Dilemmas in Science: What, Why, and How

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Knowledge in Ferment

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Dilemmas in Science, Scholarship and Society

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Preface

Dilemmas, fundamental controversies, basic oppositions between methods and approaches, occur in all fields of science and scholarship. Often dilemmas arise at the interface where science and society meet, or whenever several sciences or disciplines clash. The paradox of dilemmas is that although one might prefer to do without them, they are nevertheless indispensable. Without dilemmas progress in science and scholarship would be unthinkable. New paradigms come into existence and compete with the old for acceptance. Thus, by inciting researchers to make new efforts and pose new questions, dilemmas reveal new insights and sustain the ferment of knowledge.

As the Rector Magnificus of Leiden University for six years, from 2001 to 2007, Professor Douwe Breimer devoted his great talents and his best endeavours to developing and improving teaching and research inside and outside Leiden. As Professor of Pharmacology in Leiden from 1975, of Pharmacology and Pharmacotherapy from 1981, Breimer was the architect of, first, the Center for Biopharmaceutical Sciences (1983), then the Center for Human Drug Research (1987) and finally the research school, the Leiden/Amsterdam Center for Drug Research (1992). In 1984 he became Dean of the Faculty of Mathematics and Natural Sciences. Breimer's meritorious services to scientific research and to the organisation and development of science have been recognised in the seven honorary doctorates which he has received from universities all

over the world. But as Rector Magnificus, Douwe Breimer has been much more than the champion of the natural and life sciences, for he has also upheld Leiden's pre-eminence in the humanities, jurisprudence and the social and behavioural sciences. As a scientist, an administrator and especially as Rector Magnificus Breimer has been accustomed to act with circumspection, but also with decisive vigour. He has always shown himself to be one of the *esprits préparés* of Louis Pasteur's dictum, 'Le hasard ne favorise que les esprits préparés', a saying very dear to his heart. But he is also the embodiment of a proverb in his own mother-tongue, Frisian, 'Sizzen is neat, mar dwaen is in ding' (talk is nothing, but doing is something). He always was, and is, a man with style.

During his rectorship Douwe Breimer has enjoyed the deep respect and warm sympathy of the whole University. The University continues to regard him with pride and admiration. On his retirement as Rector Magnificus his friends and colleagues wished to demonstrate their gratitude by offering him this volume of studies. They have chosen as its theme 'Knowledge in ferment: dilemmas in science, scholarship and society'. In the word 'ferment' one may detect an allusion to a phenomenon in Breimer's own field of study; but it also refers to the catalytic role that dilemmas play in the development of science and scholarship. Colleagues from all Faculties and many departments of the University have contributed with enthusiasm to this volume. Authors and editors offer it to Douwe Breimer as a tribute of their gratitude, respect and friendship.

Leiden, 8 February 2007

Adriaan in 't Groen
Henk Jan de Jonge
Eduard Klasen
Hilje Papma
Piet van Slooten
Editors

To Douwe Breimer

on the occasion of his retirement as Rector Magnificus
of Leiden University
after a six-year term of office (2001-2007).
During these years he has inspired the University through
the example of his exceptional scientific achievements and his ideal
of the university
as promoter of welfare, well-being and culture.

He has exercised his office with unflagging energy, uncontested authority,
a rigorous insistence on the highest academic standards,
the wisdom of his judgement and experience,
his profound humanity
and grand style.

Introduction: Dilemmas in science: what, why, and how

James W. McAllister

Dilemmas are important turning points in the development of science and in the experience of scientists. They probably create more perplexity and even distress for scientists than any other predicament. If only for this reason, it is worthwhile attempting to understand what dilemmas are, why they occur, and how they can be resolved. In this introduction, I develop a concept of scientific dilemmas as conflicts between the epistemic values acknowledged by scientists, for which no wholly satisfactory resolution is available. This means that scientific dilemmas resemble moral dilemmas in important respects, and differ from scientific controversies. After having explained what features of science make it possible for scientific dilemmas to arise, I give an example of scientific dilemma in the development of quantum physics. I conclude by arguing that the practical resolution of scientific dilemmas often depends on the emotional responses of scientists to the epistemic values in conflict.

Controversies and Dilemmas

In order to clarify the nature of scientific dilemmas, it is useful to review in what respects they differ from scientific controversies and in what regards they resemble better-known dilemmas in other spheres. By doing so, we will be able to judge what is common to dilemmas of all kinds and what makes a dilemma specifically scientific.

A scientific controversy is a dispute arising from a difficult choice

between incompatible beliefs. During a controversy, adherents of each of the alternative beliefs adduce arguments and empirical evidence in its support. In due course, the arguments and evidence for all but one of the conflicting beliefs come to be regarded as mistaken or as having been interpreted incorrectly, while the remaining belief is accepted as correct. Occasionally, the belief that is eventually adopted is not one that sparked the controversy, but was formulated at a later stage, perhaps in the effort to combine insights of different competing beliefs. Nonetheless, at the closure of a controversy, one belief is accepted as correct while beliefs incompatible with it are rejected.

Controversies are a routine occurrence in science. Scientific controversies may hinge on various issues: what the empirical data indicate, which of two theories is superior, what the explanation of an effect is, and so on. A famous controversy occurred in cosmology between adherents of the big-bang and the steady-state theories of the universe from around 1940 to 1965. The big-bang theory prevailed in this controversy, largely on the strength of logical considerations as well as of the great expansion of the empirical basis of cosmology. Another controversy occurred in palaeontology between those who believed that the mass extinctions at the end of the Cretaceous period were due to an asteroid impact and those who attributed them to volcanic eruptions. It appears that this controversy, which started around 1980, has now been resolved in favour of the asteroid hypothesis.[1]

Dilemmas, by contrast, are cases of conflicting obligations. A person caught in a dilemma has an obligation to perform two or more actions that are incompatible. In a dilemma, a person seems condemned to fall short of what is required: irrespective of the choice that he or she makes, some obligation will be violated. Whereas controversies generate divisions between different participants, dilemmas give rise to intellectual and emotional tensions within each participant.

