early 1980s, this biopsychosocial approach gained broader resonance in psychiatry with the third edition of the *DSM* – the *Diagnostic and Statistical Manual of Mental Disorders*. For the first time, psychiatric conditions were systematically classified along five axes, allowing biological, psychological, and social factors to be distinguished in a structured way. This made diagnoses more consistent, but treatments also more complex. How, after all, can one develop targeted drugs if every disorder is determined by a mosaic of factors?

From a pharmacological perspective, such a biopsychosocial model in fact calls not for a purely biological strategy, but for multidimensional medicines that:
– first, restore biological dysregulations (of sleep, stress, or nutrition);
– second, correct disturbed emotions and perceptions (such as depression or delusions);
– third, enhance resilience to external stressors (such as overstimulation or anxiety); and
– fourth, remove obstacles that stand in the way of recovery (such as psychedelics).
Each of these aspects involves different mechanisms of action, and it is therefore unrealistic to expect them to be addressed by a single drug. Yet the neuroscientific factors that the DSM so systematically disentangles are, in diagnosis, recombined into broad and heterogeneous disease categories. By this clustering, drug developers – but also clinicians and insurers – are effectively forced to search for a shotgun rather than for a precisely aimed *silver bullet*.

In the second half of the last century, neurophysiology, neurobiology, and experimental psychology gave rise to an ever-growing number of specialized subdisciplines, each with its own language, methods, and institutions. Later, molecular genetics, new imaging techniques such as fMRI and PET, and computational neuroscience were added – to mention only a few developments. These differentiations brought unprecedented progress, but also increasing fragmentation. Philosophers of science have analyzed the tension between differentiation and integration in various ways. Sandra Mitchell emphasized that pluralism in science is not a sign of weakness, but can in fact be a source of strength – provided that the different levels of explanation are integrated – a view entirely in keeping with Hofmann's kaleidoscopic vision.[8] Nancy Cartwright, in *The Dappled World*, painted a mottled picture of reality: nature does not appear as a single pyramid of laws, but as a patchwork of local patterns that researchers themselves construct – acting more like engineers than explorers.[9] The historian of science Peter Galison showed that progress in physics is made possible by the interaction of distinct traditions of theory, experiment, and instrumentation.[10] Philosophers and scientists nowadays seem to agree that differentiation is both inevitable and necessary for scientific progress. The same is true for the neurosciences. Scientific depth leads to specialization and subspecialization; new techniques create new perspectives; and new concepts take root in new disciplines.

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[8] Sandra D. Mitchell, *Unsimple Truths: Science, Complexity, and Policy* (Chicago: University of Chicago Press, 2009), 2. 'My philosophical view, which I call integrative pluralism, explains how these modern scientific practices can be well grounded in an expanded epistemology of science that embraces both traditional reductive and new, multilevel, context dependent approaches to scientific explanation and prediction.'

[9] Nancy Cartwright, *The Dappled World: A Study of the Boundaries of Science* (Cambridge, UK: Cambridge University Press, 1999), 1: 'The dappled world is what, for the most part, comes naturally: regimented behaviour results from good engineering.'

[10] Peter Galison, "Chapter 9: The Trading Zone, Part I: Intercalation," in *Image and Logic: A Material Culture of Microphysics* (Chicago: University of Chicago Press, 1997), 781–82: 9.1: '[S]cience is disunified, and—against our first intuitions—it is precisely the disunification of science that brings strength and stability.'

Science resembles an expanding universe with an exponentially growing number of publications. What is far less automatic is connection: the ability to see that all these partial perspectives do not merely coexist, but can also complement and reinforce one another.

Hofmann's mind-expanding insights stand in sharp contrast to neuroscientific practice. He did not see rival realities, but kaleidoscopic facets of a single greater whole. His image of the brain as a receiver that can be tuned to different wavelengths suggests that there is more than one way in which reality can present itself to us. The significance of these perspectives lies not in their separateness, but in their coherence. That insight – that knowledge acquires meaning only through coherence – did not grow out of psychedelic illusions for me, but from other intense experiences with psycho- and neuropharmaceuticals. Those experiences revealed to me how fragmented the neuroscientific landscape truly is: richly textured for the insider, yet full of blind spots for the outsider. It was precisely that experience that led me to search for patterns that connect the different colour fields.

