EXPERIMENTAL PHARMACOLOGY AND THERAPEUTIC INNOVATION
IN THE EIGHTEENTH CENTURY

by

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ABSTRACT

In the historiography of pharmacology and therapeutics, the 18th century is regarded as a period of transition from traditional, Galenistic materia medica to the beginnings of modern, experimental drug research. Ackerknecht (1973) characterized the pharmacotherapy of this period as a "chaotic mixture of chemiatric and Galenistic practices", yet acknowledged an "increasing tendency toward empiricism, partly even true experimentalism". This thesis explores this transitional phase for the first time in depth, examining the relations between pharmacological experimentation, theory-building, and therapeutic practice. Furthermore, ethical aspects are highlighted.

The general introduction discusses the secondary literature and presents the results of a systematic study of pharmacological articles in relevant 18th-century periodicals. The identified main areas of contemporary interest, the spectrum of methods applied, and the composition of the authorship are described and interpreted. It is shown that lithontriptics ("dissolvents" for urinary stones), opium, and Peruvian bark were of major concern to 18th-century pharmacology. These substances are the subjects of three "case studies", which form the body of the thesis. Issues discussed here include, in lithontriptics, the role of proprietary remedies and links with analytical chemistry; in opium, the different interpretations of its mode of action, toxicity, and addictive properties; and in Peruvian bark, the widening of its therapeutic indications, changes in its pharmacological understanding, and problems of its quality assessment.

The thesis provides evidence of a previously unknown wealth of 18th-century pharmacological works, which were characterized by an increasingly sophisticated methodology and critical discussions of their consequences for the theory and therapeutic uses of drugs. It argues in conclusion for a positive revision of current historical judgements about 18th-century pharmacology and therapeutics.
ACKNOWLEDGEMENTS

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My work with the sources was carried out in the Wellcome Institute Library, the British Library, and the university libraries of Göttingen, Newcastle, Durham,
Edinburgh, Glasgow, and Freiburg. Thanks to the librarians of all these institutions for their friendly assistance.

Preliminary findings have been presented in research seminars at the universities of Göttingen and Durham, in lectures at the University of Kiel and the Medical Academy of Magdeburg, at the Wellcome Symposium on the History of Medicine 'Narcotics, Drugs and Medicine' 1991 in London, and at the 1994 annual meetings of the Deutsche Gesellschaft für Geschichte der Medizin, Naturwissenschaft und Technik in Halle and of the Pybus Society for the History and Bibliography of Medicine in Newcastle. Questions and comments at these occasions have contributed to my research.

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## CONTENTS

**Abstract** 2

**Acknowledgements** 3

**General Introduction** 7

**Tables 1-5** 44

A. The Search for Lithontriptics 49
1. Introduction 49
2. Traditions 52
3. Early trials in vitro, animal experiments, and case histories 60
4. Mrs Stephens's remedies: evidence and evaluation 66
5. Reactions to Stephens's lithontriptic: criticism, more research, and a new theory 71
6. A "new" London and an Edinburgh lithontriptic: Jurin's soap-lye remedy and Whytt's lime-water 84
7. Continental ways: Carlsbad waters and the bearberry plant 99
8. Fixed air, mineral waters, and calculi: the impact of chemistry 108
9. Chemical analysis of calculi and the differentiation of lithontriptic therapy 119
10. Conclusions 132

B. Opium: Studies into an Ambiguous Drug 137
1. Introduction 137
2. The medical importance of opium 142
3. Seventeenth-century views on the pharmacology of opium and their basis 147
4. Iatromechanical interpretations around 1700 155
5. Some early therapeutic conclusions 165
6. Opium and the nervous system around 1750 176
7. Effects on the heart and irritability 194
8. Stimulant or sedative? 205
9. Pharmacology and therapeutics 215
10. Opium as a habit-forming drug 229
11. The identification of morphine 247
12. Ethical aspects 254
13. Conclusions 258

C. Peruvian Bark: from Specific Febrifuge to Universal Remedy 263
1. Introduction 263
2. Early controversy on the new febrifuge 267
3. Experiment and speculation: efforts to explain the bark's action around 1700 280
4. The Stahlian critique of cinchona treatment 301
5. A surgeons' matter: the bark in "gangrene" 305
6. New pharmacological experiments: the bark as astringent and antiseptic 323
7. Clinical inferences: the bark as a tonic 333
8. Early "clinical trials" 340
9. Which bark is best? 353
10. The isolation of quinine 366
11. Conclusions 370

General Conclusions 379

Bibliography 386
I. Primary Sources 386
II. Secondary Literature 433
GENERAL INTRODUCTION

The origins of modern pharmacology and scientifically founded therapeutics are generally thought to lie in the first half of the nineteenth century. Often-cited landmarks are Friedrich Wilhelm Sertürner's isolation of morphine from opium, i.e. the discovery of the first plant alkaloid, published in 1805; François Magendie's *Formulaire pour la préparation et l'emploi de plusieurs nouveaux médicaments* (1821) as the first textbook on chemically pure drugs; and Rudolf Buchheim's creation of the first laboratory for experimental pharmacology at the University of Dorpat, where he had become professor of materia medica in 1847.¹ The role of analytical chemistry and experimental physiology in the emergence of the science of pharmacology is usually - and rightly - emphasized. However, this focus on the nineteenth century has sometimes resulted in a lack of attention to developments in the older materia medica during the previous two centuries.²

From time to time historians of medicine and pharmacy have tried to remedy this. Studies into the beginnings of experimental pharmacology, which gave full attention to the eighteenth century, were carried out around 1960 by Melvin P. Earles. He traced the gradual recognition of


² E.g. Gernot Rath, 'Zeiteinflüsse in der Pharmakologie des 16. bis 19. Jahrhunderts', *Sudhoffs Archiv*, 1963, 47: 1-18, who argued that the transformation of pharmacology from a part of therapeutics to an experimental science did not originate from materia medica itself, but was induced by the development of pathology and physiology.
pharmacological animal experimentation as a valid research
method, described contemporary theories of the mode of
action of drugs and poisons, and examined the first
contributions to the knowledge of dose-effect relations.³
Earles' discussion of the eighteenth century chiefly
referred to British publications. In 1971/72 Rolf Winau also
analyzed some of this material, but in addition drew
attention to trials with drugs and poisons by a number of
Continental researchers, especially at the University of
Göttingen.⁴ This work was supplemented in the following
years by more detailed studies of some "pioneers" of the
field, such as those by Karl-Werner Schweppe on the Vienna
clinician Anton Störck (1731-1803),⁵ by Peter K. Knoefel on

³ Melvin Peter Earles, 'Studies in the development of
experimental pharmacology in the eighteenth and early
nineteenth centuries', Ph.D. thesis, University of London,
1961; idem, 'The experimental investigation of viper venom
by Felice Fontana (1730-1805)', Ann. Science, 1960, 16: 255-
268; idem, 'Early theories of the mode of action of drugs
and poisons', Ann. Science, 1961, 17: 97-110; idem,
'Experiments with drugs and poisons in the seventeenth and

⁴ Rolf Winau, 'Experimentelle Pharmakologie und Toxikologie
im 18. Jahrhundert', Habil.Schrift Mainz, 1971; idem,
'Experimentelle Pharmakologie an der Universität Göttingen
also the early collections and summaries of eighteenth-
century pharmacological experiments, out of Paul Diepgen's
Institut für Geschichte der Medizin und Naturwissenschaften
in Berlin, Pawel Bernknopf, 'Tierversuche mit Arzneimitteln
Lindenberger, 'Pharmakologische Versuche mit dem
Berlin, 1937.

⁵ Karl-Werner Schweppe, 'Experimentelle
Arzneimittelforschung in der Älteren Wiener Schule und der
Streit um den Schierling als Medikament in der Zeit von
1760-1771', Med. Diss. TU München, 1976; idem and Christian
Probst, 'Die Versuche zur medikamentösen Karzinomtherapie
des Anton Störck (1731-1803)', in Kurt Ganzinger, Manfred
Skopek, and Helmut Wyklicky (eds), Festschrift für Erna
Lesky zum 70. Geburtstag, Vienna, Verlag Brüder Hollinek,
1981, pp. 105-122; Schweppe, 'Anton Störck und seine
the Florence naturalist Felice Fontana (1730-1805), and my own on the Schaffhausen town physician Johann Jakob Wepfer (1620-1695). Moreover, a number of medical dissertations have systematically reviewed the further unfolding of experimental pharmacology in Germany during the nineteenth century. As for therapeutics, the well-known hallmarks of the eighteenth century, the trials of James Lind and others on the cure and prevention of scurvy, and William Withering's use of digitalis in the treatment of dropsy, have been critically assessed and put into their historical context.


context over recent years. Examples of protostatistical or "arithmetic" observations in contemporary British therapeutics have been discussed by Ulrich Tröhler.

On the whole these historical investigations have shown that experimental pharmacology and "scientific" therapy were not entirely new creations of the nineteenth century, coming into being only with the help of modern chemistry, physiology, pathology, and clinical statistics. Rather, the old "pharmacology" or materia medica itself had developed an experimental tradition. It went back to the late seventeenth century, and chemical analysis, in vitro tests

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on blood, animal experimentation, and trials on both healthy subjects and patients were all part of it. Yet, the actual extent and role of this experimental tradition within eighteenth-century pharmacology and therapeutics did not become fully clear. Frequently outstanding experimental work has been discussed in isolation rather than as part of wider research efforts and therapeutic needs. Historians of pharmacology have often tended to select those sources and authors that seemed to have contributed in a major way to its development in terms of methodology, results, and concepts. In other words, there has been a certain bias towards events that appeared significant from the perspective of modern medicine. This "positivist" approach runs also through the relevant chapters of general histories of pharmacology and therapeutics. In this way the role of experiment and innovation in the eighteenth century may have been overemphasized.

On the other hand, historical judgements drawn from such reviews have sometimes been coloured by the contrast of enormous progress during the following two centuries. Erwin H. Ackerknecht characterized the pharmacotherapy of the

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eighteenth century as "dominated by eclecticism" and "a chaotic mixture of chemiatric and Galenistic practices", noted "a very dangerous therapeutic activism", and thought that the "mad desire... to systematize" was "not always conducive to reasonable therapeutics". Yet he acknowledged that the pharmacopoeias were "relieved of magic and ineffective medicaments", that "useful folk remedies" were adopted, and he observed an "increasing tendency toward empiricism, partly even true experimentalism". Chauncey D. Leake spoke of a "protopharmacology" that "led into real pharmacology at the close of the eighteenth century".

Only occasional efforts have been made to examine this "protopharmacology" and contemporary pharmacotherapeutic practice in detail and to understand their inner logic. Studies of this kind have been performed by J. Worth Estes concerning medical practice in colonial New England, by Guenter Risse and Estes on the use of drugs at the Royal Infirmary of Edinburgh, and most recently by Almut Lanz on the remedies of Friedrich Hoffmann, as prescribed or recommended in his "medical consultations". However,

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14 Leake, op. cit., note 12 above, p. 118.

focusing on therapeutic practice, these works do not specifically discuss its relation to pharmacological experimentation.

The general aim of the present study is to elucidate the relations between experimental approaches, theories, and therapeutic principles in eighteenth-century pharmacology. As a side issue ethical considerations are traced, particularly with regard to human and animal experimentation, to supplement my earlier studies in this area. Necessarily, I have had to be selective as well, and I needed also to concentrate on methods, results, and concepts. However, I have not simply turned to the "classics" of the period, such as Lind and lemon juice or Withering and the foxglove.

Intending to identify and study the main fields of interest of the eighteenth century, rather than those of modern historiography, my research started with systematic


screening and analysis of relevant contemporary periodicals for articles on "pharmacology" in a broad sense. Because of the blurred boundaries of the field in the eighteenth century, my search included not only contributions on materia medica (observational and experimental), but also such dealing with pharmacotherapeutical and toxicological topics. This initial part of my research was restricted to British publications. As the country's leading scientific journal, the Philosophical Transactions of the Royal Society of London have been examined for the whole of the eighteenth century, i.e. from volume 22 (1700/01) to 90 (1800). In addition I have studied the Edinburgh periodicals Medical Essays and Observations (5 vols, 1733-1744), Essays and Observations, Physical and Literary (3 vols, 1754-1771), Medical and Philosophical Commentaries (6 vols, 1773-1779), Medical Commentaries (14 vols, 1780-1795), and Annals of Medicine (5 vols, 1796-1800).

Though covering shorter periods, the latter periodicals can broadly be taken as a historical "unit". The first four volumes of the Medical Essays and Observations were edited by Alexander Monro primus, professor of anatomy, on behalf of the Edinburgh Medical Society, which had been founded in 1731 by the medical professors of the University of Edinburgh and a number of local physicians and surgeons. In 1737 the Medical Society was superseded by the Philosophical Society of Edinburgh, which had wider scientific aims, but in which medicine was still strongly represented both in terms of its membership and the contents of its publication, the Essays and Observations, Physical and Literary. The Philosophical Society - with Colin MacLaurin, professor of mathematics, and Andrew Plummer, professor of medicine, as secretaries - also published the fifth and last volume of the Medical Essays and Observations, which appeared in two parts in 1742 and 1744. Already before the Philosophical Society was transformed into the more broad-based Royal Society of Edinburgh (1783), Andrew Duncan senior, then
extra-mural lecturer in medicine in Edinburgh, provided a new forum for medical and surgical communications with his *Medical and Philosophical Commentaries*, which started in 1773. These were renamed *Medical Commentaries* in 1780, the new title reflecting their actual contents. Andrew Duncan senior, who became professor of the institutes (theory) of medicine in 1789, continued the *Medical Commentaries* from 1795 as *Annals of Medicine* with the help of his son, the physician Andrew Duncan junior. In 1805, finally, the *Annals of Medicine* were replaced by the *Edinburgh Medical and Surgical Journal*. In view of these continuities and institutional links it can be assumed that the selected Edinburgh periodicals reflected major interests of what may be called "eighteenth-century medical science", forming thus a kind of counterpart to the London-based *Philosophical Transactions.*

Articles identified in these periodicals as belonging to the broad area of materia medica, pharmacotherapy, and poisons were subsequently categorized into "fields". A minimum of three articles has been set as a requirement for inclusion as a "field". Though some contributions could have been allocated to more than one such field, multiple assignations have been avoided. In such cases the allocation was made on the basis of the most prominent characteristic of the article in question. In long contributions, which were published in several parts, every part was counted as one article. This was done in order to recognize their

significance as reflected in the space allowed to them in the periodical. My results are summarized in Tables 1-5.

Screening of the volumes 22 to 90 of the Philosophical Transactions revealed 240 articles in the area of materia medica, pharmacotherapy, and poisons, published between 1700 and 1799 (Table 1). 148 (61.7 %) of them could be allocated to sixteen rather narrowly circumscribed, specific fields under contemporary headings. 92 articles (38.3 %) could be assigned only to five broad categories of "various" (materia medica and therapeutics; exotic drugs and plants; poisons; pharmaceutical chemistry; pharmacology), which were constructed from the historian's perspective. The years of the first and last article in a certain field have been given here in order to allow the reader to distinguish between topics which attracted contributions throughout the eighteenth century and those which were of particular interest only during shorter periods.

Of the specific fields, "mineral waters" was the largest, about every tenth of the identified articles in the Philosophical Transactions belonging to it (Table 1). It was also the leading "pharmacological" topic in the Medical Essays and Observations with nearly one fifth of the identified articles (Table 2). The preoccupation of the eighteenth-century with the chemical and therapeutic properties of "waters" is indeed well known. The socio-economic side to this interest was the growing "spa business" in Britain, which followed the same trend in Continental Europe. In fact most of the articles considered here dealt with the properties of particular wells or spas in England or Scotland. Physicians were usually those who had the necessary chemical knowledge and skills to analyze

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18 Under "pharmacology" articles have been counted here, which dealt with questions of the subject in a modern sense, such as absorption, mode of action of medicines, or dosage in relation to age, and which could not be allocated to a particular field.
waters. Moreover, they claimed the professional authority to conclude a certain water's medical indications, or to determine them on the basis of therapeutic experience, which was sometimes illustrated with case histories. Although doctors traditionally warned that indiscriminate use of mineral waters could be dangerous, indications were usually wide-ranging, a fact which probably had economic as well as medical reasons. The identification of "fixed air" (i.e. carbon dioxide) in certain waters in the second half of the eighteenth century provided a further stimulus, including increased efforts to produce artificial mineral waters.

An important indication for many waters were urinary stones. In this respect the field "mineral waters" overlapped with the category "lithontriptics" (i.e. so-called dissolvents for bladder and kidney stones), to which over 6 per cent of the identified articles in the Philosophical Transactions could be assigned, and which was also prominent in the Essays and Observations. Physical and Literary (Tables 1 and 3). Additional bibliographical research revealed a wealth of monographs and further articles on lithontriptics in the eighteenth and early

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nineteenth centuries. Other than in the case of mineral waters, very little historical work has been done on this topic, and there was no general account of the development of this kind of medicines. I therefore decided to carry out a first "case study" into lithontriptics. Its results constitute part A of the present thesis.

"Opium" was chosen as the topic of a second case study. It featured prominently in the Medical Essays and Observations and Essays and Observations, Physical and Literary (Tables 2 and 3). Yet it did not "qualify" for inclusion as a field of its own in the other Edinburgh periodicals and in the Philosophical Transactions. On the other hand, my bibliographical research indicated that it was without doubt one of the major topics of seventeenth- and eighteenth-century pharmacological writings. An earlier "pilot study" of mine on experimentation with opium in the eighteenth century had further revealed the considerable scientific influence of some of the articles on this drug published in the above two Edinburgh journals. On this basis, and in agreement with the secondary literature, I assumed that the medical use of opium in the eighteenth century was indeed so common, that - besides experimental studies - only "extraordinary" observations on the drug found their way in the analyzed periodicals. The character of such contributions, dealing with poisonings or unusual phenomena and successes in opium treatment, supported this hypothesis. "Opium" is of course a rather familiar territory

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20 See below, part A, 1.

21 See below, part B, 2.

for historians. However, with the exception of the work of Earles and a few other authors, the general pharmacological and therapeutic aspects have clearly been neglected in favour of analyses of the concept of opiate addiction and its social implications in the nineteenth and twentieth centuries. It therefore seemed justified to perform a special study into opium, the results of which are presented in part B.

Another main topic identified by my analysis of periodicals was cinchona or "Peruvian bark" (as it was commonly called in the eighteenth century). In the Philosophical Transactions it turned out to be the fourth largest of the specific "pharmacological" fields, after mineral waters, vipers and other venomous snakes, and lithotriptics (Table 1). It furthermore ranked second in the Medical Essays and Observations, and fifth, on a par with tobacco, in the Medical (and Philosophical) Commentaries (Tables 2 and 4). Again, bibliographical research revealed great numbers of contemporary monographs and additional articles on the bark, which was known as a "specific" remedy against intermittent fevers (i.e. malaria). The "first phase" of the drug's history, from its introduction from South America in the 1630s up to its more general acceptance in European medicine in the early eighteenth century, has recently found extensive scholarly attention by Saul Jarcho. Moreover, Mauricio Nieto Olarte has studied botanical, pharmaceutical, and commercial aspects of cinchona in the Spanish Empire during the late eighteenth and early nineteenth centuries. Yet the medical

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23 For details see below part B, 1. and 2.

24 See below.

25 See below, part C, 1.

26 Saul Jarcho, Quinine's predecessor: Francesco Torti and the early history of cinchona, Baltimore and London, The
history of the bark in the later eighteenth century remained largely in the dark. Historical work in this field "restarts" only with the isolation of the alkaloids cinchonine by Gomès (1811) and quinine by Pelletier and Caventou (1820). Peruvian bark thus offered itself as the topic for a third case study, which makes part C of this thesis.

The choice of these three case studies allowed me to investigate the history of a number of important issues: for example, in opium, the various interpretations of its complex mode of action, the therapeutic problem of its relative toxicity, and perceptions of its addictive properties; in lithontriptics, the links with the rise of modern chemistry and the role of proprietary remedies, such as Mrs Stephens's medicines and James Jurin's Lixivium lithontripticum; and in Peruvian bark, the notion of a "specific", the widening of its therapeutic indications, and questions of its quality assessment. All three studies are not strictly limited to the eighteenth century, but include also relevant developments in the seventeenth and early nineteenth centuries. In the case of lithontriptics, the tradition of this type of medicines is traced back to antiquity.

With more detailed research into the history of the three selected substances not only the true wealth of primary sources on each of them became apparent. It also became clear that a limitation to British publications, as initially planned, would not have been adequate in view of the internationality of the medical and scientific


discourses in the eighteenth century. The "Republic of Letters" was found to extend to pharmacology and therapeutics. Therefore Continental sources had to be included as well, chiefly from the contemporary centres of "medical science", such as the universities of Halle and Göttingen, and the Académie Royale des Sciences in Paris. The nature of the substances (respectively groups of substances) chosen for the case studies furthermore directed my research generally more towards therapeutics and its relations to pharmacology than into the opposite direction of toxicology.

For this reason, and from considerations about a manageable scope of my investigation, the field of vipers and other venomous snakes, which was strongly represented in the Philosophical Transactions (Table 1), but not in the Edinburgh periodicals, was not used as a topic for a further case study. In view of the obvious eighteenth-century interest into this toxicological area, however, a few explanatory remarks seem to be in place here.

Ever since Andromachus, physician to the Roman Emperor Nero, had substituted lizards for vipers in the recipe for the famous antidote Mithridatium, viper flesh had become a regular item of the materia medica. Together with opium it became an essential ingredient of the antidote, soon known as "Andromachus' theriac", which in the Middle Ages developed into a panacea and an important article of commerce. Besides theriac, viper wine, broth and jelly of

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viper flesh, powder and salt of vipers, and other "viperine" preparations were recommended as remedies. Based on Galen's doctrine of primary qualities, they were thought to have a heating and drying effect on the body. Viper catchers provided physicians and apothecaries with the live animals. Against this background, the seventeenth century witnessed eminent scientific controversies, involving numerous animal experiments, between Francesco Redi, physician to the Grand Duke of Tuscany, and Moyse Charas, pharmacist to the Duke of Orleans, on the nature of the viper venom, and between Redi and the Jesuit Athanasius Kircher on the antidotal efficacy of the so-called snakestones. In view of the culture and epistemological status of experimentation in the early modern period, Redi's viper trials especially have recently been examined in detail by Jay Tribby, Paula Findlen, and Martha Baldwin. My own research into early experiments with vipers has revealed their remarkable extent. Alone in seven pertinent writings by six authors, published between 1640 and 1688, 95 descriptions of trials with vipers have been found, 57 of which seem to have been original.


31 The writings included in this search were: Ulysses Aldrovandi, Historiae serpentum et draconum libri duo, Bologna, Marcus Antonius Bernia, 1640; Marco Aurelio Severino, Vipera Pythia, Padua, Typis Pauli Frambotti, 1651;
In the early eighteenth-century volumes of the *Philosophical Transactions*, the experimental evaluation of olive oil as a new "antidote" against viper bites played a major role. The oil had originally been the secret remedy of an English viper catcher named William Oliver, who used it both externally and orally. It was not only of interest to the Royal Society for this particular purpose, but also as a possible remedy against the stings of scorpions and bites of rattlesnakes, which would have been of use in the colonies.\(^2\) The alleged antidote appears to have been discredited.

\(^2\) William Burton, 'Part of a letter...concerning the viper-catchers, and their remedy for the bite of a viper', *Phil. Trans.*, 1736, 39: 312; Cromwell Mortimer, 'A narration of the experiments made...on a man, who suffer'd himself to be bit by a viper, or common adder; and on other animals likewise bitten by the same, and other vipers', ibid., pp. 313-320; Joseph Atwell, 'A letter...containing some observations on a man and a woman bit by vipers', ibid., pp. 394-399; Stephen Williams, 'Extract of a letter...concerning the viper-catchers...and the efficacy of oil of olives in curing the bite of vipers', *Phil. Trans.*, 1737, 40: 26-27; Cromwell Mortimer, 'An abstract...of an inaugural dissertation published at Wittemberg 1736. by Dr. Abraham Vater, F.R.S. concerning the cure of the bite of a viper, cured by sallad-oil', *Phil. Trans.*, 1738, 40: 440-444; idem, 'Abstracts of two letters from M. Dufay, F.R.S....concerning the efficacy of oil of olives in curing the bite of vipers', ibid., pp. 444-445. See also Abraham Vater and Friderich Gensler, 'De antidoto novo adversus viperarum morsum praesentissimo in Anglia haud ita pridem detecto' (Wittenberg 1736), in Albrecht von Haller (ed.), *Disputationes ad morborum historiam et curationem facientes*, 7 vols, Lausanne, Sumptibus Marci-Michael Bousquet & Socior. and Sumptibus Sigismundi D'Arnay, 1757-1760, vol. 6, pp. 593-609.
however, after the apothecary Claude Joseph Geoffroy and the anatomist François-Joseph Hunauld had examined it by order of the Paris Academy of Sciences and shown its lack of efficacy in controlled animal experiments in 1737. Vipers and rattlesnakes themselves (and other serpents) were moreover objects of curiosity within natural history, which is reflected in several other articles in the Philosophical Transactions. No doubt the interest in vipers and other snakes was also a continuation of the learned debates of the seventeenth century. Finally, it should be remembered that Felice Fontana's toxicological work was chiefly concerned with the mode of action of the viper venom and the testing on animals of numerous alleged antidotes against it, most of which he found useless. Fontana's contribution in this area has been thoroughly discussed by Earles and Knoefel.

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34 For example John Ranby, 'The anatomy of the poisonous apparatus of a rattle-snake...together with an account of the quick effects of its poison', Phil. Trans., 1728, 35: 377-381; Sir Hans Sloane, 'Conjectures on the charming or fascinating power attributed to the rattle-snake: grounded on credible accounts, experiments and observations', Phil. Trans., 1734, 38: 321-331; John Ellis, 'A letter...on the Colubar Cerastes or horned viper of Egypt', Phil. Trans., 1766, 56: 287-290; Edward Whitaker Gray, 'Observations on the class of animals called, by Linnaeus, amphibia; particularly on the means of distinguishing those serpents which are venomous, from those which are not so', Phil. Trans., 1789, 79: 21-36.

35 The interest in snakestones, for example, was still alive. See Sir Hans Sloane, 'A letter...containing accounts of the pretended serpent stone called Pietra de Cobra de Cabelas', Phil. Trans., 1749, 46: 118-125. See also the wide-ranging and detailed discussion of the viper (incl. the rattlesnake) by Richard Mead, 'A mechanical account of poisons', in idem, The medical works, 3 vols, Edinburgh, A. Donaldson and J. Reid, 1765, vol. 1, pp. 1-158, on pp. 21-58.
Mercury, and various preparations made from it, were another prominent topic in the analyzed periodical literature. In the Edinburgh journals (Tables 2-5) contributions on mercurial remedies made about 10 to almost 40 per cent of the identified articles. In the Philosophical Transactions, on the other hand, they did not constitute a "field" of their own. The only two articles dealing specifically with mercury, which were published here during the eighteenth century, dealt rather with toxicological than curative aspects. A possible explanation for this discrepancy could be that mercury treatment was more a matter of medical practice than of scientific inquiry, though a number of animal experiments of the seventeenth and eighteenth century with crude mercury, sublimate (mercuric chloride), and calomel (mercurous chloride) are known. The considerably more, or exclusively, medical periodicals of Edinburgh may have been seen as more appropriate places of publication than the more general, "scientific" Philosophical Transactions.

In the eighteenth century mercury had in fact become very widely accepted as the most effective agent against venereal disease, i.e. syphilis and gonorrhea, which were not regarded as different entities for most of the period.

36 Felice Fontana, Traité sur le vénin de lavipère, sur les poisons Americains, sur le laurier-cerise et sur quelques autres poisons vegeaux, 2 vols, Florence, Avec Approbation, 1781; Earles, 'The experimental investigation', note 3 above; Knofel, 'Fontana on poisons', note 6 above; idem, F. Fontana, note 6 above, pp. 267-283.

37 T. Madden, 'An account of what was observ'd upon opening the corpse of a person who had taken several ounces of crude mercury internally', Phil. Trans., 1736, 39: 291-294; Andrew Cantwell, 'Extract of a letter...containing an account of a large glandular tumor in the pelvis; and on the pernicious effects of crude mercury given inwardly to the patient', Phil. Trans., 1737, 40: 139-142.

38 See Bernknopf, op. cit., note 4 above, pp. 23-26; Maehle, J. J. Wepfer, note 7 above, pp. 103-110.
Although the substance's harmful side effects, such as stomatitis and gingivitis, and its neurotoxicity, were well known, its various preparations were not only used against "the pox", but in many other skin affections, various "tumours", against worms, intestinal obstruction, and many other conditions. Salivation and a purging effect (the latter especially after calomel) characterized mercury as an evacuant medicine, which expelled the "venereal poison" or other morbific matter. It thus fitted the still prevailing humoral theory, but also iatrochemical and iatromechanical reasons were given for its application. Claude Quétel has observed that much of the contemporary literature was concerned with the question of how the mercury should be given, and he noted that towards the end of the eighteenth century internal administration (orally and rectally) took over from the traditional ointments and frictions. Gerard van Swieten's famous antivenereal liquor (i.e. sublimate dissolved in water and alcohol), which was taken internally, formed an important part of this development. Quétel has also mentioned the numerous other proprietary medicines (with and without mercury) against venereal disease in the eighteenth century, that were propagated both by doctors and "empirics" and which were sometimes "tested", with rather dubious results, in military hospitals, prisons, or on the venereal patients of the Bicêtre hospital in Paris.39

The articles on mercurial remedies in the Edinburgh periodicals reflect the above general characteristics and tendencies. As a new mercurial medicine "Plummer's pills" (combining calomel and antimony sulfides) were tried out in

venereal and other diseases. Some reports dealt with particulars of the usual mercurial treatments of lues and constipation, but others were concerned with new indications: convulsive disorders (5 articles), hydrocephalus (5 articles), yellow fever (2 articles), and croup (2 articles). Virtually all of them presented one or more case histories, some of which illustrated also failures and intoxications. The widening of the use of mercury, from a "specific" antivenereal remedy to a "panacea", is


tangible in these articles. The study of mercurial therapy was evidently a largely empirical enterprise. There was no mention of pharmacological animal experiments in this sample.

Certainly the mercury remedies of the eighteenth century would have made a fascinating topic for a separate case study, yet it probably would have steered my work away from pharmacology and far into therapeutics and the numerous "quack" medicines of the time. Undoubtedly the topic deserves monographic treatment in its own right.

As mentioned above, mercury was also given against intestinal worms, yet it was only one of many anthelmintics known and tried in the eighteenth century. Daniel Le Clerc's *Historia naturalis et medica latorum lumbricorum* (1715), a standard work of the field, listed 416 simple drugs against worms, 368 of which were of vegetable, 18 of mineral, and 30 of animal origin, as Charles Alston (1683-1760), professor of botany and materia medica in Edinburgh, counted. The efficacy of many, however, appears to have been doubtful. Commonly used anthelmintics were male fern, flowers of Artemesia species and of Chrysanthemum, American wormseed, and filings of tin. Usually these medicines were combined

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44 Also van Swieten's remedy was tried in this way. See John Gardiner, 'A particular method of giving the solution of corrosive sublimate mercury in small doses, as an anthelmintic', *Ess. Obs. Phys. Lit.*, 1771, 3: 380-390; David Clerk, 'Remarks on Dr Gardiner's paper on the use of corrosive sublimate, as an anthelmintic', ibid., pp. 391-394.

with purgatives in order to facilitate the expulsion of the parasites. In the Medical Essays and Observations, for example, Alston reported favourable experiences with powder of tin, which he thought to act chiefly by getting between the worms and the inner coat of the intestines, thus making the action of the purgative remedies more effective. Not surprisingly, anthelmintics were a major topic in the subsequent Essays and Observations, Physical and Literary and the Medical (and Philosophical) Commentaries (Tables 3 and 4). Characteristically, physicians and surgeons practising in the West Indies and American colonies reported about indigenous plant remedies against worms, such as Indian Pink, bark of the cabbage tree, couhage, and Angeline tree bark. Case histories were sometimes given to illustrate their efficacy. Occasionally in vitro trials on worms were carried out in order to test and compare the anthelmintic power of various substances - a method, which had already been used by Redi in the late seventeenth century. Experiments on worm-infected horses were performed


49 Thomas Kilgour, 'The history of a case, in which worms in the nose, productive of alarming symptoms, were successfully removed by the use of tobacco', Med. Comm. (2nd edn), 1781/82, 8: 75-83; Thomas Fowler, 'Observations and
in the late eighteenth century in the context of veterinary medicine. Yet, as in the case of mercurial remedies, contemporary work on anthelmintics seems to have been mainly empirical, i.e. a matter of therapeutic practice. It appeared therefore from my perspective less suitable as a topic for a study into the relations between pharmacology and therapeutics. Microbiologists have in recent years dealt with the history of anthelmintics as part of the general history of helminthology. A comprehensive historical study into these remedies, however, remains a desideratum.

A number of smaller fields, partly of temporary, but at the time strong interest, deserve to be mentioned. The analysis of Duncan's Medical (and Philosophical) Commentaries, for example, has revealed a strong therapeutic interest in flowers of zinc (zinc oxide) and cuprum ammoniacum (ammoniated copper) since the 1770s and 1780s, respectively (Table 4). Both substances were given as antispasmodics in a variety of convulsive disorders, from epilepsy, hysterical fits, and chorea St. Viti to dysphagia and obstinate cough. Convulsions were understood as arising from an excessive "mobility of the nervous system", and the copper and zinc compounds (sometimes also given in combination) were thought to help through their "tonic" property. The case histories presented on these treatments were usually "successes", though failures were not withheld. There was no reference to animal experimentation

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experiments on the effects of different anthelmintics applied to earth-worms', ibid., pp. 336-345; Enigk, op. cit., note 46 above, p. 241.

50 See ibid., pp. 240, 243.


52 See for example Benjamin Bell, 'The case of a man affected with an obstinate epilepsy, considerably relieved by the use of the flowers of zinc', Med. Phil. Comm., 1773, 1: 204-208; Patrick Dugud, 'The history of a convulsive disorder,
with the two compounds. The generally positive assessment was entirely clinical, i.e. based on improvements in individual patients.

It has already been briefly mentioned that tobacco was another field of interest in the Medical (and Philosophical) Commentaries. Introduced from the New World into Europe around the middle of the sixteenth century, tobacco had soon gained a reputation as a medicinal plant, despite the moral controversies surrounding its early medical and recreational use. By the eighteenth century it was firmly established as a therapeutic agent. A common form of application, for example, were clysters with tobacco smoke against various intestinal obstructions. Accordingly, the identified articles deal with details of the drug's form of application in particular diseases, for instance Thomas Fowler's Infusum Nicotianae in dropsy, or with intoxications, rather than with principally new developments.


noxious damps and airs, and antiseptics as topics of considerable interest. In rabies, of course, the prognosis was hopeless. Euthanasia in patients in the final stages of the disease, performed either by medical men through excessive blood-letting or by others through suffocation with the bedding, seems to have been a not uncommon practice in the eighteenth century. On the other hand, even the remotest chances of effecting an early cure were sought. Besides local treatment of the bite with resection and cauterisation, and general measures, such as cold baths and submerging the hydrophobic patient, a multitude of medicines were tried. In particular mercury (to expel the rabies "poison" by salivation and purgation) and Richard Mead's Pulvis antilyssus or Dampier's powder, a mixture of the lichen cinereus terrestris (ash-coloured ground liverwort) with black pepper, were thought to be effective. The identified articles were typically case histories of human rabies with accounts of the particular therapy or remedy used. As one would expect in this topic, experiences with treatments on rabid animals (dogs, horses) were also reported. Yet, despite these efforts, other medical men,


such as the military doctor John Hunter (1754-1809), remained sceptical, arguing that the alleged successes were cases of people bitten by merely enraged (not rabid) dogs, and that the only method to prevent real rabies consisted in rigorous local treatment of the wound.

Styptics (i.e. substances for local application to stop bleeding, especially after amputations) had already been a matter of debate in the 1690s, when John Colbatch's "Vulnerary Powder" had been tested on dogs and subsequently - with controversial results - on patients of St. Bartholomew's Hospital. The topic continued to be of occasional interest in the early eighteenth century, as articles on "Dr. Eaton's styptick" and the Pulvis stypticus Helvetii (alum with the gum resin "sanguis draconis") document. Yet it was fully revived in the middle of the eighteenth century by a report of a French surgeon about successes with agaric (i.e. fungus) of oak as a new effective styptic. Within a few years a number of English surgeons repeated the "experiment" and communicated their findings.

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58 Robert James, 'A letter...containin some experiments made upon mad dogs with mercury', Phil. Trans., 1736, 39: 244-250; John Starr, 'A letter...containin an account of an horse bit by a mad dog', Phil. Trans., 1750, 46: 474-478.

59 Not to be mistaken with the famous anatomist John Hunter (1728-1793).

60 Théodoridès, op. cit., note 56 above, pp. 154-155.


63 James Theobald, 'Mons. Faget's remarks on the use, etc. of the styptic, purchased by His Most Christian Majesty', Phil. Trans., 1751/52, 47: 560-565.
own success cases. Following French trials on horses, Lycoperdon (puff ball mushroom) was used as a further styptic. The enthusiasm seems to have been short-lived, however. The last article of this kind in the Philosophical Transactions appeared in 1755, and there was also none after that time in the examined Edinburgh periodicals. The application of styptics could obviously not prevail over the conventional methods of controlling haemorrhages, i.e. cauterisation, application of the tourniquet, and tight bandaging.

