Eur J Clin Pharmacol (2016) 72:13–17
DOI 10.1007/s00228-015-1964-2

SPECIAL ARTICLE

‘The principles of a future pharmacology’: Johann Christian Reil (1759–1813) and his role in the development of clinical pharmacology

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Received: 26 July 2015 / Accepted: 6 October 2015 / Published online: 9 October 2015

Abstract
Aim Johann Christian Reil was an eighteenth-century German physician and clinical academic with wide interests. These included building the scientific foundations of modern medical practice. In 1799, he published a work specifically calling for a scientific approach to pharmacology in medical practice. In this paper, I aim to present the key parts of that work for the first time in English translation.
Methods Reil’s 1799 work was translated into English and evaluated against current standards of practice in clinical pharmacology to highlight his ‘modern’ approach to our subject.
Results Reil defines pharmacology and presents a series of eight rules or principles that should be followed by those wishing to evaluate drugs in humans. These rules highlight the need for scientific rigour, including the use of multiple controlled experiments, and call for the introduction of a specialized vocabulary to facilitate the exchange of ideas between pharmacological researchers.
Conclusions Although rarely mentioned in the pharmacological literature today, Reil’s work in the late eighteenth century is an important precursor of our modern approach to the evaluation and testing of drugs in clinical practice. This English translation of the key sections of his work may now allow others to properly evaluate his contribution.

Keywords History · Pharmacology · Reil

Introduction

Today, the name Johann Christian Reil is best known to neuroanatomists and those working in mental health. Reil, who was born over 250 years ago, made seminal contributions to both these fields, and as his legacy, we have several structures in the brain that bear his name as well as ‘psychiatry’, a specialty that he named.

However, earlier in his career, Reil was responsible for another, perhaps even more generally applicable piece of work, when he set forth the principles on which the modern evaluation of drugs in humans should be based [1, 2]. In this paper, I shall present and examine the first English translation of this work, and assess its importance to the developing science of clinical pharmacology.

Biography

1759 Born in Rhaude, Northwest Germany [3].

1779 Began his medical education in Göttingen, but three semesters later, transferred to Halle, where he graduated in 1782.

1783 After a year in Berlin completing the clinical course required of all those wishing to practice in Prussia, he returned home to the northwest and practiced medicine.

1787 Invited to become a lecturer in Halle.

1788 Appointed as full Professor [4].

1799 Publishes his *Contribution to the Principles of a Future Pharmacology.*

1807 Published his studies of neuroanatomy and expanded on his previous work in mental health.

1808 Coins the term *Psychiaterie* to emphasize that the management of mental illness was a core medical remit and that physicians rather than other professional groups should lead.

Electronic supplementary material The online version of this article (doi:10.1007/s00228-015-1964-2) contains supplementary material, which is available to authorized users.

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1810 Moved to the new Berlin University established by Wilhelm von Humboldt, who had consulted Reil on the structure of the medical curriculum [3, 5] and who now invited him to become Dean of the Medical Faculty [6].

1813 Volunteered for military service in the Prussian Army during the Napoleonic Wars, contracted typhus. He returned to Halle where he died at the age of 54. One month later, his widow would die in childbirth [6].

His approach to pharmacology

In 1799, while he was the Professor of Medicine at the University of Halle, Reil published his *Beitrag zu den Prinzipien für jede künftige Pharmakologie* (Contribution to the Principles of a Future Pharmacology), in which he proposed and enumerated a set of rules for the conduct of pharmacological research [1]. These were presented as a theoretical framework on which to build a scientific approach to the study and evaluation of drugs.

This work, while receiving some critical evaluation in the German literature [2], has never before been translated into English and, as such, has not received the wider attention it deserves.

Reil begins his treatise with his definition of the subject. 'Pharmacology' he notes, 'should explain the effects of certain substances, i.e. drugs, on the human body.' [1]. He goes on to expand upon this when he asks, 'What does pharmacology have to offer?' He answers his own question: 'it has to explain factually and scientifically to the last detail those changes that arise in the interaction between a medical substance and a living being. The drug may also undergo changes which interest us only insofar as they contribute to the explanation of the changes to the human body.' Here, Reil puts forward the notion that not only do drugs affect the body, but that the body also affects drugs, thus presciently proposing the idea of drug metabolism long before such a concept would be confirmed.

To understand this interaction of drug and living system, Reil goes on to say that we need,

> A complete understanding of every aspect of the nature of drugs, especially with regard to their chemical make-up…, a complete understanding of the physical nature of the human being, the basic combination of his various organs, his strengths, the combination of the organs in the whole body through nerves and vessels, and the individuality of people with reference to age, sex, temperament, idiosyncrasy, etc. [1].