In the remainder of this lecture, I would like to show how that quest has shaped my career – how multidisciplinary collaboration brought colour to the development of new research methods, to teaching, to the organization of research, and ultimately to philosophical reflection on the question of why there are so many ways to illuminate the world. Time and again, the drug was the agent that made new pieces of the patchwork visible.

The overview I will offer may, to some of you, appear as a motley collection of borrowed feathers – or of old cows dredged from the ditch. That comes with the retroscope of a farewell lecture, but it is also a natural result of decades of collaboration. If you recognize something of yourself, please take it as acknowledgment, not appropriation: you have filled one of my many blind spots.

To my younger colleagues and students, I mainly wish to show how varied and colourful a career can become when one dares to look beyond the boundaries of disciplines and expertise – even when that means exchanging the specialist's magnifying glass for the philosopher's owl-spectacles.

I begin my journey from pharmacology to philosophy with the drug itself. It has been

said that developing a new medicine ultimately amounts to compiling its product information – the *Summary of Product Characteristics* (SmPC), the package insert. On paper, it looks like a complete dossier: composition, dosage, contraindications, interactions, side effects.[11] But the SmPC rarely explains *how* a drug actually works, how side effects arise, or how the dose should be adjusted to the individual patient. At the time of my inaugural lecture, this essential information was still missing from ninety percent of all package inserts.[12] Twenty years later, most labels did contain more information on age, organ function, interactions, and mechanisms of action.[13] Yet it is still rarely explained how that information should be used to tailor the dose to the individual patient.[14]

It is precisely this understanding of the interaction between drug, person, and disease that is essential for the individual patient. At present, registration, guidelines, and reimbursement are still largely based on average effects from randomized clinical trials with a given drug – trials in which, in neurology or psychiatry, often only one in ten patients actually benefits. That is hardly surprising, given the heterogeneity of diagnoses I mentioned earlier. But without a careful integration of the pharmacological properties of the drug and the clinical characteristics of the individual patient, the doctor's desk remains, in effect, a roulette table.

Professor Piet Hein van der Graaf of the Leiden Academic Center for Drug Research (LACDR) and colleagues at Pfizer have shown that the likelihood of success for a new drug increases substantially when, at an early stage of development, three pillars of efficacy can be demonstrated: brain

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[11] European Commission, *Guideline on the Summary of Product Characteristics (SmPC)*, Revision 2, in *The Rules Governing Medicinal Products in the European Union*, Vol. 2C (Brussels, 2009).

[12] D. A. Spyker et al., "Assessment and Reporting of Clinical Pharmacology Information in Drug Labeling," *Clinical Pharmacology & Therapeutics* 67, no. 3 (2000): 196–200.

[13] C. Hsieh et al., "Clinical Pharmacology Considerations of Orphan versus Nonorphan New Drugs and Biologics Approved by the U.S. FDA between 2017 and 2019," *Clinical and Translational Science* 15, no. 12 (2022): 2780–2791.

[14] A. M. Bailey et al., "Labeling of Concurrent Intrinsic and Extrinsic Factors Influencing Pharmacokinetics in New Drug Approvals from 2019 to 2023," *Clinical Pharmacology & Therapeutics* 117, no. 2 (2025): 370–380.

penetration, target binding, and functional effect.[15] That is precisely what our work at CHDR has focused on: making this entire chain visible through a coherent clinical-pharmacological framework, illustrated at the front of the booklet. For this purpose, we developed a systematic model that, as it were, follows every step a drug must take before it can do what it is meant to do: produce a pharmacological effect at the right site that improves a disease process. Because this framework essentially represents the blueprint of both my career and CHDR's working method, I would like to walk you through it at an easy pace.