"Noxious" damps and airs was already a traditional topic in the eighteenth century. Richard Mead, for example, discussed "venomous exhalations from the earth, poisonous airs, and waters" in a separate essay within his highly successful Mechanical account of poisons (1st edn 1702), starting with the knowledge of the ancients about the "Mephitis" (venomous steam) of Hierapolis and the "stinking deadly air" of the cave Corycius in Cilicia. Modern examples were the "fumes" in mines and pits, yet the prototype was the Grotta de' Cani near Naples, named after the practice of

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65 James Latterman, 'Extracts of two letters...concerning the effects of the agaric of the oak...to which are added some remarkable experiments made upon the arteries of horses, with the powder of the Lycoperdon, or Lupi Crepitus; by Monsieur La Fosse, Farrier to the King of France', Phil. Trans., 1755, 49: 36-38; James Parsons, 'A letter...concerning the use of Lycoperdon, in stopping blood after amputations', ibid., pp. 38-43.


demonstrating its poisonous exhalations on dogs. Mead had visited the place himself, described it at length, and speculated about the nature of its "fume" on the basis of experiments on dogs and frogs.\(^6^8\) It is therefore no surprise that some of the identified articles in the Philosophical Transactions also dealt with this Grotta.\(^6^9\) Other contributions reported about damps in a well, poisoning by coal fumes, and effluvia from putrid marshes.\(^7^0\) The latter, of course, and other "bad" airs were regarded as causes of fevers. As Christopher Lawrence has emphasized, Joseph Priestley's chemical work on different "kinds of air" had many of these medical connotations.\(^7^1\) Against "putrid fevers" so-called antiseptics, i.e. substances delaying or preventing putrefaction, were hoped to be effective. Especially the renowned military physician John Pringle and the Dublin doctor David Macbride engaged in numerous in vitro experiments in this field. They were followed by the Edinburgh surgeon William Alexander, who proceeded to trials

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\(^6^8\) Mead, op. cit., note 35 above, vol. 1, pp. 141-158.

\(^6^9\) Johann Philipp Seip, 'Relatio de caverna vaporifera sulphurea in lapicidina Pyrmontana, quae similis est foveae Neapolitanae Grotta del Cane dictae', Phil. Trans., 1738, 40: 266-272; Thomas Stack, 'Extract of the observations made in Italy by the Abbé Nollet on the Grotta de Cani', Phil. Trans., 1751/52, 47: 48-61.

\(^7^0\) For example Benjamin Cooke, 'An observation of an extraordinary damp in a well in the Isle of Wight', Phil. Trans., 1738, 40: 379-383; Matthew Guthrie, 'Account of the manner in which the Russians treat persons affected by the fumes of burning charcoal, and other effluvia of the same nature', Phil. Trans., 1779, 69: 325-331; Joseph Priestley, 'On the noxious quality of the effluvia of putrid marshes', Phil. Trans., 1773/74, 64: 90-95.

with antiseptics on whole animals and his own body.\textsuperscript{72} Peruvian bark was among the substances found to have "antiseptic power" in such experiments, some of which will therefore be discussed in part C.\textsuperscript{73}

The special interest in a number of further substances, as revealed by my analysis of the Philosophical Transactions (Table 1) may be ascribed to their unusual origin (ambergris and spermaceti),\textsuperscript{74} their therapeutic importance (ipecacuanha, antimony),\textsuperscript{75} their ambiguous role as remedy and poison


\textsuperscript{73} See below, part C, 6.

\textsuperscript{74} Ambergris and spermaceti are formed in the intestines and head of the sperm whale, respectively. They were seen as one substance and valued as relaxing demulcents and emollients. Cf. J. Worth Estes, Dictionary of protopharmacology: therapeutic practices, 1700-1850, Canton, MA, Science History Publications, 1990, pp. 8, 181. Towards the end of the 18th century its medical use seems to have become obsolete, the substance being used almost exclusively for perfumery. Cf. Schwediawer, 'An account of ambergrise', Phil. Trans., 1783, 73: 226-241.

\textsuperscript{75} Antimonial preparations and ipecacuanha were widely used as emetics, the former also as diaphoretics and the latter also as an expectorant. On antimony see Hermann Fischer, Metaphysische, experimentelle und utilitaristische Traditionen in der Antimonliteratur zur Zeit der "wissenschaftlichen Revolution" (1520-1820), Braunschweig, 1988 (Braunschweiger Veröffentlichungen zur Geschichte der Pharmazie und der Naturwissenschaften, vol. 30). On the introduction of ipecacuanha from South America since the middle of the 17th century see Sigrun Engelen, 'Die Einführung der Radix Ipecacuanha in Europa', Med. Diss. Düsseldorf, 1967/68.
Finally it can be seen that the interest in exotic plants and drugs was not only a characteristic of the sixteenth and seventeenth centuries, but continued throughout the eighteenth century.

An at first glance surprising, "negative" finding is the absence of digitalis as a "field" of its own in the examined periodicals, though the drug came to prominence only with Withering's work in 1785. Merely two articles on therapy with foxglove, both inspired by Withering, were found in Duncan's *Medical Commentaries*. They did not deal with the "classic" indication of dropsy, but with the use of the drug in two cases of insanity and one of haemoptysis. In the insanity cases digitalis was given as a diuretic on the supposition that the disease was caused by extravasated fluid in the brain; and in the patient who coughed up blood the drug was used to slow down his pulse. This relative

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76 On Anton Störck's trials with hemlock as an internal and external remedy for cancer see Schwepppe, 'Experimentelle Arzneimittelforschung', note 5 above; *idem* and Probst, op. cit., note 5 above. On J. J. Wepfer's observations and experiments on water hemlock poisoning, see Maehle, J. J. Wepfer, note 7 above. As a reflection of the hemlock's "double" role see William Watson, 'A letter...concerning some persons being poisoned by eating boiled hemlock', *Phil. Trans.*, 1744, 43: 18-22; *idem*, 'An account of the Cicuta, recommended by Dr. Storke', *Phil. Trans.*, 1761, 52: 89-93. William Alexander almost killed himself in self-experiments with camphor; see Alexander, op. cit., note 73 above, pp. 127-137. See also *idem*, 'Experiments with camphire', *Phil. Trans.*, 1767, 57: 65-71.

77 On the experiments with Indian arrow poisons (curare), especially by Fontana, and on the toxicological observations and experiments on cherry laurel (contains hydrocyanic acid), as reported in the *Philosophical Transactions*, see Earles, 'Studies', note 3 above, and Knoefel, F. Fontana, note 6 above, pp. 283-287, 301-302. On henbane poisoning see for example Sir Hans Sloane, 'An account of symptoms arising from eating the seeds of henbane, with their cure', *Phil. Trans.*, 1733, 38: 99-101.
scarcity of articles on digitalis might be taken as a warning not to overestimate the contemporary significance of drugs, which have been traditionally regarded as important in medical historiography. Similarly, the history of rhubarb has recently been examined in great detail (including a chapter on the eighteenth century) by Clifford M. Foust, yet our search of periodicals has brought to light only one article dealing specifically with this drug. However, both examples also show that our results are very much a reflection of our choice of sources. Withering did publish in the *Philosophical Transactions*, yet not on the foxglove, but on mineralogy, chemistry, and physics. As it is well known, his digitalis studies appeared as a monograph, his famous *Account of the foxglove* (1785). The picture would probably have been somewhat different, if our analysis had been extended to include also some of the "newer" London-based medical journals, such as the *Medical Transactions* (1768-1820) of the Royal College of Physicians, the *Memoirs of the Medical Society of London* (1787-1805), and the *London Medical Journal* (1781-90), which contain the pertinent papers on digitalis by Erasmus Darwin, Sir George Baker, and others.

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78 William Jones, "An account of two cases of insanity, one of which was cured by the use of the fox-glove: also a case of hemoptysis, cured by the same remedy", *Med. Comm.*, 1786, 11: 302-316; Joseph Mason Fox, "History of a case of insanity, cured by the use of the digitalis purpurea", *Med. Comm.*, 1789, 14: 261-270.


80 John Hope, "Extract of a letter...to Dr. Pringle; dated Edinburgh, 24 September, 1765", *Phil. Trans.*, 1765, 55: 290-293.

81 See Withering's bibliography in Aronson, op. cit., note 9 above, pp. 265-267.

John Coakley Lettsom, William Currie, and John Warren. Foust's account of rhubarb in eighteenth-century medicine is based on different, often monographical sources. The examples of foxglove and rhubarb thus remind us of the limitations of the above analysis of selected periodicals. It cannot be more than a first step towards a more objective historiography of pharmacology. Indirectly, its results underline the importance of detailed "case studies" of particular substances, that include a wide variety of sources, as they will follow in the main parts of this thesis.

Still the analysis of periodicals provides some orientation about two further aspects: the methodology, on which the identified "pharmacological" articles were based, and the professional status of their authors. Research into these two areas has been limited to the selected Edinburgh periodicals, which, taken together, carried the sufficiently high number of 160 contributions within the broad area of materia medica, pharmacotherapy, and poisons, during the years 1733 to 1800. An analogous search could in principle have been performed for the 240 identified articles in the Philosophical Transactions as well. Yet an adequate interpretation of the results of such an extensive study would require more background knowledge about the role of medicine in the Royal Society than is at present available. While the Society's early scientific development in the seventeenth century has been investigated in considerable detail, its history in the eighteenth century has to a

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83 On all of these see Aronson, op. cit., note 9 above. See also Estes, op. cit., note 9 above. For the quoted periodicals as such see W. R. LeFanu, British periodicals of medicine, 1640-1899, rev. edn, ed. Jean Loudon, Oxford, Wellcome Unit for the History of Medicine, 1984.

84 See for example Michael Hunter, The Royal Society and its Fellows 1660-1700: the morphology of an early scientific institution, Chalfont St Giles, The British Society for the
great extent remained a "valley of darkness", as David P. Miller has put it in 1989.® Only very recently a first step into the exploration of medicine at the Royal Society during this period has been made by Philip Wilson, who has analyzed the surgical articles in the Philosophical Transactions from 1727 to 1778.®

Similarly, much work on medicine in the eighteenth-century Edinburgh periodicals remains to be done, though Roger L. Emerson and Jacqueline Jenkinson have provided background concerning the Medical Essays and Observations, Essays and Observations, Physical and Literary, and Medical Commentaries.® Accordingly, the following results are meant to give just some general orientation. As can be seen in Tables 2-4, drawing up and presenting one or a few case histories was the predominant method used in the vast majority of contributions. It was found in more than two thirds of the identified articles in the Medical Essays and


®® Wilson, op. cit., note 64 above.

® See note 17 above.
Observations and Essays and Observations, Physical and Literary and in over 80 per cent, respectively over 90 per cent, of those in the Medical (and Philosophical) Commentaries and Annals of Medicine. These results principally confirm, and actually accentuate, a finding of Jenkinson, who counted a total of 217 medical articles in the five volumes of the Medical Essays and Observations (1733-1744), of which 88 (41 per cent) were case histories.** In our samples (Tables 2-4) the case histories were further supplemented by a considerable number of articles presenting "general therapeutic experience", i.e. an intellectual digest of cases without going into the details of particular patients. Only exceptionally, simple arithmetics ("protostatistics") were applied to evaluate treatment in a number of similar cases (Table 4), and there were only a few attempts to give detailed iatrophysical explanations (Table 2). The experimental approach was on the whole much less used in the study of drugs and poisons than the clinical with cases histories. Chemical experimentation with the drug in question, to learn about its components or its acidity/alkalinity, was here the most common method, being used in about one fifth of the identified articles in the Medical Essays and Observations and Essays and Observations, Physical and Literary. Self- and human experimentation, animal experiments, and pharmacological in vitro trials were described only in a very small proportion of articles (Tables 2-4).

Typically the experimental methods were chiefly used by the Edinburgh professors of medicine, Andrew Plummer, Charles Alston, Alexander Monro primus and secundus, and Robert Whytt, who contributed considerably to the Medical Essays and Observations or Essays and Observations, Physical and Literary. Conversely, among the articles identified in

** Jenkinson, op. cit., note 17 above, p. 29.
the Medical (and Philosophical) Commentaries and Annals of Medicine, none of which came from a medical professor, the experimental approach played a very small or no role. As one would expect in (broadly) pharmacological articles, physicians dominated as authors (Tables 3-5), except in the Medical Essays and Observations, where surgeons were the stronger group. In this case the influence of the editor, Alexander Monro primus, who was surgically trained himself, may have been a reason. However, a remarkable finding are the generally very high proportions of surgeons, who published on the topics of materia medica, pharmacotherapy, and poisons. In the Medical Essays and Observations, Medical (and Philosophical) Commentaries, and Annals of Medicine between 40 and 48 per cent of the contributors of the identified articles were surgeons (Tables 2 and 4-5). Only in the more broadly "science-oriented" Essays and Observations, Physical and Literary their proportion was lower, yet with more than one fifth still considerable (Table 3). This result indicates that many surgeons actually practised to a great extent internal medicine, probably as surgeon-apothecaries. More than this, they took actively part in the assessment of new remedies as well as in the finding of new indications for known medicines. In other words, they were, like the physicians, part of therapeutic innovation in the eighteenth century. At least this can be said for Britain (including her colonies), from where almost all of the identified contributions to the examined Edinburgh periodicals came. Only about 4 per cent of the articles of this sample were sent from the European Continent.

These results, emphasizing the role of case histories and of "common" medical practitioners in eighteenth-century British pharmacology and therapeutics, can serve as a "quantitative" background to the following three detailed studies into lithontriptics, opium, and Peruvian bark. Yet again, also these findings should not be overestimated. The
"qualitative" approach taken in these case studies will show that the experimental method, if it was used, was sometimes very influential. And the discourse on these remedies was an international one.
Table 1: Articles on materia medica, pharmacotherapy, and poisons in the Philosophical Transactions of the Royal Society of London, 1700-1799 (n = 240).

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<td>25</td>
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<td>1707-1792</td>
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<tr>
<td>Vipers and other snakes</td>
<td>19</td>
<td>7.9</td>
<td>1700-1789</td>
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<td>15</td>
<td>6.3</td>
<td>1701-1798</td>
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<tr>
<td>Cinchona bark</td>
<td>14</td>
<td>5.8</td>
<td>1704-1784</td>
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<tr>
<td>Rabies remedies</td>
<td>11</td>
<td>4.6</td>
<td>1709-1765</td>
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<tr>
<td>Styptics</td>
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<tr>
<td>Noxious damp and airs</td>
<td>10</td>
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<td>Antiseptics^2</td>
<td>9</td>
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<td>1702-1758</td>
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^1 including chemical analysis of urinary stones.

^2 including putrefaction.
Table 2: Articles on materia medica, pharmacotherapy, and poisons in the *Medical Essays and Observations*, 1733-1744, of the Medical Society and Philosophical Society of Edinburgh (n=31).

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¹ For some articles several methods had been applied in combination.
Table 3: Articles on materia medica, pharmacotherapy, and poisons in the *Essays and Observations, Physical and Literary, 1754-1771*, of the Philosophical Society of Edinburgh *(n = 25)*.

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¹ For some articles several methods had been applied in combination.
Table 4: Articles on materia medica, pharmacotherapy, and poisons in the Medical and Philosophical Commentaries, 1773-1779, and Medical Commentaries, 1780-1795, edited by Andrew Duncan senior, Edinburgh (n = 86).

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1 Includes one article on combined therapy with Flowers of zinc and Cuprum ammoniacum (counted only once).
2 Includes one article on tobacco as an anthelmintic (counted only once).
3 Includes one article that covers also mercurial remedies (counted only once).
4 For some articles several methods had been applied in combination.
Table 5: Articles on materia medica, pharmacotherapy, and poisons in the *Annals of Medicine*, 1796-1800, edited by Andrew Duncan senior and junior, Edinburgh (n = 18).

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A. THE SEARCH FOR LITHONTRIPTICS

1. Introduction

Substances and compound remedies with a capacity to "destroy" urinary stones, the so-called lithontriptics, formed a major field of interest of eighteenth-century pharmacology and therapeutics. Articles on this subject figured prominently in the Philosophical Transactions of the Royal Society of London and the Essays and Observations, Physical and Literary of the Edinburgh Philosophical Society. A special bibliography, compiled in the early 1830s by the Norwich surgeon John Green Crosse (1790-1850), listed no less than 103 monographs and 74 articles on lithontriptics, published internationally since 1700. Several experimental studies and clinical observations came from authors that were well-known and widely respected in the eighteenth-century medical world, such as Stephen Hales and James Jurin in London, Robert Whytt and Charles Alston in Edinburgh, Thomas Percival in Manchester, Claude Joseph Geoffroy, Sauveur-François Morand and Antoine François de Fourcroy in Paris, Anton de Haen in Vienna, and Johann Andreas Murray in Göttingen.

Historians, however, have so far concentrated only on the more spectacular or external aspects of the topic. Arthur Viseltear has described the events which, in 1740, induced Parliament to grant the empiric Joanna Stephens the high reward of 5,000 pounds for revealing the recipe of her "Medicines for the Cure of the Stone". The death

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of Sir Robert Walpole in 1745, which some contemporaries believed to have been hastened (if not caused) by the use of Jurin's "Lixivium lithontripticum", has been studied by Viseltear, too, and, more recently, by Edmund Anthony Spriggs. Viseltear also summarized some of the controversial trials that were made to evaluate Mrs Stephens's medicines. A full historical account and analysis of eighteenth-century research on these and other supposed lithontriptics has not yet been provided, however. This is particularly true for the many remedies and substances tested before and after those two early proprietary medicines. The relevance of the subject in eighteenth-century medicine, on the other hand, has recently been pointed out again. Philip Wilson has shown that remedies for bladder stones were frequently listed in contemporary domestic manuals, obviously being perceived by the public as an alternative to the dreaded, though technically improved, lithotomy operations. According to him, experimentation with the "dissolvents" led physicians to claim competence in advising the right therapeutic choice in a particular patient. Moreover,


4 Viseltear, op. cit., note 2 above, pp. 206-216.


David Harley has recently suggested a political faction over the issue of Mrs Stephens's medicines, the project of a reward for her having been "mainly supported by Whig physicians and opposed by Tory surgeons."⁷

In contrast to this previous work, the present chapter focuses on the more internal, scientific aspects of the subject. In particular, it analyzes the methods used in evaluating the efficacy and harmlessness, or noxiousness, of lithontriptics and looks into the contemporary debate on the validity of these methods. Attention is also drawn to the theories on the mode of action of remedies against urinary stones. In doing this the influence of advances in chemistry is studied as well, with respect to ideas both about the properties of lithontriptics and the constituent elements of their target, the urinary concretions. The present study concentrates on the period from about 1730, when Stephen Hales conducted a first series of experiments on the stone dissolving powers of various substances and mixtures,⁸ to the second decade of the nineteenth century, when Alexander Marcet outlined a full scheme for the pharmacotherapy of calculi based on recent insights in animal chemistry.⁹ Beforehand, however, some remarks on the long tradition of lithontriptic medicines have to be made.


2. Traditions

The idea that certain substances, taken orally, had the power to destroy stones in the urinary tract was by no means new in the eighteenth century. The recommendation of such remedies can in fact be traced back at least to the materia medica of Graeco-Roman antiquity. As in other areas of pharmacology, Dioscorides (fl. c. AD 40-80) was influential here, by describing several medicines that would "break" bladder stones. He attributed such a power to the vegetable remedies cardamom, laurel, kotyledon, semen paliuri, gum of the plum tree, lithospermon, and saxifrage, as well as to the so-called lapis Judaicus (i.e. fossil spines of sea urchins imported from Judaea) and to "stones found in sponges". The last four of these recommendations seem to have been based on an argument by analogy: like the urinary calculus, the lapis Judaicus and the lime-like concretions in sea sponges were kinds of "stones"; the saxifrage was known to be a shrub growing on rocky ground, thus "breaking" its way through the stones; and lithospermon was so called, because its seeds were "hard as stone". In addition to their lithontriptic property, Dioscorides ascribed a diuretic effect to some of these remedies. Very similar knowledge was reproduced by Pliny the Elder (AD 23-79) in his Natural history. He too mentioned "sponge stones", which, taken in wine, would cure bladder affections, and break and expel calculi. Probably meaning the same as had Dioscorides with saxifrage, Pliny wrote that "empetras" or "calcifraga",

10 John M. Riddle, Dioscorides on pharmacy and medicine, Austin, University of Texas, 1985, pp. 39, 67, 162.

growing on rocks in the coastal mountains, had a diuretic and stone-breaking effect. Like Dioscorides, he also regarded the seeds of paliuros as lithontriptic and its root as diuretic. A different tradition is reflected in the works of Aretaeus (c. AD 150). Among others he named water-parsnip as a simple medicine for breaking urinary stones and as a compounded remedy one made from vipers and the lizard "skink". Both vipers and the "skink" were also included in the materia medica of Dioscorides, but neither for bladder stones nor other diseases of the urinary tract.

A whole range of lithontriptics, grouped according to their strength, was eventually given in the writing De affectuum renibus insidentium dignotione et curacione, which has been ascribed to Galen (c. 130-199 or after 212), but is now regarded as a later compilation. The first category, "stone grinding" remedies, included a decoction of roots of quick-grass, damasonium cress, and maidenhair fern. If this had no success, the use of "stone destroying" medicines was advised, such as roots of asparagus, bdellium Arabiae, marshmallow seeds, lithospermon, betony, saxifrage, pennyroyal, the root of the Egyptian caper bush, and seeds of domestic figs. The lapis Judaicus was put in a third group of more effective, "strongly stone breaking" remedies, which also included vitrum ustum, lapis Cappadox (i.e. sponge stones), and semen paliuri. For the first group of lithontriptics this pseudo-Galenic text provided a pharmacological explanation: plants such as damasonium and maidenhair had a lukewarm quality and thus

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counteracted excessive body heat, which was thought to harden "thick matter" in the urine and to form stones in this way. For the same reason the use of hot, diuretic substances was forbidden here. Generally, however, an explanation for the choice of certain substances as lithotriptics was not given in the texts of antiquity. Their efficacy was merely affirmed. Yet, that slight scepticism in this respect existed already at that time, can be inferred from some contemporary remarks. Those who sought to win belief in the assurance that "calcifraga" could break bladder stones, noted Pliny, asserted that pebbles boiled with it were broken up. Also, the pharmacological explanation in the pseudo-Galenic text on kidney affections was given explicitly for those who might doubt that plants of a lukewarm quality had a lithotriptic power. And Galen himself, in his De simplicium medicamentorum temperamentis et facultatibus, emphasized that the "stones found in sponges" could break only renal calculi, but not bladder stones, and that those who had maintained this in their writings had made this up. The same applied, according to his own experience, to the lapis Judaicus.

Despite such occasional doubts, medicines against urinary stones continued to be passed on, figuring largely in the materia medica of medieval Arabic medicine. Rhazes (c. 854-925 or 935) gave a number of


18 Ibid., vol. 12, pp. 199, 205-206.

formulas for remedies "which break the stone", as did Avicenna (980-1037), who also listed many simple substances for this purpose. The recipes of both authors included numerous vegetable ingredients, several of which had been recommended as lithotriptics by the authors of antiquity, e.g. the root bark of the caper bush, cardamom, laurel, marshmallow seeds, bdellium, and the gum of the plum tree. Rhazes and Avicenna also continued to advise the use of sponge stones and the lapis Judaicus. In addition, melon seeds, wild carrot seeds, parsley and the ashes of scorpions were repeatedly mentioned by the Arabic authors. Their pharmacopoeia against urinary stones was larger and more differentiated than that of the Graeco-Roman writers, but - as one would expect - not basically different. Also, the ideas on the formation of stones, and on the properties of remedies against them, were those of antiquity. As Avicenna put it, excessive body heat, being an "active force", formed stones out of viscous humours, which represented "passive matter". Lithotriptic remedies, therefore, should not be too hot, otherwise they contributed to the cause of stones. Thus the best of them broke the stone powerfully without heating too much.

The Arabic tradition of lithotriptics, in turn, survived well into the early modern period. A "Confection of Rhazes" against bladder stones was still "highly praised" in the early seventeenth century. The complicated recipe brought together many of the ingredients that Rhazes had named in his original formulas. An equally popular lithotriptic was the pharmacologie Grecque dans le monde Arabe. Une vue d'ensemble', Medicina nei Secoli Arte e Scienza, 1995, 7: 159-189.


21 Ibid., pp. 228, 237.
"Confectio ex cineribus", which deviated only slightly from an original recipe in the Canon of Avicenna, containing, among others, glass, cabbage roots, scorpions, hare, and eggshells, all burnt to ashes.  

The seventeenth century, however, saw not only a continuation of lithontriptic therapy in the tradition of the ancients and the Arabs. Against the background of the rise of iatrochemistry, the classical doctrine of stone formation began to be challenged, and radical doubts that effective lithontriptics existed at all were expressed. In his Ortus medicinae (posth. 1648) Johann Baptiste van Helmont (1579-1644) questioned the evidence usually put forward in support of the ancient theory that phlegm was heated to form stones. The fact that patients with vesical calculi felt heat in their groins and voided mucus in their urine was in his view not an indication of stone formation, but a consequence of it, following from lesions caused by the stone. Moreover, the urine of stone carriers was known to form a sediment when it cooled in the glass. How then could heat be the cause? Instead, van Helmont applied the Paracelsian doctrine of the "tartarus". Like the tartar in wine, urinary calculi coalesced from a "stonifying juice", ultimately arising from "seeds" of stone, which lay "hidden in the juices". A true lithontriptic thus had to reverse this coagulation process. The remedies of the ancients, however, as van Helmont saw it, were good only to expel smaller calculi. They had neither the power to dissolve stones, nor to prevent their formation. To achieve the latter aim, he suggested to make the "over-exquisite separating Faculty" of the kidneys sleep by administering sedating plants, such as vitex agnus-castus and mandrake. An effective

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dissolvent for urinary calculi not having been found yet, van Helmont listed the criteria it would need to fulfill. It had to enter the urine, reach all relevant parts, own a specific (not secondary) "Power of loosing the Bolts of the Stone", and to be "friendly to Nature". Corrosives, which had been suggested by other authors, were excluded by the last criterion.^[24]

By the early eighteenth century the question whether stone-dissolving medicines actually existed had become a current subject of learned debate. The London physician Joannes Groenevelt, for instance, denied it in his Compleat treatise of the stone and gravel (1710), though only ten years earlier optimistic reports on therapeutic successes with powder of "ostracites" (? oyster shells) and the Ceylonese plant acemella had been published by the Royal Society.^[25] Yet Groenevelt was a well-known lithotomist, and his view may have been regarded as biased for this reason. Obviously foreseeing such criticism, he assured the reader that he would "cut no more" as soon as someone could show him that there was an effective lithontriptic. He admitted that it was "perhaps from the Art of Chymistry that we may expect this Miracle".^[26]

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^[25] John Greenfield (Joannes Groenevelt), A compleat treatise of the stone and gravel...with an ample discourse on lithontriptick; or stone-breaking medicines, London, Ralph Smith and B. Lintott, 1710, pp. 277-280; Cay, 'Part of a letter...to Dr. Lister, concerning the vertues of the ostracites', Phil. Trans., 1699/1700, 21: 81-85; Peter Hotton, 'Excerpta ex literis...de acemella et ejus facultate lithontriptica', Phil. Trans., 1700/01, 22: 760-762.

In 1729, the Rostock professor of medicine Georg Christoph Detharding (1671-1747) had the question of lithotriptides answered in a doctoral disputation, as did five years later his Halle colleague Johann Heinrich Schulze (1687-1744). Detharding's student, Ernst Wilhelm Schaumkell, was confronted with the case history of a 70-year-old man who had been diagnosed as having a bladder stone. After taking a traditional remedy, containing, among others, saxifrage, cardamom, and parsley, the patient had started to void stony "lamellae". Was this due to a lithotriptic effect of the medicine? Schaumkell's answer was "no". In his opinion the so-called stone-breaking remedies of the ancients were nothing else but strong diuretics. In friable stones, as in the present case, the increased flow of urine might just wash off some flakes. The same view was expressed rather poetically by the prominent London physician and writer Sir Richard Blackmore (1650-1729): while porous and friable calculi might crumble, "harder and more solid Stones...cannot be broken, or cut in pieces, by Remedies given at the Mouth, but they defy the Edge of the keepest Lithotriptick Weapon in all the Arsenals of Greece." Schulze's student, Johann Ernst Graberg, however, came to the opposite conclusion that there was in fact a true stone-destroying remedy. He based his argument mainly on two cases of seemingly successful lithotriptic therapy, which had been published already in 1597 by the Padua professor Orazio Augenio (1527-1603), and on the case of Wilhelm Lauremberg (1547-1612), professor of medicine in Rostock, who had reported the cure of his own bladder stone in 1610. Augenio and Lauremberg had both used

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compound remedies containing prepared millipedes, a classic ingredient recommended in Avicenna's *Canon*. Yet Graberg suggested that it was not the millipedes that were lithontriptic, but the oil of vitriol (sulfuric acid), which was used in the process of their preparation. In support of this hypothesis he quoted a more recent "cure" of urinary stones with another remedy containing oil of vitriol, performed by the iatrochemist Johann Konrad Dippel (1673-1734).  

As can be seen from these examples, the long-lasting confidence in the classic lithontriptics had faded away, or, as Schaumkell put it:

> That medicines which grind down the calculus exist was believed by almost the whole choir of ancient physicians and supported in their writings with great songs of praise; whereas most of the recent authors distrust the virtue put in these remedies.  

It was in this climate of doubt that the first systematic experimental studies in this field were carried out.

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30 See Koning, op. cit., note 20 above, pp. 240-241.

31 Johann Heinrich Schulze and Johann Ernst Graberg, 'Dissertatio medico-chirurgica, quaerens an dentur medicamenta quae calculus in vesica comminuant' (Halle 1734), in Haller, op. cit., note 22 above, vol. 4, pp. 329-353.

32 Cf. Detharding and Schaumkell, op. cit., note 27 above, p. 360 (This and all following translations of quotations into English are mine, unless otherwise stated). See, however, as a defender of lithontriptic treatment, Nicholas Robinson, *A compleat treatise of the gravel and stone*, London, W. and J. Innys, 1721, who argued that effective dissolvent medicines did in fact exist, giving three recipes which included both classic ingredients, such as saxifrage, millipedes, burnt glass and scorpion, and more recent chemical substances, such as spirit of nitre and oil of vitriol.
3. Early trials in vitro, animal experiments, and case histories

In his two-volume work *Statical essays* (1733) the Reverend Stephen Hales (1677-1761) not only reported on his well-known studies into haemodynamics and plant physiology, but also extensively on his experiments on bladder and kidney stones. Only in recent years has this part of Hales' work been reappraised positively, in particular for its role in the development of chemical theory, having been dismissed before by his biographer A. E. Clark-Kennedy as "a hundred worthless pages". In Hales' own days his studies in urinary stones were clearly appreciated: they were instrumental in earning him the Copley Medal of the Royal Society in 1739.

Hales' starting point for his investigations in calculi lay more in physics and chemistry than in therapeutics. Following on from observations of Robert Boyle and Isaac Newton, he studied the air content of a wide variety of mineral, vegetable, and animal substances, extracting the latent air in a kind of distillation apparatus. In doing this he found the highest air content in urinary and gall bladder stones, the volume of the released air being nearly 650 times larger than that of the respective concretion. This was comparable only to the amount of air set free from tartar of wine. Hales drew two conclusions from this. Firstly, urinary calculi, as well as gall bladder stones and gouty

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34 Allan and Schofield, op. cit., note 5 above, pp. 92-99.


36 Allan and Schofield, op. cit., note 5 above, p. 93.

concretions, were "true animal Tartars". Consequently he joined van Helmont's view on stone formation. Secondly, the high air content of the calculi should encourage the search for a "proper dissolvent of the Stone in the Bladder". The task of such a medicine would be to release the air particles in the stone from their unelastic state, in which they strongly attracted and united salt, sulphur, and earth, to a free, elastic state, which would lead to the stone's dissolution. Hales assumed that "fermenting" (i.e. effervescing) mixtures, injected directly into the bladder, might achieve this by shaking and rousing the air particles.38

Accordingly, he performed several in vitro experiments with urinary stones, immersing them into various fermenting liquors and observing the rise of air bubbles and the loss of stony substance after several "affusions". Mixtures of oil of sulphur (sulfuric acid), salt of tartar (potassium carbonate), and water in certain proportions turned out to be the most promising. They wasted and dissolved softer concretions, especially gravel stones which had only recently descended from the kidneys, yet failed in hard, solid calculi of the bladder. In one of these experiments only, Hales measured the weight of the calculus before and after the period of immersion, thus quantifying the lithotriptic effect.39

In accordance with his hypothesis, he explained the observed efficacy with "certain harmonic Proportions" between the vibrations of the fermenting liquor and the tone of the stone's particles, "Just as when two Strings are equally tense, the striking of one will make the other sound".40 His "dissolving Menstruum", as he termed the mixture, was weak enough to be taken into the mouth "without Inconvenience". But it was also so weak that


40 Ibid., pp. 204-205.
many repeated injections of it into the bladder would be necessary, and Hales felt that this disadvantage could make it unsuitable for medical practice. Dissuaded therefore from proceeding with trials on human beings at this stage, he tested the long-term tolerance for his dissolvent in animal experiments. In two dogs he injected the liquor repeatedly over several days into the bladder, using a catheter which was inserted through an artificial fistula in the perinaeum. Except for occasional uneasiness, no harmful effects were observed in these animals. One of them was killed afterwards for postmortem examination. Its bladder showed no pathological changes. In the second dog Hales also continually perfused the bladder with the menstruum and warm water, using a double catheter. Again he did not perceive any harm caused by this.\footnote{Ibid., pp. 199, 209-213.}

Apparently Hales did not go beyond this stage in his research on fermenting mixtures as lithontriptics. Instead he reported on two other approaches: diuretics and diet. Inspired by earlier trials of the Paris Royal Academy of Sciences to dissolve calculi by laying them for several weeks in water,\footnote{Billeret, professor of anatomy and botany at Besancon, had shown \textit{in vitro} that the water of the local river Bougeaille dissolved bladder stones within about three weeks. Commissioned by the Académie, Littre thereupon examined several waters in and around Paris for their lithontriptic effect. In comparative \textit{in vitro} tests he found that they dissolved calculi within some months, the duration of the process depending on the type of water and the compactness of the stone. Seeing the problem of transferability to the clinical situation, he welcomed Billeret's announcement to try the Bougeaille water on a child suffering from bladder stone. In particular, Littre feared that the water could not be kept long enough in the bladder and that its strength was weakened by the mixture with urine. See Littre, 'De la dissolution des pierres de la vessie dans des eaux communes', \textit{Histoire (Mémoires) de l'Académie Royale des Sciences}, année 1720 (Paris 1722), pp. 436-446, and the comment on this article, ibid., pp. 23-26.} he made own \textit{in vitro} experiments along these lines, studying the lithontriptic
effect of cold and warm, stagnant and running water. The results of these experiments, which were supposed to simulate the effect of diuretic medicines, were disappointing, however. Hales therefore did not expect more from diuretics than "the washing down of the Gravel if not grown too large." The dietary approach seemed more promising. In vitro trials with "hot alkaline Plants", such as onions, scurvy-grass and horse-radish roots, showed that onion juice seemed to have "some considerable Efficacy in dissolving the Calculus". Rather uncritically concluding here from the phial to man, Hales assured that onions "frequently eaten should, if not waste, at least prevent the Increase of, the Calculus." In addition other dietetic precautions should be observed. Assuming that food and drink, especially "tartar" forming fluids, were responsible for urinary stones, Hales furthermore examined the incrustations of hard waters. On this basis he generally recommended the use of "Meats and Drinks" that would prevent the stone's growth. A few years later this dietetic approach was fully developed by a co-Fellow of his in the Royal Society, the physician Theophilus Lobb (1678-1763).

Suffering from urinary stones himself, Lobb was anxious to find an effective lithotriptic, but like Blackmore and others he doubted that any orally taken "dissolvent" could keep its power on its long way through the gastrointestinal tract and the blood circulation, before it reached the kidneys and the bladder. Thinking about this problem, he claimed, led him to his idea of therapy by aliment:

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45 Hales, op. cit., note 8 above, vol. 2, pp. 234-236, 249.
... as I was musing on this Subject, it came into my mind that, surely the Stone derives its Origin from some Things, or other, taken into the Stomach as Aliment; and then I thought, why may not other Things of a contrary Nature, taken as Aliment, be effectual to dissolve it?

It may be questionable whether Lobb's idea was truly original, since he knew Hales' work on the subject, quoting it in a different context (see below). Still, the extent to which he put this idea to the experimental test was certainly new. In two hundred in vitro trials on calculi, some of which had been given to Lobb by the president of the Royal Society, Sir Hans Sloane, the lithontriptic effects of a wide variety of vegetable infusions and decoctions were studied. Lobb summarized his extensive experiments in tables, stating the substance or vegetable tested, the initial weight of the calculus, the days of "digestion" in the fluid including the hours of "warm digestion" at body temperature, and the "event" of each trial. The latter was given in purely qualitative terms, i.e. the stones were described as still "hard", or "softened", "partly dissolved", "dissolved" etc. On the basis of these experiments Lobb distinguished three classes: "stronger" dissolvents, "weaker" dissolvents, and substances with "no dissolvent quality". His first class included 27 aliments, reaching from bread, celery, and cucumbers, via leeks, lettuce, milk, and onions, to turnips, green tea, vinegar, and white Port wine. Some of the classic lithontriptics, such as asparagus roots, cabbage, carrots, parsley, and parsnip, appeared in the class of weaker dissolvents.

Lobb concluded from his experiments optimistically that urinary stones "compact and hard as they are,... are dissoluble, and dissoluble by Things the most mild, and

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46 Theophilus Lobb, A treatise on dissolvents of the stone; and on curing the stone and gout by aliment, London, James Buckland, 1739, p. xi.