The concept of dilemma occurs prominently in two areas of scholarly inquiry: game theory and moral philosophy. The prisoner's dilemma in game theory is in many respects the archetype. It arises in a two-player game in which each player must decide whether to cooperate with the other player or to defect from the implied pact between them. The optimal outcome for the two players combined would be attained if both players cooperated. However, irrespective of the other player's actions, each player can improve his or her own outcome by defecting. The

dilemma arises because it is not possible to conform both to the dictates of individual rationality, which suggest that a player defect, and to those of group rationality, which suggest that he or she cooperate. Each possible decision is good in some respects but poor in others – a point made in the technical language of game theory by the statement that the Pareto optimum and the Nash equilibrium do not coincide.[2]

The dilemmas discussed in moral philosophy involve conflicts between moral requirements. Some moral dilemmas are caused by the impossibility of discharging distinct obligations. An example is a situation in which telling the truth conflicts with preventing harm. Other moral dilemmas arise because contingent features of the world do not allow us to discharge a single precept consistently or universally. For example, saving the life of one person may, because of contingent circumstances, necessitate letting another person die.

Some past philosophers thought that moral dilemmas were impossible, or even that the concept of moral dilemma was unintelligible. Immanuel Kant held that his moral monism prevented moral commitments from conflicting, for example, and utilitarian thinkers such as John Stuart Mill believed that any apparent dilemma between courses of action could be resolved by a more general application of the principle of utility. Most present-day philosophers, by contrast, accept that moral dilemmas occur. Dilemmas have their root in the structure of our moral systems. If our moral codes were axiomatic systems, in which each precept were a consequence, specification or application of a more general precept, any apparent clash between two precepts on one level could be resolved by consulting the precept from which they both followed. Instead, our moral codes do not form stable hierarchies, so there is no principled way to resolve all conflicts.

Any practical resolution of a moral dilemma, because it involves violating an ethical principle, leaves a moral residue, consisting typically of sentiments of regret, remorse, or guilt. Citing this phenomenon, Bernard Williams has argued that, in important respects, moral dilemmas resemble conflicts of desires more than conflicts of beliefs. When we accept just one of two conflicting beliefs, we reject the other belief wholeheartedly. There is no regret at losing a belief that we now regard as false. By contrast, when we act on one of two conflicting desires, the overridden desire is not rejected: it manifests itself in regret for what we miss. Our experience of moral dilemmas shares this feature.[3]

The Rise of Scientific Dilemmas

Among the domains in which moral dilemmas arise are scientific research and the application of scientific techniques. Biomedical science and health care are an example. When experiments are conducted with human or animal subjects, conflicts can arise between the interests of the subjects, the experimenters, science as an ideal institution, people with certain illnesses, the wider public, and other stakeholders. One of the most widely cited ethical frameworks in health care is that of Tom L. Beauchamp and James F. Childress, which centres on the four principles of respect for autonomy, beneficence, non-maleficence, and justice. Because they acknowledge a plurality of principles, Beauchamp and Childress implicitly allow that moral dilemmas occur. They therefore rightly emphasise the need to exercise individual judgement in health care decisions.[4]

Moral dilemmas also arise, of course, in the management of scientific institutions. For example, Max Planck worked to reach a succession of uncomfortable accommodations between political forces, scientific values, and his own world view during his stewardship of German science in the 1930s.[5]

However, alongside moral dilemmas such as these, scientists also face dilemmas of a different kind: specifically scientific dilemmas, caused by conflicts between epistemic values. Science acknowledges a system of values that is similar in structure to our moral codes. The practice of science is frequently described as having an overarching goal. This goal is usually formulated in terms of attaining truth, empirical adequacy, or practical applicability. In practice, however, scientists acknowledge a variety of epistemic values. These include predictive accuracy, completeness, consistency, simplicity, objectivity, intelligibility, tractability, metaphysical acceptability, and aesthetic merit. It is plausible to assume that many of these epistemic values are functionally related in some way to the goal of science. For example, if we formulate the goal of science as the attainment of truth, it sounds plausible to say that the value of logical consistency follows from that goal. In fact, however, the relation between the goal of science and individual epistemic values acknowledged by scientists is never precisely determined. Instead, the various epistemic values take on a life of their own: scientists attach importance to them irrespective of their relation to the goal of science and of their mutual

compatibility. In consequence, the system of epistemic values acknowledged by scientists, like our moral codes, contain a plurality of values that do not form a stable hierarchy.

In many cases, no conflict occurs between the epistemic values acknowledged by scientists: the pursuit of intelligibility may coincide with the pursuit of predictive accuracy. In other cases, however, these values pull in different directions: predictive accuracy may conflict with simplicity, for example, or simplicity with intelligibility. This is the origin of specifically scientific dilemmas.[6]

Whereas the obligations on scientists in a scientific dilemma arise from epistemic rather than from moral values, its structure parallels that of a moral dilemma: a scientist has an intellectual obligation to apply two or more methodological precepts that are incompatible. Any practical resolution of a scientific dilemma thus involves violating a methodological precept that scientists acknowledge as applying to them.

Scientific dilemmas have the following features, which are counterparts of aspects of moral dilemmas. First, scientific dilemmas, unlike mere controversies, do not consist primarily of a disagreement about matters of fact. Instead, they centre on methodological tensions. A scientific dilemma arises from the impossibility of simultaneously obeying all the rules of scientific procedure that are acknowledged to apply in a given situation. It is likely that different practical resolutions of a scientific dilemma will lead scientists also to adopt different beliefs about matters of fact, but that is not the crucial aspect of a scientific dilemma.

Second, participants in a scientific dilemma acknowledge that any possible practical resolution of it has disadvantages. These disadvantages stem from the fact that some applicable methodological precept is violated. This means that a scientific dilemma, like a moral dilemma but unlike a scientific controversy, admits no resolution that is satisfactory in all respects.

Third, because of this, a practical resolution of a scientific dilemma leaves a residue analogous to that which follows from moral dilemmas. The residue in scientific dilemmas usually falls short of the anguish that we experience in some moral cases: rather, it takes the form of epistemic dissatisfaction or a sense of lack of understanding. We may take the existence of this residue as indicating that an episode has constituted a scientific dilemma rather than merely a controversy: a scientist who has resolved a controversy may experience nothing other than self-

congratulation at having ascertained the facts, but the resolution of a true scientific dilemma does not afford such unalloyed satisfaction.