The action of a drug begins with its administration. Its absorption into the body depends on formulation, route, and dosage, and these in turn influence every subsequent step: distribution across tissues, passage through the blood–brain barrier, binding to the neurobiological target, and ultimately the clinical effect. Since brain concentrations in humans are not easily measurable, cerebrospinal fluid can be used as an approximation. Through the circulation, the compound also reaches other organs, where side effects may arise. Sometimes receptor or enzyme binding can be demonstrated directly using imaging techniques such as PET or MRI. When the drug binds, it alters the function of those receptors or enzymes, which in turn affects physiological processes and ultimately leads to clinical outcomes – improvements in disease symptoms or the emergence of adverse effects.

Each link in this chain from absorption to effect requires its own methods of measurement – from determining concentrations in body fluids to identifying biomarkers of physiological responses and surrogate measures of clinical effects.[16] In essence, CHDR is devoted to mapping out these steps and connecting them to one another.

This systematic analysis – from administration through distribution to effect – forms, in the words of the FDA, 'the

[15] P. Morgan et al., "Can the Flow of Medicines Be Improved? Fundamental Pharmacokinetic and Pharmacological Principles toward Improving Phase II Survival," *Drug Discovery Today* 17, nos. 9–10 (2012): 419–424.

[16] A. F. Cohen et al., "The Use of Biomarkers in Human Pharmacology (Phase I) Studies," *Annual Review of Pharmacology and Toxicology* 55 (2015): 55–74.

cornerstone of drug development.' [17] This applies especially to rare diseases, where large trials are impossible. But in fact, this holds for every drug. Regulatory authorities increasingly recognize that evidence of efficacy need not come solely from large randomized studies. The new ICH M15 guideline on *Model-Informed Drug Development* recognizes that effectiveness can also be supported by systematically modelling how a compound moves through the body, reaches its target, and influences disease processes.[18]

The efficacy of an orphan drug therefore no longer needs to be inferred from average clinical effects in large populations, but from a coherent picture of the pharmacological chain through which the compound acts. This aligns perfectly with our clinical-pharmacological framework.

Later I will show that this framework is not only useful for the development of orphan drugs, but also for the treatment of individual patients in the consultation room – and that physicians today, unfortunately, are still insufficiently trained to recognize and guide each step in this process.

One important reason for this is that our framework of absorption, distribution, binding, and effect in practice forms a patchwork of separate domains. Each step – each patch – belongs to its own area of scientific attention, which medical education often fails to illuminate adequately.

You can therefore also regard this framework as a chain of disciplines that are, in fact, connected *through* the drug itself. For just as the neurosciences have branched into disciplines and subspecialties, so too did medical and pharmaceutical sciences drift further apart during the last century. When CHDR was founded in the 1980s by Douwe Breimer and Adam Cohen, drug studies in healthy volunteers were conducted in separate institutes, by pharmacists with little medical involvement, physicians with limited pharmacological background, and

[17] Bashaw, E. D., Huang, S.-M., Coté, T. R., Pariser, A. R., Garnett, C. E., Burckart, G., Zhang, L., Men, A. Y., Le, C. D., Charlab, R., Gobburu, J. V., & Lesko, L. J. (2011). Clinical pharmacology as a cornerstone of orphan drug development. Nature Reviews Drug Discovery, 10(11), 795–796.

[18] International Council for Harmonisation (ICH), *ICH M15 Guideline: General Principles for Model-Informed Drug Development* (Draft, Step 2b) (Amsterdam: European Medicines Agency, November 2024).

psychologists with little of either.

That independence has never entirely disappeared, but CHDR was conceived as an attempt to build a single workshop where all those experts could conduct drug research together. Our framework shows how these domains of knowledge are connected through the drug. Kinetics – absorption and distribution – falls primarily within the domain of pharmacists and biopharmaceutical scientists. Dynamics – the site of action and the functional effect – are measured by neurophysiologists, neuropsychologists, or neuroendocrinologists. Physicians and biomedical scientists can demonstrate what the compound does to pathophysiology and disease.

At the same time, our framework also makes clear that the drug does not act solely on the central nervous system, but also on the autonomic nervous system, through which it can influence the cardiovascular system, the gastrointestinal tract, or the pupils.