47 Ibid., p. vii. The greatest part of Lobb's A treatise had been read at several meetings of the Royal Society.
gentle in their own Nature, and most suitable, and benign to the Nature of our Bodies". Believing by extension that the lithomtriptic aliments were also effective against concretions in gout, he devised detailed rules of diet against those "two of the most painful, and torturing Diseases".48

Like Hales, Lobb tried to give an explanation for the dissolution of the calculi, which was based on the contemporary knowledge about their chemical components. Referring to experimental work in this field by Boyle, Nehemiah Grew, Frederick Slare, and Hales, he assumed that urinary stones consisted of a very large quantity of air, a considerable quantity of volatile alkaline salt, some animal oil, and a little earth or caput mortuum. Accordingly there were four ways in which a stone might be dissolved: the air could be forced out of it, as Hales had imagined; the texture and configuration of the alkaline salts could be altered, particularly by acids; the figure and quality of the particles of the animal oil might be destroyed - an effect, which Lobb attributed especially to onions, leeks, and cabbage; and finally, the particles of earth might be attracted by the lithomtriptic agent.49

On the whole, the emphasis of Lobb's work on lithomtriptic aliments lay clearly on the method of in vitro experimentation, as in Hales, and like him he did not seem to have worried much about the direct transfer of the experimental results to the situation in vivo. Still, as a doctor, Lobb put forward a few case histories of patients who had "found great Relief against the Stone, and Recovery from nephritick Symptoms by Vegetables in common Use as Aliment". One of the patients had supposedly benefited from the consumption of juice of onions, a second of onion water, and a third from eating dry bread in the morning, while otherwise fasting.

48 Cf. ibid., pp. 242-255.

49 Cf. ibid., pp. 255-260.
The diagnosis of urinary stones was reasonably well established in all three patients, but the authorities for their histories, and thus the alleged therapeutic effects, must have been seen as doubtful, even for contemporary standards of medical evidence. The first case history rested on the report of a neighbour of the patient (who had died in the meantime), the second was quoted from hearsay, and only the third was based on the patient's own account.

Despite these apparent shortcomings, Hales' and Lobb's work set the methodical standards for testing the efficacy of any potential lithontriptic: in vitro experiments on calculi, tolerance tests in animals, and case histories of patients suffering from "the stone" remained the three essential "tools" of investigation in this field throughout the eighteenth century. This methodical triad did not stay uncontested, however, and the most elaborate criticism was formulated with the event of the best remembered lithontriptic, Joanna Stephens's medicines against the stone.

4. Mrs Stephens's remedies: evidence and evaluation

The story of Mrs Stephens's lithontriptic medicines has been reconstructed in detail by Viseltear, so that

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50 The first patient had already undergone lithotomy and kept a box of voided stones, the second was to be cut for the stone, and the third reported to have voided considerable quantities of gravel.


53 Hales' Statical Essays were translated into French (Geneva 1744), German (Halle 1748), and Italian (Naples 1752). A French translation of Lobb's A treatise was published in Paris in 1744.
only some basic facts of it need to be mentioned here. The following sections will therefore rather concentrate on the ways in which evidence for the supposed efficacy of her remedies was produced, how it was confirmed or contested, and how this further shaped the methodology for the study of lithotriptics, that had been introduced by the work of Hales and Lobb.

In spring 1738 the empiric Joanna Stephens publicly offered to disclose the recipe for her secret medicines against urinary stones, as soon as the sum of 5,000 pounds had been paid in an account of hers with the London banker Drummond. Her offer was simultaneously supported by the young clergyman and practitioner David Hartley (1705-1757), now better known for his contribution to the development of human psychology.\(^5^4\) Having symptoms of a bladder stone himself, Hartley had started to take her medicines in the form of a powder and a liquid, and he now published the cases of ten fellow-sufferers, who had undergone the same treatment with apparent success.\(^5^6\) Apart from some improvement in the symptoms, they had begun to void stony scales or flakes with their urine, which were regarded as fragments of their calculi, separated by the action of the remedy. In four of the ten cases the diagnosis of bladder stone was explicitly said to have been confirmed through examination by a surgeon, i.e. in peranal palpation or catheterization of the bladder. Nine of the case histories were witnessed by the patients themselves, one rested on the conjoined authority of Hartley, the physician Peter Shaw and the Royal surgeon Caesar Hawkins.

\(^5^4\) Viseltear, op. cit., note 2 above.

\(^5^5\) See David Hartley, Observations on man, his frame, his duty, and his expectations, 2 vols, London, S. Richardson, 1749.

\(^5^6\) Idem, Ten cases of persons who have taken Mrs. Stephens's medicines for the stone. With an abstract of some experiments, tending to illustrate these cases, London, S. Harding and J. Roberts, 1738.
In addition, Hartley reported over sixty in vitro trials on various human as well as animal calculi (or fragments of them), in which he had studied the lithotriptic effect of Mrs Stephens's liquid, a watery solution of her powder, and his own urine while taking these remedies. The latter had acquired an alkaline quality, as chemical tests showed. The experiments were carried out against several controls, such as new river water, pump water, and common urine, and the calculi were regularly weighed in a dried state before and at the end of the trial. The test fluid was exchanged daily, and the calculi were rubbed with a wet sponge each time before immersed anew. The main result was that the greatest weight loss appeared in the tests with Hartley's own "medicated", alkaline urine. From this and the evidence of the case histories Hartley concluded that he was justified to speak at least of "strong Presumptions in Favour of Mrs. Stephens's Medicines".

Already in the next year, 1739, Hartley was able to publish a collection of 155 case histories of patients who had taken Mrs Stephens's remedies. These histories included again the earlier ten cases, which had partly been updated, as well as his own case and, most prominently, that of the well-known Irish presbyterian divine and physician James Kirkpatrick (d. 1743), who suffered from kidney gravel. As before, the authority for the histories were mostly the patients themselves, or the cases were said to have been communicated to Hartley "by good Hands". In 35 cases the clinical diagnosis of bladder stone was explicitly said to have been confirmed either by catheter examination or peranal palpation or, in some cases, in lithotomy or extraction, or eventually in a postmortem. The therapeutic success was again seen as being obvious from the fact that many of the patients voided stony flakes under the treatment, though in some cases no improvement was noted, and in eight out of nine

57 Ibid., p. 38.
cases, where re-examitations or re-catheterizations were performed, the stone was still found being present after several weeks' therapy. Quite frequently also side effects, particularly sickness, were mentioned. Still, Hartley remained optimistic, assuring that Mrs Stephens's medicines were generally "innocent and safe" and had "done great Service in the Stone and Gravel". Yet, by this time Hartley had been confronted already with three basic objections: that the medicines caused so much pain that it was better to submit to lithotomy; that the stony bits would have been voided without taking any remedy; and - most seriously - that this stony matter did not originate from the urinary calculi at all, but was actually generated by the medicines. Against this last objection he adduced the authority of Kirkpatrick: having studied under the microscope the flakes and sediment, which he excreted during treatment, Kirkpatrick had affirmed that they clearly came from urinary stones. So Hartley maintained in conclusion that the "Flakes and Fragments" were not made by the medicine, that the effect could not be accounted for from accident in all these cases, and that, after all, his in vitro experiments (which he summarized again) had shown that the alkaline urine of those taking the medicines had a stone-dissolving power. As for the latter, he saw an analogy with putrefaction, which was known to be associated with alkalinity. As putrefaction was "very apt to propagate itself in contiguous Bodies", so the alkaline salts in the urine attenuated and finally dissolved the stone.  

With his two publications on Mrs Stephens's medicines, the last of which was dedicated to the Royal College of Physicians, Hartley had clearly made a valiant

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effort: the number of case histories he had collected to substantiate the claim of efficacy exceeded any before in the history of lithontriptics, and his in vitro trials could well compare with those of Hales and Lobb. In some respect (use of controls, obligatory weighing of the calculi before and after the trial) they were even more advanced.

When it became clear that the requested sum of 5,000 pounds was not going to be reached through payments by the public, Joanna Stephens petitioned Parliament for the full amount. A Parliamentary committee subsequently agreed to pay the sum, provided that a group of Trustees set up for this particular issue was satisfied as to the claimed efficacy of her medicines. She agreed on these terms, and in June 1739 her recipe was published in the London Gazette and in the next month in other newspapers as well. It consisted of a powder, a decoction, and pills. The powder was made from calcined eggshells and snails; the decoction was produced by boiling in water some herbs together with soap, burned swines-cresses, and honey; and the pills consisted of calcined snails, wild carrot seeds, burdock seeds, ash, hips, and haws, all burnt to blackness, soap, and honey. It was obvious that several of her ingredients were well-known classic lithontriptics (as some critics soon pointed out), and the mode of preparation (calcination, burning to blackness) resembled closely that of the old "Confectio ex Cineribus" (see above). The evidence, which the Parliamentary Trustees eventually acknowledged as showing the efficacy of these remedies, and which in March 1740 earned Mrs Stephens the requested sum, came mainly from a very limited clinical trial including four patients. The procedure of this trial was well elaborated, however. In

59 The group of Parliamentary Trustees consisted of seventeen noblemen, politicians and high ranking clergymen, the president and four censors of the Royal College of Physicians, three surgeons, including the renowned lithotomist William Cheselden, the physician Peter Shaw, David Hartley, and Stephen Hales.
each case the diagnosis of bladder stone was confirmed by way of a catheter examination, before the medicines were administered. After several months' therapy, during which the voiding of stony material was recorded, a second (and in two cases a third) catheter examination was made. Examinations were always carried out by more than one person, in one case by thirteen physicians and surgeons. In all of the four cases the stone could not be found any longer in the re-examination, which was taken as evidence of the lithotriptic power of the medicines.60

The promotion of Mrs Stephens's medicines through Hartley and the official certification of their efficacy aroused wide-spread scientific and medical interest, also outside Britain. More evidence was produced to confirm the efficacy, and efforts were made to find the active component and thus to simplify the recipe. Other authors considered the benefits and limitations of the medicines' clinical use. On the other hand, critics put forward arguments and evidence to the contrary that Mrs Stephens's remedies were useless, if not harmful.

5. Reactions to Stephens's lithotriptic: criticism, more research, and a new theory

An early negative reaction came from Henry Bracken (1697-1764), surgeon, physician, and manmidwife in Lancaster, who also practised as a lithotomist.61 In a published letter to Hartley, dated 19 March 1739, he denounced Joanna Stephens's medicines as "a Piece of Quackery" and predicted that "in twelve Months Time the Nostrum will be blown up, and follow the rest of the

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60 David D'Escherny, A treatise of the causes and symptoms of the stone and of the chief remedies now in use to cure this distemper, London, J. Haberkorn, 1755, pp. 11-20, and Viseltrear, op. cit., note 2 above, pp. 201-206.

61 See Harley, op. cit., note 7 above.
Tribe of such short-liv'd and indigested Compositions". On a different level, however, he voiced quite sober criticism of the evidence that Hartley had produced so far. In Bracken's view, the cases in favour of her medicines were questionable, because the outside of the bladder stones might just have been softened into a mucilage, and a cure might thus have been erroneously assumed. In those cases where a catheter examination had been carried out before and after treatment, the surgeon handling the catheter might have been "deceived". Bracken emphasized how important it was that the diagnosis of a bladder stone was really established in order to make trials with the medicines meaningful. It was therefore better to lay the trials in the hands of "an ingenious Surgeon in every County, together with a Physician or two" and of "the Gentlemen of the several Hospitals in London" than to rely on the histories of grateful patients. Bracken made it clear that he principally advocated the search for lithotriptic remedies, quoting as an example his revered teacher Herman Boerhaave, who was said to have made considerable, though fruitless, efforts in this field. Despite this assurance, an answer to Bracken's letter, published by one Omnelio Pitcarne, M.D. in the same year, indirectly insinuated that the Lancaster surgeon opposed Mrs Stephens's medicines, because he feared a decrease in his practice as a lithotomist. It thus basically tried to undermine the credibility of Bracken's counter-arguments.

Another early attack on the remedy, published anonymously in 1740 by the physician Dennis de Coetlogan, almost discredited itself, though its main point might

62 Henry Bracken, Lithiasis Anglicana: or, a philosophical enquiry into the nature and origin of the stone and gravel, in human bodies, etc. Wherein is considered, the possibility of dissolving such animal tartar or calculous concretion, London, T. Cooper, 1739, pp. 2-3.

63 Cf. ibid., pp. 1-4, 29-32.

64 Quoted in Harley, op. cit., note 7 above, p. 57.
have been seen as reasonable in view of the results of Lobb. Coetlogan argued that the success cases of Hartley got better only because the patients' diet was improved during therapy, i.e. that the success had nothing to do with the remedy at all. But at the same time he maintained to have made known the principal ingredients of Mrs Stephens's medicines long before she made them public, and therefore claimed the reward for himself. Moreover he complained that her medicines had "in reality been robbed from the Profession", since "Soap Draughts" had "frequently and many Years ago been advised for Gravel, etc."  

By this time, however, Hartley and Hales, both of whom belonged to the group of Trustees, had produced new "evidence" in favour of Stephens's lithotriptic. Hartley published drawings of the stones of five patients, who had used the remedy for some time and had died in the meantime. Taken out in the postmortem examination, the stones showed rugged surfaces, which were interpreted as erosions caused by the lithotriptic treatment. Hales and Hartley together also tried to invalidate experimentally the objection that the stony material voided with the urine of patients taking the remedy was actually produced by the latter. They heated specimens of calculus, of stony matter voided by a patient taking the medicines, and of the urinary sediment of such a patient. While the first two specimens both proved to be volatile,  

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65 [Dennis de Coetlogan], A full examination, and impartial account of all relating to Mrs. Stephens's cures, and medicine for the stone and gravel, London, T. Cooper, 1740. For a case of a patient, who had taken soap against his bladder stone since February 1739, see John Pringle, 'An account of the virtues of soap in dissolving the stone, in the case of the Rev. Mr. Matthew Simson', Phil. Trans., 1757, 50: 221-227.  

66 David Hartley, A supplement to a pamphlet intitled, A view of the present evidence for and against Mrs. Stephens's medicines, annexed to Stephen Hales, An account of some experiments and observations on Mrs. Stephens's medicines for dissolving the stone, London, T. Woodward, [1740].
leaving almost nothing behind, the third was only reduced in its mass. The former two specimens were therefore believed to be identical, i.e. the voided material was regarded as "true calculous Matter" eroded from the stone, whereas the rest of the third specimen was seen as the "true calx" of the medicines.  

In addition, Hales performed a series of comparative in vitro experiments on calculi in order to isolate the effective principle in Mrs Stephens's medicines and thus to make them "both less nauseous, and more efficacious". These trials showed that soap-lye, made from potash and quicklime, was a strong dissolvent of urinary stones, and consequently Hales assumed that it was the soap included in Mrs Stephens's recipe, together with the lime stemming from the calcined eggshells and snails, that was the active, lithontriptic component. A pharmacological explanation was given as well. In the process of calcination the lime had stored "fiery Particles", which gave their energy to the alkaline, "lixivious" salts of the potash. This enabled the salts to penetrate and mix with the oily part of the urinary stones, which was seen as their "principal Band of Union", and thus to dissolve them. As in his earlier theory on the lithontriptic effect of fermenting mixtures, Hales drew upon an analogy from the realm of physics. The lixivious salts, he speculated, acquired "an erect lancinating Polarity" from the fire of the lime, "as a Loadstone makes Filings of Iron erect themselves into bristle-like Spires". Additional in vitro trials with lime-water seemed to support this theory. Except for very hard calculi, lime-water was found to be "a most powerful Dissolvent", particularly if freshly calcined quicklime had been used for its preparation: "...the fresher the Lime is from the Fire, so much the greater Energy it has, as I found in

67 Hales, op. cit., note 66 above, p. 8.

68 Cf. ibid., p. 3.
these Trials". Unlike in his previous work on lithontriptics, Hales this time addressed the critical question, whether his in vitro observations could be transferred to the clinical situation, i.e. whether soap-lye given orally to patients with urinary stones would have a therapeutic effect. Though there was no clinical experience with this yet, he thought that his results were transferable, believing that Hartley's cases of patients taking Mrs Stephens's medicines and his own in vitro experiments corroborated each other's evidence "to the degree of full demonstration".

Support for Mrs Stephens's medicines came also from physicians and natural scientists on the Continent. As early as September 1739 her recipe was made known to the German academic world by the Halle professor of medicine Johann Heinrich Schulze, who had shown his interest in lithontriptics before (see above). In a medical disputation one of his pupils published in detail the ingredients and the method of preparation and commented positively on the British remedy's efficacy. In view of its active components, the remedy was recommended for sufferers from the stone who had a good appetite and no fever, whereas for weak and feverish patients the milder preparation of Augenio was still preferred.

Extensive research on Stephens's lithontriptic was carried out at the Académie Royale des Sciences in Paris, where the chemist Claude Joseph Geoffroy (1685-1752) and the surgeon Sauveur-François Morand (1697-1773) had been commissioned with its investigation. From his chemical examination of the remedy Geoffroy concluded - like Hales - that the alkaline salts of the soap were the actual

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69 Ibid., p. 29.

70 Cf. ibid., pp. 25-26.

dissolvent, and additional experiments with the serum and urine of patients taking Mrs Stephens's medicines convinced him that the soapy component really entered the blood circulation and was excreted by the kidneys. His other results basically confirmed, but differentiated the "evidence" of Hartley. In vitro experiments on a "rough bladder-stone", comparing the "medicated" urine from a patient at the beginning and at a later stage of the treatment, showed that a lithontriptic effect could be expected only after the remedy had been taken for about one or two months. Moreover, Geoffroy's knowledge of several cases seemed to suggest that the medicines were "only beneficial to grown persons", not to children.72

The therapeutic value of the remedy was further explored by Morand, who conducted a clinical trial including 40 patients. They were divided into four groups. The first group consisted of five patients with diseases of the kidneys and bladder other than "the stone"; the second group of eight patients suffering from kidney gravel; the third of five patients with symptoms of bladder stone, who had not been "searched" with a catheter, however; and the fourth group of twenty-two patients, who had all been "examined by the Catheter, and found to have the Stone". Twelve of these had been "searched" by Morand himself, the rest by surgeons "of character". After the patients had taken Mrs Stephens's medicines for some time, the success was assessed by their subjective condition. Some patients of the first group appeared to have received "benefit", but in others (Morand gave no number), who had voided purulent urine,

the medicines were said to have "increased the disorders". Of the second group two "reckoned themselves perfectly cured", four "relieved", and two experienced "no benefit". Some of this group voided stones during therapy. In the third group one patient believed himself to be freed from his disorders, and four considered themselves "relieved", having brought away entire stones or scales. Of the fourth group two patients were left out for assessment, because they had only recently begun to take the medicines. Of the remaining twenty patients four had undergone the lithontriptic treatment "but a very little while". One of these said to be "considerably relieved", two experienced "neither benefit nor hurt", and in one lithotomy had to be performed because of great pain. The remaining group of sixteen patients, who had taken Mrs Stephens's remedy "for a considerable time", consisted of eleven adults and five children. Whereas of the adults four judged themselves "perfectly cured", another four "greatly relieved", and three to have had "no benefit" by the medicines, only one of the children "said he was relieved". Being "not relieved", the other four children underwent lithotomy, which revealed stones without any signs of dissolution. Several patients of the fourth group observed that they excreted stones, or parts of stones, or a white urinary sediment during treatment. Morand concluded from these results that Mrs Stephens's medicines were in fact effective, though - as Geoffroy had already suspected - not in children. Also, they were not to be used in patients with bladder ulcers (voiding pus in their urine), because they made the condition worse. Although Morand had to admit that only very few patients considered themselves actually cured, he thought that it was prudent to try the medicines in view of the risks of lithotomy, which he regarded as "always hazardous, notwithstanding the great Improvements made in it".73

73 Sauveur-François Morand, 'Examen des remèdes de Mad.ille Stephens pour la pierre', Histoire (Mémoires) de
Morand did not comment further on the different results in his four groups, which may indicate that he was stronger in designing his trial than in interpreting it. He recognized one weakness in his clinical trial, however, particularly when compared to the English one: in none of his patients did he manage to perform a second catheter examination after the apparently successful treatment. "Cured" patients refused to undergo the unpleasant procedure a second time, being aware of the ethical issue involved here. As one of them explained to Morand, "before he begun the Medicines, he submitted to be searched for his private benefit; but being now cured, he did not incline to be searched for the benefit of the public".74 Like Hales and Geoffroy, Morand made in addition comparative in vitro trials on calculi. They led him also to the conclusion that it was the soap contained in Mrs Stephens's medicines, respectively its alkaline salts activated by the quicklime from the calcined snails and eggshells, that was the stone-dissolving agent.75

The reaction of the Paris Medical Faculty to both the work of Hartley and Hales, and Geoffroy and Morand, appears to have been positive. Two disputations of the year 1742, under Louis Marie Pousse and Jacques Albert Hazon (1708-1779), examined the question whether Stephens's remedy was a valuable alternative to lithotomy in bladder stone. With reference to the experiments and observations of the above authors the question was both times answered in the affirmative, at least for some

74 Ibid., pp. 30-32. Morand consoled himself, however, with the consideration that even the search with a catheter could lead to different conclusions according to the prejudice of the examiner. For instance, a surgeon who does not believe that medicines can cure the stone, and who finds no stone after the treatment, will still assume that there is a stone (which he only fails to detect).

75 Cf. ibid., p. 20.
softer types of calculi. One of the disputants, Andrew Cantwell (d. 1764), was able to substantiate this view further with some cases of his own and in vitro trials. Also Hales' theory that fire particles in the lime moulded the alkaline salts of the soap into sharp spikes was acknowledged as an explanation for the lithontriptic effect.

Meanwhile more research supporting the conclusions of Hartley and Hales had been conducted by the Dublin physician John Rutty (1698-1775), who presented his results to the Royal Society of London in January 1742. Rutty joined issue with them over the question whether the calcareous matter, which patients treated with Mrs Stephens's medicines usually voided, might be generated by the remedy itself. In own experiments he confirmed their physical distinction that - put in the fire - this matter as well as genuine urinary stones were volatile, whereas the so-called calx of the medicines remained 'fixed'. In addition he provided a chemical distinction, showing that the calcareous matter as well as bladder stones made an ebullition with aqua fortis (nitric acid), but not with weaker acids, such as vinegar and spirit or oil of vitriol (diluted sulfuric acid). The calx of the medicines, however, produced a strong ebullition also with these latter substances, and this difference was taken as further evidence that the voided calcareous matter was identical with the substance of bladder stones (from which it had thus been separated by the medicines). Apart from this contribution in a crucial question, Rutty had performed in vitro trials on fifteen different

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77 Ibid., pp. 404-408.
calculi, comparing the lithontriptic effect of soap-lye, soapy decoctions, lime-water, spirit of nitre (nitrous acid), spirit of salt (hydrochloric acid), and — inspired by the work of Lobb — of juices of onions, leeks, and cellery. Since the main ingredients of Mrs Stephens's remedy proved to be lithontriptic in these tests, Rutty believed that it was efficacious. Going beyond this "proof" of efficacy, he emphasized the different strengths of the examined substances. The strongest was spirit of nitre, which he regarded as the only true dissolvent of urinary stones, followed in declining order by the lithontriptics spirit of salt, soap-lye, and lime-water, and finally the vegetable juices, to which he attributed a mild lithontriptic effect. Rutty used this differentiation in an obvious attempt to keep lithontriptic therapy in the hands of doctors, claiming that "it will still require the Sagacity of a Physician to determine which of these Medicines is to be preferred; when it may be proper to use the milder, when the sharper, and when to premise or interpose the Use of one or the other". This professional motive featured also prominently in the title of his publication on his experimental work, stating that he gave hints for reducing Joanna Stephens's medicines "from an empirical to a rational use".

From these reactions it may seem that, after initial resistance, Joanna Stephens's empirical medicines were going to be accepted by doctors, who analyzed them and developed modified lithontriptic treatments with the ingredients that they found most effective. In the end this was what actually happened, but before that, substantial and detailed criticism was voiced, which

78 John Rutty, An account of some new experiments and observations on Joanna Stephens's medicine for the stone: with some hints for reducing it from an empirical to a rational use, London, R. Manby, 1742.

79 Ibid., p. 38. See on this aspect also Wilson, op. cit., note 6 above.
radically called into question all the scientific evidence which had hitherto been produced in favour of the remedy. It came from James Parsons (1705-1770), a London doctor and Fellow of the Royal Society, who in 1742 published his comment as a long appendix to an anatomical work of his on the human urinary bladder.\textsuperscript{80} Parsons principally criticized the facts that Mrs Stephens's medicines were nauseous, that the duration of treatment with them was indefinite, and that they were to be prescribed uniformly in every case, thus precluding the possibility of varying the therapy according to the patient's individual condition and needs. The latter argument was in fact generally used around this time by traditionally minded physicians, whenever they opposed new, "specific" remedies.\textsuperscript{81}

In particular, he tried to demolish the evidence provided by Morand and Hartley. Among the French surgeon's forty subjects there was "not a positive Instance of a perfect Cure", and the medicines proved to be useless in children and harmful in patients with ulcers in the kidneys or bladder. That some of the patients felt ease after treatment did not mean that their stones had been dissolved. Intervals without symptoms were a common phenomenon in this disease.\textsuperscript{82} In a similar way Parsons dismissed the evidence of Hartley's 155 cases. He was not impressed at all by the overall success here, and he questioned the validity of the case histories, since the majority of them had been drawn up by the patients themselves. In Parsons' opinion only "a

\textsuperscript{80} James Parsons, \textit{A description of the human urinary bladder, and parts belonging to it: anatomical figures shewing its make, situation, etc. to which are added, animadversions on lithontriptic medicines, particularly those of Mrs. Stephens}. London, J. Brindley, 1742, pp. 51-283. His work was translated into French (Paris 1743) and German (Nuremberg 1759).

\textsuperscript{81} See Cook, 'Practical medicine', General Introduction above, note 61.

\textsuperscript{82} Cf. Parsons, op. cit., note 80 above, pp. 70-79.
very few" patients were "capable of giving a proper Account of their own, or that of any other". Neither was the examination with a catheter absolutely reliable. Bladder stones could be enclosed in cysts or covered by membranes or mucus and therefore not be felt with the instrument. Also, Hartley's specimens of apparently eroded bladder stones from treated patients did not prove the efficacy of Mrs Stephens's medicines. Such stones were merely one naturally occurring type of calculus and could be found in patients who had never taken her remedy. As for the in vitro experiments on urinary stones, Parsons principally doubted that their results could be transferred to the conditions in vivo.83

His strongest criticism, however, was directed against the "evidence" of the calcarius matter voided by patients under treatment. Parsons joined the objection that this matter came from the remedy itself, being "the Calx of the Medicines". Rutty's chemical argument against this objection was seen as inconclusive: the calcarius matter in the patients' urine, argued Parsons, was really the calx of the medicines they had taken, its alkaline quality had merely been diminished on its long way through the body. It was therefore no surprise that it raised an ebullition only with strong acids, such as aqua fortis, whereas the unchanged calx of the remedy, abounding with "fiery particles", effervesced already with weak acids, such as vinegar.84 Yet, Parsons' main blow against the evidence of "white flakes" and "chalky matter" was based on a human trial made to decide this question:

But, to conclude, the Experiment made in one of our Hospitals proves it undeniably: The Medicines were given to a Man who never had the Stone, nor any Symptoms like it, who, during the Time of his taking them, voided Flakes, Scales, Bits, Sediment, and all the Train of Form the Calx of the Medicines could produce. Sure the

83 Cf. ibid., pp. 79-92, 114-115.

84 Cf. ibid., pp. 121-122.
greatest Infidel must now be convinced, that the calcareous Matter of the Medicines alone produced these, and not any calculous matter whatsoever. 85

Parsons concluded that Mrs. Stephens's medicines were "Sediment-generators, Flake-generators, etc." and that they were therefore not only useless, but dangerous: stony particles in the urine might be taken up by the calx of the medicines, which thus became the starting point of concretions. 86

Thoughtful and pertinent as Parsons' criticism was, there do not seem to have been many reactions to it. The Petersburg professor of anatomy and surgery Johann Friedrich Schreiber (1705-1760) joined Parsons' views in a published letter to Albrecht von Haller in Göttingen, having found Mrs Stephens's remedy useless in a patient with bladder stone and having been unable to observe a lithontriptic effect of soap-lye in a controlled in vitro trial. 87 Also the eminent London physician Richard Mead (1673-1754) recommended Parsons' critical book in his Monita et praecepta medica (1751). 88 Generally, however, research on Stephens's medicines continued unabated. In particular, other investigators followed the avenue of Hales, Geoffroy, and Rutty to identify the active principle contained in the compound remedy, thus preparing the way for the transition from its "empirical" to its "rational" use. 89

85 Ibid., pp. 111-112.
86 Ibid., pp. 123-124, 188.
88 Richard Mead, 'Medical precepts and cautions', in idem, The medical works, London, C. Hitch and L. Hawes, 1762, pp. 449-575, on p. 531. From his own experience Mead particularly supported Parsons' argument that calculi with seemingly eroded surfaces were only a natural variation.
6. A "new" London and an Edinburgh lithontriptic: Jurin's soap-lye remedy and Whytt's lime-water

One of those who simplified and modified Mrs Stephens's medicines was the prominent London physician and one-time secretary of the Royal Society, James Jurin (1684-1750). Suffering himself from symptoms of a vesical calculus, such as haematuria and pain in the bladder during movements, Jurin considered taking the remedy, but was neither fully convinced of its efficacy nor of its harmlessness. He therefore turned to soap-lye, which, in an in vitro experiment, he had found to dissolve a stone voided earlier by him. From March 1740 onwards he took soap-lye in varying doses for six months, after which time he considered himself "perfectly cured". Jurin then standardized his soap-lye, also trying to make it less nauseous. The exact mode of preparation was not revealed by him, however. Instead patients were referred to the London apothecaries Beckington and Littlebury, who prepared the remedy, by now known as "Jurin's Lixivium lithontripticum", according to his directions. Jurin justified this procedure by asserting that the quality of the remedy was guaranteed in this way. The price - 1

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89 Even Hartley eventually joined this line, having recognized that the calcined eggshells and the soap were the essential components in Mrs Stephens's medicines and that her other ingredients might be omitted. In 1746 he published a simple recipe to form troches out of Alicant soap, pulverized quicklime, and fixed alkaline salt. Another six simple recipes using the same ingredients were given by Hartley in 1751. Cf. David Hartley, De lithontriptico a Joanna Stephens nuper invento dissertatio epistolaris, Leyden, Joh. and Herm. Verbeek, 1741, pp. 3-7; idem, De lithontriptico...editio secunda. Cui adicitur methodus exhibendi lithontripticum sub forma commodiore, Bath, T. Boddely, 1746, p. 69; idem, Ad virum clarissimum Ric. Mead, M.D. epistola, varias lithontripticum Joannae Stephens, exhibendi methodos indicans, Bath, T. Boddely, 1751.

90 [James Jurin], 'The case of James Jurin, M.D.', annexed to Rutty, op. cit., note 78 above, pp. 41-56.
shilling 6 pence per half pint bottle - was, as he thought, quite low anyhow, being an adequate compensation for the apothecary's efforts.\(^91\)

With the death of the former prime minister Sir Robert Walpole in 1745, however, Jurin's "Lixivium" soon appeared in an unfavourable light. Walpole, suffering from bladder stone in his last illness, had been treated by Jurin with this remedy for several weeks. In the published postmortem report Walpole's surgeon John Ranby revealed that the bladder was found distended, containing several small stones and clots of blood. Ranby expressed his view that Jurin's "Lixivium" was at least partly responsible for Walpole's death, and this insinuation caused a typical eighteenth-century pamphlet war for and against, including an anonymous piece of sarcasm by Henry Fielding.\(^92\) Jurin himself, in a second edition of his own case history, discussed Walpole's case without naming him, yet practically admitting that the remedy had contributed to this patient's death. The "Lixivium", he explained, had divided the stone into several sharp pieces, which, wounding the bladder, had caused severe bleeding followed by an obstruction of the organ by coagulated blood that led eventually to death. Jurin

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\(^92\) For detailed accounts see Viseltear, op. cit., note 3 above, and Spriggs, op. cit., note 3 above.
emphasized, however, that this was an isolated, unfortunate case, "one in ten thousand". This statistical argument had already been used by him in his well-known work on the relative benefits and risks of inoculation, and he actually drew a direct comparison with this issue: there had been strong opposition against the preventive practice of inoculation as well as to the introduction of Peruvian bark into therapy, and still, in the end both had "since triumphed over all Opposers". The same, he hoped, would happen with his "Lixivium". Such vigorous rhetoric might well have been necessary for Jurin, since there is evidence from his correspondence that patients, apparently made uncertain by the case of Walpole, hesitated taking the "Lixivium", being "discouraged from it by the thoughts of Pain or Danger". In fact, at this time another lithotriptic was coming up, which was also derived from Mrs Stephens's medicines, but seemed to be more harmless than Jurin's remedy: lime-water.

Based on the theory that active, "fiery particles" were stored in calcined lime, affusions of water with

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95 Cf. Jurin, op. cit., note 91 above, pp. 28-29. On the arguments against Peruvian bark see below, part C.

96 Letter by Thomas Worsley to Jurin, 25 November 1746, in Rusnock, op. cit., note 91 above. In early 1746 the surgeon William Cheselden had reported (without comment) the case of another patient who had died after oral treatment with soap-lye, and whose bladder was subsequently found filled with a multitude of stones; see Cheselden, 'The effects of the lixivium saponis, taken inwardly by a man aged 75 years, who had the stone, and in whose bladder, after his decease, were found two hundred and fourteen stones', Phil. Trans., 1746, 44: 36-40.
quicklime had been tested in vitro for its lithontripticity by Hales and Rutty, and also by Jurin, all of whom had found it efficacious. Actually, this was not new knowledge, since already in 1663 the Danish physician and chemist Ole Borch (1626-1690) had reported that - according to his own, repeated experience - bladder stones removed in lithotomy could be dissolved to a mucilage within some days, if they were put into lime-water made from calcined oyster and mussel shells and kept there warm by a small fire. Yet, it was only in 1744, when Robert Whytt (1714-1766), later professor of the institutes of medicine at the University of Edinburgh, had published his first study of lime-water, that this substance became known as a lithontriptic for clinical use. Also, with the work of Whytt, which was soon joined and challenged by that of his colleague Charles Alston (1683-1760), the professor of botany and materia medica, the centre of research on lithontriptics temporarily "moved" from London (and Paris) to the rising Edinburgh medical school.

Based on the work of Hartley and Hales, Whytt had successfully treated a 60-year-old patient suffering from urinary stones by a course of soap and lime-water. This success, which was attested by the patient, subsequently

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97 Hales, op. cit., note 66 above, pp. 28-29; Rutty, op. cit., note 78 above; Jurin, op. cit., note 90 above.

98 Ole Borch, 'Epist. LXXVI. De vesiculis pulmonum, ranarum anatomoe, aere in cor penetrante, vesicae tunica, modo solvendi calculos per aquam calcis vivae', in Thomas Bartholinus, Epistolarum medicinalium centuria IV. variis observationibus curiosis et utilibus referta, Copenhagen, P. Haubold, 1667, pp. 446-453.

led Whytt to carry out extensive experimental research on the properties and lithontriptic effect of lime-water. That he chose the latter as his main object of investigation (instead of soap or soap-lye as Geoffroy and Jurin had done) was explained partly with the results of Hales' work on Mrs Stephens's medicines, partly with his own observation that soap alone did not seem to have helped much in that case.\(^{101}\) Compared to previous work on stone-dissolving medicines, Whytt's on lime-water was much more systematic and comprehensive, studying not only its efficacy at such, but also the question which factors relevant to the clinical situation might influence this efficacy. A first series of experiments dealt with the production of different kinds of lime-water and their effect on urine, sediment, and calculi. Assessing the "dissolving power" in the by then customary way of determining the weight loss of calculi immersed into the test fluid for a definite period, Whytt found that lime-water made from calcined oyster and cockle shells had a greater effect than that made from burnt limestone. Moreover, he confirmed the observation of Hales that the water made from freshly calcined shells was stronger than that of older material. Following this line, Whytt tried to increase the "strength" of lime-water even further by pouring it on quicklime, thus producing a so-called "double lime-water". Judging from his criteria of "strength", e.g. taste, specific gravity, and lithontriptic effect, he thought that this trial had been successful - a point, which was soon to involve him into a controversy with Alston (see below).\(^{102}\)

\(^{100}\) Whytt gave reasons for this: "As Authors have sometimes been accused of framing Histories to support a certain Theory, or raise the Value of some favourite Medicine, I thought it might be proper to add the Gentleman's own Attestation of the Truth of what has been above related." Whytt, op. cit., note 99 above, p. 11.

\(^{101}\) Ibid., pp. 11-16.

\(^{102}\) Ibid., pp. 17-44.
The second series of Whytt's experiments studied the effects of body fluids, such as saliva, bile, blood serum, and urine, on the lithontripticity of lime-water. The tests were carried out in vitro by adding the respective fluid to the lime-water, in which a piece of calculus had been immersed. The stone-dissolving power was not found to be diminished in these trials, which convinced Whytt that lime-water would not lose its efficacy on the way from the mouth to the bladder. With the same view and method the possible effects of various foods and drinks and of different purgative medicines were tested. The latter were thought to be necessary, because lime-water was known to make patients costive. On the basis of these experiments Whytt recommended avoiding certain fermented, alcoholic drinks during therapy and using vegetable laxatives, e.g. aloe, rhubarb or jalap powder, instead of purgative salts, such as Glauber and Epsom salt. With his dietary experiments and recommendations Whytt stood in the tradition of Hales and Rutty, both of whom he quoted in this context, strangely leaving the extensive work of Lobb unmentioned, however. Some of Whytt's in vitro trials studied also the stone-dissolving power of soap and soap-lye, and of "Liquid Shell", another nostrum that had been launched in view of the success of Mrs Stephens's medicines. None of these showed the efficacy of lime-water. In his final therapeutic suggestions, however, Whytt recommended the combined intake of three pints of oyster or cockle shell lime-water with one ounce of Alicant soap because of the latter's additional, albeit limited, lithontriptic effect and its capacity to prevent the costiveness otherwise caused by the former.