Reil then defines his scientific approach to pharmacology:

> The only way pharmacology can improve is to carry out tests, note the results carefully and subsume the isolated observations into higher-level rules… at the same time this will serve to explain the effects of drugs… Now I have stated above that we are not able to explain the action of drugs because we do not know their composition or the disposition of the human body in sickness or in health, or how they act on one another....Until now an explanation of how drugs work, and therefore a science-based pharmacological discipline has not been possible. The way forward is clear, namely: a) painstaking research into the nature of drugs, especially their composition; b) research into physiology and especially animal chemistry; c) accurate observation of what happens in the interaction between drugs and the human body and an accurate integration of these phenomena into higher rules. All other methods are wrong and all attempts to find a principle to explain these things in any other way is a waste of time [1].

To complete his scientific approach to pharmacology, Reil enumerates a set of eight rules for the evaluation of drugs in his 1799 paper and these merit closer study [1, 2].

Reil's rules

Reil's rules are presented in English translation. For comments on each, please see the online supplement to this article.

1) The observer must have good common sense, good understanding, judgement, know how to make observations but also have a healthy degree of scepticism. He should not allow himself to be influenced by egotism, doctrine, an attachment to his school, or any prejudice, but by the simple love of truth.
2) If the results of experiments, that is the changes brought about in the human body by the drugs, are consistent, they can be considered to be undoubtedly valid only if both the drugs and the human beings used in the series of tests are of a standardized nature. If the reagents which are working on one another are sometimes of one quality, sometimes of another, then the results will be correspondingly inconsistent. With regard to the drugs it is very difficult to get them always with the same quality. How variable poppy juice, musk, napell [aconite] extract and hemlock extract are in the chemist shop! Herein lies often the reason for contradictory results! However, the experimenter can make this possible. It is only with regard to human beings that no uniformity is possible. Every individual is different from another, and the same individual is not the same all of the time. With human beings a standard, average type has to be established, and before the experiment the test subjects must be assessed to identify exactly how they deviate from the standard so that variations in

the results can be compensated for accurately for each individual according to how they deviated from the norm. How difficult this point is and yet how inexact efforts are with regard to it.

3) If we are experimenting on invalids the same things apply. Their illness must not be hypothetical, but real, identifiable from recognizable symptoms and deemed by the experimenter as really being present. If he should say of a drug that it cures the 'Black Bile', his statement is incomprehensible as this 'malady' is hypothetical. If he extols the efficacy of another drug saying it was good for blockages of the mesentery, I would doubt whether he had had a reliable diagnosis of this condition. How many mistakes have wormed their way into pharmacology because of confused terms about the nature of diseases and an imperfect semiotic of the same.
4) The experiments must be repeated often and under exactly the same conditions and in each repetition the results have to be the same. This alone can convince us that the results are effects of the drug. If, after one or more tests, a given effect sometimes is seen and sometimes not, the possibility remains that it was due not to the use of the drug but some other possible cause. How often the results of an experiment, or one successful and ten unsuccessful experiments, are reported as practical knowledge! How many things have got into the materia medica through this failing, which are either totally ineffective or have quite different powers than those ascribed to them!
5) A drug must be tested on its own, not in conjunction with others, because otherwise it remains uncertain which of the substances used has brought about the effect in question. I am not suggesting, however, that in practice no compound substances should be used. Some are excellent, for example Theban tincture used as eyewash. At present, I am simply speaking of the determination of the powers of substances, which must precede their application. First of all, we must determine the powers of the simple, individual substances in order to be able to work out the effect of compounds of them. The compounded substance must then be thoroughly tested, the same as for a simple, to understand the alteration of its effect which has been caused by its compounding.
6) The effects of drugs must be described specifically, not in terms that are too general, as otherwise they are of no practical use. If you say a drug acts as a stimulant (causes one substance to have an effect on another substance) you are saying something that everyone knows and therefore nothing at all. It is not a question of whether the substance simply has an effect, but the 'what' and the 'how' of this effect.
7) The effects of drugs must be established either through direct experience or from conclusions, which were clearly able to be drawn from direct experience. Their characteristics have to be clearly described. That tartar emetic causes vomiting is a judgement that is understandable to everyone; but it is part hypothesis, part unfounded conclusion to state that it causes looseness. Isolated observations must be collated and general results deduced according to certain rules (e.g. frequency, causality).
8) Finally, the terminology used in pharmacology deserves sharp criticism. The meaning we give to words needs to be more precise, more expansive and more accurate. Without this improvement we will remain virtually unintelligible to each other.