Drug development depends on collaboration between diverse areas of expertise, all connected through the compound. True insight only arises when these domains can be brought together into a single pattern. For that purpose, we use models that describe what the body does to the drug – *pharmacokinetics* or PK – and, conversely, what the drug does to the body – *pharmacodynamics* or PD. By linking kinetics and dynamics, PK/PD modelers can relate the full spectrum of doses, concentrations, and patient characteristics to the resulting effects. Preclinical data from animal studies can likewise be integrated into this pattern. In this way, the drug becomes the lens that focuses the colourful spectrum of specialized knowledge into a clear and predictable image.

That is precisely the intention of ICH M15 as well: not to collect information about kinetics, target binding, and functional effect as separate outcomes, but to integrate them into a single model – *Model-Informed Drug Development*. What the guideline does *not* explain is how to do this in practice: how to measure tissue uptake, target binding, and system response, and how to relate them meaningfully to clinical efficacy or side effects. Each link in the chain belongs to its own scientific domain, with its own instruments and methods.

That brings me from the drug to test development. I will begin with a few

glimpses of the problem. In the 1980s and early 1990s, CHDR was still small. We conducted bespoke studies, often in collaboration with colleagues from industry, LACDR, and LUMC. Each sponsor or researcher would bring their own preferred test. Sometimes this led to rather creative gymnastics – such as parachute trousers hanging from the ceiling, so that patients with hyperekplexia would not injure themselves during their extreme startle reactions.[19] This approach worked, but it was slow and fragmented, and each time we had to find a way to align the diverse methods that collaborators brought with them into coherent dose-dependent and PK/PD relationships.

That heterogeneity was by no means a Leiden peculiarity. In the international literature on drug research in healthy volunteers, hundreds of different tests appeared – each with its own way of measuring and interpreting – making results difficult to compare. To make sense of this diversity, we developed a deliberately simple system – 'a brutally simple meta-analysis,' as one reviewer called it – in which we grouped comparable methods so that the sample size per test cluster became large enough to reveal dose–response relationships.[20] That formed the basis for what later became the NeuroCart: a compact and repeatable test battery that brings together the most sensitive pharmacodynamic measurements – regardless of their neuroscientific origin.

The versatility of the NeuroCart not only opens many windows onto the brain, but also provides an open, practical approach for integrating new technologies – from pain assessments and brain stimulation to neuroimaging. Its real strength, however, lies in efficiency: all tests are standardized and most can be repeated frequently, making it possible to relate them closely to changing concentrations and doses of a drug through PK/PD modelling. As a result, a NeuroCart study does not produce a colourful collage of isolated datapoints, but a coherent pattern of

[19] M. A. Tijssen et al., "The Effects of Clonazepam and Vigabatrin in Hyperekplexia," *Journal of the Neurological Sciences* 149, no. 1 (1997): 63–67.
[20] J. M. A. van Gerven, "Functional Measurements of Central Nervous System Drug Effects in Early Human Drug Development," in G. Nomikos and D. Feltner (eds.), *Translational Medicine in CNS Drug Development* (Amsterdam: Elsevier, 2019), 39–61 (*Handbook of Behavioral Neuroscience*, Vol. 29)

relationships – linking absorption and distribution, via (indirect) indications of brain penetration and target interaction, all the way to physiological and clinically relevant effects.[21]

Earlier, I described the drug as a lens that focuses a multicoloured spectrum of effects. The NeuroCart functions more like a prism: it separates that beam into an orderly pattern that allows us to compare compounds and make rational decisions – about dosing, about follow-up studies, and ultimately about clinical use in patients.

The lesson from those early years was simple and lasting: one gains less insight from ever more specialized tests than from the right combination of instruments – carefully chosen for their sensitivity to different mechanisms of action *and* their practical repeatability in humans.

By focusing on coherence rather than specialization, we created a framework that accelerates early development and prepares the translation to the clinic – precisely the connection at the heart of clinical pharmacology.