103 Ibid., pp. 45-46.
104 Ibid., pp. 46-59.
105 Ibid., pp. 81-104.
106 Ibid., pp. 114-117.
In his pharmacological theory Whytt followed basically Hales' concept of "fiery particles" in quicklime. The relevance of his experimental studies lay more in their therapeutic consequences. During Whytt's lifetime his essay on lime-water, initially published in the Edinburgh Medical Essays and Observations, went through three separate editions, each time enlarged by case histories of sufferers from the stone that had been "cured" or got "better" by the use of lime-water with soap. The most prominent of these cases was that of the Whig politician and diplomat Horace Walpole (1678-1757), the younger brother of Sir Robert Walpole, whose history, written up by himself, was also published in the Philosophical Transactions of the Royal Society. Whytt openly used Horace Walpole's case to advertise his therapeutic innovation, stating that "the Histories of those, in conspicuous Stations of Life, are wont to make the strongest Impressions upon the Generality of Mankind". Another prominent patient following successfully Whytt's soap and lime-water course, the Reverend Dr Newcome, Canon of Windsor and later Lord

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107 See ibid., pp. 36, 77-78, 83, 105-107.


109 'An account of the Right Honourable Horace Walpole Esq; drawn up by himself', Phil. Trans., 1751/52, 47: 43-48; 'A sequel of the case of the Right Honourable Horace Walpole, Esq; relating to the stone', ibid., pp. 472-473. See also the report of Walpole's last months of life and of the findings in the postmortem examination, given by John Pringle, together with Whytt's comment on this, in 'An account of the case of the late Right Honourable Horace Lord Walpole', Phil. Trans., 1757, 50: 205-220.

110 Whytt, op. cit., note 99 above, 'Advertisement'.
Bishop of Llandaff, even performed his own in vitro trials testing the lithontriptic effect of his "medicated" urine.\footnote{See Whytt, ibid., 2nd edn, pp. 202-210, and 3rd edn, pp. 206-207.} As Charles Alston observed in 1757, there had been "more Lime-water made use of in London and Edinburgh, in One Year, not long after the Publication of the Essay [by Whytt] than in almost Half the Century preceding".\footnote{Charles Alston, A third dissertation on quick-lime and lime-water, Edinburgh, G. Hamilton and J. Balfour, 1757, p. 46.}

With respect to the mode of administration of lithontriptics, Whytt's work was influential, too, though here his influence did not go beyond the stage of therapeutic experimentation. In his initial essay of 1744 he had suggested complementing oral therapy with additional injections of lime-water into the bladder.\footnote{Whytt, op. cit. (1744), note 99 above, pp. 733-736. The theoretical possibility of injecting lithontriptic substances directly into the bladder of patients suffering from the stone had been briefly discussed by Blackmore, op. cit., note 28 above, p. 50, as well as by the physician W. Shaw in his anonymously published A dissertation on the stone in the bladder, London, H. Goslin, W. Meadows and T. Cooper, 1738, pp. 16, 26-28. Whytt did not refer to these two authors, however.} In part this suggestion was inspired by Hales' injection trials on dogs with his "dissolving Menstruum" (see above). Yet Whytt followed also certain surgical models here. Intravesical injection of warm water through a catheter was a common preparation for the so-called high operation for the stone, in which the bladder wall was opened through a suprapubic incision. Eminent lithotomists, such as Joannes Groenevelt, John Douglas, and William Cheselden had introduced and advertised this new method of operation into Britain earlier in the century.\footnote{It was clear from the experience gained here...}
that patients would tolerate the procedure, if the injected volume was not too large. Moreover, Whytt was able to refer to a case of seemingly successful treatment by regular injections into the bladder. It had been communicated by the renowned Paris surgeon Henri-François LeDran (1685-1770), who claimed to have cured, in 1725, a patient with an inflamed and contracted bladder by injecting through a catheter a decoction of marshmallow roots twice a day for a month's time. Not surprisingly therefore, Whytt asked an Edinburgh surgeon, John Campbell, to make the trial with lime-water on human subjects. The first of these was a ten-year-old boy, taken into the Royal Infirmary to be cut for the stone. His bladder having been injected with two ounces of oyster shell lime-water with a bit of starch (to "soften" the former), he retained the fluid for nearly three hours "without any Pain or Uneasiness". A man having subsequently been injected with pure lime-water showed the same tolerance, retaining it "a considerable Time".

The date of these trials was given as 1745, i.e. a year before the London physician Browne Langrish (before 1700-1759), a friend of Hales, published a systematical study of the tolerance for intravesically injected lithontriptics in dogs.

Taking up Whytt's suggestion of 1744, Langrish not only tested the tolerance for long-term injections of lime-water of different strengths (two injections through


117 These early human trials as well as the preceding injection experiments on dogs by Hales (1733) are not noted by Arthur J. Viseltreer, op. cit., note 5 above, who consequently quotes Browne Langrish as the first to have designed experiments with direct injections of lithontriptics into the bladder.
a catheter per day over several weeks), but also for increasing doses of soap-lye, lime-water with various proportions of soap-lye, Jurin's "Lixivium", and lime-water with Alicant soap. Strainings to make water, excretion of mucus, and bloody urine were recorded as signs of irritation and damage of the bladder. They appeared quite soon in the soapy preparations, whereas lime-water was always tolerated without problems, even if a small amount of soap-lye had been admixed. Two dogs, to which such a lime-water and soap-lye mixture had been administered for a long period, were killed and their bladders examined. No signs of inflammation or thickening of the bladder walls could be found.¹¹⁸ On the basis of these experiments - and obviously unaware that Whytt and Campbell had already made trials on patients - Langrish suggested next trying the "solvents" on convicts, a proposal, that was not unusual in his time and had actually been carried out in the case of smallpox inoculation in 1721.¹¹⁹ No such trials seem to have been performed with lithontriptics, but Whytt further pursued his programme of tests on patients.

Seeing particularly the problem that repeated catheterization would irritate the bladder, Whytt induced the Edinburgh medical student William Butter to devise a suitable injection apparatus and to try it on patients of the Royal Infirmary. The instrument constructed by Butter

¹¹⁸ Browne Langrish, Physical experiments upon brutes: in order to discover a safe, and easy method of dissolving the stone in the bladder, by injections, London, C. Hitch, 1746, pp. 3-36.

consisted of a sheep's bladder (as a reservoir for the lithontriptic fluid) contained in bellows, and connected over a stopcock to a tin pipe, which could have different lengths and shapes depending on the age and sex of the patient. Unlike a catheter, the pipe was inserted only into the urethra, which meant that the tone of the closing muscles of the bladder had to be overcome by the pressure of the fluid during injection. After initial technical difficulties, in 1752, and again in 1754, Butter injected each time two male subjects with lime-water. Both the technical procedure and the injected fluid were reported to have been well tolerated. Though the last two men suffered from bladder stones, being clinical patients of the professor of medicine, John Rutherford (1695-1779), these trials were not therapeutical. They rather studied, apart from the technical side of the method, the acute tolerance for intravesically applied lime-water. Only one therapeutic experiment was quoted by Butter, which had been carried out in 1753 by Rutherford himself. A man who had been admitted to the Infirmary for lithotomy (the diagnosis of a large bladder stone having been confirmed by catheter examination) was instead taught to treat himself with Butter's "machine". After two lime-water injections per day, supported by an oral course of soap and lime-water, for about two months, the patient was catheterized again and his stone found reduced to a small nucleus. Being "impatient to return to home", the man was subsequently discharged from the hospital.\footnote{ Cf. Whytt, op. cit. (1752), note 99 above, pp. 132-139; William Butter, A method of cure for the stone chiefly by injections. With descriptions and delineations of the instruments contrived for those purposes, Edinburgh, Hamilton, Balfour, and Neill, 1754. Drawings of Butter's injection apparatus are reproduced from his publication in Viseltear, op. cit., note 5 above, p. 480.}
not gain ground. It was obviously too inconvenient and complicated for patients, particularly if injections had to be performed for months. Oral treatment remained the only alternative to lithotomy, regardless of its side effects, such as nauseousness, and despite ongoing suspicions that a lithontriptic taken by mouth would lose its efficacy on its long way through the body. Although injections of "solvents" into the bladder were tried anew at the turn to the nineteenth century, after the eminent Paris chemist Antoine François Fourcroy (1755-1809) had propagated them on the basis of his recent insights into the chemical composition of urinary stones (see below), the method seems soon to have been given up again. As the London physician and chemist Alexander Marcet noted in 1819, those trials had "not led to any decisive results" and had "for some years, been almost entirely abandoned." 

By the time Butter made his injection experiments, Whytt had already been involved in a long scientific controversy with his colleague Alston concerning the physico-chemical properties of lime-water. Alston, who had used lime-water in experiments on the vegetation of plants since 1743, had found that from one pound of quicklime up to 500-600 pounds of lime-water could be produced in successive infusions. Each of the infusions appeared to have the same strength, provided that enough time was allowed for impregnation. This meant that the solubility of lime in water was limited, or that the

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122 Marcet, op. cit., note 9 above, p. 188.

123 For detailed accounts of this controversy see Henry Guerlac, 'Joseph Black and fixed air: a bicentenary retrospective, with some new or little known material', Isis, 1957, 48: 124-151, 433-456; French, op. cit., note 5 above, pp. 17-26.
strength of lime-water could not be increased once the point of saturation had been reached. These findings clearly contradicted those of Whytt. According to his experiments, quicklime made from oyster shells had still its "virtue" after 270 times its weight of water had been poured on it, but the successive infusions had been found to become gradually weaker. Alston's findings furthermore excluded the possibility of Whytt's "double lime-water" being stronger than normal lime-water. Neither could Alston confirm that lime-water made from oyster and cockle shells was stronger than that made from limestone. The dispute about these issues started in 1749/50 with two letters by Alston to the Royal Society, later published in its _Philosophical Transactions_, and ended only with his death in 1760. Alston produced in this period three dissertations on quicklime and lime-water (the first of which had a second edition); Whytt not only responded in the various editions of his essay, but also by a new article, in which he insisted, on the basis of more physical and chemical experiments, that his different lime-waters really differed in strength.


125 Whytt, op. cit. (1752), note 99 above, pp. 43-44.

126 'Extract of two letters from Dr. Alston, Bot. Prof. at Edinburgh, to Dr. Mortimer, Secr. R.S.', _Phil. Trans._, 1751/52, 47: 265-266; Alston, op. cit., note 124 above; _idem_, _A dissertation on quick-lime and lime-water_. The second edition, with additions, Edinburgh, G. Hamilton and J. Balfour, 1754; _idem_, _A second dissertation on quick-lime and lime-water_, ibid., 1755; _idem_, op. cit., note 112 above.

A problem underlying this dispute was of course that of how to measure the "strength" of lime-waters. The methods used for this, such as comparing the specific gravity with that of common water, weighing the "earthy crusts" formed by lime-water exposed to air, colour reactions with silver and with claret wine, precipitation after the admixture of salt of tartar, and tasting, were all open to accidental influences or errors, that could lead to considerable variations. Moreover, the materials were certainly not pure. Lime-water made from calcined shells, for instance, contained remains of organic matter and sea salt. Although these problems were addressed within the dispute, neither of the two opponents changed his views. Another circumstance, partly explaining the discrepancies between Alston's and Whytt's results, has been pointed out by Roger French: Whytt must actually have produced weaker lime-waters than Alston, because he slaked the lime in boiling water, whereas the latter used cold water slaking. As is now known, calcium hydroxide is less soluble in hot than in cold water.¹²⁸

Whytt and Alston also disagreed over the therapeutic relevance of their different physico-chemical findings. The former believed that it was "of no small importance" for patients to know how to prepare a lime-water of the right strength, both for oral therapy and injections into the bladder. The latter thought that, if it was really true that some lime-waters were weaker than others, this could easily be compensated by increasing the dose, which would be safer anyway.¹²⁹ Finally, they had different ideas about the mode of action of lime-water on urinary stones. While Alston's theory was more chemical, deriving the lithontriptic effect from the generally detergent power of lime-water, Whytt adhered, as mentioned above, to Hales' fire particle theory, at least initially. Later,

¹²⁸ French, op. cit., note 5 above, p. 18.
¹²⁹ Whytt, op. cit, note 127 above, pp. 384-385; Alston, op. cit. (1754), note 126 above, p. 73.
under the influence of the work of Joseph Black (1728-1799), he changed to the view that quicklime lacked fixed air and that the lime-water prepared from it therefore attracted such air from the calculus.\footnote{Idem, op. cit., note 124, p. 38; Whytt, op. cit. (1752), note 99 above, pp. 36, 77-78; Guerlac, op. cit., note 123 above, pp. 143-144; French, op. cit., note 5 above, pp. 19, 25.}

These differences of opinion should not hide the fact, however, that Alston agreed with Whytt that lime-water was really an effective lithotrétic, though its efficacy might vary with the type of stones. Alston's \textit{in vitro} trials showed, for example, that it acted more on calculi of old than of young people (thus confirming the observations of Geoffroy and Morand), and that it had a greater effect on stones of a clay colour than on such that were either more whitish or dark brown. Similarly Whytt found that extremely hard, dark brown stones "dissolved a good deal slower" than the - also very hard - calculi of "a grey sandy colour".\footnote{Alston, op. cit., note 124, pp. 35-38; Whytt, op. cit., note 108 above, pp. 351-355.} Not least, Alston himself was one of the patients who, following Whytt's recommendation of 1744, had successfully treated their bladder stones by drinking lime-water, and he expressed his gratefulness for this throughout the dispute.\footnote{Alston, op. cit., note 124 above, p. 29; \textit{idem}, op. cit. (1755), pp. vi, 61.} In his third dissertation (1757) Alston moreover listed thirteen case histories illustrating the "success" of lime-water in a variety of affections: not only in cases of stone and gravel, or in gout, which was seen as a related disease, but in conditions ranging from irregular menses and disordered judgement via tertian fever to scurvy skin eruptions and aphthae in the mouth and throat.\footnote{Cf. \textit{idem}, op. cit., note 112 above, pp. i-iv, 2-8.} This spectrum reflected the wide range of pharmacological effects soon attributed to lime-water, going far beyond
its lithontripticity. According to Alston, it was also diluent, detergent, attenuating, diuretic, vulnerary, antiseptic, and anthelmintic.\footnote{Idem, op. cit., note 124 above, p. 29. Alston also studied experimentally the antiseptic effect of lime-water (i.e. its power to prevent or delay putrefaction) on meat, fish, and various body fluids, as well as its capacity to kill worms, snails, and insects. See ibid., pp. 31-34, 40-46; idem, op. cit. (1754), note 126, p. 36; idem, op. cit., note 112 above, pp. 38-40; idem, op. cit., General Introduction above, note 45, vol. 1, pp. 264-271. See also Pringle, op. cit., General Introduction above, note 72; John Clephane, 'Experiments by Francis Hume, M.D. on fish and flesh preserved in lime-water', Phil. Trans., 1753, 48: 163-164; Stephen Hales, 'An account of some trials to keep water and fish sweet, with lime-water', Phil. Trans., 1754, 48: 826-831.} Not surprisingly therefore, both Alston and Whytt reacted with indignation, when new experiments were reported from the Continent, which seemed to disparage lime-water as a lithontriptic.

7. Continental ways: Carlsbad waters and the bearberry plant

These new experiments had been carried out by Gottlob Carl Springsfeld (1714-1772), town physician of Weissenfels in Saxony, who was a member both of the German Imperial Academy of Naturalists (Leopoldina) and the Berlin Royal Academy of Sciences. His study, originally published as a Latin monograph in 1756, was made known in Britain already in the same year through a summary in the Philosophical Transactions of the Royal Society, given by one of its Fellows, the apothecary William Watson. In repeated, comparative \textit{in vitro} trials Springsfeld had found that the lithontriptic power of the thermal waters of Carlsbad in Bohemia was up to 6-7 times greater than that of lime-water made from calcined eggshells or oyster shells. Being familiar with the work of Hales, Hartley, Rutty, and Whytt, he had measured lithontripticity with the usual and accepted method of...
determining the weight loss of immersed calculi in a given time. Moreover, he had shown in this way a considerable efficacy of the so-called medicated urine, i.e. urine of a patient taking the Carlsbad waters, using the urine of a healthy, untreated person as a control.\(^{135}\)

The experiments had partly been performed together with the renowned Berlin anatomist and physician Johann Nathanael Lieberkühn (1711-1756), when the latter visited Carlsbad in 1755, bringing a number of calculi with him. Not least it was this association with Lieberkühn's good name that provoked attention. Watson, in his summary of the trials, emphasized Lieberkühn's general "exactness" and "fidelity" and praised Springsfeld's experiments as "well devised, and to appearance carefully executed"; and in the next issue of the *Philosophical Transactions* the Reverend Jeremiah Milles, F.R.S., gave - inspired by Springsfeld's work - a positive account of the current practice of taking the Carlsbad waters and its medical uses.\(^{136}\) These rather friendly reactions of the Royal Society in London contrasted, however, with those of the two "experts" in Edinburgh, Alston and Whytt.

Alston called Springsfeld's experiments and their results "curious" and "almost incredible", and Whytt suspected that the German's trials with lime-water were "somehow not just".\(^{137}\) Accordingly, both of them were prompted to carry out additional trials in order to examine Springsfeld's contentions. An earlier analysis of


\(^{137}\) Alston, op. cit., note 112 above, p. 33; 'Postscript to Dr. Whytt's observations on Lord Walpole's case', *Phil. Trans.*, 1757, 50: 386.
Carlsbad water by the latter had shown that it contained "sal medium amarum" (magnesium sulfate), alkaline salt, and calcareous earth, and that it seemed similar to lime-water in turning milky and forming an earthy crust when standing for some hours exposed to the open air. In admixing Epsom salt (magnesium sulfate) and salt of tartar (potassium carbonate), the purest known alkaline salt, to lime-water, Alston tried to imitate the properties of the Carlsbad water. In his subsequent in vitro tests with this mixture he found the lithontriptic "virtue" neither increased nor decreased compared to pure lime-water, which meant that Springsfeld's and Lieberkühn's observations could not be reproduced. Whytt performed some more experiments on stones with Spanish soap and oyster shell lime-water and calculated that these lithontriptics had a much higher "dissolving power" than Springsfeld had given for Carlsbad water. In addition he compared the latter's experimental results for medicated urine with those of the analogous trials of Newcome, now Lord Bishop of Llandaff (see above), concluding that Carlsbad water and lime-water gave "at least an equal dissolving power to the urine". The alleged superiority of the Carlsbad waters had thus successfully been called into question - or, that was the impression that Whytt and Alston obviously wanted to create. Without "presuming to decide certainly as to the comparative virtue of the Carlsbad waters and lime-water", Whytt could now compare their respective advantages. The former were more digestible, but the latter could be drunk "equally good in all places, and at all seasons of the year; which is not the case with the Carlsbad waters."

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139 Alston, op. cit., note 112 above, pp. 33-38.
140 R. Whytt, 'Some observations on the lithontriptic virtue of the Carlsbad waters, lime-water, and soap', Phil. Trans., 1757, 50/1: 386-392.
The vigour and promptness with which Alston and Whytt defended lime-water against Springsfeld (their experiments were published in the following year, 1757) indicates that other than purely scientific issues may have been involved here. Given the high methodological level that experimentation in this particular area had reached since the early 1730s, it must have been clear also to the contemporary observer that neither Alston's nor Whytt's control trials were conclusive. Alston had — for obvious geographical reasons — been unable to make use of real Carlsbad water to repeat the comparison; and Whytt was not justified in comparing the "dissolving powers", since he could not be sure that Springsfeld had used the same type of urinary stones. The latter problem was already known by that time, not least through Alston's and Whytt's own work, and it was usually circumvented by performing comparative tests on fragments of one and the same calculus (as Springsfeld had in fact done). The indignant and methodologically inadequate response of the two Edinburgh professors may have had to do, as intimated above, with the high therapeutic value that they attributed to "their" lime-water. Other reasons might have played a role as well. On the basis of negative experiences in a few of his cases, Springsfeld had judged Mrs Stephens's remedy as inefficacious, if not noxious, thereby joining its severest critics, Parsons and Schreiber, both of whom he quoted. Though Whytt and Alston had also criticized Mrs Stephens's medicines, but only for their nauseousness and unnecessarily high number of ingredients, it was from them that their therapy with lime-water had actually been derived. As if sensing this difficulty, Springsfeld had dedicated his work to the Royal Society of London, as an explicit "tribute" to the fact that most research to find a

141 Springsfeld, op. cit., note 135 above, pp. 3-5.

dissolvent for the bladder stone had been carried out in Britain.\textsuperscript{143} Whytt was a F.R.S. by that time, but did this mean that Springsfeld's tribute included the Edinburgh school of medicine? Perhaps most important, however, might have been the fact that the treatment with Carlsbad waters could be seen as a retrograde step. Taking the waters against the stone and gravel was by no means new. Already van Helmont had justified his interest in a chemical lithontriptic with the high numbers of patients who went to take the Spa waters, hoping to be freed from "the Monster of the Affect of the Stone".\textsuperscript{144} More recently, the analyses of many German mineral springs by the well-known Halle professor Friedrich Hoffmann (1660-1742) had made it both medically respectable and popular on the Continent to take the waters against all kinds of stones, gout, and many other diseases.\textsuperscript{145} More particularly, Carlsbad saw, as Milles reported, about 200 patients per season (May to August) each year.\textsuperscript{146} Lime-water, being a carefully prepared remedy, based on experimentation and chemical theory, was probably seen as a progress over the spa "business", which had grown in Britain, too.\textsuperscript{147} Springsfeld's results, indicating that the natural mineral water of Carlsbad, just as it came out of the earth, was so much a better lithontriptic than Whytt's best oyster shell lime-water, in a way belittled the many years of scientific work put into lithontriptics. It was probably this that made it so urgent for Alston and Whytt to try an experimental rebuttal.

About the same time that Carlsbad water was made known as a lithontriptic, another remedy against urinary stones was tried and discussed on the Continent. From

\textsuperscript{143} Springsfeld, op. cit., note 135 above, dedication.

\textsuperscript{144} Van Helmont, op. cit., note 24 above, p. 704.

\textsuperscript{145} Habrich, op. cit., General Introduction above, note 15.

\textsuperscript{146} Milles, op. cit., note 136 above.

\textsuperscript{147} See General Introduction above.
1756 Anton de Haen (1704-1776), professor of the practice of medicine in Vienna, made therapeutic trials with the pulverized leaves of the bearberry plant (uva ursi), which had been recommended to him by his senior colleague Gerard van Swieten.\textsuperscript{148} In the Mediterranean region uva ursi had been used in urinary diseases, including lithiasis, earlier on in the century, particularly by the Spanish Royal surgeon and botanist Joseph Quer. It was only after de Haen, however, that Quer reported a few of his own successful cases.\textsuperscript{149} The hospital patients, on whom de Haen tried the bearberry plant, not only included those with a confirmed bladder stone, but also those who voided foetid, purulent urine (i.e. who suffered from urinary infection without sure evidence of a calculus).

Accordingly he differentiated his results. While those with purulent urine were "all cured", many of those with stones got better or became eventually free of symptoms, but some of them were only better as long as they took the remedy, or did not get better at all and had to resort to lithotomy.\textsuperscript{150} De Haen admitted that uva ursi was not a true lithontriptic in the strict sense of the word, yet so was neither, in his view, lime-water and soap, which he also gave sometimes. The benefit of his plant remedy, he speculated, lay rather in a factor that took away pains and spasms in the urinary system.\textsuperscript{151}

Objections against de Haen's remedy followed soon on the grounds of chemical analysis. The Berlin physician


\textsuperscript{151} Ibid., vol. 1, pp. 228-229, 339, vol. 2, pp. 197, 337-339.
Karl Abraham Gerhard (1739-1821), who became well-known as a mineralogist, argued in 1763 that the chemical components he had found in the uva ursi proved its being not only useless against stones, but harmful. On the other hand, further experimentation and clinical experience with this plant led to the conclusion that just the opposite was true: Michele Girardi (1731-1797), later on professor of anatomy in Padua together with Morgagni, reported in 1764 his extensive \textit{in vitro} experiments on the lithontriptic effect of extracts of the uva ursi on various calculi. The results of these experiments indicated a real lithontriptic power of the plant, whereas comparative trials with lime-water (made from limestone or shells) and shell lime-water with soap showed little or no effect. Although Girardi did not dare to doubt the veracity of Whytt's experiments, he made it clear in his conclusion that he now regarded uva ursi as the "summum remedium" in lithiasis. Following the example of Hales and Langrish, he had also convinced himself in trials on dogs and cats that his extract caused no harm, either given orally or injected into the bladder. Moreover, he had been able to give six of his own case histories illustrating its therapeutic efficacy in stones and other urinary diseases. His somewhat enthusiastic, though experimentally well-founded evaluation of the bearberry plant was qualified, however, in the same year by the freshly appointed Göttingen professor of botany and medicine, Johann Andreas Murray (1740-1791).

Murray presented two of his own cases of stone patients, whose symptoms were reduced under treatment with leaves of the bearberry, but in whom this improvement lasted only - as in some of de Haen's


\textsuperscript{153} Michael Girardi, \textit{De uva ursina ejusque, et aquae calcis vi lithonthryptica novae animadversiones, experimenta, observationes}, Padua, Conzatti, 1764.
patients - as long as they actually took the remedy. Inspired by the experiments of Lobb, Hales, Hartley and others, he therefore examined the lithontripticity of a decoction of uva ursi in in vitro trials on stone fragments, using fountain water as a control. Though after several weeks' immersion in the decoction the fragments became friable, they showed no signs of dissolution. The fragment immersed in water, by contrast, not only became friable, but lost some of its weight.\(^{154}\) Murray concluded therefore, like de Haen, that the uva ursi had no stone-dissolving power and that its therapeutic effect might rather have to do with its well-known astringent property and bitterness.\(^{155}\)

It seems that this view became the accepted one. In a Göttingen medical dissertation of 1765, republished in German translation in 1774, the current spectrum of remedies against urinary stones was critically reviewed and classified.\(^{156}\) Uva ursi was put into the category of palliatives, along with oily, mucous, and emollient medicines, anodynes (Sydenham's Laudanum, opium), and some other plant remedies, such as juniper berries and plantago aquatica latifolia, which had also been recommended by de Haen.\(^{157}\) True lithontriptics were, according to this survey, the juice of onions, the Dutch nostrum "Harlem oil" (known to contain turpentine), lime-water and Venetian soap, Carlsbad water, and - as the strongest - Liquor nitri fixi (solution of potassium carbonate). The efficacy of oil of vitriol and millipedes

\(^{154}\) Johann Andreas Murray, Commentatio de arbuto uva ursi, Göttingen, Pockwitz and Barmeier, 1765, pp. 41-46, 54-55.

\(^{155}\) Ibid., pp. 57-58.


as inferred from Augenio and Lauremberg was questioned, as was that of Dippel's remedy. Mrs Stephens's medicines were dismissed here as actually increasing calculi by producing stony matter - a view also held by de Haen.\textsuperscript{158} The same verdict was given on an analogous lithontriptic of Friedrich Hoffmann, which was based on "pearl ash" (potash, potassium carbonate).\textsuperscript{159} Although de Haen's trials with uva ursi were translated into English in 1763,\textsuperscript{160} his method of treating stones did not gain ground in Britain, nor did Carlsbad water, regardless of the early positive responses in the Philosophical Transactions. Whytt's lime-water with soap remained the predominant lithontriptic. Also soap-lye kept its place, despite the misfortune of Jurin's lixivium in the case of Robert Walpole. In the 1760s and early 1770s it was more or less disguised in new nostrums, such as Dr. Chittick's medicated veal broth and another "lixivium", composed, tested \textit{in vitro}, and propagated by the Bromley apothecary Alexander Blackrie (d. 1772).\textsuperscript{161} It was only in the mid-1770s that the search

\textsuperscript{158} Ibid., p. 328.

\textsuperscript{159} Cf. Cohen, op. cit. (ed. Niemann), note 156 above, pp. 79-84.

\textsuperscript{160} 'An account of de Haen's diss. on the stone, translated from his \textit{ratio medendi}', \textit{The Medical Museum}, 1763, 1: 15, 89, 601 (quoted from Crosse, op. cit., note 1 above).

\textsuperscript{161} Alexander Blackrie, \textit{A disquisition on medicines that dissolve the stone. In which Dr. Chittick's secret is considered and discovered}, London, D. Wilson, 1766, and enlarged 2nd edn London, printed for the author, 1771. Another safe and effective dissolvent for urinary stones was announced - without revealing what it was - by Henry Boesnier de la Touche, \textit{A short account of the disease of the stone in the human body. Also of the method of cure}, London, P. Vaillant and W. Nicoll, 1765, pp. 34-35. Francis Home tested Chittick's medicine with little success on stone patients in the Edinburgh Royal Infirmary, yet found their "medicated urine" to have a lithontriptic effect \textit{in vitro}. See F. Home, \textit{Clinical experiments, histories, and dissections}, 2nd edn, London and Edinburgh, J. Murray and William Creech, 1782, pp. 483-493.
for lithontriptics went into a new direction, following recent developments in chemistry.

8. Fixed air, mineral waters, and calculi: the impact of chemistry

From early on the knowledge of "fixed air" (i.e. carbon dioxide) had been linked with the search for lithontriptics. When Stephen Hales studied, around 1730, the air content of various substances, including urinary stones (see above), he already spoke of "fix'd" air which could be released to its elastic state by his distillation process. For him this fixed air was not yet distinct from the normal air in the atmosphere. Also the bubbles rising from his stone-dissolving "fermenting" mixture of oil of sulphur (sulfuric acid) and salt of tartar (potassium carbonate) - nowadays explanable as carbon dioxide gas - were still simply seen as bubbles of air.\(^{162}\) It was only with the studies of Joseph Black on magnesia alba (magnesium carbonate) in the 1750s that fixed air was recognized as a specific, chemically distinct "kind of air". Black's work, now considered as having laid the foundation for pneumatic chemistry, was initially also linked with the question of stone-dissolving substances. Attracted by the lime-water controversy between the professors Alston and Whytt, the young Black had chosen magnesia alba as the subject of his Edinburgh medical dissertation in the hope of finding "a new quick-lime and lime-water, different from the common sort, and perhaps more powerful in dissolving the calculus".\(^{163}\) While in this respect his hopes were disappointed, he was led instead into his famous series

\(^{162}\) Cf. Hales, op. cit., note 8 above, p. 166.

\(^{163}\) Quoted in A. L. Donovan, Philosophical chemistry in the Scottish Enlightenment: the doctrines and discoveries of William Cullen and Joseph Black, Edinburgh, University Press, 1975, p. 188.
of experiments, in which he established the specific chemical nature of fixed air and its relation to the causticity and solubility of calcareous earths.\textsuperscript{164}

Despite their direct connection with the study of potential lithontriptics, neither Hales' work on fermenting mixtures nor Black's work on magnesia alba had great immediate impact in this field. Though Hales' \textit{in vitro} tests on calculi became methodically a model for later researchers, such as Lobb and Hartley, his early work on lithontriptics was soon overshadowed by his subsequent study of Mrs Stephens's medicines. As mentioned above, Black's work caused Whytt to change his explanation for the lithontripticity of lime-water, but this was a purely theoretical issue. Recent developments in the chemistry of mineral waters, however, drew again attention to fixed air and calculi in the 1770s.

In 1765 the Whitehaven physician William Brownrigg (1712-1800) had suggested that the "air" contained in the Belgian Spa and other mineral waters was identical with the "choak-damp" of the coal mines; and two years later Henry Cavendish had published his experiments on water from a pump in Rathbone Place, London, demonstrating among others that the volatile component of this water was a mixture of fixed air with common air.\textsuperscript{165} It thus became clear that the old mysterious "mineral spirit" in many waters was nothing else but Black's fixed air, a


\textsuperscript{165} William Brownrigg, 'An experimental enquiry into the mineral elastic spirit, or air, contained in Spa water; as well as into the mephitic qualities of this spirit', \textit{Phil. Trans.}, 1765, 55: 218-243; Henry Cavendish, 'Experiments on Rathbone-Place water', \textit{Phil. Trans.}, 1767, 57: 92-108. See also Coley, 'Physicians and the chemical analysis', General Introduction above, note 19.
knowledge, which subsequently provided an incentive to produce artificial "aerated" mineral waters. In fact the production of artificial mineral waters had a rather long tradition by that time. Since the late seventeenth century salts had been extracted from natural waters, e.g. Epsom salt (magnesium sulfate), which were then sold by apothecaries for re-dissolution in common spring water. Friedrich Hoffmann had also given a recipe for making sparkling waters ("acidulae"): salt of tartar (potassium carbonate) had to be shaken with spirit of vitriol (diluted sulfuric acid) and pure water in a corked earthenware vessel. As mentioned above, Alston for example did not hesitate to produce an artificial Carlsbad water in order to examine Springsfeld's claims. A new step was now the so-called impregnation of waters with fixed air. Joseph Priestley, in 1772, was the first to publish instructions for a device for this purpose, which was subsequently modified and successfully commercialized by the Bristol apothecary John Mervin Nooth.

Brownrigg had taken a keen interest in Mrs Stephens's medicines as soon as they had become known in 1739. Having carefully abstracted Hartley's A view of the present evidence, he concluded that this remedy was in fact an effective lithontriptic and accordingly prescribed it to some of his patients who suffered from urinary calculi. Likewise he had studied in detail Lobb's A treatise on dissolvents of the stone. Cf. Jean E. Ward and Joan Yell (ed. and transl.), The medical casebook of William Brownrigg, M.D., F.R.S. (1712-1800) of the town Whitehaven in Cumberland, London, Wellcome Institute for the History of Medicine, 1993 (Med. Hist., suppl. no. 13), pp. 107-119.


Seen against this background, it is not surprising that fixed air, in particular water impregnated with fixed air, was soon suggested and tried as a lithontriptic. For long "gravel and stone" had been a main indication for the taking of mineral waters at the spas. Now that fixed air had been recognized as a major component of these waters, attention was naturally drawn to its possible therapeutic value in calculous complaints. A first step in this direction was made even before artificial "aerated" waters could be produced. In 1771 Nathaniel Hulme (1732-1807), physician to the Charterhouse in London, published cases of patients with urinary stones, whom he claimed to have cured by a combined treatment with salt of tartar and weak, diluted spirit of vitriol. While this was nothing else but Hoffmann's recipe for "acidulae", and basically the same as Hales' "dissolving Menstruum", Hulme's explanation for the apparent therapeutic effect was new. The remedy's efficacy was attributed to its content of fixed air, which came from a reaction of the two components when they were mixed in a sealed container before giving them to the patient, or when they met in the patient's stomach, if they had been administered separately.\(^\text{108}\)

Two years after Priestley had published his method for impregnating water with fixed air, his friend Thomas Percival (1740-1804) of Manchester, nowadays best remembered for his Medical Ethics (1803), started to test this kind of water as a lithontriptic. Percival had heard that William Saunders (1743-1817) in London, physician to Guy's Hospital and known as a lecturer in chemistry, had employed fixed air as a solvent for human calculi, but he was not yet informed about the method and outcome of these trials. In patients with "pulmonic disorders" and as an antiseptic in so-called putrid diseases, such as "gangrenous sore throat", "malignant fevers", and "foul

\(^{108}\) Cf. Nathaniel Hulme, A safe and easy remedy proposed for the relief of the stone and gravel, the scurvy, gout, &c., London, G. Robinson, 1778 [1st edn 1771].
ulcers", Percival had already tried fixed air and reported the cases. As for the air's possible value as a lithontriptic, he formed a particular hypothesis. Recollecting that "Dr. Black and Mr. Cavendish have proved the solubility of various earthy bodies in water, either by abstracting from, or superadding to the fixed air which they contain", he assumed (like Whytt) that lime-water and soap-lye dissolved calculi in the former way. Impregnated water, he reasoned, should dissolve them in the latter way, i.e. by superadding to their content of fixed air.

Using normal spring water as a control, Percival immersed human urinary stones for two to three days in water impregnated with fixed air. After this time he noted a considerable loss of their weight which exceeded that in the control trials. Calculi suspended in an atmosphere of fixed air for the same time slightly gained weight, obviously through absorption, but became friable. Comparative in vitro experiments with lime-water, soap-lye, and oil of vitriol (sulfuric acid) confirmed their known lithontriptic powers. Percival felt that these results were "favourable" to his hypothesis and proclaimed that water impregnated with fixed air, or "mephitic water" as it also became to be known, was the new lithontriptic of choice. Knowing from his trials on patients with other diseases that this water was easily tolerated, and concluding from his in vitro tests that it was efficacious in every kind of urinary stone, he preferred it to lime-water, which was known to be "nauseous", as well as to soap-lye preparations, which

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carried the risk of causing bladder pains and bloody urine.\textsuperscript{170}

Saunders subsequently communicated his trials and conclusions in a letter to Percival, dated 1 February 1776, which was published by the latter in the same year along his own work. For Saunders, it had been particularly Stephen Hales' experiments with "fermenting" mixtures that had led him to try fixed air as a lithontriptic. With the chemical knowledge meanwhile provided by Black, Cavendish and others, he interpreted the lithontriptic effervescence of Hales' "dissolving Menstruum" as an effect of released fixed air. Like Percival he had therefore made \textit{in vitro} trials with water saturated with fixed air, using simple distilled water as a control. Experimenting on fragments of a urinary stone, Saunders had observed a lithontriptic effect of the impregnated water already within some hours, and he took this as sufficient proof of the "solubility of the human \textit{Calculus} in the mephitic acid" (i.e. carbonic acid).\textsuperscript{171} He therefore strongly advocated its further study in patients, hoping particularly to replace the current soap-lye containing nostrums, which he regarded as dangerous quackery:

\begin{quote}
We shall be usefully employed if by a rational inquiry of this kind, we can extricate the present practice, in such cases [i.e. of calculus], from the hands of empirics, and prevent a deluded public from blindly confiding in the boasted remedies or \textit{nostrums} on this subject, all of which, so far as I have examined by analysis, are the lixivium in disguise...\textsuperscript{172}
\end{quote}


\textsuperscript{171} 'A letter to Dr. Percival from William Saunders, M.D. physician to Guy's Hospital; concerning the solution of stones of the bladder by fixed air', \textit{ibid.}, pp. 295-329.