Reil's rules in perspective

In the second half of the eighteenth century, medical practice was in turmoil after a period of relative stagnation lasting more than 500 years. Through numerous discoveries and a wholly different approach, mediaeval medicine was giving way to a more enlightened system [7]. As part of this, there was a growing desire to place medical practice on a much more solid scientific foundation. The term *pharmacology* itself was probably coined in the late seventeenth century but acquired its modern definition in 1791 from Friedrich Albrecht Karl Gren, a German chemist, physician and friend of Reil [2, 8]. Gren distinguished the science of the action of drugs from the mere description and collection of drugs. This cataloguing of drugs was *materia medica*, while pharmacology was a science. A science, however, needed a rational framework and a method, and these Reil sought to provide [9].

Reil's rules may be seen as a natural development in this context. However, Reil was not the first to propose a set of rules to formalize the study and evaluation of drugs. The ancient Roman physician and philosopher Galen and the eleventh-century Persian polymath Avicenna, as well as mediaeval physicians who followed them, did the same [10–12].

An obvious question to address is how much was Reil influenced by his predecessors?

Galen and Avicenna had dominated the medical curriculum for centuries. Galen's works were widely read and studied in their original Greek and from the fifteenth century in Latin translations [13]. They formed part of the core curriculum in most European medical schools, but by the Renaissance, their authority was being questioned. By the mid to late seventeenth century, they were no longer taught at the European medical schools [14].

Similarly, Avicenna's famous *Canon of Medicine* was available in Latin throughout the later mediaeval period and was probably first translated in the second half of the twelfth century by Gerard of Cremona [15]. The Canon continued to be used in medical schools up until the late seventeenth to early eighteenth centuries. However, by the time Reil attended

medical school, it would have fallen out of favour, to be replaced with more contemporary texts of the medical enlightenment.

In parallel with the upheaval in medical practices in the eighteenth century, there was a corresponding overhaul of medical education. Medical curricula were changing to accommodate new subjects such as chemistry, botany and physiology. While the classic texts such as those of Galen might still be read, they no longer formed part of the core syllabus [7].

Thus, Reil would have had access to the works of Galen and Avicenna, but it is questionable whether his medical education in the 1780s would have focussed on, or even included, these classic authors' works. It is perhaps unsurprising then that Reil's rules differ significantly in their emphasis from those of the ancients. Like Galen and Avicenna, Reil recognized the need for appropriate experimental design, but he goes much further than his forebears in his calls for scientific rigour and for a new vocabulary to report our findings.

In the late eighteenth century, when 'pharmacology' had advanced little beyond the cataloguing of mediaeval herbalists, when the principle drugs in use were the same as those that had been used for the last thousand years, when the concepts of what constituted a drug, how it was metabolized and how it exerted its action were in their infancy, Reil's contribution to the debate seems almost anachronistic. He realized the power of rationality in our approach to therapeutics and sought to build a new pharmacology on a scientific foundation.

Conclusion

Reil, like many physicians of his day, was not content to specialize in one area. His contributions to several branches of medicine, including pharmacology, are significant, but partly because of his premature death and partly because of his shifting interests, we had to wait until later in the nineteenth century to see a truly scientifically founded pharmacology.

It was not until 1847 that the first chair of pharmacology was filled by Rudolf Buchheim (1820–79) [8, 16]. Buchheim is not credited so much with any fundamental discovery as with the development of the framework in which pharmacology would develop as a science. This framework consisted of two closely related elements: first that there should be a 'natural system' for the classification of drugs, based on their mode of action, and second that an experimental approach was required to unravel these mechanisms of action. The latter, as we have seen, was proposed by Reil almost 50 years earlier.

Perhaps Buchheim's greatest contribution was as a teacher and mentor for it was the achievements of his students that would be his greatest legacy. One student in particular would not only carry his torch but would bring global recognition to the new discipline of pharmacology. In 1869, Oswald Schmiedeberg (1838–1921) took over from his supervisor as Professor of Pharmacology [8] and subsequently moved to the University of Strassbourg in 1872 where he would remain for the rest of his professional life and establish what at the time would be the most important centre for the study of pharmacology in the world. During a long and highly productive career, he made many discoveries and contributed significantly to his developing field. However, like Buchheim, Schmiedeberg was also a mentor and one of his legacies was the training of a whole new generation of pharmacologists who would go on to sit in more than 40 chairs in universities around the world [17]. Today, it is Schmiedeberg rather than Buchheim or Reil who is regarded as the father of modern pharmacology, but Schmiedeberg himself was always the first to acknowledge the debt he owed his former professor.

The debt, however, that both men and the developing science of pharmacology owed to Reil remains largely unacknowledged. Nevertheless, without physicians of the enlightenment such as Reil, who questioned the status quo and called for the application of scientific rigour, it is hard to imagine that pharmacology as we understand it today could have developed and flourished to become one of the central pillars of modern medicine.

Acknowledgments This work could not have been done without Alexander Gaw, who translated Reil's paper from the original German, and SJ Littleford who helped me access key literature in Oxford.

Compliance with ethical standards

Competing interests The author declares that he has no competing interests.

Funding None.

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