With this image of connection and profiling in mind, I would like to pause briefly on two other domains in which coherence has proved equally crucial: organization and education.

First, the organization. A research institute such as CHDR is called a *centre* for good reason. The development of a neuro- or psychopharmaceutical requires the integration of diverse forms of expertise – from formulation to effect measurement. The NeuroCart is a good example of this: it is composed of tests developed by scientists from different disciplines. The same breadth is reflected in our organization. Within the CNS group, physicians, psychologists, pharmacists, modellers, nurses, engineers, and data specialists work together every day – usually in collaboration with academic and industrial partners.

That this does not descend into chaos rests on a clear organizational framework which, in a sense, mirrors our clinical-pharmacological approach. The drug is prepared, administered, measured, and analyzed according to a single system – from

[21] G. J. Groeneveld, J. L. Hay, and J. M. van Gerven, "Measuring Blood–Brain Barrier Penetration Using the NeuroCart, a CNS Test Battery," *Drug Discovery Today: Technologies* 20 (2016): 27–34.

administration to effect assessment – in which each step connects seamlessly to the next, thanks to the collaboration of specialists who can take over and complement one another's work effortlessly.

Multidisciplinary research is essential to follow the pathway of a drug step by step, but genuine insight arises only when those disciplines work together coherently. That requires not only coordination on the work floor, but also oversight and perspective at a higher level. This is why CHDR has always maintained a broadly composed Scientific Advisory Board. Every new protocol was discussed there in light of previous studies with the same compound, summarized in the *Investigator's Brochure* (IB). The IB brings together all separate preclinical and clinical studies in a single document. The result is a kaleidoscope of study data, from which each reader must construct a coherent picture.

To make the dose–effect pattern across all these studies more transparent, we developed the IB-DeRisk method. The principle is, once again, brutally simple. Each study with a compound yields a set of doses, concentrations, and effects – across all species or human populations in which it has been tested. These effects are colour-coded: from light blue for purely pharmacological changes, through green for desired functional effects, to yellow, orange, and red as adverse effects become more severe.

When these data are sorted by dose or concentration, a single overview emerges that shows at a glance whether the dose–effect relationships between species are translatable and predictable – and thus likely also to apply to humans – and which doses form the green, therapeutically active range. A compound that displays comparable dose–response curves across all those models no longer produces a kaleidoscopic blur of colours, but a clear rainbow – from blue-green to orange-red.

The IB-DeRisk charts enable in-depth discussions among advisors and team members from different disciplines – and also with sponsors. They contribute greatly to informative *and* safe phase-I studies. The method has also proved to be a powerful educational tool. Research by Jeroen van Smeden, CHDR's Director of Education, showed that even inexperienced clinical pharmacologists, using only a blinded IB-DeRisk analysis, were able to recognize the high-risk concentration–effect patterns of notorious compounds such as BIA 10-2474

and TGN 1412.[22] Such compounds caused disastrous reactions at other institutions during their first administration – precisely because of a lack of insight into the dose–response relationship. Governmental bodies such as the EMA and the CCMO have also shown interest in the IB-DeRisk approach.[23] The method is now being further automated in collaboration with the CCMO and TNO. This growing interest shows that creating oversight within a multidisciplinary process is important not only for researchers but also for regulators. An integrated and verifiable quality system therefore forms one of CHDR's strongest pillars – essential for reliable data, effective collaboration, and the training of new researchers.

From this conviction, I devoted the final ten years of my career to promoting coherence and quality (among other roles) as chair of the CCMO, the Central Committee on Research Involving Human Subjects. During that period, the pressure to develop therapies more rapidly increased, while requirements for privacy and transparency became ever stricter. This demanded a better balance between speed and diligence. Because CHDR was built on a foundation of quality, we were able to use the legal pressures to strengthen the organization further. For many academic research institutions, this was not the case. That is why we – both at CHDR and at the CCMO – tried to show researchers that regulation may not always make research easier or more enjoyable, but it *does* make it better: at CHDR by showing partners how detailed procedures and agreements can actually make research more efficient; and at the CCMO by using review as a quality and learning instrument for applicants, not merely as a form of control.