\textsuperscript{172} \textit{Ibid.}, pp. 320-321.
Saunders recommended not only water impregnated with the help of Nooth's apparatus, but also waters which naturally contained fixed air, such as Seltzer, Bristol, Rathbone Place, and Chislehurst water, artificial saline draughts "in the state of effervescence" and - as if to make therapy pleasant - "brisk vinous liquors", such as Champagne.

Still in the same year, 1776, William Falconer (1744-1824) of Bath, known through his study of the local waters, repeated and confirmed Percival's in vitro trials, also concluding that water impregnated with fixed air might be an effective remedy against the stone. Of course the old question concerning any orally taken lithontriptic, whether it actually reached the urinary tract, was posed for fixed air as well, and it was again Percival, who studied it experimentally. Having persuaded "a young gentleman, Mr Thomas Smith", to drink large quantities of mephitic water for two weeks, Percival demonstrated chemically and physically that his subject's urine contained fixed air: a precipitation was produced with lime-water, and placed under the receiver of an air pump, the urine copiously emitted bubbles. Urinary stones put into the test person's urine for some time were eventually dissolved.

173 Ibid., pp. 318-319.

174 William Falconer, Experiments and observations in three parts...Part II. On the dissolvent power of water impregnated with fixible air, on the urinary calculus, London, W. Goldsmith, 1776.

175 Cf. 'A review of the discovery of the solvent powers of fixed air on the urinary calculus; of the application of this remedy to other disorders of the kidneys and bladder; and of the success which has attended the use of it', Med. Phil. Comm. (ed. by Andrew Duncan senior), 1778, 5: 442-453. Stimulated by the work of Percival and Saunders, Francis Home tried mephitic water orally and intravesically on a bladder stone patient in the Royal Infirmary of Edinburgh - without success. His in vitro trials with mephitic water and the patient's "medicated urine" were inconclusive. Cf. Home, op. cit., note 161 above, pp. 493-498.
Nooth's apparatus, modified by John Hyacinthe Magellan and manufactured by William Parker in Fleet Street, London, was said to have been sold over 1,000 times already in 1777. By the beginning of the nineteenth century the "gasogene", as the apparatus was marketed, had become a familiar feature in many households. In addition, carbonated waters produced in a high-pressure process in the factories of Jean-Jacob Schweppe and associates in Geneva, Paris, and London became available in the early 1790s. It may be assumed therefore that aerated waters were increasingly used for self-medication in calculous complaints and other diseases, apart from their growing role as an article of regular consumption. On the other hand, doctors in the late eighteenth century refined and "medicated" this perhaps all too simple remedy, partly, it seems, to have their own share in the business with artificial waters.

William Falconer, for instance, introduced the so-called aqua mephitica alkalina, i.e. a solution of salt of tartar (potassium carbonate) in water, which was then impregnated with fixed air. It had been used with apparent success in a self-trial by his Bath colleague Benjamin Colborne in 1778, who suffered from urinary stones. Colborne had also performed some in vitro experiments, showing the lithontriptic effect of alkaline salts (such as salt of tartar). As Falconer explained, water impregnated with fixed air was chosen by Colborne as a weak acid that would combine loosely with the rather caustic and nauseous alkaline salts to form an agreeable neutral salt. In the patient's body this neutral salt would be divided again into its active components. Yet,


this explanation may well have been made *ex post*. The alkaline mephitic water had, as Falconer admitted, natural precursors in the chemically similar Carlsbad and Selters waters, both of which had been recommended against gravel and stone by Friedrich Hoffmann.\(^{178}\) (Interestingly, Springsfeld's work was not quoted.) Moreover, a very similar preparation, "Bewley's julep", had already entered the medical market. The Norfolk surgeon and apothecary William Bewley (1726-1783), a friend of Priestley, impregnated a solution of fixed alkali (sodium carbonate) with fixed air and sold the mixture as a digestive.\(^{179}\)

In order to substantiate the efficacy of the aqua mephitica alkalina, Falconer gave twenty-four case histories, including Colborne's and all of them successes, noting that only one case had occurred to him, in which it had been "of no service". In addition he reported more *in vitro* experiments, performed together with Colborne, that showed the remedy's lithotriptic power as well as that of the urine of persons taking it, tested against normal urine as a control.\(^{180}\) Falconer claimed that his, respectively Colborne's, alkalinized mephitic water worked more mildly and in another way than simple impregnated water. Referring to Percival's and his own earlier *in vitro* trials with simple mephitic water, he speculated that it acted mainly on the "mucus" or "animal gluten", which connected the "sandy particles" of urinary stones. By contrast, judging from the "corroded and worm-eaten appearance" of immersed calculi, the new


\(^{180}\) Falconer, op. cit., note 177 above, pp. 16-107, 124-125.
alkaline water acted upon the "sandy particles" themselves. On the basis of recent analytical results of the Uppsala professor of chemistry and pharmacy, Torbern Bergman (1735-1784), Falconer assumed that these stony parts consisted of acid of sugar and calcareous earth and suggested that the mode of action was a "double attraction": alkaline salt attracted the former, fixed air the latter component, resulting in the dissolution of the calculus.\(^{181}\) This quite differentiated pharmacological theory went hand in hand with the commercialization of the remedy. Both a footnote to Falconer's scientific text and an attached advertisement pointed out that his aqua mephitica alkalina could be obtained ready-made in half-pint bottles from John Killick near Black Friars Bridge in London at six shillings per dozen. Not surprisingly, Killick sold also Falconer's book on this water.\(^{182}\)

A simple alternative to alkaline mephitic water was suggested in 1793 by the Bristol physician and chemist Thomas Beddoes (1760-1808): sal sodae or natron (sodium carbonate), either formed to pills with soap or dissolved in water. The motive for this suggestion reflected less pharmacological considerations than Beddoes' political radicalism and zeal as a medico-social reformer, that has recently been studied in detail by Roy Porter.\(^{183}\) As Beddoes wrote, his aim had been to provide "a cheap, safe, and efficacious formula, adopted to the poor, who are by no means exempted from calculous disorders". Though chemically derived from the aqua mephitica alkalina, his remedy did not require the expensive and brittle Nooth-Parker apparatus for preparation. Moreover, it did not cause the "dizziness" that had been reported

\(^{181}\) Ibid., pp. 145-147.

\(^{182}\) Ibid., pp. 10-11 (footnote) and advertisement.

after the use of waters impregnated with fixed air. In support of his therapy Beddoes presented the case histories of ten patients suffering from calculi and other diseases of the urinary tract, all of whom were said to have been cured or got "much better". His alkaline remedy, he speculated, led to the expulsion of concretions by causing movements in the pelvis of the kidney and the ureters, and in some cases actually seemed to have dissolved the stone.

In one sense, Beddoes' initiative was an anti-commercial one, tying in with his general medical ethics that criticized doctors who profited from "the sick trade" and made business agreements with apothecaries. It was also an example of his vision that chemistry would transform medicine into a rational, scientific practice. In this sense he constructed a positive and a negative history of lithotriptics. The negative history comprised the various remedies in the tradition of antiquity and the Arabs, of alchemical writers, but also de Haen's bearberry plant. The positive history was that of alkaline remedies, starting - not surprisingly for an author of the Enlightenment - only in the early eighteenth century with the recommendation of salt of tartar in Nicholas Robinson's *Treatise on the gravel and stone* (1721) and Friedrich Hoffmann's praises of the hot alkaline springs of Germany and the salt of the Carlsbad waters. Evidently referring to Mrs Stephens's medicines,

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186 See Roy Porter, 'Plutus or Hygeia? Thomas Beddoes and the crisis of medical ethics in Britain at the turn of the nineteenth century', in Baker et al., op. cit., note 7 above, vol. 1, pp. 73-91.

Beddoes pointed out that later "alkaline substances enriched the English empirics, and obtained the commendation of Hartley, Whytt, Kirkpatrick, De Haen, and other physicians of great celebrity". They relieved the pain caused by the stone, but did not dissolve it. As an important next step Beddoes noted that Bergman, in 1776, had confirmed lime-water and "caustic alkaline lixivium" (soap-lye) as the right lithontriptics on the basis of his studies into the chemical composition of urinary stones. Perhaps even more important for Beddoes, however, was the self-experiment of Colborne, leading to the alkaline mephitic water as the immediate precursor of his own remedy. Accordingly he dedicated his book on this subject to Colborne as the "discoverer of the virtues of vegetable alkali, supersaturated with carbonic acid". This positive story in the search for lithontriptics exemplified the way that medicine should go in the future, or as Beddoes put it:

From Chemistry, which is daily unfolding the profoundest secrets of nature, and, among the rest, the delicate play of living machinery, your [i.e. Colborne's] example alone would justify us in entertaining the most sanguine expectations: since the earliest discoveries in that department of chemistry, which has been so successfully cultivated by Black, Cavendish, Priestley, Scheele, and Lavoisier, suggested to you a safe and efficacious remedy for one of the most frequent, painful, and hopeless of diseases.

9. Chemical analysis of calculi and the differentiation of lithontriptic therapy

When Beddoes wrote these optimistic lines, chemistry had in fact started to have yet another impact on the field of lithontriptics than that of leading to the alkaline and/or carbonated remedies outlined above. In the late eighteenth century improved methods of

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188 Beddoes, op. cit., note 184 above, pp. 2-6.
189 Ibid., p. v.
analytical chemistry were developed (often in connection with the study of mineral waters), which permitted the detection of increasingly smaller quantities of substances and compounds in specimens.¹⁹⁰ These methods being also applied in the emerging field of animal chemistry, urinary stones were subjected to this kind of scrutiny as well. As will be shown in the following sections, this led not only to chemical classifications of calculi, but also to a differentiation of lithotriptic treatments and eventually to important insights into their limits and fallacies.

Until well into the second half of the eighteenth century, urinary stones had been characterized merely by their anatomical location, size, form and surface, hardness, and colour. Though it was known through the experimental studies of Alston, Whytt and others that some kinds of calculi, such as the dark, hard "mulberry" stones (i.e. calcium oxalate stones), resisted lithotriptics much more than others (see above), there had been no specific chemical explanations for this. Urinary stones were generally believed to consist of salt, air, and earth, and a sticky oil or animal gluten, that connected their particles.

A first reference to a differentiation going beyond this can be found in the Göttingen dissertation of 1765, mentioned above. Its author Meyer Kalman Cohen quoted a personal communication of the renowned Berlin chemist Andreas Sigismund Marggraf (1709-1782), who distinguished two types of calculi according to his findings in calcining them. While one type left back much "earth" after calcination (probably calcium phosphate stones), the other type left no earthy residuum, being completely volatile. This latter type, as Cohen concluded, contained no earth, but only "salt", which he believed to have been formed from a "phosphorous acid" (i.e. uric acid). This

¹⁹⁰ See Coley, 'Physicians and the chemical analysis', General Introduction above, note 19; idem, 'Physicians, chemists', General Introduction above, note 19.
chemical distinction was moreover correlated with a structural one. The earth containing stones had an irregular structure, "as composed of many granules", whereas the pure "salt" stones showed regular layers or "cortices". On the basis of Marggraf's chemical distinction Cohen assumed that alkaline remedies, such as lime-water, soap, Carlsbad water and Liquor nitri fixi, would dissolve only these "salt" stones. In "earthy" stones little could be expected from alkalies, except that they might smoothen the calculus' surface, having thus a palliative effect. As for therapeutic practice, he therefore suggested a trial with the alkaline remedies and to see whether the patient started to void sand and gravel. If this did not happen despite a long period of treatment, lithotomy was the only resort.

As Cohen noted, Marggraf had performed in vitro trials, showing that alkaline fluids dissolved calculi. It was the London apothecary and Fellow of the Royal Society Timothy Lane, however, who demonstrated experimentally, about five years after Cohen's dissertation had been printed, that alkaline lithontriptics acted selectively on concrements, depending on their chemical nature, as the latter had suggested.

Yet the starting point for Lane's investigation did apparently not lie in the work of Marggraf or Cohen, but in a disturbing practical observation: the efficacy of the then customary "Lixivium Saponarium" (soap-lye), prepared after the precepts of the latest Pharmacopoeia, had been found to be "very unequal". Studying comparatively the effect of calcination and of a three days' ingestion in "Lixivium" on fourteen different specimens of urinary stones, Lane found that those which

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191 Cohen, op. cit., note 152 above, pp. 5-6.

192 Ibid., pp. 32-34.

were most volatile (i.e. the "salt" stones of Marggraf) were also the most soluble. This explained, as he pointed out, the lack of therapeutic success of alkaline remedies, such as "Lixivium", soap, and lime-water, in some cases, whereas they showed "salutary effects" in others. On these grounds Lane did not recommend a "try and wait" policy like Cohen, but suggested a chemical pre-test in vitro whenever this was possible:

It frequently happens, in fits of the gravel and stone, that gravel or small pieces of calculi are discharged, which should be examined. If perfectly soluble in lixivium (Aq. kali puri), the remedy is obvious; if imperfectly, doubtful; if insoluble, lixivium will only irritate, without benefit.

Lane's study was read to the Royal Society only in May 1791, and published in its Philosophical Transactions in the same year - twenty years after the experiments had been carried out. By this time the Swedish chemist Carl Wilhelm Scheele (1742-1786) had identified uric acid, which he called "lithic acid", as a chief constituent of urinary calculi (1776), a finding, which - though subsequently confirmed by Bergman - became accepted knowledge only after some controversy. The London physician George Pearson (1751-1828), a disciple of Lavoisier, argued in 1798, on the basis of his own extensive analyses of urinary stones, that Scheele's lithic acid was actually an "animal oxide", for which he consequently coined the name "uric oxide". This, in

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195 Ibid., p. 227. Also Thomas Percival reported about own chemical trials with calculi, including calcination. Having experimented on five different specimens, he concluded that "an absorbent earth often enters into the composition of the urinary calculus" and speculated that this earth was ingested by the drinking of hard spring water. Cf. his 'Experiments and observations on the nature and composition of urinary calculi', in op. cit., note 170 above, pp. 159-170.
turn, was challenged by Fourcroy, who pointed out that moist "uric oxide" turned litmus red and should therefore be regarded as a true, albeit weak, acid, which he suggested to call "acide ourique".\(^{197}\) Having studied not only human, but also animal calculi, from carnivores (dog) as well as from herbivores (rabbit, horse), Pearson further stated that his "uric oxide" could be found only in humans, explaining this through differences in the urinary organs and food and drink. Yet also in this he was soon refuted, when the presence of "lithic acid" in the kidney stone of a sheep was demonstrated in 1801.\(^{198}\) Other components of urinary calculi found by Pearson were phosphate of lime, ammoniac, phosphoric acid united with ammoniac, water, and animal mucilage.

Pearson was still too cautious to make any therapeutical inferences from his analytical results. He expressed his conviction, however, that "more efficacious and innocent practice, in diseases from these concretions, can only be discovered by a further investigation of their properties".\(^{199}\) In fact this line of research was soon followed by Fourcroy, who had started to perform experiments on human urinary calculi in 1787. For him this was part of a larger research programme in animal chemistry, carried out together with his junior colleague Nicolas Louis Vauquelin (1763-1829), in which they explicitly aimed at therapeutically relevant analytical knowledge.\(^{200}\) It was Pearson's work that

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\(^{196}\) George Pearson, 'Experiments and observations, tending to show the composition and properties of urinary concretions', Phil. Trans., 1798, 88: 15-46.


\(^{198}\) William Stephen Jacobs, Experiments and observations on urinary and intestinal calculi, Philadelphia, Carr and Smith, 1801, p. 25.

\(^{199}\) Pearson, op. cit., note 196 above, p. 19.

\(^{200}\) See Smeaton, op. cit., note 197 above, pp. 136-162.
stimulated Fourcroy, after his political commitment to
the French Revolution, to take up the subject of urinary
stone analysis again. By 1800 Fourcroy and Vauquelin had
already examined over 500 different specimens, which
enabled them to set up a classification on chemical
principles and to estimate the relative frequency of
certain types of calculi.201

According to Fourcroy seven constituent substances
could be identified in urinary stones: uric acid, urate
of ammonia, phosphate of lime, ammoniaco-magnesian
phosphate, oxalate of lime, silica, and animal matter.
Since these substances were found in various combinations
(only animal matter being always present as a connecting
substance), twelve "species" of calculi could be
distinguished. About two thirds of all examined stones
consisted of the two "earthy" phosphates and oxalate of
lime, about one third were composed of uric acid. Silica
stones were found very rarely.202 Knowing from own in vitrino
experiments that diluted ley of potash and soda dissolved
uric acid and that weak nitric acid and muriatic acid
(hydrochloric acid) dissolved phospate of lime and
ammoniaco-magnesian phospate (and to a lesser degree also
oxalate of lime), Fourcroy concluded that one of these
liquid reagents would normally dissolve the calculus,
when injected into the patient's bladder. As a solvent
for oxalate of lime stones, he also suggested diluted
nitric acid, and for silica stones fluoric acid.
Concerning oral administration of lithontriptics he
shared the doubts of his predecessors that the reagent
would keep its efficacy until it reached the bladder.203

201 Fourcroy, op. cit., note 121 above, vol. 10, p. 293.
See also Johannes Büttnner and Christa Habrich, Roots of
clinical chemistry, Darmstadt, GIT Verlag, 1987, pp. 67-
68.

202 Fourcroy, op. cit., note 121 above, vol. 10, pp. 330-
343, 357.

203 Ibid., pp. 352-355; see also Smeaton, op. cit., note
197 above, p. 151.
An obvious practical problem was of course the diagnosis of the chemical type of a urinary stone in situ in order to choose the right solvent. Fourcroy recommended examining voided gravel, to analyze the urine, and to consider the patient's family history. If this was not possible or gave no information, a probatory injection with ley of potash should be made. If it met with an uric acid stone, the used solvent fluid would contain traces of uric acid, that could be discovered by forming a precipitate with muriatic acid. In case this was not found, muriatic acid could be tried next as a solvent, and in a stone containing phosphates the used fluid would then show a precipitate after adding a few drops of ammonia. Apart from this the diagnosis could be made ex iuvantibus, i.e. when the symptoms diminished after some injections, or when the calculus was found smaller in a repeated catheter examination.²⁰⁴ Fourcroy was quite optimistic about the practicability of his therapeutic suggestions, referring to five persons, who had been using alkaline injections without sensing any harmful effect, and he expressed his belief that patients would prefer these to the "pain and danger" of lithotomy. Like William Butter nearly half a century before, he imagined that patients would perform the injections themselves. Though the technical preconditions for such a treatment had become better (Fourcroy recommended the use of a permanent elastic gum catheter and a tin syringe for up to eight injections per day over several months), his method did not get beyond the stage of an experimental therapy (see above).²⁰⁵ Like his Edinburgh predecessor, Fourcroy had evidently underestimated the patients' resistance to the inconvenience and unpleasantness of catheterization and intravesical injections.


Still, for the history of lithontriptics Fourcroy's work was important in two respects. For the first time a therapeutic scheme had been developed on the basis of detailed knowledge about the chemical nature of both the solvent remedy and its target, the calculus. In this respect Beddoes' vision had been fulfilled. And secondly, the history of lithontriptics began to be seen in another light. Against the background of his new chemical knowledge, Fourcroy regarded the search for lithontriptics as a long road of trial and error. Only by chance was something "hit upon", that was appropriate for a certain species of calculi: for example, Mrs Stephens's medicines, Whytt's lime-water, and soap-lye might have succeeded in cases of calculi formed of uric acid or urate of ammonia, but not in stones consisting of earthy phosphates and oxalate of lime. Moreover, Fourcroy offered an explanation for the phenomenon of "stony flakes" voided by patients under treatment with alkaline remedies, that had caused so much controversy. As he had observed in his own five cases, injected ley of potash formed precipitates with free phosphoric and uric acid in the urine.

While Fourcroy and Vauquelin had examined many calculi, in England some analyses of this kind had also been carried out by William Hyde Wollaston (1766-1828), who had come to very similar results and conclusions. In the next years the chemist William Thomas Brande (1788-1866) and the surgeon Everard Home (1756-1832), who had been brought together in the Animal Chemistry Club of the Royal Society, took up the question of stone analysis and

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207 William Hyde Wollaston, 'On gouty and urinary concretions', Phil. Trans., 1797, 87: 386-400. See also Smeaton, op. cit., note 197 above, p. 151. Marcet later criticized that Fourcroy had failed to acknowledge Wollaston's (previously published) work. See Louis Rosenfeld in his forthcoming history of clinical chemistry. Thanks to Professor Rosenfeld, New York, for sending me an extract from his manuscript.
lithontriptic therapy. Also Brande's analysis, carried out on specimens from the Hunterian Museum and Home's private collection, confirmed Fourcroy's results for human calculi. In addition he found that some animal calculi contained carbonate of lime, besides the usual phosphates. Linking the anatomical location of calculi with the results of their chemical analysis, Brande furthermore observed that concrements which had been voided immediately after their descent from the kidney consisted almost always of uric acid, whereas bladder stones frequently contained phosphates. Of particular importance, however, became Brande's views on the therapeutic value of lithontriptics. He agreed with Fourcroy and others that in vitro uric acid stones would eventually be dissolved by a solution of caustic alkali, but this could not happen in the body. Here the alkaline remedies united with uncombined phosphoric and carbonic acids in the urine (an observation actually made by Fourcroy himself), and this made them incapable of exerting any action upon the calculus. Lime-water was the worst choice in this respect, since it formed insoluble compounds with the free acids (the "stony flakes" of earlier observers). Alkaline substances, Brande believed, were good only for preventing the formation of uric acid and thus of an increase of existing bladder stones. Similarly critical was his opinion about the use of muriatic acid as a dissolvent for phosphate stones. Though the phosphates in the urine might be diminished and ultimately disappear under this therapy, and the phosphate containing parts of a calculus might actually be dissolved, its usual nucleus of uric acid would remain, if not be augmented. Brande objected also to Fourcroy's suggestion of injecting the "solvents" directly into the bladder. The frequent insertions of an instrument would make the patient's suffering only worse. Moreover, the French chemist's tests for diagnosing the
type of bladder stone could identify at best the nature of its surface, but not its full composition.\textsuperscript{208}

On these grounds Brande finally reinterpreted and restated the role of lithontriptic therapy:

It has been shown that in the majority of cases, the nuclei of calculi originate in the kidneys [sic], and that of these nuclei by far the greater number consist of uric acid; the good effects therefore so frequently observed during the use of an alkali, arise, not from any actual solution of calculous matter, but from the power which it possesses of diminishing the secretion of uric acid, and thus preventing the enlargement of the calculus, so that, while of a very small form, it may be voided by the urethra.\textsuperscript{209}

Everard Home, in a comment on Brande's work, published together with the latter in the Philosophical Transactions of 1808, fully supported these chemical views and tried to substantiate them with case histories. The soft exterior laminae of some calculi, which had been extracted from patients after a course of alkaline medicines and which had usually been regarded as proof of their lithontriptic effect, were - in the sense of Brande - just a newly formed mass, deposited on their surface. The mitigation of symptoms that could sometimes be observed in stone patients taking alkalies, had, argued Home, very different reasons. In older men, for example, the growth of the prostate gland might have formed a barrier between the stones and the orifice of the bladder. In other patients calculi might be enclosed in cysts between the muscular fascicles of the bladder wall. From this perspective he pointed out that Mrs Stephens's medicines had not been evaluated in postmortem

\textsuperscript{208} William Brande, 'A letter on the differences in the structure of calculi, which arise from their being formed in different parts of the urinary passages; and on the effects that are produced upon them, by the internal use of solvent medicines...to Everard Home, Esq. F.R.S.', Phil. Trans., 1808, 98: 223-243.

\textsuperscript{209} Ibid., pp. 242-243.
examinations, when Parliament granted her the remuneration.210

Brandie and Home were not merely critical of the value of traditional and new lithotriptics. Subsequently they made a positive contribution on the basis of their concept of stone prevention (rather than dissolution). Home suggested the intake of magnesia (magnesium oxide), believing that it would remain long in the stomach (because of its insolubility in water) and combine with "any acid", therefore reducing the formation of uric acid. At his request Brande pursued this question in therapeutic trials. By 1813 he had been able to present the cases of six patients suffering from "uric" gravel or calculi, in whom the magnesia treatment had apparently diminished the uric acid levels in the urine and stopped or reduced the voiding of concretions. In addition Brande claimed to have used citric and carbonic acid successfully in four patients with phosphate-type stones.211

With the work of Fourcroy and Vauquelin in Paris, and Brande and Home in London, the history of lithotriptics had definitely taken on its modern face. The pharmacotherapy of urinary stones was from now on based on the results of chemical analysis. Also the therapeutic aim had been qualified: it was no longer a cure by actually "breaking" or dissolving calculi that was expected. The alkaline and acid medicines of the late eighteenth and early nineteenth centuries were rather supposed to prevent stone formation by influencing its chemical preconditions, the patient's particular

210 Everard Home, 'Some observations on Mr. Brande's paper on calculi', ibid., pp. 244-248.

211 W. T. Brande, 'Observations on the effects of magnesia, in preventing an increased formation of uric acid; with some remarks on the composition of urine', Phil. Trans., 1810, 100: 136-147; idem, 'Additional observations on the effects of magnesia in preventing an increased formation of uric acid; with remarks on the influence of acids upon the composition of the urine', Phil. Trans., 1813, 103: 213-226.
"diathesis". These new concepts also characterized the first full monograph on the chemistry and medical treatment of urinary stones published in 1817 by the chemist-physician Alexander Marcet (1770-1822) of Guy's Hospital, London. According to him, any proper pharmacotherapy of urinary stones required a previous analysis of voided sediment or gravel, in order to determine the chemical type of the present calculous disorder and thus to select the appropriate chemical remedy. For uric acid stones he recommended soda water (i.e. alkali containing water supersaturated with carbonic acid by mechanical pressure), and for phosphate calculi muriatic acid. Marcet also referred to the new magnesia treatment of Home and Brande, which by this time already seems to have gained wide-spread acceptance. It actually illustrated, in Marcet's account, the dangers of a chemical treatment by practitioners and by patients themselves without a proper chemical diagnosis. For patients with the "most common species" of ammoniacomagnesian stones the habitual taking of magnesia, "merely in compliance with the popular practice", had proved harmful by adding to, or confirming, their disease. As Marcet had experienced, "the patients, mistaking the neutralizing and aperient properties of the alkaline earth for its supposed solvent powers, had continued this baneful practice, till the examination of the sand deposited in the urine, or of some fragment of the calculus, had made them aware of their error." Even worse, some patients had been reported to have died from masses of magnesia, which had accumulated in their intestines. Reading Marcet here between the lines,


214 Ibid., pp. 172-173.
reveals his view that lithontriptic treatment belonged only in the hands of physicians with sufficient knowledge of (animal) chemistry. Not surprisingly, he is known to have added optional lectures on the identification of urinary calculi to his course on general chemistry, which he gave to the medical students at Guy's, and his book contained instructions for methods of stone analysis that required "little chemical skill or knowledge" and "extremely simple apparatus".  

When in this sense Marcet propagated the medical therapy of calculi as a branch of applied animal chemistry, mechanical techniques for the treatment of bladder stones started to be developed. From 1817 Jean Civiale (1796-1867) began to construct devices for the intravesical destruction of calculi, initially combined with the local application of solvents through an inserted tube, to be followed by the "lithotrites" of James Leroy d'Etiolles (1798-1860) and Charles Louis Heurteloup (1793-1864) in the 1820s and 1830s. By the middle of the nineteenth century lithotripsy, as the technique became known, had developed into a serious alternative to lithotomy.  

The introduction of anaesthesia in the mid-1840s took not only the horror of pain from bladder stone operations, but eased the method of suprapubic cystostomy, which had before been hampered by the straining of the abdominal muscles. With improved techniques the well-known complications of lithotomy - incontinence, impotence, and the formation of fistulae - could better be avoided, as could be wound infections after the introduction of Lister's antisepsis. All these developments may have contributed to the fact that the search for lithontriptics, which had been so intense in the

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217 Idem, op. cit., note 114 above.
eighteenth century, became less prominent in the nineteenth.

Still, it was never really given up, and has in fact survived into the present day. In the current "management" of urinary stone disease the oral intake of alkali together with a large quantity of fluids is recommended for uric acid and cystine stone disease, not only to prevent further stone growth or recurrence, but in the hope of being able to actually dissolve concrements in situ in some patients. Conversely, acidifying the urine of patients with a history of calcium phosphate and magnesium ammoniate phosphate stones is part of the efforts to prevent the re-growth of these calculi. In these therapeutic recommendations, it seems, the historical search for lithontriptics, from Hales to Marcet, still lives on.

10. Conclusions

The history of lithontriptics, as reconstructed above, raises several issues. An obvious, though not primarily historical question is whether the long tradition of oral "stone-dissolving" therapy, backed up by reports of numerous success cases, was founded on the use of at least some substances, which we would in fact regard as efficacious from the point of view of modern pharmacology. In looking at other properties of the classic lithontriptics of antiquity and the Arabs, attributed to them either at their time or in the

218 See e.g. Henry Bence Jones, 'On the dissolution of urinary calculi in dilute saline fluids, at the temperature of the body, by aid of electricity', Phil. Trans., 1853, 143: 201-216. Thanks to Professor L. Rosenfeld for pointing out this reference.

seventeenth and eighteenth centuries, it is striking that many of them were characterized as diuretics.\(^{220}\) It is quite clear from this that one old idea behind lithontriptics was to wash off stone fragments and to expel smaller calculi through an increased, strong flow of urine. A diuretic property has been confirmed and explained by modern pharmacologists in several plants that had traditionally been recommended as lithontriptics: in quick-grass, asparagus, and caper it is the content in saponines, and in pennyroyal, wild carrot, and parsley in ethereal oils that is now seen as being responsible for their diuretic effect.\(^{221}\) The bearberry plant (Arbutus uva-ursi Lin.) is now known to contain arbutine and methylarbutine. Excreted by the kidneys, these are hydrolyzed in alkaline urine to form hydrochinone and methylhydrochinone, which have an antiseptic and disinfecting effect.\(^{222}\) This, in retrospect, explains de Haen's and Murray's observation that patients with purulent urine were "cured", while the symptoms of stone carriers improved as long as they took the remedy, although it had no apparent lithontriptic effect. The leaves of the bearberry (Folia uvae ursi) actually entered the pharmacopoeias of the nineteenth century as a remedy against various bladder and kidney diseases. They were still listed in the Deutsches Arzneibuch of 1968.\(^{223}\) Finally, that Mrs Stephens's medicines, lime-water and soap-lye, and aqua mephitica alkalina may have had some therapeutic, or at least preventive effect on certain types of urinary calculi (especially uric acid stones)

\(^{220}\) See Estes, op. cit., General Introduction above, note 74.


\(^{222}\) Ibid., pp. 176-178.

can be gathered from their often reported alkalising effect on the patients' urine. As mentioned above, alkalisation of the urine has survived as a principle in the present "management" of uric acid and cystine stone disease. Moreover, the high fluid intake in a course of lime-water, of artificial "aerated", or natural mineral waters (e.g. Carlsbad waters) surely facilitated the excretion of small calculi and may well have helped in preventing further stone growth.

As for the history of pharmacology in general, the example of lithontriptics illustrates the strong influence that chemistry gained in the course of the eighteenth century on this branch of knowledge. Hales' initial work on stone-dissolving "fermenting" mixtures was performed in the context of a chemical investigation; Alston's and Whytt's studies on lime-water were to a large extent purely chemical; the work of Black, Priestley, Cavendish and others on fixed air induced a new lithontriptic treatment; and, most importantly, the analytical studies on urinary stones by Fourcroy and Vauquelin, Wollaston, Pearson, and Brande led to a differentiated scheme of stone therapy, that was based on chemical principles. Occasionally the direction of influence went also the other way round, pharmacology fertilizing chemistry, as in the case of Black's work on magnesia alba, which started off as a search for a lithontriptic better than lime-water. The growing importance of chemistry is also reflected in the development of pharmacological theories of lithontriptic effect. While Hales' early theories were essentially physical (vibrations caused by "fermenting" mixtures, "fiery particles" in lime and "lancinating" salts in soap), later explanations became increasingly chemical, e.g., attraction or superaddition of fixed air (Whytt, Percival), or "double attraction" on the chemical components of stone particles (Falconer).

The story of lithontriptics helps also to qualify the common historical opinion that eighteenth-century
therapeutics was still dominated by the traditions of Galenic humoralism (enriched with Paracelsian iatrochemistry), being basically about purging, vomiting, and bloodletting, with a few remarkable exceptions, such as James Lind's study on the treatment of scurvy or William Withering's on the fox-glove. As has been shown in detail, controlled in vitro experiments, tolerance tests on animals, self-experimentation, and clinical trials were used throughout the century in an innovative way within the extensive search for new, effective lithontriptics. Moreover the validity of results obtained with these methods was amply discussed at the time. Large numbers of case histories were, as we have seen, another important tool in substantiating claims of therapeutic efficacy. Only recently have historians begun to realize, and to demonstrate, the great importance of case histories for the development of the practice of medicine in the eighteenth century. The example of lithontriptic treatment does not only illustrate this point, but throws also some light on contemporary views on the epistemological value of case histories, such as Bracken's and Parsons' objection that accounts drawn up by grateful patients were scientifically unreliable.

Last but not least the history of lithontriptics reflects the commercialization of medicine in eighteenth-century Britain. On the one hand the proprietary remedy

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of an empiric, Mrs Stephens's medicines, was appropriated by academic physicians and scientists, who tried to reduce it to a simple, "rational" therapeutic substance. But on the other hand doctors and apothecaries were quick to commercialize their own remedies, as Jurin's Lixivium lithonatripticum, Chittick's medicated broth, Blackrie's lixivium, and Falconer's aqua mephitica alkalina amply testify. The Nooth-Parker apparatus for impregnating water with fixed air and Schweppé's manufactured "aerated" waters eventually foreshadowed the connection with industry that was to characterize pharmacology and pharmacotherapy in the nineteenth and twentieth centuries.
B. OPIUM: STUDIES INTO AN AMBIGUOUS DRUG

1. Introduction

Since at least the 1960s, when increasing drug abuse became an issue of political and public concern in the West, the history of opium has been of considerable interest. As in other areas of historical investigation inspired by today's problems, the focus tended to be on precursor stages or roots of present phenomena, i.e., attention was devoted mainly to earlier perceptions of the drug's psychotropic and addictive properties, and to medical and social responses to this. The by now classical study in this field was published in 1962/63 by Glenn Sonnedecker, who gave an overview of the development of the concept of opiate addiction from the sixteenth to the twentieth century. Sonnedecker documented Western knowledge about the dangers of habitual consumption of the drug since the Renaissance, mainly from reports of travellers to countries of the Near, Middle and Far East about indigenous opium-eaters. Yet he also pointed out that an awareness of opium addiction as a serious medical or even social problem could not be found in the West before the nineteenth century.¹ This was confirmed by John C. Kramer in a brief survey of the medical uses and misuses of opium in Western countries during the seventeenth and eighteenth centuries, and more recently in a comprehensive study of the history of opium addiction by Margit Kreutel.²


Accordingly most of the scholarly work on historical aspects of opium has been devoted to developments from the late eighteenth or early nineteenth century onwards, when the non-medical, recreational use of the drug became popular in the Western world. Alethea Hayter's book on opium-eating writers of the Romantic period, such as Samuel Taylor Coleridge and Thomas De Quincey, was followed in the 1980s by detailed studies into the social history of opium consumption in nineteenth- and twentieth-century Britain and North America by Virginia Berridge, Terry M. Parssinen, and David Courtwright. They elucidated changes in the public perception of addiction and the beginnings of modern drug control. The Chinese


Compared to this body of historical knowledge on issues related to opium addiction and recreational consumption, only a little disparate work has been done on the history of the therapeutic uses of the drug and on the development of pharmacological knowledge about it. The existing studies into opium therapy have usually concentrated on some specific aspect or period. Most recently, John Scarborough has examined the knowledge about opium in Hellenistic and Roman medicine, especially as documented in the materia medica of Dioscorides. J. Worth Estes investigated the potency and contents of seventeenth-century opium preparations on the basis of data published by the English physician John Jones in 1701. Andreas Niklaus Bindler traced attitudes towards the use of opium as a painkiller as reflected in a number of German and Swiss medical inaugural dissertations of the seventeenth and eighteenth centuries. Luzius von Rechenberg and Huldrych M. Koelbing looked into the opium therapy of Christoph Wilhelm Hufeland, who introduced the term "Opiumsucht" (opium addiction) in 1829. The psychopharmacological use of opium in nineteenth-century German psychiatry has been reviewed by Matthias M. Weber. Finally, some insights into its more general medical usage in the nineteenth century have been provided by John S. Haller Jr. on the basis of articles in Anglo-American medical journals.\footnote{John Scarborough, 'The opium poppy in Hellenistic and Roman medicine', in Porter and Teich, op. cit., General Introduction above, note 22, pp. 4-23; J. Worth Estes, 'John Jones's Mysteries of Opium Reveal'd (1701): key to historical opiates', *J. Hist. Med.*, 1978, 34: 200-209; Luzius von Rechenberg and Huldrych M. Koelbing, 'Hufelands Opiumtherapie im zeitgenössischen Vergleich', *Gesnerus*, 1985, 42: 97-119; Andreas Niklaus Bindler,
Studies of Brunonian therapeutics, such as those by Verena Jantz and Guenter B. Risse, have discussed opium, since John Brown and his followers regarded it as the strongest stimulant and applied it therefore frequently in so-called asthenic diseases. Recently Claudia Wiesemann has argued that the genesis of the modern concept of drug addiction around 1800 was closely linked with Brownianism. Finally, some historical accounts of concepts of pain have touched upon opium as an analgesic.