The idea that a scientific advance on one dimension may be accompanied by a retreat on another dimension was put forward by Thomas S. Kuhn. He suggested that scientific revolutions invariably involve losses in conceptual performance in some areas as well as gains in other areas – a phenomenon that later authors have dubbed 'Kuhn loss'. An instance of Kuhn loss creates a dilemma for the scientists involved in it, since any choice between the old and the new paradigms incurs some cost. Let us turn for an example to the transition from the Cartesian to the Newtonian account of the solar system. Newtonian celestial mechanics was superior to its Cartesian predecessor in many respects. However, it involved a loss of explanatory power in regard to certain features of the solar system. The Cartesian account was able to explain with ease the facts that the orbits of the planets lie in approximately the same plane, and that the planets orbit the sun in the same direction: these facts are consequences of the origin of the solar system in a vast vortex. By contrast, the Newtonian account regarded these facts as arbitrary initial conditions of the physical system, for which no explanation could be offered within the theory. A seventeenth-century natural philosopher who weighed this loss of explanatory power against the advantages of the Newtonian theory would have experienced a dilemma in theory choice.[7]

Dilemmas in Quantum Physics

If the concept of scientific dilemma has validity, then in order to identify examples of scientific dilemmas we must search for scientific advances that involved the violation of an acknowledged methodological precept for the sake of conforming to another precept.

The development of quantum theory in the 1920s and 1930s is a rich source of examples. Quantum theory was created in the attempt to account for experimental findings about some phenomena that had proved inexplicable to classical physical theories: black-body radiation, the photoelectric effect, and the absorption and emission spectra of atoms. However, quantum theory soon showed itself to be quite different from the theories of classical physics: it was indeterministic, portrayed the world in some respects as discontinuous, and did not lend itself to consistent visualisation. These features of the theory led to a dilemma

between the precept of accounting for empirical data and the precept of maintaining the style of theorising that had proved so successful in classical physics.

A particular manifestation of this dilemma pertained to the nature of the fundamental constituents of the physical world. Some experiments appeared to confirm both that electrons were particles and that electromagnetic radiation, including light, was a particle phenomenon; other experiments seemed to indicate both that electromagnetic radiation was a wave phenomenon and that electrons behaved as waves. A few experiments, such as the two-slit diffraction experiment, even provided support for both conclusions simultaneously. These outcomes meant that a conflict arose between three methodological precepts that had been in harmony in classical physics: the precept of formulating theories that have internal logical consistency, the precept of formulating theories that accord with empirical data, and the precept of visualising submicroscopic phenomena in classical terms. Physicists discovered that obeying any two of these precepts entailed violating the third. This predicament was often described by early quantum physicists as the wave/particle dilemma.[8]

On a more general level, the dilemma presented by quantum phenomena took the form of a conflict between the precepts of formulating theories that were deterministic and that provided visualisations of phenomena in classical terms on the one hand, and the precept of choosing the theories that best accorded with empirical data on the other. This dilemma split the physics community into two. One group, including Niels Bohr and Werner Heisenberg, judged the loss of determinism and visualisation a price worth paying for an empirically successful theory of subatomic phenomena. The other group, which included Albert Einstein and Erwin Schrödinger, acknowledged the empirical success of quantum theory but found the theory unacceptable in virtue of its violation of the classical precepts of theorising. Schrödinger was repelled especially by the abstractness of quantum theory: he strove to find a visualisation of the Schrödinger equation in classical terms, but it quickly emerged that none could be provided. By contrast, Einstein was displeased by the theory's indeterminism: for him the beauty of the world would be marred if God decided occurrences on the cast of a die.

Both groups could claim to be acting with justification. Bohr and Heisenberg followed well-established epistemic values in embracing the best-performing theory of subatomic phenomena available. But the other

group, too, could claim empirical support: the lesson of classical physics seemed to them that adherence to the principles of determinism and visualisation is crucial in the long term for scientific progress.

However, both groups also perceived the disadvantages of the practical resolution of the dilemma that they advocated. Bohr, Heisenberg, and other members of their group were not left unperturbed at the indeterminism and lack of visualisation of quantum theory: many of them found it unsettling not to be able to trust their classical intuitions in developing and applying physical theory. For instance, Bohr wrote that acceptance of quantum theory was made possible 'only by a conscious resignation of our usual demands for visualisation and causality'.[9] Einstein, Schrödinger, and like-minded physicists, for their part, recognised the disadvantage of rejecting the empirically best-performing theory of submicroscopic phenomena available. For example, Einstein accepted that quantum theory had demonstrated good empirical adequacy even as he resolved on balance to reject the theory. In the following passage, he formulates his objection in terms of an alleged incompleteness of quantum theory:

Experiments on interference made with particle rays have given a brilliant proof that the wave character of phenomena of motion as assumed by the theory does, really, correspond to the facts. In addition to this, the theory succeeded, easily, in demonstrating the statistical laws of the transition of a system from one quantum condition to another under the action of external forces, which, from the standpoint of classical mechanics, appears as a miracle .... In spite of this, however, I believe that the theory is apt to beguile us into error in our search for a uniform basis for physics, because, in my belief, it is an incomplete representation of real things .... The incompleteness of the representation is the outcome of the statistical nature ... of the laws.[10]

The participants thus acknowledged that none of the conceivable practical resolutions of the situation was ideal in all respects, and accepted the residue of epistemic dissatisfaction that would unavoidably follow. This acknowledgement and acceptance mark this case as a scientific dilemma rather than a simple controversy.

In the end, the dilemma was resolved in the way Bohr, Heisenberg, and their group advocated: by abandoning the classical precepts of theorising,

by deciding to base theory choice purely on empirical performance, and by accepting the concomitant loss of determinism and visualisation. For the specific wave/particle dilemma, this resolution entailed abandoning the classical terms of the discussion: the constituents of the physical world are neither classical particles nor waves, but rather radically new entities that may be termed 'quantum particles' or 'wavicles' and that have no precise counterpart in previous theories.