I take that conviction with me into my new role as chair of the medical-ethical review committees at Amsterdam UMC, and possibly also of the NedMEC in Utrecht. I

[22] A. F. Cohen, J. van Smeden, and D. J. Webb, "De-Risking Clinical Trials: The BIAL Phase I Trial in Foresight," *Clinical Pharmacology & Therapeutics* 111, no. 2 (2022): 362–365.

[23] J. M. A. van Gerven and M. Bonelli, "Commentary on the EMA Guideline on Strategies to Identify and Mitigate Risks for First-in-Human and Early Clinical Trials with Investigational Medicinal Products (EMEA/CHMP/SWP/28367/07 Rev. 1)," *British Journal of Clinical Pharmacology* 84, no. 7 (2018): 1401–1409

want to continue working on that connection between researchers and regulators – not merely to supervise or judge, but to demonstrate that the quality of academic research largely arises from multidisciplinary collaboration.

The success of collaboration ultimately depends on how we educate new researchers, clinicians, and regulators. Unfamiliarity breeds indifference: those who do not understand one another's work are less inclined to appreciate it. For everyone working with medicines, a shared framework is therefore indispensable – a framework in which the development of new treatments goes hand in hand with the optimization of therapy in individual patients, step by step within a clinical-pharmacological model.

Such a binding framework does not arise by itself. Researchers, practitioners, and regulators all work within their own patches, even when they recognize the need for collaboration. In that light, it is disappointing that earlier attempts to create a joint training programme for everyone involved in drug research have failed – not out of unwillingness, but because of the shortsightedness of a system that gives few people an incentive to look beyond their own border of the patchwork.

I therefore call upon all relevant organizations to educate their new generation of scientists, physicians, and regulators within a coherent framework such as the ICH M15 guideline – or our own clinical – pharmacological model similar to it.

CHDR has always taken a leading role in this respect. If I am not mistaken, it remains the largest training site of clinical pharmacologists in the Netherlands – and certainly the only CRO with a full-time Director of Education and Dean. With the Teaching Resource Centre Pharmacology, we have developed a digital platform with a unified visual language that integrates pharmacology, pharmacotherapy, and clinical practice.[24] I will not have time to present this in detail, but I do want to mention that students from all over the world are using the free TRC app to learn that pharmacotherapy is not only about *which* condition a drug treats, but also *how* – and *in whom*.

[24] E. A. Dubois et al., "Integratie van Onderwijs in Farmacologie en Farmacotherapie in het Leids Geneeskundecurriculum," *Nederlands Tijdschrift voor Geneeskunde* 148, no. 4 (2004): 194–199.

For medical specialists, we expanded on our clinical-pharmacological framework with the advanced six-step method, which teaches physicians to follow the journey of a drug from administration to effect.[25] This helps them better understand why a drug may fail to work or cause side effects. When the number needed to treat (NNT) or to harm (NNH) is ten, that understanding matters far more to the ninety percent who *do not* benefit than to the few who happen to do so.

In this way, education in pharmacotherapy itself can become a model in action – an exercise in connecting domains of knowledge along the same chain that the drug itself follows: from administration based on pharmacological properties, through monitoring of tissue concentrations and biomarkers, to the measurement of clinical efficacy.

I hope to have sketched for you a kaleidoscopic yet coherent picture: from a century of neuroscientific fragmentation toward integration around the drug – from test battery to effect profile, from framework to organization, from brutally simple data reviews to regulatory oversight, and from educational system to individual therapy. The neurosciences provide a colourful kaleidoscope of data which – through the lens of the drug – are focused into a clear image of concentration-dependent effects. That image is then, with prismatic instruments such as NeuroCart, IB-DeRisk, and TRC, dispersed again into an interpretable spectrum.