As for the history of the pharmacology of opium, some pertinent eighteenth-century experiments have been described and analyzed in the early 1960s by Melvin P. Earles, particularly those which dealt with the then controversial question whether the drug acted directly on the nervous system or indirectly via absorption into the blood. After Earles' work this area attracted only scant interest of historians, however. In the 1970s Rolf Winau reviewed some trials with opium in his account of experimental pharmacology and toxicology in the eighteenth century, and Claire Salomon-Bayet drew attention to auto-experiments with the drug by the seventeenth-century pharmacist Moyse Charas. Another survey by John C. Kramer, published in 1980, dealt with the isolation of the opium alkaloids (especially morphine) in the early nineteenth century and the subsequent medical use and abuse of opiates. This was followed by a short paper by Ronald K. Siegel and Ada E. Hirschman, in which they cited excerpts from the extensive pharmacological self- and animal experiments with opium, morphine, and narcotine carried out in 1826 by the French physician Pierre-Alexandre Charvet. Only recently has the topic been taken up again by the present author with an overview of experimental research on opium in the eighteenth century and a brief study into self-experiments in this field during the same period.

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9 Earles, 'Early theories', 'Experiments with drugs', and 'Studies', General Introduction above, note 3.


This chapter aims at providing a more comprehensive picture and better understanding of early pharmacological experimentation with opium and its implications. In particular, it looks into the leading questions in this area, the methods employed in answering them, the relevance of experimental results for pharmacological theories as well as for therapeutic practice, and also into some ethical considerations. The period under study begins in the second half of the seventeenth century, when concerns among doctors about the safety of opium therapy were coupled with a strong interest in the drug's pharmacological properties, leading to first experiments. It ends in the early nineteenth century, when the isolation of morphine and other opium alkaloids gave new directions both to therapeutics and pharmacology.

2. The medical importance of opium

Though well-known as a powerful substance at least since Greco-Roman antiquity, opium became a very widely used remedy in the West only in the seventeenth century.\textsuperscript{13} Thomas Sydenham's dictum that without opium medicine would be a "cripple" has often been referred to in this context.\textsuperscript{14} This qualitative statement had its counterpart

\textsuperscript{12} Maehle, 'Pharmacological experimentation' and 'Selbstversuche', General Introduction above, note 22.


in the number of pertinent publications. In the part on plants (1787) in his *Systematisch-Literaerisches Handbuch der Naturgeschichte* Georg Rudolph Boehmer, "senior" of the University of Wittenberg, listed internationally 76 monographs and 73 articles dealing specifically with opium and/or poppy plants (papaver) since the early seventeenth century. In view of these numbers one may well agree with recent authors, such as Weber and Kreutel, who referred to an "opium or opiology literature" as a genre of medical writing. On the other hand, my systematic analysis of the *Philosophical Transactions* of the Royal Society of London, from 1700 to 1800, and of the leading Edinburgh medical journals of this time, at first glance seems to arrive at a different result. The *Philosophical Transactions* had just one article (published in 1701) specifically on opium in the whole eighteenth century. Of the Edinburgh journals, *Medical Essays and Observations* (1733-44) and *Essays and Observations, Physical and Literary* (1754-71) each published three, *Medical (and Philosophical) Commentaries* (1773-95) two, and *Annals of Medicine* (1796-1800) one such article during the periods stated. These rather small numbers (compared to other pharmacological and

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granted to the human race, as a comfort in their affections, no medicine of the value of opium, either in regard to the number of diseases that it can control, or its efficiency in extirpating them... So necessary an instrument is opium in the hand of a skilful man, that medicine would be a cripple without it; and whoever understands it well, will do more with it alone than he could well hope to do from any single medicine."  


17 See also General Introduction above.
therapeutical topics, such as lithontriptycs, mineral waters, and Peruvian bark) should not be taken, however, as representing a relatively minor importance of opium in the eighteenth century. Some of the articles, such as those by the Edinburgh professors Charles Alston, Robert Whytt, and Alexander Monro secundus, were major studies into the pharmacology of the drug, that were quoted, translated, and discussed internationally.\(^{18}\) Other articles reported cases of poisoning or some unusual phenomenon or remarkable success in therapy with opium.\(^{19}\)

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18 Charles Alston, 'A dissertation on opium', Med. Ess. Obs., 1742, 5/1: 110-176; German transl.: 'Eine Abhandlung von dem Opio', in Die medicinischen Versuche und Bemerkungen, welche von einer Gesellschaft in Edinburgh durchgeesehen und herausgegeben werden, vol. 5/1, Altenburg, Druck und Verlag Paul Emanuel Richters, 1752, pp. 125-214; Robert Whytt, 'An account of some experiments made with opium on living and dying animals', Ess. Obs. Phys. Lit., 1756, 2: 280-316; German transl.: 'Eine Nachricht von einigen Versuchen, die mit Opiun an lebendigen und sterbenden Thieren gemacht worden sind', in Neue Versuche und Bemerkungen aus der Arztneykunst und übrigen Gelehrsamkeit einer Gesellschaft zu Edinburg vorgelesen und von ihr herausgegeben, vol. 2, Altenburg, Richterische Buchhandlung, 1757, pp. 316-358; French version: 'Expériences faites avec l'opium sur des animaux vivans', Journal de Medecine, Chirurgie, Pharmacie, etc., 1758, 9: 25-44. Alexander Monro sec., 'An attempt to determine by experiments, how far some of the most powerful medicines, viz. opium, ardent spirits, and essential oils, affect animals by acting on those nerves to which they are primarily applied, and thereby bringing the rest of the nervous system into sufferance, by what is called sympathy of nerves; and how far these medicines affect animals, after being taken in by their absorbant veins, and mixed and conveyed with their blood in the course of its circulation; with physiological and practical remarks', Ess. Obs. Phys. Lit., 1771, 3: 292-365; reviewed in Medicinischchirurgische Bibliothek, 1776, 3/II: 132-137. For a discussion of these works, see this chapter below.

This may in fact be seen as reflecting a widespread medical use of the drug, so that - apart from the scientific, experimental studies - only some "extraordinary" practical observations were published in those journals. Reports on contemporary efforts to produce opium in Britain (chiefly in order to solve the problem of varying strength and quality, which existed in the customary opium imported from Oriental countries) point in the same direction.  

While there is agreement in the secondary literature about the medical importance of opium during the seventeenth and eighteenth centuries (John C. Kramer entitled one of his articles "Opium rampant"), different explanations have been given why it may have gained this prominence. In an essay published in 1971 Richard Toellner argued that with Cartesian dualism pain was re-evaluated in the seventeenth century. It was no longer seen as a God-given evil, following from the original sin, but as a corporeal symptom, which could be accepted as a useful warning sign in diseases, yet also be fought and eliminated with bodily means. On this basis Ulrich Tröhler and his student Bindler have looked into the use


21 Kramer, op. cit., note 2 above.

of opium as a painkiller in the late seventeenth and early eighteenth centuries. They suggested a link between a liberal use of opium and an empirical attitude in therapeutics (inclined to purely symptomatic treatment), which was combined with an anatomical understanding of disease. While they found this view reflected in medical dissertations at the University of Basle, medical faculties still largely devoted to Galenic humoral pathology, such as Altdorf and Jena, appeared to be reluctant to give much space to opium in therapeutics. After all, it was hard to integrate into their therapeutic system. Opium was only in part an evacuant medicine: it was known to be a diaphoretic (sudorific), but on the other hand it stopped or diminished diarrhoea, vomiting, and cough (expectoration), thus being an anti-evacuant as well. Yet also the followers of either Friedrich Hoffmann's iatromechanical system or of Georg Ernst Stahl's animism in Halle were rather critical towards opium therapy, preferring - as Bindler has argued - intervention into the assumed causes of disease to symptomatic measures.23

While Tröhler and Bindler thus made therapeutic empiricism responsible for a more permissive medical use of opium since the seventeenth century, Kreutel emphasized from a pharmaceutical perspective the contemporary belief in the ability to "correct" the harmful powers of the drug by admixing "contrary" substances. In addition, she linked the increase in the use of opium preparations with the rise of the iatrochemical school, which advocated the use of the drug in the tradition of Paracelsus' famous "laudanum" (though his original recipe probably did not contain opium).24 In fact, the same point had been made already at the

23 Bindler, op. cit, note 6 above; Tröhler, op. cit., note 8 above.

beginning of the last century by the medical historian Kurt Sprengel:

Incontestably the chemiatric school of the seventeenth century has the merit of having promoted and more generally recommended this excellent remedy [i.e. opium], while it was decried by the Galenists as a cooling agent, which thickens the humours.\(^{25}\)

These historical interpretations lead us to the question of seventeenth- and eighteenth-century theories of the modus operandi of opium and their possible influence on therapeutic practice. In connection with this we need to explore to what extent and how these theories were shaped by experimental work with the drug—a topic, which has, with the exception of Earles, virtually been left untouched in the secondary literature. The following sections are meant to provide some insights into these aspects of the history of opium.

3. Seventeenth-century views on the pharmacology of opium and their basis

As in other areas of medicine, such as anatomy and physiology, traditional, Galenic knowledge started to be questioned in the materia medica of the seventeenth century. This applied particularly to opium. Traditional doctrine, going back to Dioscorides and Galen, taught that opium had a strongly cooling and drying effect, which led to a thickening of the humours, diminution or loss of sensitivity, and sleep.\(^{26}\) The inconsistencies of


\(^{26}\) Riddle, op. cit., part A above, note 10, p. 38; Sarborough, op. cit., note 6 above, p. 7; Zekert, op. cit., note 16 above, pp. 21-24; Kreutel, op. cit., note 2 above, pp. 24-28; Georg Harig, Bestimmung der Intensität im medizinischen System Galens. Ein Beitrag zur theoretischen Pharmakologie, Nosologie und Therapie in
this view were now sharply exposed by iatrochemists, most notably by Johann Baptiste van Helmont in his *Ortus medicinae* (1648). He pointed out that opium had, as everyone agreed, a bitter taste. According to the Galenic doctrine of qualities, however, bitterness as a secondary quality was a sign of excessive warmth as a primary quality. In fact from the sixteenth century onwards some medical authors, such as Pierandrea Mattioli, Felix Platter, and Michael Döring, had attributed a warm quality to opium.\(^\text{27}\) How then, asked van Helmont, could this drug be hot and cold at the same time?\(^\text{28}\) Moreover, other anodynes (i.e. pain-relieving substances), such as hyoscyamus and mandrake, were not bitter, or were even sweet, e.g. "vitriol and sulphur" (i.e. probably ether). Some plants traditionally regarded as having a cooling quality, such as nightshades (solanacea), made people "mad", but they did not induce sleep.\(^\text{29}\) Even if opium was cooling, how could its cold drive narcotic vapours up to the head? And if it could, how could these vapours penetrate the dense substance of the brain and spinal marrow to reach the origins of the nerves and block their openings?\(^\text{30}\) Van Helmont concluded that the doctrine of

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primary qualities in remedies (i.e. hot, cold, wet, dry) and the old method of predicting the effects of a substance from its taste were wrong, even "ridiculous". Instead he suggested that opium contained a specific, hypnotic "bitter oil" or "sulphur", combined with an "acrid, sudorific salt".  

Whether these chemical characterizations had a material basis in a detailed chemical analysis of the drug, or whether they were used more symbolically in the language of the Paracelsians, cannot be decided from the text. Also, van Helmont's idea of the mode of action of opium was rather vague and only loosely connected with his chemical interpretation. In diseases caused by an enraged archeus (van Helmont's personified vital principle) opium helped by calming him down. On the other hand van Helmont warned against using opium to induce sleep, for it had not only a hypnotic but also a poisonous component, which could cause "confusions and impetuousness".

Still, the importance of his critique lay in its demand for a new, chemical understanding of opium and other drugs. Writers on opium in the second half of the seventeenth century followed his line, rejecting explanations with Galenic primary qualities. Likewise, they would not accept any longer the doctrine of super-

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30 Ibid., vol. 1, p. 566, vol. 2, pp. 855-856. Nerves were thought to be hollow to allow the flow of the spiritus animales as mediators of sensation and motion.

31 Ibid., vol. 1, pp. 221, 515, vol. 2, p. 855. A "sulfur" as the effective principle of opium had also been assumed by the Paracelsian doctor Joseph Quercetanus (1521-1609), personal physician to Henri IV of France. See Kreutel, op. cit., note 2 above, pp. 111, 122-125.


elementary, occult qualities in drugs and poisons, which also went back to Galen and had been propagated recently by the Wittenberg professor Daniel Sennert (1572-1637). It was usually assumed now that opium contained a specific, effective chemical principle. In agreement with van Helmont it was also referred to as a volatile "fetid sulphur" combined with an "acrid salt".

Disagreement arose, however, over the precise nature of this active principle and especially how it acted on the body. A common speculation was that it somehow hindered the flow of the spiritus animales in the nervous system by binding, fixing, condensing, coagulating, or actually destroying them. Painlessness, sleep, and the stoppage of excretions were thought to result from this. Sweating was seen as an indirect effect, following from relaxed, dilated pores. Actually this view was not too far away from the traditional Galenic idea of a cooling effect of opium. But it was couched in the terms of contemporary physiology and was held by prominent iatrochemists, such as Thomas Willis (1621-1675) in Oxford, François de le Boë (1614-1672) in Leyden, Michael Ettmüller (1644-1683) in Leipzig, and Georg Wolfgang

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35 See e.g. Waldschmied, op. cit., note 34 above, pp. 8-9.
Wedel (1645-1721) in Jena. Yet, in the late seventeenth century some authors started to formulate different concepts of the modus operandi of opium, arguing that it had an effect on the blood as well, or that it acted even primarily on the blood.

A methodical precondition for these ideas had been the development of intravenous injection in the 1650s and 1660s. In fact some pioneers of this new technique had used opium solutions when trying it out on animals. In probably the first recorded experiment of this kind, in 1656, Christopher Wren (1632-1723) and Robert Boyle (1627-1691) injected a warm solution of opium into the crural vein of a large dog. The animal soon "began to nod with his head, and faulter and reel in his pace, and presently after appeared so stupified, that there were wagers offered his life could not be saved." In animal experiments of the same kind, Thomas Willis and the Germans Johann Daniel Major (1634-1693) and Johann Sigismund Elsholtz (1623-1688) induced drowsiness and sleep with injections of opium. The latter convinced himself of the drug's hypnotic and analgesic effect with

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simple tests: his experimental animal being a hound, he tried to wake him up by shouting hunting commands, and occasionally he pricked the sleeping dog's tongue or leg with a needle. Less carefully, and as Willis had done before, William Courten (1642-1702) beat and whipped a dog that had been put into deep sleep with a high intravenous dose of opium. It should be noted, however, that these initial experiments had not been performed to explore the pharmacology of the drug. Rather they had been concerned with the new method of application, and the observed effects had been relevant insofar as they were principally the same as those after oral administration (which were well-known from medical practice). Yet, towards the end of the seventeenth century intravenous injection became a tool for investigating the nature and mode of action of opium.

In 1693 the student Samuel Schroeer presented his thesis to the medical faculty of Erfurt. Though conventional in its title, De opii natura et usu, it reported some original experiments. The student had injected half a drachm of "fetid oil of opium" into the jugular vein of a dog. Dissecting the animal some hours later, he found the auricles and ventricles of the heart filled with coagulated blood. Repetitions of the trial on three more dogs, including injection of "fetid oil of horn" as a comparable substance, led to similar effects. The "sulphuric" parts, believed to be contained in both these oils, thus rather "placated and sedated" the movement of the blood than inciting it, ran the conclusion.

Additional in vitro tests led Schroeer to

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39 Willis, op. cit., note 36 above, part 1, pp. 149-150; Johann Sigismund Elsholtz, Clysmatica nova, 2nd edn, Berlin, 1667, Reprint Hildesheim, Olms, 1966, pp. 14-16; Paul Scheel, Die Transfusion des Blutes und Einspritzung der Arzeneyen in die Adern, Copenhagen, Friedrich Brummer, 1802, pp. 206-208, 211-212; Hans Sloane, 'Experiments and observations of the effects of several sorts of poisons upon animals, etc. Made at Montpellier in the years 1678 and 1679, by the late William Courten Esq.', Phil. Trans., 1712, 27: 485-500.
assume that the bitter taste of opium was due not to a
"volatile sulphuric salt" (in the sense of van Helmont
and his followers), but an "acid sulphuric principle":
solutions of opium in water as well as in alcohol
effervesced and precipitated when alkaline spirits were
admixed, but not when acids were added. Also, a watery
solution of the drug coagulated blood serum and milk like
other acids. Going one step further, he argued that the
"acid-sulphuric particles" were the actual narcotic
agents in opium, adducing the indirect evidence of more
animal experiments. "Fetid oil of opium", thought to lack
the acid component, caused vomiting and salivation, but
failed to induce sleep, when given orally to a cat, even
in a sufficiently large quantity. A solution of the whole
drug in water, however, given to the cat some days later
in a smaller dose, made the animal sleep for an entire
day, and this effect was confirmed in experiments on
dogs. When mixed with spirit of wine (alcohol), a watery
solution of opium became even more effective - because of
an increase in its acidity, as Schroeer thought. Such a
mixture injected into the crural vein of a dog initially
caused convulsions, followed quickly by a state of
narcosis, which ended - with respiration and heart action
failing after half an hour - in the animal's death.

On the basis of these chemical and pharmacological
experiments Schroeer formulated his own theory of the
modus operandi of opium. Taken orally and dissolved by
the acid gastric juice, its "sulphuric particles" first
"stifled and bound" the nutritive spiritus naturales, and
then - because of the mutual connection between stomach
and brain - affected the whole nervous system. Meanwhile,
however, they also coagulated the blood, and some
particles of the drug were carried with the blood

40 Schroeer, op. cit., note 34 above, p. 7.
41 Cf. ibid. Emphasis added.
42 Ibid., pp. 7, 10-11.
43 Ibid., pp. 8, 11.
circulation to the head. They entered the ducts of the brain, slowed down and suppressed the cerebral circulation and thus put the spiritus animales to rest as well. "As a subject, on which opium acts, we declare both the spiritus and the blood", concluded Schroeer."

In support of his thesis that the blood was equally affected he listed five "proofs". The first was that his experiments with intravenous injection in dogs had produced the same effects as were known from oral taking in man, thus suggesting action on, or via, the blood. While this followed clearly from his experimental work, the other four "proofs" were given almost as afterthoughts. When handling opium in distillation or preparation of solutions, "exhalations" had hurt and inflamed his eyes, and he had noted increased diuresis in himself while occupied with this work. The diaphoretic power of opium was well known, as he pointed out, and finally, he had observed in three dogs that it killed their worms. According to contemporary understanding, all these effects could be explained with one uniform cause, namely coagulation of the blood and other humours, and they therefore strengthened Schroeer's point. In a self-confident manner he thus finished his considerations: "In conclusion, opium not only acts on the spiritus, as Ettmüller holds to have convinced himself so very well..."

Yet, seen as a whole, Schroeer's criticism of the conventional iatrochemical view of opium was rather moderate. He had changed the Helmontian chemical interpretation more in detail than in principle, and his pharmacological theory rather enlarged than radically altered the previous ones of Ettmüller and others. After all, Schroeer's experimental work and his arguments belonged to the same intellectual framework:

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44 Ibid., pp. 11-12.
iatrochemistry. Less than ten years later, however, representatives of the iatromechanical school came forward with a new theory of opium, which in fact challenged and eventually replaced the usual idea of spiritus being fixed or bound.

4. Iatromechanical interpretations around 1700

The first in a small series of publications, offering a new, mechanical understanding of the effects of opium, came from the school of the Halle professor of medicine Friedrich Hoffmann (1660-1742), the most prominent proponent of iatromechanics on the Continent at the time. In his inaugural dissertation of 1700, Hoffmann's pupil Jacob Descazals critically discussed current pharmacological theories of the drug, such as the traditional notion of its cold quality, the modern views of Willis, Ettmüller, and Wedel on its interaction with the spiritus animales, as well as the ideas of the Kreuznach physicus Johann Peter Gladbach (1647-1701) and the Cartesian Theodor Craanen (1620-1690), who had suggested, similar to Schroeer, additional effects on the blood.

Gladbach believed that the "volatile salt" and "thick oil" of opium "wrapped up" the spiritus vitales in the blood, so that less and thicker spiritus animales were produced in the brain, leading to obstruction of their flow in the nerves and slowing down of heart activity. Craanen had assumed that the "spirituous and


volatile parts" of the drug coagulated the blood, which would eventually cause sopor, and that its "acrid volatile salt" further made the nerve fibres lose their tension, resulting in a failure of sensation and thus painlessness.48

None of these theories, maintained Descazals, could sufficiently explain all the known effects of opium. For instance, the drug was known as an aphrodisiac, and according to the travellers, Oriental soldiers took it to become alert and courageous in battle. Such effects, however, required rather excitement of the spiritus than their extinction. Moreover, if it was the acid property of the "sulphur" in the drug that fixed the spiritus and coagulated the blood (as Schroeer and others had suggested), why was it, asked Descazals, that strong acids, such as oil of vitriol, concentrated spirit of vinegar, and spiritus nitri, did not act as narcotics? And if it was a "volatile oily salt" that was the analgesic and diaphoretic principle, as for example Cornelis Bontekoe (1640-1685) had stated, why was it that the small amounts of it contained in opium (as well as in mandrake and nightshade) were so effective, but not volatile oily salts in general, even if given in large doses? Similar to van Helmont, Descazals furthermore doubted that a "sulphuric vapour" could penetrate the brain and obstruct the pores of the nerves. If it really reached the origins of the nerves, he argued, it should rather be dissipated through their pores.49

Instead Descazals referred to some clinical observations of his teacher Hoffmann, which had obviously given the clues for a new theory. In patients who had taken opium the vessels of the head appeared turgid and swollen, their faces turned red, and sometimes nosebleeds followed. Moreover, those who suffered from "ardent and inflammatory fevers", became delirious even from small

48 Ibid., pp. 15-16.
49 Ibid., pp. 16-19.
doses of the drug, yet their delirium subsided after prolonged bleeding.\textsuperscript{50}

Following the opinions of Hoffmann, Descazals suggested that opium contained a "resolvable and evaporable sulphur". Absorbed into the circulation, this fine "sulphur" was thought to increase the expansion of the blood, when the latter was exposed to air during its passage through the lungs. The unnaturally thin, "rarefied", "inflated" blood then overfilled and distended the arterial vessels of the brain, leading to impeded or stagnating cerebral circulation. All effects of opium, maintained Hoffmann's pupil, could be explained in this way. Extravasated serum caused sleep, and, in larger quantity, severe headache, torpidity, loss of memory, and amentia. The remaining, thicker blood, stagnating in the cerebral vessels, could lead to turbulent and frightful phantasms and even furious insomnia. Diminished cerebral circulation meant that less spiritus animales were generated in the brain. A lesser flow of the spiritus through the nerves resulted in painlessness and in relaxation of muscular spasms. Relaxed pores in turn allowed sweating. The activity of the heart (believed to depend on the inflow of spiritus animales) decreased, which accounted for the weaker and slower pulse that was observable after taking opium. The aphrodisiac effect was explained by the rarefied, slowly circulating blood, which, by expanding the "muscles" of the penis, led to a long lasting erection. Finally, Descazals quoted pathological observations in those who had died of narcotic remedies: the ventricles of the brain were found filled with coagulated blood. Also this seemed to support the idea of stagnating cerebral circulation.\textsuperscript{51}

Hoffmann's and Descazals' "rarefaction theory" of opium (as one may briefly call it) was thus to a great

\textsuperscript{50} Ibid., pp. 19-21.

\textsuperscript{51} Ibid., pp. 20-23.
extent a iatromechanical speculation, which rested on some clinical and pathological findings. In this respect it was not principally different from the conventional "spiritus animales theory" favoured by the iatrochemists. Indeed Descazals was cautious or diplomatic enough to admit at the very end of his thesis that opiates and other narcotics might not exclusively act on the blood, but in addition also affect the spiritus immediately.\textsuperscript{52}

Yet, support for Hoffmann's theory was provided three years later on an experimental basis by his colleague at the nearby University of Wittenberg, the medical professor Johann Gottfried Berger (1659-1736). Dissecting cats which had been poisoned orally with opium, Berger and his student Christoph Fimmler observed that the animals' blood was "never coagulated, but more dissolved, serous and fluid". Likewise, in opening the skulls of dogs that were stupefied from intravenous injections of the drug, they found the cerebral vessels "turgid and distended". When cut, "florid, thin and serous blood" flowed out. The same observation was made in the blood of the heart and other vessels.\textsuperscript{53} These findings clearly contradicted the experimental observations made ten years earlier by Schroeer in Erfurt.

Like the Halle researchers, Berger and Fimmler concluded that opium "rarefied" the blood. The distended blood vessels, they speculated further, compressed the fibres of the brain and of adjoining nerves, and this led to an intermission of sensation and motion. As they believed, too, all effects of the drug could be explained with this theory.\textsuperscript{54} Not doing without reference to modern

\textsuperscript{52} Ibid., p. 24.

\textsuperscript{53} Johann Gottfried Berger and Christoph Fimmler, \textit{Dissertatio solennis de vi opii rarefaciente, a qua, ostenditur, omnia illius effecta in homine proficisci}, Wittenberg, Gerdesianus, 1703, pp. 9-11.

\textsuperscript{54} Ibid., pp. 12-23.
authorities, they pointed out that Ole Borch had found thin, fluid blood in his animal experiments with the drug as well, and that the renowned iatromathematician Archibald Pitcairne (1652-1713) had taught a theory of opium similar to their own in his Leyden lectures in the early 1690s. Strongly declaring themselves for mechanical explanations, it is not surprising that Berger and Fimmler also referred to Hoffmann's work on opium, albeit only briefly.

The "rarefaction theory" of opium was propagated at the same time, yet without overt reference to the Continental work, in England as well. In his work Emmenologia (1st edn 1703) the iatromechanist Oxford physician John Freind (1675-1728) discussed medicines which would promote or inhibit menstruation by rarefying or coagulating the blood, respectively. His methods to ascertain either quality of a substance included examination of its "sensible effects" (taste, smell, obvious physiological changes, such as acceleration of the pulse or increased body heat and sweating), in vitro trials on freshly drawn blood, testing for acidity or alkalinity by admixing syrup of violets, and intravenous injection in living animals.

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56 Berger and Fimmler, op. cit., note 53 above, pp. 2, 5, 38.
In the case of opium everything pointed to its being an "emmenagogum", i.e. a remedy that would bring forward menstruation by attenuating the blood. Firstly, the drug had an acrid and bitter taste, indicating a rich content of "volatile salt", which would thin the blood. Secondly, when Freind mixed fresh arterial blood from a dog with Sydenham's Laudanum Liquidum (a solution of opium in wine) or Dr Jones's Liquid Panacea of Opium (solution in water), the blood appeared thinner and kept its shining red colour. Similarly, human serum became thinner, and stayed like this for a day or two, after those opium solutions had been added. Thirdly, an aqueous solution of the drug turned syrup of violets green, which meant that it had an alkaline quality. Alkalies were known to dissolve coagulated blood. Finally, in a dog killed by intravenous injection of a very high dose of the Panacea of Opium, the Vena cava, the ventricles of the heart, and the descending aorta were found to contain thin and bright red blood without a trace of coagulation, and the lungs appeared red from turgid blood vessels. These observations were confirmed in another dog, which had been poisoned orally with Laudanum.57

Freind did not leave it at this experimental characterization of opium as an emmenagogum. Like Hoffmann and Berger, he developed a comprehensive theory of the drug's action based on its rarefaction of the blood. Freind distinguished between effects after a "moderate" dose, e.g. stimulation of the heart and increased perspiration, and effects after an excessive dose. As in Berger's theory, turgid blood vessels were believed to compress nerves and the brain, leading eventually to the more severe symptoms of opium intoxication, such as somnolence and "quasi paralysis".58

57 John Freind, Emmenologia: in qua fluxus muliebris menstrui phaenomena, periodi, vitia cum medendi methodo, ad rationes mechanicas exiguuntur, Rotterdam and Leyden, J. Hofhout & C. Wishoff, 1711, pp. 172-185.

58 Ibid., pp. 166-169.
Almost simultaneously, Freind's friend Richard Mead adopted a similar notion of the *modus operandi* of opium. Included in the latter's highly successful *Mechanical account of poisons* (1st edn 1702, internationally at least sixteen editions until 1765), it became probably the best known iatromechanical interpretation of the drug's effects in the eighteenth century. Having studied with Pitcairne in Leyden, Mead's general concept in this work was to apply "mechanical considerations", the "laws of motion", and "geometrical reasoning" to the field of toxicology. His theory of opium consisted basically of two parts: the first described the immediate effects of the orally taken drug on the stomach, and the second the effects after it had passed the so-called *primae viae* (i.e. the gastro-intestinal canal) and had entered the blood circulation. This second part resembled closely the mechanical ideas of Pitcairne, Hoffmann, Berger, and Freind. Rarefied by opiate particles, the blood was believed to distend the cerebral and other vessels, which pressed on the nervous "tubuli, or canals" and thus diminished the influx of "nervous fluid" containing the spiritus animales.

In the first part of his theory, however, Mead suggested that opium caused a "pleasant titillation" of the nervous coat of the stomach, leading to the feeling of "an agreeable plenitude", which he compared to that

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61 Ibid., p. 133.
after a good meal. The mind, entertained by "ideas of satisfaction and delight", would be distracted from sensations of pain. Moreover, the fibres of the body were relaxed, and immoderate secretions were stopped in this way. To some extent these notions, which were rather vitalistic than mechanistic, reflected the earlier Helmontian ideas about an effect on the "archeus" located in the stomach. But they were much more similar to a third theory of opium (besides the spiritus animales and rarefaction theories), which had shortly before been published by the physician and chancellor of the diocese of Llandaff, John Jones (1645-1709). In his book *The mysteries of opium reveal'd* (1st edn 1700) Jones had propagated his view that all the known effects of the drug could be explained by its causing a "pleasant Sensation", which led to relaxation of all sensible parts of the body.

At first glance it may appear surprising that Mead did not refer to this work, which after all had been authored by a member of the College of Physicians in London and recommended for publication by its president Thomas Burwell. Mead's silence may well have had to do, however, with the book's peculiar nature and style. Jones' text was written in a proselytizing manner, replete with repetitions and italicized emphasis characteristic of the pamphlet literature of the time. Repeatedly Jones thanked God for having revealed this new knowledge of opium to him and compared it with Harvey's discovery of the blood circulation and Columbus' of America, adding a triple "Amen". The euphoric style of Jones' book suggests that it may actually have been written under the influence of the drug. In fact it contained quite detailed observations on the consequences

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62 Ibid., pp. 131-133.


64 Ibid., pp. 98, 253, 370-371.
of habitual opium-taking. Considering this, one may understand why Mead obviously omitted to mention Jones in his own study, which being branded "mechanical" promised a rational inquiry based on the most modern scientific, Newtonian principles.

Mead's account of opium was not purely speculative, but had experimental components as well. He gave quantitative results of a chemical analysis of the drug, which was found to contain "volatile alcaline spirit", "foetid oil" and "coal, void of salt", and he employed animal experimentation, too. The latter, however, had a rather subordinate role, compared to that in Berger and Freind. On the basis of his theory Mead predicted that a large quantity of opium would inflame the stomach and rarefy the blood so much that the vessels would lose their tone, resulting in apoplectic symptoms. "To be convinced of this" he performed just one experiment on a dog. Having been poisoned orally with about two drachms of opium (i.e. ca. 120 times the usual therapeutic dose of one grain in man), the animal died under convulsions within an hour. The postmortem examination revealed in fact "beginning inflammation" of the stomach, "very full" cerebral vessels, and coagulated blood in the Sinus longitudinalis of the brain, "as is not uncommon in apoplectic carcases".

Seen as a whole, we can thus identify at the beginning of the eighteenth century two new pharmacological theories of opium, that competed with the older view of "fixed" or "bound" animal spirits: rarefaction of the blood, indirectly and mechanically

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65 See ibid., pp. 31-33, and below.

66 Mead, op. cit., General Introduction above, note 35, vol. 1, pp. 131, 136-137. This result partly contrasted with an earlier oral poisoning experiment reported by Willis, in which a dog survived the same dose of 2 drachms (120 grains) of opium. Willis had attributed this outcome to the "acid Ferment" of the stomach, by which the "narcotick Sulphur" might have been "somewhat broken and overcome". Cf. Willis, op. cit., note 36 above, part 1, p. 149.
affecting the nervous system; and the "pleasant sensation" theory, which operated more in vitalistic or psychophysical terms. It is quite remarkable that Mead felt able to use both of them alongside, perhaps an early indication of his flexibility in theoretical explanations, which was to become obvious in later editions of his toxicological work. By contrast, referring to a German review of Jones' *Mysteries*, Berger and Fimmler condemned the notion of an "ideal" or "virtual" effect of opium via "pleasant titillation of the stomach". For them, this was "playing games with the very term of spiritus animales". They scathingly compared such a mode of action with getting children to sleep by an old woman telling them fairytales, and added sarcastically: if this were true, it was to be hoped that opium could procure death as suddenly as the children are caused to sleep.\(^6\)

In fact it was rather the iatromechanical theory of rarefied blood than Jones' ideas, that eventually replaced the notion of fixed animal spirits, as can be seen from later standard works in the field, such as Etienne-François Geoffroy's *Tractatus de materia medica* (1741), William Lewis' *New dispensatory* (1753), George Young's *Treatise on opium* (1753), and Balthasar Ludwig Tralles' *Usus opii salubris et noxius* (1st edn 1757-1762).\(^6\) Yet by the middle of the eighteenth century the rarefaction theory had already come under attack itself.

\(^6\) Berger and Fimmler, op. cit., note 53 above, pp. 34-35.

Before we look into this and further developments in theories on opium, however, the question of therapeutic implications needs to be addressed. What were the current opinions on opium therapy? And more specifically, which therapeutic conclusions were drawn from the new theories of opium in the late seventeenth and early eighteenth centuries?

5. Some early therapeutic conclusions

Significantly, those new pharmacological theories were formulated in a period when concern about an all too liberal use of the drug in therapeutics became prominent. Opium was widely used and praised for its singular effectiveness as an analgesic, hypnotic, antitussive, sudorific, and antidiarrhoeal remedy, and it had also been recommended as an excellent cordial. Inevitably, it seems, lethal opiate intoxications during treatment were observed more frequently. The Marburg professor of medicine Johann Jakob Waldschmied (1644-1687), writing in 1679, compared the problem with the damage that was often caused by excessive use of purgatives. Opium, he pointed out, was like a double-edged sword or like a coin showing an angel's face on one side and the devil's on the other. Similar views were expressed by other medical writers of the time, for example Willis and Wedel. Like


69 For example Sydenham, op. cit., note 14 above, p. 173 on opium: "To know it only as a means of procuring sleep, or of allaying pain, or of checking diarrhoea, is to know it only by halves. Like a Delphic sword, it can be used for many purposes besides. Of cordials, it is the best that has hitherto been discovered in Nature. I had nearly said it was the only one."

70 Waldschmied and Chunon, op. cit., note 34 above, pp. 3-4, 14, 22.
Willis, Waldschmied complained that "empirics, foolhardy medics, and anyone equipped for bloodsucking" savaged mankind by giving opiates indiscriminately in any kind of disease. Though their wish to restrict opium therapy to the learned, academic physicians may well be understood in terms of professional motives, it would probably go too far to doubt that their concerns were genuine.

Careful dosage, the obvious way to avoid intoxication, was not sufficient because of the greatly varying strength of the crude opium, which was imported chiefly from Turkey, Egypt, and East India. Though quality criteria, such as its colour, consistency, taste and smell, and simple quality tests, such as colour changes when mixed with saliva or burned in a flame, were known since Dioscorides, exact methods of standardization were not developed until the nineteenth century. It was even controversial whether the imported "opium" was really the dried juice of slit poppy capsules, or whether it was the weaker "meconium", i.e. the pressed and dried juice of the whole plant or an extract of a decoction of it. Moreover, there were suspicions that merchants adulterated opium with other drugs, such as wild lettuce juice, to increase its quantity.

71 See Willis, op. cit., note 36 above, part 1, p. 144; Schroeer, op. cit., note 34 above, pp. 12-14; Hoffmann and Descazals, op. cit., note 36 above, pp. 3-4; Berger and Fimmler, op. cit., note 53 above, p. 5. See also Kreutel, op. cit., note 2 above, p. 129. On opium as a poison see William Ramesey, Tractatus de venenis. Or, a treatise of poysons, London, D. Pakeman, 1661, pp. 94-96.


Yet there were basically two other ways to counter the danger of iatrogenic opium poisoning. The traditional way, going back to antiquity, was to "correct" the drug's effect by combining it with other substances, which were believed to have a contrary quality. The theriac of Andromachus (1st cent. A.D.), for example, had viper flesh among its many ingredients, which was thought to be warm and dry and thus to compensate partly the cooling effect of opium contained in the remedy. Pepper, cinnamon, saffron, castoreum, and other drugs with a warm quality were used as "correctives" of opium. With the challenge of the Galenic primary qualities in the seventeenth century, however, the methods of pharmaceutical correction needed to be reconsidered as well. The second way was to define those diseases or states of illness, in which the giving of opiates was harmful and thus contraindicated. In these two areas, especially the latter, theories of opium became practically relevant.

An example for therapeutical conclusions drawn from the iatrochemical theory of opium binding or "fixing" the spiritus animales was provided by Waldschmied. As he saw it, acrid and lethal exhalations of the drug "fixed" the

Storch, 1796, pp. 193-216, on pp. 194-195; Kreutel, op. cit., note 2 above, pp. 27, 34, 155; Scarborough, op. cit., note 6 above, pp. 16-17.


"liquor animalis" (containing the spiritus) and caused it to degenerate into an acid. Consequent inhibition or failure of nutrition, blood circulation and nervous functions led to the known symptoms of opium poisoning, such as a cold sweat and sopor.⁷⁶ Against the background of this theory Waldschmied discussed a long list of contraindications for the use of opium, issued under the title of "Medical Admonitions" (Monita medica circa opii et opiatorum usum) and publicly defended by one of his students at Marburg University.