As this narrative shows, practical resolutions have now been found for some of the initial dilemmas of quantum theory. Nonetheless, the idea that quantum phenomena confront us with dilemmas remains a standard trope in present-day expositions of the theory. Physicists use it to remind students that quantum theory inaugurated an unprecedented phase in the development of physical science.[11]

The Role of Emotion in the Resolution of Dilemmas

How do scientists arrive at a practical resolution of a scientific dilemma? The crucial fact about scientific dilemmas is that they arise from a conflict between epistemic values. Any practical resolution of a dilemma violates an epistemic value. If epistemic values formed a stable hierarchy, it would be possible to adjudicate between them by appeal to some higher value. As we have seen, however, the epistemic values that scientists acknowledge do not form a stable hierarchy. Because of this, it is not obvious which epistemic value should be privileged in a dilemma.

The structure of scientific dilemmas means that they are not resolvable by algorithmic reasoning. Take the ideal of a rational calculator as a reference point. A rational calculator is a perfectly rational agent: it makes decisions by following all applicable instructions and taking account of all relevant information. A rational calculator is able to deal with a conflict between precepts only if it is provided with principles for adjudicating between the conflicting precepts. Since a dilemma is a situation in which such principles are absent, a rational calculator would grind to a halt in a true scientific dilemma: it would be unable to arrive at any practical resolution.

This suggests that, to the extent that scientists are able – albeit with a degree of conceptual unease – to reach a practical resolution of scientific dilemmas, their behaviour deviates from that of a rational calculator. It must be, instead, that scientists rely on some faculty to leapfrog the

obstacles that would halt the rational calculator. It is reasonable to conjecture that this faculty is a scientist's emotion system.

Work on emotions over the last twenty years has undermined the view that emotions are merely the antagonists of cognition and rationality. Instead, the view has gained ground that reliance on emotional responses is a necessary condition for making sound inferences and decisions in many circumstances. The contribution of the emotion system is most important for inferences and decisions of a practical nature where the relevant values and information are not complete or not consistent. A rational calculator is not able to reach a conclusion in such cases. A person's emotion system, however, is able to break the deadlock. The emotion system attributes salience to aspects of situations, enabling the decision-maker to overcome the incompleteness or inconsistency of the relevant values and information.

Since dilemmas are characterised by the inconsistency of values, we can expect emotions to play an important role in our reactions to them. There is strong evidence that emotional responses help determine the practical resolution of moral dilemmas. There is now a growing realisation that scientists' emotional responses play a similar role in the resolution of scientific dilemmas. Only by relying on their emotional responses can scientists adjudicate between two conflicting epistemic values when there are grounds for holding to both values and insufficient evidence for disqualifying either of them.[12]

The development of quantum physics in the 1920s and 1930s provides an illustration of the role of emotion. Bohr, Heisenberg, Einstein, and Schrödinger were confronted by the need to decide between epistemic values that were entrenched to a similar degree in the history of science: empirical adequacy, determinism, and visualisation. A rational calculator faced with the competing values would never resolve this dilemma: it was precisely the unavailability of higher principles that sparked it. The scientists involved were thus compelled to base their decisions to a large extent on their emotional responses to epistemic values and to theories.[13]

We thus see the exceptional place of scientific dilemmas in the practice of science: they constitute not only important turning points in the development of a discipline, but also the locus at which emotion necessarily enters scientific work.

Notes

1 On the controversy in cosmology, see Helge Kragh, *Cosmology and Controversy: The Historical Development of Two Theories of the Universe* (Princeton, N.J.: Princeton University Press, 1996); on that in palaeontology, see William Glen, ed., *The Mass-Extinction Debates: How Science Works in a Crisis* (Stanford, Cal.: Stanford University Press, 1994). Broader literature on scientific controversies includes H. Tristram Engelhardt, Jr., and Arthur L. Caplan, eds., *Scientific Controversies: Case Studies in the Resolution and Closure of Disputes in Science and Technology* (Cambridge: Cambridge University Press, 1987); Bruno Latour, *Science in Action: How to Follow Scientists and Engineers Through Society* (Milton Keynes: Open University Press, 1987) p. 21–62; and Peter Machamer, Marcello Pera, and Aristides Baltas, eds., *Scientific Controversies: Philosophical and Historical Perspectives* (New York: Oxford University Press, 2000).

2 On the prisoner's dilemma, see Robert Axelrod, *The Evolution of Cooperation* (New York: Basic Books, 1984).

3 Bernard Williams, 'Ethical Consistency' (1965), reprinted in Bernard Williams, *Problems of the Self: Philosophical Papers 1956–1972* (Cambridge: Cambridge University Press, 1973) p. 166–186. Some classic discussions are reprinted in Christopher W. Gowans, ed., *Moral Dilemmas* (New York: Oxford University Press, 1987). Popular examples are collected in Martin Cohen, *101 Ethical Dilemmas* (London: Routledge, 2003).

4 Hugh LaFollette and Niall Shanks, *Brute Science: Dilemmas of Animal Experimentation* (London: Routledge, 1996); Tom L. Beauchamp and James F. Childress, *Principles of Biomedical Ethics*, 5th ed. (New York: Oxford University Press, 2001).

5 John L. Heilbron, *The Dilemmas of an Upright Man: Max Planck as a Spokesman for German Science* (Berkeley: University of California Press, 1986).

6 The axiology of science is discussed by Larry Laudan, *Science and Values: The Aims of Science and Their Role in Scientific Debate* (Berkeley: University of California Press, 1984). I have treated the relation between empirical and aesthetic values in James W. McAllister, *Beauty and Revolution in Science* (Ithaca, N.Y.: Cornell University Press, 1996).

7 Thomas S. Kuhn, *The Structure of Scientific Revolutions*, 2nd ed. (Chicago, Ill.: University of Chicago Press, 1970) p. 99–100. On the Cartesian theory of the solar system, see E. J. Aiton, *The Vortex Theory of Planetary Motions* (London: Macdonald, 1972).

8 On the wave/particle dilemma, see Mara Beller, *Quantum Dialogue: The Making of a Revolution* (Chicago, Ill.: University of Chicago Press, 1999) p. 227–232.