Many of you would gladly forgive me for stopping here, Ladies & Gentlemen. Yet I would like to take you briefly into the final part of my career: philosophy. Philosophers of science have long reflected on the inevitable differentiation of the sciences. My story has shown how widely the neurosciences have branched out – but also that integration around a single theme, the drug, can yield new insight and greater coherence. In practice, however, that very integration proves to be the most difficult. Why is it that we cannot, even within the neurosciences, arrive at a single,

[25] G. A. Rongen, P. Marquet, and J. M. A. van Gerven, "The Scientific Basis of Rational Prescribing: A Guide to Precision Clinical Pharmacology Based on the WHO 6-Step Method," *European Journal of Clinical Pharmacology* 77, no. 1 (2020): 1–14, https://doi.org/10.1007/s00228-020-03044-2

comprehensive model of the brain? This is seldom a matter of unwillingness – so perhaps something more fundamental stands in the way.

This is where the American philosopher Hilary Putnam comes into view. In the 1980s, drawing on logical theorems from model theory, he demonstrated that even a perfect theory can always have multiple, mutually different models that all satisfy the theory. Each model interprets the same set of rules in a different – but logically valid – way.[26] Logic itself, however, does not tell us which model is the right one. At the time, Putnam's model-theoretic argument was a shocking realization, for it meant that there is no fixed anchor connecting our descriptions or theories one-to-one with reality.

For the neurosciences, this implies that there will never be a single, all-encompassing model of the brain. But, as Hofmann inferred from his kaleidoscopic experience, different images can in fact complement one another and together reveal more than any single perspective ever could. The question is how we can *see* the coherence between models – and how we can distinguish it from illusion.

That realization, for me, forms the bridge between philosophy and science. If one comprehensive model is in principle unattainable, then the task of the scientist shifts. She need no longer search for a single true model, but for ways to connect separate models so that together they form a coherent pattern.

In my philosophical work, I have explored one such direction within model theory: connection through shared structures – so-called partial isomorphisms. Different models can share elements of truth that remain valid within each individual sub-model. These shared elements form bridges between divergent descriptions of reality and together constitute a network that reflects our theories of the brain more fully than any isolated fragment could.

This idea – that truth does not reside in any single model, but in the coherence among them – has guided my scientific work as well. The drug itself can serve as such a shared structure: a bridge between the

[26] Hilary Putnam, "Models and Reality," *Journal of Symbolic Logic* 45, no. 3 (September 1980): 464–482.

Hilary Putnam, *Reason, Truth and History* (Cambridge, MA: Cambridge University Press, 1981), 49–74

pharmacological, the neurophysiological, and the biopsychosocial model. Each time a concentration-dependent effect holds simultaneously across all these domains, an overlapping zone of shared truth emerges. There, at the intersections of effects, measurements, and models, coherence becomes visible – and it is precisely there, ladies and gentlemen, that philosophy and pharmacology meet: in the search for shared structures within the kaleidoscopic brain.

Philosophy has taught me two things. First, that the coherence in which I have so long believed is, in principle, impossible. Strangely enough, that offers some understanding for all the disagreements I have encountered – and a measure of comfort for my own failed attempts to resolve them.

Second, I learned that coherence is not self-evident, but it *is* attainable – provided we do not seek it in one grand, uniform picture, but in recognizing and cultivating the overlapping structures between partial models. We should neither blend all our coloured ideas into a single shade, nor stitch them together uncritically – but discover the pattern that emerges when they complement one another.

That is precisely what neuropsychopharmacology can – and, in my view, must – do. By following the drug from administration to effect, by linking concentrations to functions and functions to experiences, we reveal shared structures along which disciplines can meet. The drug thus becomes both the lens and the framework: it focuses knowledge and connects the neuroscientific disciplines.

If we anchor this approach in science, organization, regulation, and education, then – despite all our differing perspectives – we can still tell a single, coherent story: not a story of one correct image, but of an illuminating network of overlapping truths.

That is my plea on saying farewell to you all: seek insight in shared patterns. Keep opening ever new windows for one another onto the same wondrous, kaleidoscopic brain.

This was my final lecture, ladies and gentlemen – and I would have done violence to myself if I had managed to finish on time. Still, I will take a few more minutes to thank as many people as possible for a wonderful time in Leiden.