First of all, opiates should not be used in "soporose affections", such as apoplexia, epilepsy, lethargy, paralysis, loss of memory, and vertigo, for they were characterized by a lack of active spiritus animales. With reference to van Helmont he also warned against calming down states of "mania" or "amentia" with the drug, because it caused laborious, unpleasant sleep and had something "mad" in itself, madness being "nothing but a daydream". Since opium "darkened the light" of the animal spirits, it was not to be used in people with impaired sight (and hearing). Thickening pus and mucus and diminishing respiration, it accelerated death in patients with phthisis and put asthmatics into fear of suffocation. In angina, malignant, petechial and similar fevers, as in smallpox and measles, opiates would allow the disease to "nidate" even more profoundly in the blood, because they "fixed" the vital spirits contained in the latter and bound the "active principles". Moreover opium harmed the stomach, made constipation worse, put patients with haemorrhoidal or menstrual fluxes into a dangerous weakness, and might actually kill someone with hydrops. In children and old people it should generally be avoided, because their spiritus animales were too weak. Finally, Waldschmied pointed to the dangers of habitual opium consumption: people became "inebriated and

⁷⁶ Waldschmied and Chunon, op. cit., note 34 above, pp. 10-12.
torpid" and "comatose, stupid, inconstant, saying 'yes' at one time and 'no' in the next moment"."

These last observations, however, referred to "the Turks", not to Western patients. Waldschmied relied here on the report of one of the Oriental travellers of the sixteenth century. The fact that these consequences of a chronic use of opium were mentioned at the very end of his list of "admonitions" further indicates that they were not yet regarded as a major problem. The main concern was about acute intoxications and harmful side effects in therapy.

As shown above, Waldschmied closely linked his theoretical, pharmacological considerations with his therapeutic warnings, the former sometimes actually being the reason for the latter. In some instances he also referred to cases of poisoning from the recent literature or own clinical observations. But the important feature of his work was that he could rationally predict harm in certain diseases or therapeutic situations on the basis of his pharmacological theory.

Waldschmied's admonitions were soon adopted by other medical authors. Though the major contraindications for the use of opium thus remained the same, the reasons given for them changed with the pharmacological theories. This is evident from the early adherents of the rarefaction theory of opium mentioned above. For example, Hoffmann and Descazals also warned about avoiding opium

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77 Ibid., pp. 12-20.

78 Though Waldschmied did not cite his source, it is evident that he used the report by the French physician and botanist Pierre Belon (c. 1517-1564) on his travels in Asia Minor between 1546 and 1549. Cf. Sonnedeccker, op. cit., note 1 above, p. 281. Belon's observations are also mentioned (with reference) by Hoffmann and Descazals, op. cit., note 36, pp. 10-11, and Berger and Fimmler, op. cit., note 53 above, p. 8.

79 Cf. the very similar contraindications, partly with reference to Waldschmied, in Schroeer, op. cit., note 34 above, pp. 13-14, and Hoffmann and Descazals, op. cit., note 36 above, pp. 9-10.
in "all diseases of the head", such as apoplexia, vertigo, paralysis etc., but rather because of impeded cerebral circulation than a direct effect on the spiritus animales. Likewise, Berger and Fimmler adopted Waldschmied's warning against giving opiates to children and the old, but the reason was now that their brains were too weak to withstand the pressure of distended blood vessels. A similar link between theory and contraindications can be observed in Jones as the representative of the concept of "pleasant sensation". Since the "pleasant sensation" led to general relaxation, he stated that opiates should not be given if parts of the body were unnaturally relaxed, paralysed, or ruptured, or if a "grievous sensation" was useful in promoting the excretion of harmful matter.

Occasionally the new theories led to new contraindications or differentiation in current indications: Mead, for instance, concluded that opiates should be employed only in excessive secretions due to irritation, whereas in "colliquative diarrhoea", in the course of hectic fevers, it would cause "real mischief, by relaxing the fibres, and heating and rarefying the fluids, already too thin and broken in their texture." Probably the most important contraindication, emerging from the rarefaction theory, were acute inflammations. It appeared obvious that rarefied blood and distended blood vessels would make them worse.

The new theories of opium also induced some rethinking of the current practices of preparing and "correcting" the drug. Schroer, who, as mentioned above,
believed to have identified an acid principle as the effective component of opium, suggested admixing alkaline substances, condemning simultaneously many of the more traditional correctives. Similarly, Berger and Fimmler were highly critical of the usual corrections, stating that most of them were founded on "prejudiced opinions". Someone who knows about the mode of action of opium, they argued, should not have to be too worried about corrective substances and should be able to use the crude drug or simple preparations. As they saw it, in the classic complex composita, such as theriac, opium was not really corrected, but only given in very small doses (and therefore safely). Hoffmann and Descazals were more positive about corrections, however. On the basis of their pharmacological theory they required that a corrective substance should promote the movement of the blood and animal spirits. Sudorifics, purgatives, aromatics, and diuretics appeared suitable for this purpose. In principle, they admitted, this requirement had been fulfilled in traditional preparations, such as theriac and diascordium, as well as in more recent opium remedies, such as the "pillulae Wildegansii" (with added aloe) and "Starkey's" or "Matthew's pill" (with white hellebore).

Yet the topic was obviously important enough for Hoffmann to make another student of his, Friedrich Christian Muller, explore exclusively the question of preparing and correcting opium. After testing the efficacy of water and alcohol extracts of the drug (and of their residues) in animal experiments, and lengthy considerations, this student concluded that a simple

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87 Hoffmann and Descazals, op. cit., note 36 above, p. 13. On current opium preparations around 1700, their raw opium content and relative potency see Estes, op. cit., note 6 above.
extract of opium with distilled rainwater, as John Jones had recommended it, was the safest remedy. In the extracted gum, he explained, the active "sulphur" was sheathed by viscid, mucilaginous particles. Similarly Ole Borch, who had tested various opium preparations in animals, had recommended prescribing crude opium with little or no corrections; and Muller could quote other recent authors, including the respected Wedel of Jena, who had also preferred simple extracts of the drug (with water, vinegar or alcohol) to any more complex preparations.

Obviously there was a trend towards simple opiates in the late seventeenth and early eighteenth centuries, which followed a general trend in the materia medica of the time, but was also founded upon new theories of the drug's mode of action and experimental experience. Safety of therapy with opium was aimed at by a restricted use in indicated cases rather than by complicated pharmaceutical efforts in correcting the drug. Stating that the most serious and frequent errors in contemporary medicine were committed in the use of opiates, Muller condensed therapeutic precautions into seven rules, which probably reflected the teaching of Hoffmann and thus the opinion of the German iatromechanical school: 1. to consider that some individuals might not tolerate the drug even in a very small dose because of a peculiarity in their constitution; 2. to give opium only if really

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88 Hoffmann and Muller, op. cit., note 75 above, pp. 14-21.

89 Borch, op. cit, note 55 above, pp. 25-27; Hoffmann and Muller, op. cit., note 55 above, p. 17; Michael Bernhard Valentin, Historia literaria S.R.I. Academiae Naturae Curiosorum, Gießen, Henning Müller, 1708, pp. 72-74 (Review of Wedel's Opiologia).

90 On the general trend, since the late seventeenth century, to simplify and contract the materia medica see Earles, 'Studies', General Introduction above, note 3; Kreutel, op. cit., note 2 above, pp. 154-156; Christa Habrich, op. cit., General Introduction above, note 15.
necessary; 3. to prefer weaker medicines if possible; 4. to avoid giving opiates in fevers, when the harmful "materia peccans" had to be excreted, and never to give them in the crisis of the disease; 5. not to use opium in "malignant" diseases, resulting from bad blood and humours; 6. likewise not in severe inflammations, gangrene, and in states of plethora and "cacochymia"; and 7. not in "cold affections" of the brain and nerves, chronic diseases, hydrops, and asthma. What was left as indications for the use of opium was mainly severe pain after injuries, in colics and stone disease, tooth- and earache, haemorrhoidal pain, and excessive coughing, vomiting, and diarrhoea.  

Though this may seem a rather limited use, Hoffmann's colleague at the University of Halle, Georg Ernst Stahl (1660-1734), went even further in his therapeutic criticism. In 1707 he matched Hoffmann's initiatives with a thesis entitled De impostura opii ("On the imposture with opium"), that was publicly defended by his student Johann Georg Brunschwitz. The argument of the thesis was that treatment with opium betrayed both patients and doctors, because it effected only a transient mitigation of symptoms. Even worse, since salutary physical movements and powers, guided by the soul, were "stupefied" and "dazed" by the drug, harmful matter (materia peccans) was not hindered in enhancing lesions and ultimately destroying the patient's body. If the primary affection of a disease could not be reached by therapeutic means, it was better to hope for help by "nature and time".  

Evidently, Stahl's animist theory of health and disease played a major role in this almost complete rejection of opiates.  

91 Hoffmann and Muller, op. cit., note 75 above, pp. 29-31.  
92 Georg Ernst Stahl and Johann Georg Brunschwitz, Dissertatio medica inauguralis, de impostura opii, Halle, Ch. Henckel, 1707, pp. 9-10, 36-38. See also Bindler, op. cit., note 6 above, pp. 18-20, 23-25.
some case histories from his teacher's practice to illustrate the negative effects and declared the usual corrections of the drug as "false" (i.e. ineffective). Opium should not be given except in cases where the symptoms "really urged" its use, ran the conclusion.\(^94\)

As is clear from the examples discussed above, pharmacological theories had some influence on therapeutic concepts, particularly by defining and explaining contraindications for the use of opiates. On the other hand, there was certainly no simple, direct line from theory to practice. Clinical experience of opium intoxications contributed to therapeutic caution as well, and some contraindications, once introduced into the literature by a respected medical writer, were perpetuated probably on the grounds of authority alone. Nor was there a simple relation between pharmacological experimentation and theory. Far from following strict Baconian induction, experiments were "embedded" in chemiatric, iatromechanist and vitalist speculation. Together with clinical observations and some simple chemical trials, animal experiments with opium could provide "arguments" towards a theory of the drug (as Freind put it), but they would not form its foundation.\(^95\) Neither were these pharmacological trials used as crucial tests for the truth of a particular theory. When Mead added an animal experiment to his "mechanical account" of opium, this was not really for verification or


\(^{95}\) Cf. Freind, op. cit., note 57 above, pp. 172-173, 175, 192.
falsification of a hypothesis in the modern sense, but for confirming a theory that he already believed in. Moreover, experimental observations were obviously moulded to fit the theory. Actually contrary findings in opium-poisoned animals, namely coagulated blood (Schroeer, Mead) and thin, fluid, non-coagulated blood (Berger, Freind), were both taken as a sign of impeded circulation - an assumption that had to be made in order to be able to account mechanically for the clinically known effects of high doses.

However, despite these qualifications, one should note as a characteristic of the examined early work on opium that experimentation, theory, and therapeutics were in fact linked with each other, albeit not in a very stringent manner. With his late work Pharmaceutice rationalis (1st edn 1674/75) Willis had made the bold, though not very successful attempt to build pharmacotherapy on pharmacological experiment and theory. And there is also the programmatic statement of the Essex pharmacist and licentiate of medicine Samuel Dale (1650-1739), in his Pharmacologia (1st edn 1693), that the best way to investigate the medicinal properties of natural bodies was animal experimentation, as the Swiss physician Johann Jakob Wepfer (1620-1695) had demonstrated it on the water hemlock and other poisons. In fact a number of experimental studies on opium were performed in the course of the eighteenth century, which became influential not only for pharmacological theory, but also for physiology and for therapy. The following sections will analyze this work and its implications.

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6. Opium and the nervous system around 1750

In 1742, Charles Alston (1683-1760) made a major contribution to the knowledge of opium by publishing a 'Dissertation' on the drug in the Edinburgh Medical Essays and Observations. With this work the "centre" of research on opium moved, as in the case of lithontriptics, from London to the rising Edinburgh medical school. As we shall see later on, a similar "move" happened on the Continent from the leading University of Halle (founded in 1694) to the young University of Göttingen (founded in 1737).

Alston, trained by Herman Boerhaave in Leyden like all of the first professors in the Edinburgh medical faculty, was very critical of the contemporary state of pharmacological knowledge, and this was particularly true for the case of opium. As he stated in his lectures on the materia medica:

... some strenuously maintain that opium is cold in the fourth degree; other that it is hot, yea caustic; some that it is an alcali, others an acid; some that it rarifies the blood, other that it coagulates it; some

97 Alston, op. cit., note 18 above.


99 For possible reasons see Andrew Cunningham, 'Medicine to calm the mind: Boerhaave's medical system, and why it was adopted in Edinburgh', in Cunningham and French, op. cit., part A above, note 119, pp. 40-66.

think that its virtues are lodged in its sulphureous, and other in its gummy parts, etc. each accounting for its effects from his own opinions in their own way, though none of them are founded on experience, and easily confuted.\textsuperscript{101}

With respect to these "many Controversies", which he also noted in his 'Dissertation', Alston put current views on opium to a systematic test by "Experiments and Observations".\textsuperscript{102} In doing this he employed a spectrum of methods, which by far surpassed that of previous researchers in this area: examination of the drug by taste and smell, various chemical tests and quantitative analysis, \textit{in vitro} experiments on blood and serum, toxicological trials on frogs and dogs (applying opium externally, perorally, and intravenously) including microscopic observations and postmortem examinations, self-experimentation (external application and peroral taking), and interpretation of one's own therapeutic experiences as well as of reported cases. As has been documented above, most of these methods as such had been used in studying the drug since the second half of the seventeenth century, but not all of them in combination. In this respect Alston's 'Dissertation' may be regarded as the first full-fledged pharmacological work (in the modern sense) on opium.

Remarkable is also the expert help that he was able to recruit. Andrew Plummer (c. 1698-1756), who held the Edinburgh chair of medicine and chemistry, put his laboratory to Alston's disposal and assisted in chemical analysis; Alexander Monro primus (1697-1767), the professor of anatomy and surgery, contributed his manual skills in performing an intravenous injection in a dog; and Robert Fullarton, described as "a curious Gentleman, and very dextrous in Microscopical Observations", helped in performing some of the experiments on frogs.\textsuperscript{103}

\textsuperscript{101} Ibid., vol. 1, p. 40.

\textsuperscript{102} Alston, op. cit., note 18 above, p. 110.
In his testing of current opinions Alston began with the most basic issue, i.e. the question whether the imported "opium" was really the dried "tear" or "milk" of cut or scratched poppy capsules or whether it was an extract of the whole plant, the weaker "meconium". Medical travellers to Oriental countries could be quoted in support of either view, e.g. Engelbert Kaempfer (1651-1716) for the former, Prosper Alpin (1553-1617) for the latter. The French chemist Nicolas Lemery (1645-1715) had insisted in his authoritative *Dictionnaire ou traité universel des drogues simples* (1st edn 1698) that the imported "opium" was nothing but meconium. To solve the problem Alston produced his own opium from the heads of poppy plants grown by himself in Scotland. It closely resembled the imported "opium" in colour, taste, and smell, while self-made meconium had a much less intense taste and smell. The imported "opium" was therefore "for the far greatest Part, the true Tear of the Poppy", as Alston concluded, only "some part" of meconium might be admixed in "some Places".

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103 Ibid., pp. 147, 153, 156.


105 Alston, op. cit., note 18 above, p. 115. Cf. Nicolas Lemery, *Dictionnaire ou traité universel des drogues simples*, 3rd edn, Amsterdam, Aux Dépens de la Compagnie, 1716, pp. 391-392. Pharmacologically Lemery adhered to the "spiritus animales theory" of opium, teaching that its viscous and sulphureous parts agglutinated the animal spirits in the channels of the brain and thus caused sleep; see ibid.

106 Alston, op. cit., note 18 above, pp. 116-121. Also Albrecht von Haller in Göttingen produced his own opium from poppy heads and found it equally strong as the imported drug; A. von Haller, *Enumeratio methodica*
His next step was to characterize the "virtues" or properties of the drug by tasting and smelling it, a classical method, which had been developed into a fine art by his time. Nehemiah Grew (1641-1712), for example, had presented a highly differentiated system of tastes in plants to the Royal Society. Alston, who had adopted Grew's system, taught his students to distinguish between sixteen kinds of simple and six kinds of compound tastes, which were further differentiated according to degrees of intensity, duration, increase and decrease, and place of sensation within the mouth. From tasting and smelling opium, he felt able to infer that it was "an acrid, diaphoretic, nervine, and cathartic Medicine". The last of these alleged properties, however, illustrated the limits of this method. Clinical experience taught that opium was not a cathartic or purgative substance, having mostly the opposite effect of constipation. Faced with this apparent contradiction, Alston distinguished between a sensible "stimulating" and an independent "narcotic" quality in the drug, foreshadowing later debates on, and efforts to solve, this problem of seemingly contradictory properties.

This led to his chemical examination of the drug, which formed the most extensive part of his work. Extraction trials with water, wine, vinegar, spirit of vinegar, brandy and rectified spirit of wine (alcohol)


made him conclude that the gross constituents were a gum, a rosin, and insoluble "terrestrial" matter in a proportion of 6:4:2. Self-experiments with the extracted rosin showed it to be tasteless and somniferous, without bad side effects. Alston disagreed at this point with John Jones, who had attributed the "mischiefs" caused by the drug to this component. "The World is too cautious now", commented the Edinburgh professor, "to believe implicitly every general Assertion". Numerous tests for acidity or alkalinity made him also disagree with the Paris professor of medicine Etienne-François Geoffroy (1672-1731) and Friedrich Hoffmann, who (like Schroer) believed they had identified an acid "salt" or "sulphur" as the drug's active principle. According to Alston's tests, the drug as a whole was rather alkaline, and further chemical experiments of his indicated that also its "essential Salt" was "ammoniacal" (alkaline). Moreover, contrary to other chemical authors, evaporation and distillation trials made him assume that the active principle in opium was rather fixed than volatile, which meant that the traditional method of "correcting" the drug by roasting it was quite pointless.

Assisted by Plummer, Alston then proceeded to his quantitative analysis of the drug by way of chemical distillation, which gave a phlegm, spirit and oil, volatile salt, and caput mortuum (salt and earth). Further analysis of the spirit of opium revealed that it contained only very little volatile salt. Since the amount of volatile salt obtained in the first process had also been very small, Alston was reassured in his view that Hoffmann as well as Craanen had been wrong in

109 Alston, op. cit., note 18 above, pp. 136-140. Jones thought that the rosin stuck to the stomach, causing continuous harm, and that it should therefore be separated from the crude opium. Cf. Jones, op. cit., note 63 above, pp. 202-203, 309.

identifying this component as the effective principle in the drug."11 Despite this quite detailed investigation, Alston went no further in his interpretation of the chemical results, being also here aware of the limitations of the method. With chemical distillation, he warned, the very same components had been found in deadly nightshade and in nutritious cabbage.112

Further-reaching conclusions were drawn, however, from his *in vitro* and animal experiments with the drug. With the help of Fullarton he examined microscopically the blood flow in the webbed feet of frogs, which had been given orally a solution of opium in water. While the colour and consistency of the serum as well as the size, form and colour of the red blood corpuscles remained unchanged, the velocity of the blood stream slowed down considerably - a finding that could be confirmed in repeated trials of the same kind.113 Chiefly copying Freind's and Mead's experiments, Alston came further to different results. The postmortem of a dog, that had been poisoned by Monro through intravenous injections of an aqueous solution of opium, revealed small, white, and bloodless lungs, and the Vena cava, ventricles of the heart, and aorta contained clotted and coagulated blood.

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112 Alston, op. cit., note 18 above, p. 147. See also *idem*, op. cit., General Introduction above, note 45, vol. 1, p. 26. Note, however, the highly positive opinion of chemical analysis "by fire" in *The dispensatory of the Royal College of Physicians, London*, transl. by Henry Pemberton, London, T. Longman, T. Shewell and J. Nourse, 1746, pp. 27-28: "... as heat is a primary agent in all natural operations, and fire one of the great dissolvents of bodies, no art is more fitted for detecting the internal constitution of things. It has also furnished us with many of the most powerful remedies, as it has put into our hand some of the active principles, by which the changes in nature are wrought, less clogged and obstructed from action, than in the usual compound bodies, that come in our way."

This clearly contradicted Freind's findings. Moreover, a small dog was given orally the same dose of two drachms (120 grains) of opium as in Mead's experiment. Though it temporarily lost the power of its limbs and refused food and drink, it did not show the apoplexia-like symptoms that had been described by the London doctor. Finally, in repeating Freind's in vitro trials, Alston mixed solutions of opium in water and alcohol with milk, serum, and fresh arterial and venous blood. Unlike Freind, he found rather coagulation and precipitation than rarefaction.

On the basis of these experimental observations Alston opposed the "rarefaction theory" of opium, as it had been taught by Mead, Freind, and others, stating to the contrary that the drug "rather coagulates or thickens, than dissolves or attenuates the Blood." He did not leave it at this conclusion, however, which would basically have been the older view of Craanen and Schroer. At this point he moved forward to formulate a "new" theory of opium acting directly on the nervous system.

As Alston saw it, the analgesic and hypnotic effects of opium did not depend on its action on the blood or the brain. Instead, it "first and principally" affected the nerves of the part to which it had been applied, i.e. in the usual, oral case, the nerves terminating in the walls of the stomach. The effect would then quickly be distributed over communicating nerves, and "by Consent", or sympathy, the whole nervous system would soon be affected. The "primary effect" of the "narcotic Part" of opium (as distinguished earlier from the "stimulating" part) was believed to be a relaxation of the nervous fibres. This relaxation extended either directly or

114 Ibid., pp. 156-158. Cf. Freind and Mead, above.
indirectly, via an impression on the sensorium commune in the brain, to the "moving" muscle fibres. Depending on the dose of opium, this caused in a second step its clinically known "good" secondary effects as an euphoristic, analgesic, cordial, sudorific, and hypnotic medicine, or - if overdosed - "Stagnations, Deliriums, Lethargies, Apoplexies, Death."

At first glance, Alston's theory may appear quite similar to that of John Jones or the first part of Mead's, whom he quoted in this context. Yet, judging from the reasons he gave for his theoretical views, the experimental work of Wepfer in the previous century and Alston's own clinical experience with opiates played a greater role. In fact Alston did not really derive his pharmacological theory of opium from his extensive experimental work, which, as we have seen above, rather served to evaluate and criticize the views of other authors.

Dissecting or vivisecting perorally poisoned animals, Wepfer had found that some "narcotic" plant poisons caused grave symptoms, although they had apparently not yet left the stomach and seemed unchanged. On this basis, and influenced by van Helmont's idea of the archeus, the Swiss physician had suggested that these poisons attacked primarily the nervous coats of the stomach. Per sympathiam the Praeses systematis nervosi, i.e. the personified nervous, vital principle, would be "enraged", and in his efforts to subdue and expel the poison, he caused the observable symptoms of intoxication. The latter were thus not, or at least not primarily, caused by an effect on the blood. There was also indirect evidence for such a view, for early vomiting in his experimental animals, as well as in clinical poisoning cases, led often to recovery. It was to these observations of Wepfer that Alston referred,

117 Ibid., pp. 168-170. On the roots of the concept of sympathy in antiquity see Röhr, op. cit., note 34 above, pp. 34-76.
when he justified his theory. Yet Wepfer's experiments had not included opium or poppy. His theory rested mainly on his work on water hemlock and other toxic, fast acting plants and drugs, such as napellus, white hellebore, cocculi Indici, and nux vomica.\textsuperscript{118}

In fact the speed with which the effects of opium and some other drugs showed after oral taking was Alston's second argument to support his theory, and it was here that his clinical experience came in. A few drops of Liquid Laudanum (opium in alcohol) "in a Moment" ended violent tenesmus and stopped vomiting, eased pain, and induced sleep "almost as soon".\textsuperscript{119} It was very unlikely in his opinion that such instant effects were brought about by absorption of the drug into the blood and transport to the brain. To understand this view one has to consider the current doctrine of lymphatic absorption in Alston's time. An orally taken substance would have to pass down to the guts, be absorbed by their chyle vessels and then travel the long way up the thoracic duct before entering the blood of the subclavian vein to be distributed with the circulation.\textsuperscript{120}

Alston's theory of direct action on the nerves was the beginning of another shift in the pharmacological ideas on opium. Less importance was placed on possible effects on the blood and circulation. The nervous system became (again) the prime target of the drug.\textsuperscript{121}

\textsuperscript{118} Maehle, J. J. Wepfer and 'Wepfers experimentelle Toxikologie', General Introduction above, note 7.

\textsuperscript{119} Alston, op. cit., note 18 above, p. 165.


\textsuperscript{121} See also Earles, 'Early theories', General Introduction above, note 3.
More experimental "evidence" in support of this view was provided in 1745 by the Dutch physician Abraham Kaau Boerhaave (1715-1758), a nephew of Herman Boerhaave, who basically applied Wepfer's old method of oral poisoning and vivisection to the study of opium. The stomach of dogs that had been put to deep sleep by high doses still contained the drug after several hours, while the pylorus appeared perfectly closed, the intestines contracted and almost without peristaltic movement, and the (absorbent) chyle vessels empty. In one experiment Boerhaave had weighed the remaining amount of opium in the stomach six hours after oral administration and found that the original dose of 30 grains had been reduced by less than one grain. These findings seemed to speak against a primary effect of opium via absorption and the blood circulation. Consequently he concluded, like Alston, that it acted initially on the nerves of the stomach, from which the effect spread per consensum to the central parts of the nervous system, leading to impaired sensation and motion throughout the body. Turgid veins in the brain and elsewhere, which Boerhaave (as Berger and others before) noted during his vivisections, were interpreted by him as a secondary effect, resulting from diminished motion of the heart and retarded blood circulation, after the nervous system had been affected.\textsuperscript{122}

Though forming only a small part of a large theoretical work on the physiology of sympathetic action, Boerhaave's experiments seem to have had considerable impact on the development of pharmacological ideas on opium, being repeatedly quoted by later researchers.\textsuperscript{123}

More important in this respect, however, became a series

\textsuperscript{122} Abraham Kaau Boerhaave, \textit{Impetum faciens dictum Hippocrati per corpus consentiens philologice et physiologice illustratum observationibus et experimentis passim firmatum}, Leyden, Samuel Luchtmans & Fil., 1745, pp. 401-407.

\textsuperscript{123} E.g. by Whytt, op. cit., note 18 above, p. 315; Monro, op. cit., note 18 above, pp. 298-299.
of trials in the 1750s by Alston's Edinburgh colleague Robert Whytt.\footnote{On Whytt's life and work see French, op. cit., part A above, note 5.}

Examining the question whether the blood circulation or the nervous system was more important in bringing forth the effects of opium, Whytt compared the drug's action on differently prepared frogs with that on intact ones as controls.\footnote{Whytt, op. cit., note 18 above.} In some of the animals he previously either excised the heart or cut off the head and destroyed the spinal marrow by pushing a wire down the vertebral column. He thus used three "animal models" (as one would say today): one, in which the blood circulation had been interrupted, another, in which the central nervous system had been eliminated, and a third, in which both systems worked.

Whytt's experiments showed that a solution of opium in water, injected into the stomach and guts, destroyed sensibility and motion in a frog without blood circulation as soon as in an intact one. Moreover, when such a solution was applied to muscles or injected into the body cavities of frogs without central nervous systems, it reduced the heart rate much less quickly than in the entire animal. Whytt concluded from these observations that opium produced its effects chiefly by direct action on the nervous system, not (or much less) via absorption and transport with the circulating blood.\footnote{Ibid., pp. 302-303. See also Whytt, 'An essay on the vital and other involuntary motions of animals', in The works, part A above, note 108, pp. i-viii, 1-208, on pp. 199-200.}

This seemed to be supported by experiments on dogs, performed by his student Robert Ramsey. Opium solutions injected rectally or intraabdominally almost immediately led to paralysis and loss of sensation in their hind legs, but not in the front part of their bodies - a phenomenon, which also made an effect via absorption and
circulation seem unlikely. Accordingly, Whytt endorsed Alston's theory of a direct action on nerves spreading by sympathy and simultaneously rejected the older idea of rarefied blood.\textsuperscript{127} Similar to Boerhaave, he explained the swollen blood vessels in opium-poisoned animals with stagnating circulation. In Whytt's physiological concept of "vital and involuntary motions", the heart needed to sense the stimulus of the returning blood to perform its contractions. Since opium caused "insensibility" of the heart, as it did in other parts of the body, cardiac motion necessarily slowed down and eventually stopped. With regard to intravenous injection of opiates he suggested that they acted on nerves terminating at the inner surface of the heart and blood vessels or affected the cerebral medulla itself.\textsuperscript{128}

Without doubt, Whytt's animal experiments on opium had been the most sophisticated so far in this field of research. Not only had he compared the drug's effects on specially prepared frogs with those on intact animals. In true control experiments he had also studied the physiological changes caused by preparation alone (i.e. excision of the heart, decapitation and pithing), without administration of opium.\textsuperscript{129} Moreover, although his main experiments had been conducted on cold-blooded animals (frogs), he had sought confirmation of his findings in warm-blooded animals (dogs). Yet, despite this methodical cautiousness, it was Whytt's experimental design that soon became the target of criticism by expert colleagues: at home in Edinburgh by the anatomist Alexander Monro secundus (1733-1817), the son of Alston's colleague, and on the Continent by the renowned Albrecht von Haller (1708-1777). Though Haller's critique predated that of Monro, we shall first look into the latter's work and its

\textsuperscript{127} Whytt, op. cit., note 18 above, pp. 297-299, 307-309.

\textsuperscript{128} Ibid., pp. 303, 313; Whytt, op. cit., note 126 above, pp. 195-198.

\textsuperscript{129} Whytt, op. cit., note 18 above, pp. 281-285.
consequences, because it was more closely concerned with the controversial question of opium's effect on the nerves or on the blood.

In 1761 Monro presented the results of his own, extensive experimental work on this problem to the Philosophical Society of Edinburgh. Whytt, he maintained here, had become victim of "an unlucky deception, in the chief of his experiments" by assuming implicitly that absorption and circulation continued in frogs whose central nervous system had been eliminated. Monro had observed microscopically that the blood flow stagnated in the small vessels of frogs prepared in this way, and he had found experimentally that absorption became inconsiderable as the circulation ceased. Following his wrong supposition (explained Monro), Whytt had attributed the slow effect of opium in decapitated and pithed frogs only to the lack of a central nervous system, forgetting to consider diminished absorption and circulation as well.\textsuperscript{130}

Aware of these pitfalls, Monro used modified animal models, so to speak. In one group of frogs he either excised the heart or separated one of the hind legs, leaving only the crural nerve as a connection with the trunk. Applying subcutaneously a solution of opium in water to the leg, he intended to study the effect mediated solely by nervous action in this way. In a second group he either destroyed the lower spinal marrow or cut one hind leg so that it remained connected with the body only via its large blood vessels and concomitant lymphatics. Again applying opium to the leg, these animals were supposed to show purely the effect through absorption and transport with the blood and lymph. As Whytt had done it, intact frogs were used as controls, in which both the nervous and circulatory system were unimpaired. Between these three groups Monro compared the appearance and intensity of typical effects of opium

\textsuperscript{130} Monro, op. cit., note 18 above, pp. 299-302.
intoxication, such as loss of sensitivity, diminished circulation (observed microscopically in the webbed feet after Alston's method), paralysis, and convulsions. While they showed strongly in the models for pure absorption, they appeared only locally in the hind legs, not throughout the body, in the models for pure nervous action. Not surprisingly, the systemic symptoms of poisoning came up soonest in intact animals.

On the basis of these results Monro enlarged the current theory of the modus operandi of opium. Its effects, he argued, were produced both by way of direct action on nerves (in the sense of Alston and Whytt) and via absorption into the circulating blood.\(^{131}\) He was all the more convinced of this broader concept, since he had found in further animal experiments with alcohol and camphor that these substances seemed to act even chiefly through absorption.\(^{132}\) Counterarguments suggested by the work of Kaau Boerhaave, i.e. that opium appeared to be effective while it was still in the stomach and hardly dissolved, were readily dismissed by Monro: the stomach had lymphatic vessels capable of absorption like those of the guts, and the active principle of opium probably formed only a small part of the whole drug.\(^{133}\) Yet, even so, Monro did not radically depart from Whytt's theory. Like the latter he supposed that opium, once it had been absorbed into the blood, would affect nerve endings at the inner side of the heart and blood vessels, which communicated their "sufferance" by sympathy. Instant convulsions in frogs after intravenous or intraarterial injection of opium seemed to indicate this mode of action. Rarefaction of the blood, however, if happening at all, was in his view "so inconsiderable as scarcely to merit attention" and ought "not to be considered with

\(^{131}\) Ibid., pp. 337-338, 360.

\(^{132}\) Ibid., pp. 350, 357.

\(^{133}\) Ibid., p. 339.
Pitcairn, Friend [sic!], and with the learned Dr Tralles, as the primary effect..., but only as a secondary one."\(^{134}\)

While Monro thus stopped halfway in his critique of Whytt's (and Alston's) nerve theory, some twenty years later the well-known Italian natural scientist Felice Fontana (1730-1805) rejected it altogether in favour of a theory of absorption. In a large series of experiments, involving not less than 300 frogs, Fontana had prepared the sciatic nerves on both sides. On one side the nerve was then dipped into an aqueous solution of opium, on the other side in pure water. Dividing the total number of preparations into groups of thirty, the immersion time was varied from ten to one hundred minutes in ten minute steps, and the nerves of both sides were subsequently stimulated. Since their capacity to conduct stimuli to the muscles of the hind legs decreased equally and to the same degree on both sides, Fontana concluded that opium had generally no direct effect on nerves.\(^{135}\) This meant that it had to act via the blood circulation, a conclusion, which Fontana believed to have confirmed with a number of intravenous injection trials on rabbits. Depending on the dose of an injected aqueous solution of the drug, the animals quickly showed the usual symptoms of opium poisoning, such as deep sleep, paralysis, and convulsive movements, sometimes ending in death.\(^{136}\)

Since Fontana's conclusion that opium acted primarily through the blood and not through the nerves, was diametrically opposed to that of Whytt, he repeated


\(^{136}\) Fontana, Beobachtungen, note 135 above, pp. 253-254.
some of the latter's crucial experiments with slight modifications. In one group of frogs he destroyed the brain and spinal marrow with a large needle inserted through a hole in the skull and then compared the effects of orally given opium with those in intact frogs. Examining their heart rates and stimulating their crural nerves, Fontana could not confirm Whytt's observation that the drug's effect was either weaker or appeared more slowly in frogs without a central nervous system. In another trial he gave the opium solution perorally to one group of frogs, in which he immediately after excised the heart, and to another group, in which he only opened the thorax, leaving the heart in situ. Contrary to Whytt's observations, the animals with heart showed signs of opium poisoning (here loss of voluntary movement) much earlier than those without, suggesting that an intact blood circulation was important in producing the drug's effects.

Fontana's experiments on opium in fact marked the beginning of a final shift in the theories on its primary effect, moving away again from the idea of direct action on nerves towards a theory of absorption into the circulating blood. As Melvin P. Earles has shown, such a shift took place generally in pharmacological and toxicological theories, action by way of absorption becoming eventually the accepted concept around the middle of the nineteenth century. Despite the impressive numbers of trials performed by Fontana, however, the evidence he had produced for his theory was regarded as quite weak in his own time. It was criticized as methodically inadequate, for example, that he had applied

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137 Ibid., pp. 257-258.
138 Ibid., pp. 260-261.
139 On the resistance to Fontana's theory and further experimental efforts to answer the question of opium's effect on nerves or via the blood see Earles, 'Studies' and 'Early theories', General Introduction above, note 3.
opium to the trunks of nerves, covered by "thick, cellular" coats, while the natural places of sensation were the fine extremities of nerves or specially adapted nervous surfaces. It was therefore wrong to conclude from the lacking effect here to a lack of any direct nervous action of the drug. In fact this point had already been made before Fontana's trials by Monro, who, however, in later experiments apparently ignored his own precautions and applied opium solutions directly to the brain and spinal marrow of the frog, rabbit, and pig. Since this led to convulsions followed by paralysis, Monro actually felt confirmed in his view that opium - if it was absorbed into the blood - acted on nerves terminating at the heart and vessels and affected through these the whole nervous system.

Moreover, Fontana remained rather vague on the exact mode in which opium was supposed to act through the blood circulation. He did not seem to regard the blood as a mere transport medium for the drug, but rather to assume that opium inhibited and diminished the circulation, possibly by affecting the blood's "living principle". Also this assumption of a vital element in the blood, propagated at the time most notably by John Hunter (1728-1793), became a target of criticism, e.g. by the Irish physician Samuel Crumpe (1766-1796), who experimented extensively with opium in the early 1790s.

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140 Georg Christoph Siebold, Commentatio de effectibus opii in corpus animale sanum maxime respectu habito ad eius analogiam cum vino, Göttingen, Jo. Christ. Dieterich, 1789, p. 82.

141 Monro, op. cit., note 18 above, pp. 325-326; idem, Experiments on the nervous system, with opium and metalline substances; made chiefly with the view of determining the nature and effects of animal electricity, Edinburgh, Adam Neill and Company, 1793, pp. 9-16.

repeated also some of those of Monro's experiments, which had in part supported the theory of absorption. He applied subcutaneously a solution of opium to frog legs that were left connected with the trunk merely through the thigh bone and nerve. Compared to control trials on intact frogs, death occurred equally fast in both cases. Moreover, frogs only prepared in this way, but not given the drug, survived clearly longer than the equally prepared animals that had been given opium. As Crumpe saw it, these experiments provided decisive proof that opium acted only on the nervous system. The results of Fontana's intravenous injections did not count in his view, because "many substances friendly to the animal frame, or at least not poisonous, when injected in a similar manner, produce speedy death". Likewise, changes of the blood observed in the dissection of opium-poisoned animals, or in in vitro experiments in the manner of Freind, said nothing about the drug's real effect in the body:

To me it appears pretty clear, that any conclusion deduced from experiments made on blood drawn from its

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143 For John Hunter's idea of a "living principle" in the blood see his A treatise on the blood, inflammation, and gun-shot wounds, 2 vols, London, E. Cox, 1812, vol. 1, pp. 133-165. Samuel Crumpe, An inquiry into the nature and properties of opium: wherein its component principles, mode of operation, and use or abuse in particular diseases, are experimentally investigated; and the opinions of former authors on these points impartially examined, London, G. G. and J. Robinson, 1793, pp. 104-125. Crumpe also criticized Fontana's method of applying solutions of opium directly to nerves, arguing that "the nervous matter must be organized in a peculiar manner, to enable it to receive or be sensible of these impressions." Ibid., p. 126.