9 Niels Bohr, *Atomic Theory and the Description of Nature* (Cambridge: Cambridge University Press, 1934) p. 108.

10 Albert Einstein, 'Physics and Reality', translated by Jean Piccard, *Journal of the Franklin Institute,* 221 (1936) p. 349–382, at p. 374; emphasis as in the original. For more discussion of the dilemmas of quantum physics, see McAllister, *Beauty and Revolution in Science* (cit. n. 6) p. 188–201.

11 An example is Andrew Whitaker, *Einstein, Bohr and the Quantum Dilemma: From Quantum Theory to Quantum Information*, 2nd ed. (Cambridge: Cambridge University Press, 2006).

12 Empirical evidence that the emotion system plays an important part in the consideration of moral dilemmas is presented by Joshua D. Greene, R. Brian Somerville, Leigh E. Nystrom, John M. Darley, and Jonathan D. Cohen, 'An fMRI Investigation of Emotional Engagement in Moral Judgment', *Science,* 293 (2001) p. 2105–2108. A wider philosophical discussion of the relation between emotions and moral dilemmas is developed by Patricia S. Greenspan, *Practical Guilt: Moral Dilemmas, Emotions, and Social Norms* (New York: Oxford University Press, 1995). I treat the roles of emotion in scientific practice in James W. McAllister, 'Emotion, Rationality,

and Decision Making in Science', in Petr Hájek, Luis Valdés-Villanueva, and Dag Westerståhl, eds., *Logic, Methodology and Philosophy of Science: Proceedings of the Twelfth International Congress* (London: King's College Publications, 2005) p. 559–576.

13 On the part played by emotion in the development of quantum physics, see Mara Beller, 'The Conceptual and the Anecdotal History of Quantum Mechanics', *Foundations of Physics,* 26 (1996) p. 545–557; Beller, *Quantum Dialogue* (op. cit. n. 8) p. 30–39.

1
Novel drug discovery – serendipity or design?

Meindert Danhof

Modern medicines are indispensable weapons in the war against (serious) disease. Not surprisingly, medicinal products play an integral and important role in our society. Yet, their availability and accessibility are not self-evident. For many serious disorders there are still no effective medicines available. Moreover, for those disorders where effective medicines do exist, loss of effectiveness over time is prevalent, as is amply illustrated by the worldwide development of resistance against anti-infective drugs. Finally, with time new diseases continue to develop. This underscores the need to continuously search for novel drugs and for novel concepts of drug treatment.

Another important problem is the lengthy and costly process of developing a new chemical or biological entity into an effective drug. In this respect development concerns the identification of the optimal dose of a new chemical entity and the demonstration of its efficacy and safety in clinical trials. At present, the development of a single new drug takes on average ten to twelve years, requiring an investment of approximately 1 billion Euros. Moreover, drug development is associated with high failure rates, with attrition as high as 92%. As a result, the cost of new medicines is very high. This may ultimately limit the access to important life-saving drugs to only select and privileged groups in our society or in the worst case may even preclude their development.

The above emphasises the need to advance research in the field of drug discovery and development. Specifically it will be essential to improve the

efficiency of this process both in terms of the number of novel drug molecules to be identified and the cost and duration of the development process. An intriguing question is how to approach this. Will we have to rely on the discovery of novel drugs by serendipity, in the course of biomedical research? Or will it become possible to design new drugs in dedicated investigations?

Diseases in search of drugs

The report *Priority medicines for Europe and the world* of the World Health Organization[1] analyses so-called 'pharmaceutical gaps' which affect society. In this analysis pharmaceutical gaps are identified as those diseases of major public health importance for which medicines either do not exist or are inadequate. The report analyses the total burden of disease in terms of disability adjusted life years (DALY's) using the WHO Global Burden of Disease Database. Data on the clinical efficacy of existing treatments is extracted from the Cochrane Database of Systematic Reviews as the most authoritative source of this information.

The WHO report identifies demographic changes as a major determinant of the expected burden of disease in the years to come. In the western world the population is ageing, with more people – especially women – living beyond 80 years. In the developing countries there is a sharp difference between Africa and other regions. In many African countries infectious disease (in particular HIV and AIDS) has a substantial impact in reducing life expectancy. In other regions, the rapid ageing of the population will lead to an increase not only in the number, but also in the proportion of the elderly in the population. Another trend is the rapid urbanisation taking place around the world. As a result of these trends, over the next thirty years there will be a demographic shift towards rapidly ageing populations in large cities, particularly in Asia, in Latin America and in some African countries. These demographic changes, which are very similar to the changes that we have experienced in the western world, will be marked by a continued increase in non-communicable chronic diseases worldwide.

The WHO analysis identifies 20 major diseases which account for nearly 60% of the global burden of disease. Using a variety of criteria, of which an in-depth discussion is beyond the scope of this article, the following diseases/conditions have been identified as the main disorders

where pharmaceutical gaps prevail: infectious diseases, mental and central nervous system conditions, cardiovascular diseases, (auto) immune disorders and cancer. This has led to the conclusion that innovation in drug discovery and development should focus primarily, albeit not exclusively, on these diseases.

In the WHO report, focus is not only on medicines for the treatment of disease, but ample attention is also paid to the prevention of life-threatening diseases. Specifically, the report identifies a number of preventable high-burden diseases as having pharmaceutical gaps. The most important are the secondary prevention of heart attack and stroke. Although for these diseases prevention is possible, through the use of a combination of effective medicines, in practice, for a variety of reasons, these drugs are not taken. The WHO report proposes to develop fixed-dose combinations as an approach to increase their use.

In addition to identifying priority diseases, the WHO report also reviews improved pharmaceutical delivery mechanisms for existing medicines. Medicines have to be administered to the patient to achieve maximal clinical benefit. The most commonly used delivery mechanisms are tablets or capsules for oral delivery. Over recent decades, a wide range of sustained release devices (such as patches for transdermal drug delivery) have been developed. At present such technologies are heavily under-utilised. Yet these technologies will be critically important to improve treatment in children and the elderly, and other areas where individualised dosing of medicines is imperative, such as patients with impaired liver or kidney functions, or patients with compromised immune systems. Finally, safety concerns may drive the need for targeting potent, but very toxic medicines (i.e. anti-cancer drugs, anti-viral drugs) to the pertinent site of action in the body rather exposing the whole body to the medicine.