Of course, I begin with Professors Douwe Breimer and Adam Cohen, to whom I will

always remain deeply grateful. Thirty-three years ago, they offered me a unique position as the first academic neurologist *and* clinical pharmacologist in the Netherlands. Strictly speaking, there was no vacancy in neurology at the time – so I must immediately thank the department head Raymond Roos, and his successor Jan Verschuuren, for deciding to hire me nonetheless. I spent more than twenty years working with wonderful neurologists and residents, from whom I never truly managed to say goodbye.

In 1994, I was appointed associate professor at the LACDR, even though at that point I still had everything to learn – from professors such as Meindert Danhof and Ron de Kloet, and from far too many other pharmacologists to name. My sincere thanks to all of you for your intellectual generosity and endless patience.

One of them was Professor Ron de Kloet, through whom I became increasingly involved with the Department of Psychiatry, where – thanks to the late professor Frans Zitman – my strategic chair was established. His successors Bert van Hemert, and later Robert Vermeiren and Nic van der Wee, have always continued to support me. With Bert, I also shared a fascination for philosophy, and together with him, as secretary, I took my first tentative steps in oversight – as chair of the Scientific Advisory Board of the National Epilepsy Fund.

Around the year 2000, I began joining various national and international advisory bodies – usually because Adam didn't feel like doing it himself. In 2011, that led to my membership of the CCMO, where I was appointed vice-chair in 2013 and chair in 2016. At the CCMO symposium last May, I already said farewell to all the committee members and staff, but I will remain deeply grateful for everything I learned there. I hope I will be able to work just as pleasantly and productively with my new colleagues of the Medical Ethics Review Committees in Amsterdam and Utrecht.

During all the years at the CCMO, I was fortunate to remain employed at CHDR, and for that I am especially grateful to Professors Adam Cohen and his successors Koos Burggraaf and Geert Jan Groeneveld. It allowed me to keep my feet firmly in the clay of research, while maintaining enough distance to gradually gain broader perspective and deeper insight.

I want to thank in particular Professor Geert Jan Groeneveld and Dr. Philip

Kremer, and above all Dr. Gabriel Jacobs, who have taken clinical neuropharmacology and psychopharmacology at CHDR to a higher level after my departure. Dr. Saco de Visser – my 'last PhD student,' as he likes to call himself – I wish all the best in his next step in Amsterdam in the field of drug development. This brief expression of thanks does not do them justice – but then, friends do not always need that. The same goes for many others. Professor Robert Rissmann, and especially his successor Dr. Jeroen van Smeden, have turned CHDR, after its enthusiastic early years, into an internationally recognized institute for clinical pharmacology. I have already described how difficult it is to develop cross-disciplinary education, and we owe enormous appreciation to Jeroen for his tireless, selfless efforts to make this possible through educational tools like TRC and IB-DeRisk.

All of this, of course, was only possible thanks to the talent and dedication of far too many PhD students to name – and of all the measurement assistants, nurses, and other staff who make CHDR 'the best f**ing CNS CRO in the world,' as one American sponsor once put it bluntly.

The reunited CNS group will undoubtedly continue to conduct unique academic studies in the future. I would especially like to mention the pioneering pharmaco-MRI research we were able to establish with Professor Serge Rombouts and Dr. Jeroen van der Grond, with the support of Professor Mark van Buchem from the Department of Radiology. Nor can I fail to mention the many years of collaboration with Professor Albert Dahan.

Countless other fellow researchers and inspiring students I can only thank in thought – otherwise, there will be no time left for the reception. Before I close, however, I would like to thank Alice Meijer and Helma Nederend, and their colleagues, for organizing this unforgettable farewell – and again Gabriel, Geert Jan, and all the speakers who made this afternoon's symposium such a special occasion.

I end with the most important people in my life: my dearest wife Patricia; our wonderful sons Peter, Marinus, and Jurriaan; their lovely partners and our little Otis and his even smaller brother – and all our dear family and friends, who make life so incredibly colourful.

I have spoken.

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