The above underlines the wide range of diseases with an imminent need for novel drugs as well as the multi-faceted nature of the development of such drugs and the corresponding pharmaceutical products.

The high days of drug discovery

In his fascinating book *The rise and fall of modern medicine* James le Fanu[2] describes the unprecedented medical achievements and innovations in the

years following the Second World War. The book focuses on twelve decisive moments in medical history, which have been true landmarks in the development of effective treatments for human disease. It is very interesting to see how novel medicines have played a major and often decisive role in the vast majority of these developments. Specifically, four of these twelve decisive moments concern the discoveries of novel drugs *per se*: penicillin for infectious disease, cortisone for inflammatory disorders (i.e. rheumatoid arthritis, asthma), streptomycin for tuberculosis and chlorpromazine for psychiatric disorders (i.e. schizophrenia). Moreover, for the majority of the other breakthroughs, it holds that they have become possible only through the availability of novel drugs. For example, kidney transplantation would have been impossible without the development of cyclosporine as a drug to suppress rejection of the transplant in a controlled manner. The same applies for open-heart surgery, which was made possible by the development of synthetic opiates as anaesthetics, to provide cardiovascular stability. Likewise, the cure of childhood cancer relies entirely on the use of novel anti-cancer drugs. Finally, artificial ventilation of patients in intensive care, the prevention of stroke by the treatment of high blood pressure, the birth of test-tube babies and the treatment of peptic ulcers all depend on the use of novel effective and safe medicines. It is intriguing and remarkable to see how the vast majority of these drugs were discovered largely by serendipity, without much understanding of disease processes.

Drug discovery and development in perspective

At present, novel drugs are almost exclusively discovered and developed by the international pharmaceutical industry. Not surprisingly, over the years the pharmaceutical industry has largely determined the research agenda in drug innovation. In his book *In quest of tomorrow's medicines* Dr. Jürgen Drews,[3] formerly president of global research at Hoffman-La Roche, describes in an enlightening manner the development of the pharmaceutical industry and the pharmaceutical sciences in the nineteenth and twentieth century.

Briefly, the pharmaceutical industry arose from two sources. One is the aniline dye industry which evolved in the wake of the industrial manufacturing of town gas. The other is the traditional apothecary with its focus on medicinal plants.

Town gas was originally obtained from the carbonisation of hard coal. Over the years, the by-product of this process, coal tar, was discovered to contain many compounds which could not only be used as dyes in the textile industry, but which also served as a source of organic compounds for the rapidly developing field of synthetic organic chemistry. As a result, the aniline dye industry became an important source of new chemicals, including drugs. It is of interest to see that many well-established international pharmaceutical companies such as Bayer and Novartis indeed have their roots in the aniline dye industry.

Traditionally, apothecaries were institutions where prescriptions written by physicians were filled. With the rise of chemistry in the nineteenth century, a major shift occurred when the active ingredients from previously known medicinal plants were extracted and used as drugs. Well-known examples are the extraction of morphine from opium, caffeine from the coffee plant and quinine from the cinchona bark. In order to make these new substances available to a wide public, a number of apothecaries developed themselves into 'industrial' apothecaries or in other words, pharmaceutical firms. This led to the establishment of pharmaceutical companies which still exist today, such as Merck, Schering and Boehringer.

The development of chemistry in the nineteenth century was paralleled by the development of experimental pharmacology as a scientific discipline. The hallmark of this research was the systematic description of the effects of drugs on animals and isolated organs. Important theoretical concepts on dosage-effect relationships and other aspects of modern drug research originated directly from this work. It is fair to say that, in addition to the advances in organic chemistry, in particular the development of modern pharmacology has indeed been the cornerstone of modern drug discovery and development. The key factor was the interfacing of chemistry and pharmacology. Specifically, the study of the relationships between chemical structure and the binding of molecules to biological target proteins has been the key to the discovery of many new drugs. It was Sir James Black's discoveries, first of propranolol (which blocked the beta receptors in the heart, thus relieving the symptoms of angina) and then of cimetidine (which blocked the histamine receptor in the gut, thus reducing the amount of gastric secretions and allowing ulcers to heal) that led many to believe that the effects of drugs could be predicted on the basis of their chemical structure.[4,5] Up to the present

day, novel drug molecules are designed on the basis of the study of 'structure-activity relationships'.

The dearth of new drugs

Between 1960 and 1970 a sharp decline in the success of drug innovation occurred. While the number of new drugs marketed was running at around seventy per year throughout the 1960's, by 1970 this number was down to around 30 per year, a trend which continued in the years thereafter. Moreover, many of the new drugs marketed in the last decades were improvements to existing drugs, rather than truly innovative medicinal products. There are a number of explanations for this decline in drug innovation.

The most commonly mentioned explanation for the decline in drug innovation is the tightening of safety regulations in the aftermath of the thalidomide (Softenon®) disaster. As a result, initial toxicity testing of new chemical entities in animals needed to be conducted prior to first administration in man. Moreover, the results of extensive clinical trials in humans, demonstrating efficacy and safety, were mandatory before a drug could be approved for release to the general public. This made the entire process of drug innovation more time-consuming, complicated and expensive. Ultimately this resulted in the current situation where the development of a single new drug takes approximately 10-12 years, involving the investment of on average 1 billion Euros.

Another presumably much more important factor for the decline in drug innovation is the fact that up to the 1970's the process of drug discovery was based on the classical paradigm of synthesising novel chemical compounds which could then be investigated for their potential therapeutic effect. Sooner or later pharmaceutical companies would run out of new chemicals to be tested in this manner. Moreover, drug discovery focused on a limited number of only 500 specific targets.

Meanwhile, progress in molecular biology has opened new avenues to the understanding of the mechanisms of disease. In theory this yields the opportunity to design novel drugs which specifically interact with the disease process or, in other words, correct what is wrong. Yet research from the mid-1970's onwards has not produced many genuinely useful novel drugs. It is important to analyse what may have caused this lack of success.

Multiple interactions between drug molecules and biological systems

Drug effects result from multiple and complex interactions between drug molecules and various components of the biological system. Commonly, two kinds of processes which determine *in vivo* drug action are distinguished. These are referred to as pharmacokinetics and pharmacodynamics.

Pharmacokinetics concerns the processes of the uptake of drug molecules in the body, their distribution into peripheral tissues and their elimination. These processes govern the time course of the drug concentration at the site of action and thereby, indirectly, also the time course of the pharmacological response intensity. In recent years, research has much improved our knowledge of the molecular mechanisms involved in these processes. Although the absorption, distribution and elimination of drug molecules depend on their physicochemical properties (especially the size of the molecule and the lipid solubility), the functionality of transporters and metabolizing enzymes is an important factor. A drug transporter is a protein which specifically functions to transport drug molecules from one side of a biological membrane to the other. In recent years numerous specific drug transporters have been discovered, which may be operative at various levels of the disposition. Specifically, transporters may either enhance or restrict the absorption of drug molecules from the small intestine, their distribution into the brain and their elimination. An important factor is that the functionality of transporters may change over time, causing drug resistance. The most well-known example is multi drug resistance against cancer chemotherapy, which is caused by over-expression of the active efflux transporter P-glycoprotein.[6]

In addition to drug transporters, a wide array of drug metabolising enzymes has also been identified. The role of these enzymes is the breakdown of the often lipophilic drug molecules to facilitate their excretion. Drug metabolising enzymes, which are primarily localised in the small intestine and in the liver, may substantially reduce the amount of drug that ultimately enters the body upon oral administration. Moreover, for most drugs, after absorption these enzymes also determine the rate of elimination from the body.

Pharmacodynamics concerns the mechanisms that determine the

nature, the intensity and the duration of the drug effect. With the advances in molecular biology, research has much improved our understanding of the mechanisms of drug action. Briefly, pharmacodynamics involves the binding of the drug molecule to its biological target, the activation of this target, the transduction into the pharmacological effect and the homeostatic mechanisms which may be operative. The most common targets for drug molecules are receptors. Receptors are specific proteins which, after activation by drug molecules, alter the function of cells. Over the years numerous receptors and receptor subtypes have been identified. Transduction refers to the processes of target activation into a pharmacological response. Typically this involves the activation of a cascade of electrophysiological and/or biochemical events. Transduction may operate at widely different time scales ranging from milliseconds to hours or days. This may explain why drug effects may take a long time to develop, as is illustrated for antidepressants, where the therapeutic effect is not observed until several weeks after the initiation of treatment.

Another important factor that may influence the pharmacological effect is the presence of physiological control mechanisms which may counteract the drug effect. Such counter-regulatory control mechanisms may explain loss of efficacy (i.e. tolerance development) which is often observed in chronic treatment and rebound effects that may occur upon cessation of treatment. Last, but not least, pharmacodynamic interactions must also be considered for drugs which, due to lack of selectivity, act simultaneously on different targets.

The above observations show that drug effects result from the complex interactions of a variety of biological systems and processes. This makes the prediction of the drug effects in man and thereby the design of novel drugs a formidable challenge.

Inter-individual variability: the need for 'tailor-made' pharmacotherapy

The design of novel drugs is further complicated by the wide inter-individual variability that is often observed. This important topic was addressed by Douwe Breimer[7] in his inaugural lecture at Leiden University in 1976 entitled: *Farmacotherapie op maat* (*'Tailor-made Pharmacotherapy'*). In his lecture Breimer demonstrated that the clinical

response to drug administration varies widely among patients. Specifically, drugs may prove inactive in some patients but may be highly active or even toxic in others who are given the same dose. This implies that in practice drug therapy must often be individualised.

In theory, variability in drug response may result from variability in pharmacokinetics, variability in pharmacodynamics or a combination of both. In the meantime it has been convincingly demonstrated that variability in pharmacokinetics contributes substantially. Specifically, the rates at which the processes of drug absorption, distribution and elimination occur differ widely between individuals. As a result, the same dose of a given drug results in widely different concentrations, thus causing wide differences in the response. The observed differences in pharmacokinetics can often be reduced to inter-individual variability in the expression and function of transporters and/or drug metabolising enzymes. Much of this variability is caused by genetic factors. However other factors, such as diseases, differences in age and sex, interactions with other concomitantly taken drugs etc., are often contributory and should therefore also be taken into account.

In contrast to pharmacokinetics, much less is known about inter-individual variability in pharmacodynamics. Yet, beyond reasonable doubt, variability in pharmacodynamics contributes at least equally to the observed inter-individual differences in drug response. It is well established that drug response depends largely on the level of receptor expression in a given target. Receptor expression can vary widely between individuals due to genetic factors. Moreover, receptors are in a dynamic state which means that their expression and function can be either up-regulated or down-regulated, depending on the conditions. In the meantime, there is ample evidence that variability in receptor expression is indeed an important determinant of inter-individual variability in drug response. It seems likely that variability in the efficiency of transduction and homeostatic feedback mechanisms is an equally important factor.

The aforementioned observations show that inter-individual variability is intrinsically associated with drug treatment. This has major implications for the use in clinical practice. In the meantime genetic testing is beginning to be applied clinically to predict treatment response in individual patients. The most well-known examples are the treatment of breast cancer with traztuzumab (Herceptin®) and of chronic myeloid

leukaemia with imatinib (Gleevec®), where genetic testing is used to select patients with cancers that are sensitive to the drug.[8]

Given the enormous clinical implications, inter-individual variability in response has become a key factor in modern drug discovery and development. The prediction of individual variability in drug response contributes an additional major challenge to the rational design of novel drugs.

Tomorrow's drugs: targeted treatment solutions?

In the report *Pharma 2010: The threshold of innovation,* Steve Arlington[9] unfolds his vision on novel drug discovery and development in the years to come. The novel dimension in his proposed approach is the shift in emphasis from pharmacology to disease. Specifically, it is anticipated that future drug discovery and development will be underpinned by an understanding of the mechanism of the disease at the molecular level and as part of the integrated biological system. This redefining of pathology will result in the identification of specific disease subtypes and opens new avenues towards the identification of novel drug targets. Moreover it will also enable the identification of molecules that interact specifically with the disease process.

It is expected that the aforementioned approach will yield novel drugs for the treatment of individual patients with specific disease subtypes, rather than one-size-fits-all blockbuster drugs. This implies that in the future drug treatment will become increasingly individualised. Accordingly, in Steve Arlington's vision, in future the pharmaceutical industry will produce not just drugs, but 'targeted treatment solutions' which include in addition to the drug, diagnostic tests, monitoring devices and a wide range of services to support patients. In principle, such targeted treatment solutions should enable the implementation of highly individualised drug treatment in clinical practice. The recent experience with drugs like Herceptin® and Gleevec® illustrates that for serious, life-threatening disorders with a strong genetic component, this may indeed be a feasible option. Whether this is in general the case remains to be established.

Clearly, the development of targeted treatment solutions, with its emphasis on individualisation, requires innovative approaches to drug development.

Modelling and simulation

In the preceding paragraphs it has been shown that drug effects result from multiple interactions between drug molecules and various components of the biological system. Moreover, it has been demonstrated that there is often a considerable inter-individual variability in drug response. This makes the prediction of drug effects in individual patients a formidable challenge, and indeed complicates the design of novel chemical or biological entities as innovative drugs. As a result, most drugs as we know them today have been discovered largely by serendipity rather than by design. In recent years, however, modelling and simulation of biological systems are increasingly applied in drug research. An intriguing question is to what extent modelling and simulation enable the prediction of drug effects in individual patients. If feasible, this would constitute a major step forward towards the discovery of novel drugs by design and to the implementation of tailor-made pharmacotherapy.

In recent years important progress has been made in the development of mechanistic models describing the functioning of whole body systems, to predict in a strictly quantitative manner drug effects in man. The Leiden-Amsterdam Center for Drug Research at Leiden University has been at the forefront of this research.[10] A pertinent feature of these models of whole body systems is that they contain specific expressions to characterise processes on the causal path between drug administration and response. This includes the pharmacokinetics, the distribution of the drug to target site, the binding to and activation of the target, the transduction pathways and the homeostatic feedback mechanisms. Ultimately, also the interaction of drug effects with the disease processes and disease progression are considered.

As truly mechanistic models of drug action on the whole body may become incredibly complex, their identification constitutes a major challenge. An important question is therefore whether mechanistic models could be reduced so as to contain only expressions for the most essential processes on the causal path, while maintaining their utility for extrapolation and prediction. Meanwhile it has been demonstrated that in many instances parsimonious mechanism-based models do indeed constitute a valuable basis for the prediction of drug effects in man.

It is anticipated that modelling, simulation and high-performance computing will revolutionise the way in which novel medicines are

discovered and developed. Specifically, modelling how drugs act at the sub-cellular level, in organs and ultimately in whole body systems will yield novel concepts of drug treatment. Moreover, such modelling also enables the identification and the design of novel drug molecules. Another important aspect is that, in addition to the aforementioned applications, the prediction of drug effects in man will also enable the design of accurate clinical trials. Meanwhile it has been amply demonstrated that the application of advanced modelling and simulation increases the efficiency of the drug discovery and development process. Last, but not least, modelling and simulation also yield a scientific basis for tailor-made pharmacotherapy, both with regard to the selection of susceptible patients and the individualisation of the dosing. Ultimately this will enable the management of diseases for which no one-size-fits-all treatment solutions are available.

Novel drug discovery: serendipity or design?

The previous paragraphs describe the complexity of novel drug discovery and development. It is shown that drug effects result from the complex interactions of drug molecules with multiple components of the biological system. An important observation is that drug effects may be observed only under very specific conditions. This makes the discovery of new useful drug molecules, which are efficacious, safe and easy to use, look like the proverbial 'search for the needle in the haystack'.

In recent years, however, important progress has been made with the modelling of biological systems as the basis for the prediction of drug effects. Although such models readily become extremely complex and thereby difficult to identify, it has in the meantime been amply shown that reduced, parsimonious models can indeed be used to predict drug effects. This constitutes therefore a basis for the discovery of novel concepts of drug treatment and for the design of novel drug molecules. It is foreseen that in the coming years modelling and simulation will be increasingly applied in rational drug discovery and development. An important factor is that this will also yield an improved understanding of the mechanisms of inter-individual variability in drug effect. Ultimately this may enable the implementation in clinical practice of highly individualised targeted treatment solutions for diseases where easy one-size-fits-all medications are not feasible.

Notes

1 Kaplan, W. and Laing, R., *Priority Medicines for Europe and the World*, World Health Organization, Department of Essential Drugs and Medicines Policy (Geneva 2004).
2 Le Fanu, J., *The Rise and Fall of Modern Medicine* (London 1999).
3 Drews, J., *In Quest of Tomorrow's Medicines* (New York 1999).
4 Black, J.W. and Stephenson, J.S., 'Pharmacology of a New Adrenergic Beta Receptor Blocking Compound', in: *The Lancet* 2 (London 1962) p. 311-315.
5 Brimblecome, J.W., Dunant G.J., Emmet, J.C., Ganellin, C.R. and Parsons E.M. 'Cimetidine: A Non-thiourea H_2 Receptor Antagonist', in: *Journal of International Medical Research* 3 (Worthing 1975) p. 86-92.
6 Juranka, P.F., Zastawny, R.L. and Ling, V. 'P-glycoprotein: multidrug-restistance and a superfamily of membrane-associated transport proteins', in: *The FASEB Journal* 3 (Bethesda 1989) p. 2583-2592.
7 Breimer, D.D., *Farmacotherapie op Maat* (Leiden 1976).
8 Emens, L.A., 'Traztuzumab: targeted therapy for the management of HER-2/neu over expressing metastatic breast cancer', in: *American Journal of Therapeutics* 12 (Philadelphia 2005) p. 243-253.
9 Arlington, S., Barnett, S., Hughes, S., and Palo, J., *Pharma 2010: The Threshold of Innovation* (Somers 2002).
10 Danhof M., De Jongh J., De Lange, E.C.M., Della Pasqua, O.E., Ploeger, B.A. and Voskuyl R.A., 'Mechanism-based Pharmacokinetic-Pharmacodynamic Modeling: Biophase Distribution, Receptor Theory, and Dynamical Systems Analysis', in: *Annual Review of Pharmacology and Toxicology* 47 (Palo Alto 2007) p. 21.1 – 21.44.

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