144 Ibid., pp. 137-139. Monro also tried to refute Fontana's theory, pointing among others to his earlier trials on frogs, which had indicated that opium was still effective even if the circulation had been interrupted and the blood largely evacuated. Cf. Monro, op. cit., note 141 above, p. 16, and idem, op. cit., note 18 above, pp. 318-319, 331-332.

145 Crumpe, op. cit., note 143 above, p. 131.
vessels, in proof of its [i.e. opium's] action thereon, are perfectly fallacious and inconclusive; and that the changes observed in it on dissection, have been rather the consequences of the previous state of the system, the action of the vessels on their contents, and the effects of exposure to the atmosphere, than to any immediate operation of the medicine itself on the fluids.  

Essential for the eventual change from the "nerve theory" to the theory of absorption were, according to Earles, a number of physiological studies in the early nineteenth century, particularly by François Magendie (1783-1855). They demonstrated that absorption was not only performed by lymphatic vessels, but also directly (and thus quickly) by veins, and they showed the high speed of the circulation. New chemical methods, allowing poisons to be detected in tissues of organs and the blood, helped further to discredit the theory of direct nervous action. The work of Monro and especially of Fontana, in response to Whytt, thus contributed to the general change in pharmacological theory at a very early stage, when there was still strong opposition to the idea of effect by absorption - an opposition, which was partly based, as has been shown above, on experiments too.

7. Effects on the heart and irritability

The other main response to Whytt's opium experiments, coming from Haller as mentioned above, was part of what is known to historians as the Haller-Whytt controversy over sensibility and irritability. In his famous paper on the "sensible and irritable parts", given

146 Ibid., pp. 140-141.


148 For a summary of this controversy see Earles, 'Studies', General Introduction above, note 3. See also French, op. cit., part A above, note 5, pp. 52-53, 73.
in 1752 to the Royal Society of Sciences in Göttingen, Haller had stated that opium diminished irritability (i.e. the contractility of muscle fibres) throughout the body, and in particular the peristaltic movements of the guts, but that it left the motions and force of the heart unimpaired. This assertion was founded on a number of vivisections of opium-poisoned cold- and warm-blooded animals, that Haller had performed in the preceding year together with his doctoral student Johann Adrian Theodor Sproegel (1728-1807).

A close reading of the findings in these experiments, which were first published in Sproegel's dissertation and subsequently, with additional trials, in Haller's Mémoires sur la nature sensible et irritable, des parties du corps animal, indicates that the experimental basis for this view was rather thin and not completely unambiguous. Haller claimed to have observed in three opiated frogs that the heart still retained its irritability, while the intestines had already lost it. Yet, in Sproegel's account this was less clear in one of these three trials, and both reported one opium experiment on a cat, in which the movements of the guts actually survived those of the heart. The latter finding was apparently ignored by Haller in his conclusions, where he reiterated that "the irritability of the intestines is more easily destroyed by opium, and less easily restored, than that of the heart." Still, even with these uncertainties, Haller's results sharply contrasted with those of Whytt. In

149 Albrecht von Haller, Von den empfindlichen und reizbaren Teilen des menschlichen Körpers, ed. by Karl Sudhoff, Leipzig, Johann Ambrosius Barth, 1922, p. 46.


152 Ibid., p. 386.
applying opium to frogs and vivisecting them, Whytt had found a considerable decrease of their heart rate.\footnote{153} Because of this discrepancy with Haller's observations he had conducted more experiments of this kind, which confirmed his initial observations. Moreover, excised frog hearts stopped beating sooner if immersed in an aqueous solution of opium than if put in pure water. The deceleration of the heart rate was also noted in one of the opium trials on dogs performed by Whytt's student Ramsey, mentioned above, and Alston and Kaau Boerhaave had described this phenomenon in dogs, too.\footnote{154} Accordingly, Whytt had emphasized that the irritability of the heart was not exempted from the effect of opium, adding somewhat arrogantly that Haller's "candor and love of truth" would without doubt "make him readily acknowledge his mistake, as soon as he shall discover it."\footnote{155}

As often in the eighteenth century, a scientific controversy developed. Haller quoted his and Sproegel's experiments, questioning simultaneously the validity of Whytt's by emphasizing the problem of artefacts in the latter's very invasive methods:

To open the abdomen of an animal, to cut off its head or spinal marrow, in order to find out about the more or less slow effects of a poison, is surely not the way to learn the truth.\footnote{156}

\footnote{153} Whytt, op. cit, note 126 above, pp. 197-198.


\footnote{155} Whytt, op. cit., note 154 above, pp. 212-213. See also idem, op. cit., note 18 above, p. 305.

Haller apparently ignored here the fact that Whytt had performed control experiments and that his own trials, including vivisection of the poisoned animals, were open to the same criticism. Yet, on a less polemical level, he rightly pointed out that Whytt had not performed experiments to confirm or refute his and Sproegel's crucial observation that the action of the heart survived the peristaltic movements of the guts. Moreover, he was able to quote experiments of Fontana in his favour.\textsuperscript{157} Fontana, having examined the effect of opium on the velocity and force of cardiac contractility in over a hundred trials, chiefly on frogs, actually remained undecided, because the results were too varied. But referring to experiments on warm-blooded animals, he noted that a moderate dose intensified the movements of the heart, whereas high doses appeared to diminish its force, as it reduced the liveliness of the animals in general, weakening their "vital force". Fontana pointed out that a similar mode of action could be seen in man after oral taking of the drug. In most cases cardiac movements were increased, and the few observations to the contrary would not invalidate this general rule.\textsuperscript{158}

In fact this was in keeping with the clinical testimony of George Young and Tralles, who were both quoted by Haller. Young had observed that opium heated the body and augmented fever, implying a stimulating effect on the blood circulation; and Tralles had clearly stated that the drug intensified and accelerated the pulse of the heart and arteries, and thus the whole of the circulation.\textsuperscript{159} Whytt, on the other hand, was subsequently supported by Monro in this question of

\begin{itemize}
\item \textsuperscript{157} Haller, op. cit., note 151 above, vol. 4, pp. 130-131.
\item \textsuperscript{158} Fontana, \textit{Beobachtungen}, note 135 above, pp. 261-262.
\end{itemize}
cardiac effect, on the basis of his own animal experiments.  

What at first glance may look like a quarrel about some rather minor aspect of the pharmacology of opium, had actually important implications for the general concept of sensibility and irritability, and thus for a central topic of eighteenth-century physiology. The vigour of Haller's response to Whytt can be understood in this way. The two opponents agreed that opium diminished sensibility. If this effect was linked with a decrease of irritability throughout the body, including the heart, Whytt's view was strengthened that irritability depended on sensibility. If, however, the irritability of the heart was not reduced by the drug, this gave support to Haller's doctrine, according to which irritability was a distinct property of muscle fibres, independent of the sensibility of the nerves and able to endure without any nervous influence. We see here how a drug or poison was employed as a tool to investigate questions of physiology - a method that was to be developed fully only in the nineteenth century by Claude Bernard (1813-1878). 

Yet, also for the pharmacological theory of opium itself the effect on the heart had wider implications. Not only was the question at stake whether opium was a cordial, as Sydenham had affirmed so emphatically, but more generally, whether opium was basically a stimulant or a sedative. Attracted by these problems, as by the prominence of Haller's and Whytt's names, several researchers in the second half of the eighteenth century tried to find a solution. In doing this they went beyond

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the method of animal experimentation, performing also trials on themselves and other test persons.

In his Edinburgh medical dissertation of 1764 Maxwell Garthshore (1732-1812) had stated in line with Haller, Tralles, and the lectures of William Cullen (1710-1790), that opium first of all accelerated the movement of the blood and increased body heat, referring also to "experiments conducted by myself". Only a year later, however, another Edinburgh medical student, the young American Samuel Bard (1742-1821), challenged this view on the basis of careful self-experimentation and other human trials.

On the day before his first experiment Bard registered a day profile of his pulse rate without the influence of the drug, taking hourly measurements and avoiding physical exercise. On the following morning he then took orally one and a half grains of opium, i.e. a usual therapeutic dose, and measured his pulse rate in intervals from half to one hour. In this way Bard found a significant decrease of his pulse from 71 per minute (which corresponded to his measurements the previous day) to a minimum of 57 per minute. This effect set in about an hour after taking the drug and was combined with a feeling of relaxation and loss of concentration, which increased to sleepiness. It wore off after about seven hours. Bard basically confirmed these observations in three repetitions of the experiment on himself, in three of his friends, and in six convalescent patients of the Edinburgh Royal Infirmary. The result did not change either when he modified the experiment on himself by taking the one and a half grains of opium distributed into six portions in half-hourly intervals. In addition

163 See also on this aspect Maehle, 'Selbstversuche', General Introduction above, note 22.

164 Maxwell Garthshore, Dissertatio medica inauguralis, de papaveris usu, tam noxio, quam salutari, in paturientibus, ac puerperis, Edinburgh, Typis Academicis, 1764, p. 4.
Bard measured his body temperature with a Fahrenheit thermometer: it never went beyond his usual temperature of 98 degrees.\textsuperscript{166}

On the basis of these results Bard concluded in favour of Whytt, and against Haller and Tralles, that opium slowed down the heart rate and blood circulation and that it rather lowered the body temperature than increasing it. In his opinion this could be explained with a general diminution of both sensibility and irritability in all parts of the body. His only concession to Haller's view was that the heart, because of its exquisite irritability, was less affected than other parts.\textsuperscript{167}

Yet, despite Bard's circumspect experimentation, his findings did not remain unchallenged either. The Münster physician Carl Joseph Wirtensohn (d. 1788), likewise stimulated by the Haller-Whytt controversy, also examined the effect of opium on the heart and pulse and published his results in his inaugural dissertation of 1775, which he successfully defended at the University of Harderwyk. Having swallowed each a grain of opium, he and a friend had measured their pulse rate: within half an hour it had increased from 76 to 86, respectively 71 to 84, per minute. On the other hand, when Wirtensohn had repeated Whytt's experiments with opium on isolated frog hearts, he had also found that their pulsations decelerated. If, however, the hearts of frogs were merely exposed, being left \textit{in situ}, the giving of opium actually accelerated their contractions. Taking these seemingly discrepant observations together, Wirtensohn suggested a mechanical explanation, which tried to reconcile the standpoints of Haller and Whytt. Opium, he argued in the sense of Whytt, weakened the force of the heart. But since irritability


\textsuperscript{166} Ibid., pp. 25-26.

\textsuperscript{167} Ibid., pp. 26-28.
was diminished throughout the body, this meant that the contractility of the arteries, and thus peripheral resistance, was reduced, too. Therefore the heart would initially beat faster, and the speed of the blood circulation increased. This explained the observations of Haller. Only in the later stages of opium poisoning would the weakening effect on the heart become manifest.\textsuperscript{168}

Haller kept his interest in the problem long after his move from Göttingen to Berne in 1753. The dissertations of Garthshore and Wirtensohn are in his library, as are, among other works on opium and the poppy, the monographs of Young and Tralles, Descazals' thesis under Hoffmann, and the seventeenth century studies of Borch and Waldschmied, discussed above.\textsuperscript{169} In 1776 and 1777, shortly before his death, Haller commented on the issue again, when he reported on his experiences as an opium-using patient over the last few years. Suffering from a chronic bladder disease during his last illness, he had rather reluctantly followed the advice of his British correspondent Sir John Pringle (1707-1782) and taken up a regular use of opium clysters.\textsuperscript{170}


\textsuperscript{169} Maria Teresa Monti, \textit{Catalogo del Fondo Haller della Biblioteca Nazionale Braidense di Milano}, 12 vols, Milan, Franco Angeli, 1983-94. I thank the editing group of Haller's correspondence under Professor Urs Boschung, University of Berne, for making a search at my request on their computerized version of the Monti catalogue.

\textsuperscript{170} Albrecht von Haller, \textit{Abhandlungen über die Wirkung des Opiums auf den menschlichen Körper}, transl. and ed. by Erich Hintzsche and Jörn Henning Wolf, Berne, Verlag Paul Haupt, 1962 (Berner Beiträge zur Geschichte der Medizin
this treatment Haller repeatedly noted that his pulse rate increased as the clyster eased his pains, and that it dropped again as the drug effect wore off. The same stimulation of the "vital powers" could be observed after oral taking.\footnote{171} In this way Haller was reassured in his old opinion that irritability was independent of sensibility. As for the cardiac effect of opium, he now went even a step further than in his earlier experimental work. Based on his own experience, and also with reference to Tralles' work, he stated that a moderate dose actually increased, supported and renewed the powers of the heart, accelerated the pulse, and warmed the body. Only very high doses of the drug inhibited, and eventually stopped, the action of the heart.\footnote{172}

Though not naming Whytt, but doubtlessly with the latter's experiments in mind, Haller argued anew that trials on animals with such high doses and including vivisection were not the right way to study pharmacological effects. In particular he argued that opening the body cavities of a frog would make its pulse rate drop anyway, without having given opium. Instead of vivisection he advocated careful observation of the drug's effects in the human patient, especially examination of the relation of loss of sensibility (analgesia) to changes in heart action, as he had done in his self-observations.\footnote{173}

This was also the opinion of Tralles, who a few years earlier had responded to Whytt's experimental findings, too. Quoting Young and Garthshore, he had pointed out that their experiences on their own bodies supported his view of opium's stimulating effect on the

\footnote{171} Haller, op. cit., note 170 above, pp. 16-17.

\footnote{172} Ibid., pp. 5, 17.

\footnote{173} Ibid., pp. 5-8.
heart. Simultaneously, he had discarded the self-experiments of Bard as the work of someone whose only aim had been to prove that the views of Whytt (who was then still living) were right, while his (i.e. Tralles') were wrong. More importantly, Tralles had made clear that he was not ready to give up his knowledge of the effects of opium, which was based on "thousands of experiences" in many years of medical practice, only because Whytt had found something different in "marshy frogs". Paraphrasing Erasmus, Tralles had written that someone heading for "the better and more solid" was not distracted by the unpleasant croaking of frogs along his path.174

Behind the overt polemic, a number of important questions relating both to the validity of pharmacological experimentation in general and the ambiguous nature of opium had been brought up by the Haller-Whytt controversy. Haller's objection that Whytt's vivisectional trials created artificial conditions, and were therefore questionable, was not without justification. Likewise, Tralles' criticism of Whytt's frog experiments touched the problem of transferability of results from animal to man, in this case accentuated by the fact that a cold-blooded animal had been used. Both objections - artefacts and lack of transferability - were generally discussed around this time, especially also with respect to Haller's doctrine of sensibility and irritability.175 Such debates reflected a growing awareness of the fallacies of animal experimentation. This awareness was not limited, however, to the camp of critics, but can be found in the experimental researchers themselves. As mentioned above, Whytt had performed control experiments, in which he studied the effect of


175 See Maehle, Kritik, General Introduction above, note 16, pp. 15-56.
the vivisectional procedures alone, without giving the drug. And though the majority of his trials had in fact been performed on frogs, he had made the test on a warm-blooded species (dog) as well. Alexander Monro was particularly aware of the objection of a lack of transferability. While he admitted that "the effects of a medicine may be much more speedy and violent on one species of animals, than on another", he emphasized that the basic mode of action was the same, if the used species were "provided with like systems of nerves and vessels".\textsuperscript{176}

Self- and human experiments were a way to avoid the problem of transferability, yet here the possible influence of subjective factors became apparent. When Samuel Bard in one of his trials had taken the rather high dose of two and a half grains of opium, nausea and vomiting set in, and fearing an intoxication, his pulse rate accelerated. Accordingly, this finding was not included in his assessment of the drug's cardiac effect.\textsuperscript{177} Similarly, Wirtensohn initially suspected that the increase of the pulse rate in himself and his friend had rather to do with some emotion, or their expectation to see what would happen, than with the effect of opium itself. Only after he had confirmed his findings repeatedly in the treatment of patients, did he regard the effect as authentic.\textsuperscript{178}

Another difficulty was that of dosage. Both Haller and Fontana had made clear that the effect of opium on the heart differed, depending on whether a "moderate" or a "high" dose had been taken. In the first case it consisted in stimulation, in the second in inhibition. Certainly this can be seen as a possible explanation for the discrepancy to Whytt's observations. Yet Sproegel and

\textsuperscript{176} Monro, op. cit., note 18 above, pp. 294-295.
\textsuperscript{177} Bard, op. cit., note 165 above, p. 18.
\textsuperscript{178} Wirtensohn, \textit{Dissertatio}, note 168 above, p. 10.
Haller used very high doses in their animal experiments as well, such as ten grains of opium in a frog, i.e. about ten times the usual dose in man. However, they do not seem to have had a clear notion of a ratio of dose and body weight. Sproegel often gave some indication of the size, breed, or general state of his experimental animals, such as "a middle-sized, yet very robust dog", "a yellow Molossian dog", or "a strong tom cat". But such descriptions rather had the purpose to provide some idea of the resistance to poisoning that could be expected in a particular animal. In fact Sproegel concluded from his experiments that animals generally tolerated much greater quantities of poisons than human beings, and Haller pointed out that heart action was more resilient in cold-blooded than in warm-blooded animals. On the other hand Fontana, in his studies of viper venom, did explicitly relate the amount of poison to the weight of his experimental animals. For example, he extrapolated the lethal dose of venom in pigeons of six ounces weight to that which would kill a 750 pound ox or a 150 pound man.179

A problem which may also have played a role was the variety in the purity or quality of opium. Although this element of uncertainty was in principle known (see above), it was not taken account of in the debates surrounding the Haller-Whytt controversy. Typically, neither Haller or Sproegel, nor Whytt, nor one of the later researchers mentioned above, went into any detail about the sort and quality of opium they had used in their experiments.

8. Stimulant or sedative?

Still, towards the end of the eighteenth century, an answer to the Haller-Whytt problem gained ground. Rather

than different dosage alone, different stages of the action of opium were assumed to be responsible for the observed differences in effects. In 1789, in a prize winning essay for the medical faculty of Göttingen, the student Georg Christoph Siebold (1767-1798), son of the renowned Würzburg professor of anatomy, surgery and obstetrics Carl Caspar Siebold, suggested such a theory. Based mainly on animal experimentation and some self-experiments, he proposed a first stage, in which opium raised the pulse and respiration rates as well as body temperature, followed by a second stage, in which these parameters were lowered. Moreover, he observed that this first phase of stimulation lasted the longer, the smaller the intake of opium had been.180 Probably independently of Siebold, Samuel Crumpe published similar views in 1793. In experiments on himself, which were partly repeated on another healthy test person, Crumpe studied the effect of opium on the pulse in the manner of Bard and Wirtensohn. After doses between one and two and a half grains he measured the pulse every five minutes for one or two hours and noted accompanying symptoms. In doing this he found a fuller pulse and an increase of the pulse rate during the first half hour, which was followed by a decrease to the initial rate or below. While the phase of accelerated pulse was linked with sweating, alertness and a bright mood, the phase of declining pulse was characterized by languor, headache, drowsiness, and nausea, followed by vertigo, trembling, vomiting, and a longer "stupid state".181

Crumpe's observations were relevant in two respects. Firstly, they offered an explanation for the discrepant observations of Bard and Wirtensohn, and by extension for those of Haller and Whytt. Bard had started to measure the pulse only half an hour after taking the drug. He had therefore (as Crumpe pointed out) missed the initial

180 Siebold, op. cit., note 140 above, pp. 7-9, 48-53.
181 Crumpe, op. cit., note 143 above, pp. 33-36.
increase of the pulse rate and described only the second phase. Wirtensohn, on the other hand, had measured only up to thirty minutes after the intake of opium and had therefore noted only the acceleration of the pulse in the first stage. Seen in this way, both had only in part been right. Secondly, Crumpe's experimental observations provided support for the then widely discussed doctrine of excitability of John Brown (1735-1788). As mentioned above, Brown regarded opium as the strongest stimulant, the powers of which surpassed those of ether, camphor, volatile alkali, musk, and alcohol. Though referring to trials with these drugs, his assessment of opium seems to have been largely based on his own experience with it in treating his fits of gout. The instant and reliable success of the drug in this - in Brown's understanding - asthenic disease (characterized by weakness or lack of excitement) commended it as a highly effective stimulant medicine.

Crumpe explained his two stages of the action of opium in terms of Brown's system, acknowledging simultaneously the Scotsman's originality. The first stage was that of stimulation and excitement, which, as the body's excitability became exhausted, turned into the second stage. This was characterized by insensitivity to further stimuli, resulting in painlessness, slow movements of the heart and arteries etc., followed - if a very high dose had been given - by so-called indirect asthenia or weakness (due to over-excitement), that sometimes ended with death.

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183 Wirtensohn, Dissertatio, note 168 above, p. 10.

By the camp of Brunonian physicians Crumpe's work was hailed as experimental proof of their therapeutic system. A positive review of the German edition (1796) of Crumpe's book, in Melchior Adam Weikard's (1742-1803) *Magazin der verbesserten theoretischen und praktischen Arzneikunst*, stated:

By the experiments described in this work any doubt has been removed that opium is a stimulant. The mitigation of pain follows only after a previous stimulus, an increase of pain etc. Thus opium diminishes sensibility, when it has induced indirect weakness... Almost everything fits together with Brownian doctrine.  

In fact Crumpe had made quite extensive trials to establish the stimulant power of opium. They included self-experiments in which a watery solution of opium was applied to the eye, to excoriated skin, and into the urethra, always followed by pain or burning sensations. Powder of opium inhaled into the nose acted like weak snuff. And various animal experiments also appeared to confirm the stimulant effect of the drug.  

Support for a Brownian understanding of opium as a stimulant came also from Alexander von Humboldt (1769-1859), who included the drug among the various substances which he tested for their effect on the excitability of nerves and muscles. The trials were performed by Humboldt and his friend Keutsch with alcoholic solutions of opium, which they applied to the vagus nerve of a dog, the ischiadic nerve of a lamb, the axillar and crural nerves of frogs, the forefoot of a rat, and isolated frog hearts. Humboldt claimed to have observed in these experiments an initial increase in excitability (both

187 Crumpe, op. cit., note 143 above.
spontaneously and after electric stimulation), followed by a state of atonia or lack of excitability, which he attributed to "over-stimulation". On the basis of these trials he objected to Fontana's finding that opium did not act directly on nerves; and he sided with Whytt against Haller and his followers, asserting that opium did in fact quickly destroy cardiac pulsation after a brief phase of stimulation.\textsuperscript{188} Most importantly, however, he confirmed the views of Crumpe and Brown:

These facts and experiences now convince me completely that opium ... weakens, sedates, and acts as a narcotic only through over-stimulation. What I have observed in cold- and warm-blooded animals, in voluntary and involuntary muscles, confirms the doctrines of the Brownian school...\textsuperscript{189}

Speculating in the terminology of chemistry after Lavoisier, Humboldt thought that "carbon" and "hydrogen" contained in opium might attract "oxygen" from animal fibres as well as from arterial blood, disturbing in this way the vital processes. Like other researchers of the time he applied opium solutions also to plants. Again he thought to have found here a decrease in "vital power", expressed in their reduced absorption of fluid.\textsuperscript{190}

On the other hand, those sceptical of, or in distance to, Brown's system of excitability did not give much weight to Crumpe's evidence and conclusions. In fact his work became the prime target of conservative medical men, who vigorously defended the view that opium was a sedative. As the Critical Review pointed out, for instance, pain after application to the eye was not a


\textsuperscript{189} Cf. ibid., p. 408.

\textsuperscript{190} Ibid., pp. 414-417.
certain indicator of a stimulant, because this effect could be evoked with "every extraneous body", and often pure water would do the same. Moreover, even if opium had some stimulant power (as the reviewer conceded for argument's sake), it would not follow that its sedative effects resulted from previous stimulation. If this was true, the degrees of stimulation and subsequent sedation should be proportional. Experience with increasing doses, however, taught that this was not the case, because they would eventually lead to sedation alone, without the first stage of stimulation.\textsuperscript{191}

An extensive, devastating critique of Crumpe's book was published in 1802 in the London Medical and Physical Journal by Michael Ward (1762–after 1831), surgeon to the Manchester Infirmary.\textsuperscript{192} Ward had made himself known a few years before with "successful" external opium treatments, in which he had been supported by his prominent medical colleague Thomas Percival (1740–1804).\textsuperscript{193} In sharp opposition to Crumpe's and Brown's understanding of the drug's mode of action, he now moved on to explain his own theory. For him, opium was clearly a sedative. Crumpe's own human and animal experiments, argued Ward, had shown this, since they demonstrated a decrease of the heart rate and, in the animals, also an almost immediate loss of sensibility and motion. Crumpe had therefore been misguided by Brownian prejudice in his interpretation. His theory was "erroneous" and should be "consigned by all to merited oblivion".\textsuperscript{194} As Ward saw it, it had been a particularly serious mistake to conclude from the resemblance of opium's effects to those of wine and alcohol that it was a stimulant. Referring to Cullen,

\textsuperscript{191} Critical Review, 1794, n. s. 11: 66-70.


\textsuperscript{193} See below.

\textsuperscript{194} Ward, op. cit., note 192 above, vol. 8, p. 347.
Ward regarded the latter two (as well as opium) as "narcotic sedatives".\textsuperscript{195}

Ward did not leave his criticism at this argumentative level. Using his sixteen-year-old house pupil as a test person, he examined the drug's effects experimentally, too. Having embrocated in two trials the boy's legs and feet with a mixture of opium tincture, olive oil, and egg yolk, he noted that the pulse rate dropped considerably within ten to fifteen minutes. Moreover, the boy complained of feeling cold and drowsy, and his pulse appeared soft and weak, before - after about an hour - it started to return to normal again. Also subjectively, there was no indication of opium having a stimulant effect. Rather it seemed to act as a powerful narcotic:

I now asked if he had felt exhilarated at all, either in this or the former experiment? He answered, No; and could not help smiling at the question, though he looked like one in the cold fit of an intermittent... On his saying he had often been very cold, but had never before found that sensation accompanied with such disagreeable symptoms, I mentioned the word Horror, and he said it conveyed the best idea of what he had felt.\textsuperscript{196}

Ward's own theory of opium's \textit{modus operandi} was not only based on this experimental evidence, but actually picked up on one of Crumpe's observations in animals. After injections of opium solutions into the abdominal cavity of animals, Crumpe had seen increasead redness and apparent inflammation of their viscera, which he interpreted as a sign of the drug's stimulant effect. For Ward, however, this showed that opium had made the blood vessels loose their "tone" and "action" - a view, which

\textsuperscript{195} Ibid., vol.7, p. 127. Cullen classified opium as a narcotic and described its mode of action as "diminishing the mobility, and in a certain manner suspending the motion, of the nervous fluid". Cf. William Cullen, \textit{A treatise of the materia medica}, 2 vols, Edinburgh, Charles Elliot, 1789, vol. 2, pp. 224-225.

\textsuperscript{196} Ward, op. cit., note 192 above, vol. 7, p. 137.
he believed to be also supported by Alston's microscopical observation of a reduced capillary blood flow in opiated frogs (see above). It actually was the starting point in his pathophysiological explanations. Opium taken orally, wrote Ward, acted "directly as a sedative upon the vessels and coats of the stomach and small intestines... retarding or interrupting THE NATURAL FUNCTIONS OF THESE IMPORTANT ORGANS". The well-known alleviation of vomiting, diarrhoea, and tenesmus could easily be understood in this way. Furthermore, the reduced flow in the arteries of the stomach and intestines would lead to plethora in the aorta, which extended to the heart and the pulmonary, subclavian, and carotid arteries. Their contractions consequently increased in frequency and strength, resulting in a temporary acceleration of the blood circulation with its symptoms of warmth, liveliness, and alertness. Within an hour, however, the blood would also start to stagnate in the veins of the abdominal organs, the heart therefore receiving less venous blood. The arterial plethora was now quickly taken off, frequency and strength of the pulse were reduced below standard, and this led to languor, drowsiness, headache, nausea, and tremor. This, according to Ward, was the series of changes after a moderate dose of opium. After a "large" dose, taken by an unaccustomed person, the second phase would come up immediately, resulting in a "state of suspension" of the physiological functions and often ending with death.  

Ward thus principally accepted the "two stages"-concept of Crumpe, but for him also the first stage (increased circulation, alertness etc.) was indirectly explicable with a sedative effect of opium. In comparing the rival theories of Crumpe and Ward, it becomes clear

\[197\] Ibid., pp. 346-347, 359-360.
\[198\] Ibid., vol. 8., p. 325.
that the crucial difference lay in their understanding of this first stage. For Crumpe (as for Humboldt) it was the essential prerequisite for the second phase characterized by languor, drowsiness etc.: in the sense of Brown, stimulation exhausted excitability, thus leading to this latter stage. For Ward, however, the first phase was merely a transitory side effect of the directly sedating action of opium. It could be explained haemodynamically, and after high doses it would not appear at all.

Ward's attack on Crumpe's theory of opium as a stimulant is only one - albeit a particularly elaborate - example for contemporary discussions on the nature, and thus the therapeutic place, of the drug. As Ward himself pointed out, not only Brown and Crumpe, but also Erasmus Darwin, in his Zoonomia, had called it a powerful stimulant. Cullen, on the other hand, in his Materia medica, had ranked it as a sedative. Other authors had taken an intermediary position. George Young, in his still highly regarded Treatise on opium, had described both exhilarating and cordial qualities and sedative effects. Hooper's medical dictionary listed the drug both under sedatives and stimulants.200

The belief in the stimulant power of opium was actually a cornerstone of Brown's doctrine, and the debate over the drug's stimulant or sedative property reflected the wider conflict between his followers and adversaries. As Claudia Wiesemann has recently argued concerning Germany, where the debate on Brownianism was particularly intense around 1800, socio-political connotations gave a special edge to those exchanges: Brown's new therapeutic system, with opium and alcohol as favorite stimulants, fitted the younger generation of doctors who were prone to Romantic ideas and showed revolutionary zeal, both medically and socially. Anti-Brownians, on the other hand, who saw a very liberal use of opium and alcohol as a danger to health, could be

200 As quoted ibid., vol. 7, p. 126.
characterized as conservative, bourgeois representatives of late Enlightenment ideas, the prime example being the Prussian court physician and Berlin professor Christoph Wilhelm Hufeland (1762-1836).\textsuperscript{201} For Britain such a divide seems less clear, though Thomas Beddoes (1760-1808) might be quoted as an example of the former "type".\textsuperscript{202}

To some extent the stimulant-sedative controversy over opium can also be seen as yet another edition of the old debate on the drug's ambiguous nature that went back to the seventeenth century, as has been outlined above. With the beginning of the nineteenth century pharmacological theories on opium had surely become more complex, as the example of Ward shows, being informed by the physiological knowledge accumulated in the previous fifty years by Haller, Whytt, and others. But, four years before the isolation of the first opium alkaloid by Friedrich Wilhelm Sertürner (1805), the nature of the drug and its effects were still far from being clearly understood, and there was no theory of its mode of action that would have been unanimously accepted. To a great extent theories on opium had been a mirror of the changing general medical theories and systems of the eighteenth century. Aptly the medical historian Kurt Sprengel observed in 1803:

> How the spirit of the times has changed since one and a half centuries can hardly be seen more clearly than from a short survey of the different concepts of the effect of opium within this period.\textsuperscript{203}

Before we turn to the (renewed) efforts in chemical analysis of the drug after 1800, it will therefore be appropriate to pause and ask what the string of pharmacological theories on opium since the middle of

\textsuperscript{201} Wiesemann, 'Brownianism', note 7 above.

\textsuperscript{202} See ibid., and Porter, op. cit., part A above, note 183.

\textsuperscript{203} Cf. Sprengel, op. cit., note 25 above, p. 329.
the eighteenth century had meant in terms of therapeutic practice. In this context, the views on the drug's addictive properties also need to be considered.

9. Pharmacology and therapeutics

As has been shown above for the late seventeenth and early eighteenth centuries, a connection between experimental studies of opium and recommendations for its therapeutic use existed from the beginning, although they were not very stringent. A convenient starting point for examining the further development of this connection is Charles Alston's work of 1742 with its experiment-based rejection of the then current "rarefaction theory" of opium. For Alston the replacement of this, in his view erroneous theory by his concept of direct action on nerves was not only a matter of scientific correctness, but of therapeutical importance. The theory that opium rarefied the blood, he claimed, "might be of bad Consequence, and lead into dangerous Errors in Practice".204 After an overdose of opium, for example, venesection would be the measure of choice, if rarefaction of the blood was assumed. There had been reports in the literature, however, that the giving of a narcotic shortly after venesection had been lethal; and Alston was able to quote one case of his own experience in Edinburgh, in which an accidental intoxication with opium a day after liberal blood-letting had led to the patient's death. Moreover, argued Alston, how could opium be found useful in haemorrhages and smallpox, if it rarefied the blood (implying that bleeding should get worse and smallpox turn haemorrhagic on this supposition).205

204 Alston, op. cit., note 18 above, p. 171.

205 Ibid., pp. 161-162, 171. Note that in the seventeenth century Waldschmied (see above) had opposed the use of
Apart from his warning of combining venesection and opium, Alston professed his belief in the usual indications for the drug, such as violent pains, sleeplessness, excessive evacuations, "Choleras", "Dysenteries", various fevers, gravel, gout, cough, and consumption. He actually advocated a more liberal use of opium than his predecessors in this subject about half a century earlier, stating that opium was not absolutely contraindicated in infants, weak, plethoric, or aged persons, pregnant women, and malignant diseases.²⁰⁶

Alston's indications for opiates included also "Disorders of the Nerves", which strikes as following naturally from his theory of the drug's direct effect on the nervous system, though he did not further comment on this field of therapy. This link was fully elaborated, however, in the works of his Edinburgh colleague Robert Whytt, who - as shown above - strongly supported the "nerve theory" on the basis of his numerous animal experiments.

These had convinced Whytt that opium acted directly on nerves terminating at the site of application and that its effect spread quickly through the whole nervous system by way of "sympathy" or "general consent".²⁰⁷ On these grounds opium was one of the principal palliative medicines in "nervous and hysterical people", since it weakened the "sentient power of the nerves" and consequently diminished "those pains, irregular motions, or spasms which arise from any usual irritation". The other main palliatives - camphire, castor, musk, and asa foetida (gum-resin of the root of Ferula assafoetida) - were used as stimulants.²⁰⁸

opium in smallpox and haemorrhoidal and menstrual fluxes, though on different grounds.

²⁰⁶ Alston, op. cit., note 18 above, pp. 172, 176. Cf. the contraindications of Waldschmied, Berger and Fimmler, and Hoffmann and Muller, mentioned above.

²⁰⁷ Whytt, op. cit., note 126 above, p. 494.

Following this pharmacological scheme, Whytt recommended opium in fixed spasms, convulsions of muscles, of the stomach and intestines, in tetanus, hydrophobia (characterized by convulsions of the gullet and stomach), pains without inflammation, weakness after a too great flux of the menses, flatulent colics, spasmodic asthma, and "immoderate discharge of pale urine" in hysterical people (which he attributed to "an increased motion of the secretory vessels of the kidneys"). Together with asa foetida, opiates were further valued as a means to lessen "that restlessness, and those hot flushings and sick fits, which many hypochondriacal people are liable to".

Like Alston, and unlike earlier authors, Whytt was prepared to give opium in plethoric patients. He advised here previous blood-letting to avoid "bad consequences" and to make the treatment more effective, apparently ignoring Alston's warning of combining venesection and narcotics. Whytt was cautious, however, in giving opiates to "low-spirited" patients, arguing that their relief was only temporary and that they would become even more depressed, after the drug's effects had worn off. Likewise he warned of administering opium in large doses over a long time. Lessening the sensibility and vigour of the whole nervous system, it impaired not only physical strength, but also "the faculties of the mind".

As can be seen from the example of Whytt, the understanding of opium as an immediately neurotropic agent, based to a great extent on animal experimentation, opened up a whole field of indications under the heading of nervous disorders. Furthermore, restraints in the opium treatment of plethoric patients, motivated by the earlier belief in the drug's expanding effect on blood

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210 Ibid., p. 644.

211 Ibid.
and blood-vessels, seem to have loosened. In this way the change in pharmacological theory may have had some impact on opium therapy, though its traditional main indications were obviously kept (as can be seen from Alston).

This link between opium theory and therapy can be traced further in relevant authors around the turn of the nineteenth century. As described above, Michael Ward argued that opium primarily diminished the irritability and motility of the vessels and coats of the stomach, thus reducing gastro-intestinal secretion. Announcing that his new theory would be of "practical utility", he was able to give an example that must have been plausible at the time. In contemporary understanding the proximate cause of diabetes (mellitus and insipidus) was an increased secretion of gastric juice. Opium, reducing this secretion according to Ward's theory, was thus suggested by him as a promising antidiabetic, all the more because the drug's known diaphoretic effect would additionally reduce the patients' polyuria. To a much greater extent, however, the connection between pharmacological theory and therapeutic recommendations can be traced in the author who was so severely criticized by Ward, Samuel Crumpe.

It has been outlined in previous sections how Crumpe - sympathetic to Brown's doctrine - provided ample "proof" of the latter's view that opium was a stimulant, drawing his arguments both from animal and human trials, including self-experimentation. A close examination of Crumpe's discussion of the drug's therapeutic uses (which follows in his book of 1793 after the descriptions and interpretations of his experiments) reveals the impact of his theoretical understanding.

Crumpe saw two principal therapeutic uses of opium: as an anodyne (i.e. analgesic) by giving it "in large doses, and at considerable intervals", and as a stimulant by giving it "in moderate doses frequently repeated".

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While the former was the traditional use, the latter, new use had a number of consequences for the treatment of particular diseases. In continued fevers, for example, Crumpe distinguished between a first, inflammatory stage, in which opium as a stimulant would make the condition worse and was therefore contraindicated, and a second stage, characterized by debility, in which it showed very good effects exactly because of its stimulant power.\(^{214}\) As he pointed out, these considerations were in keeping with recent clinical observations of the Oxford professor and physician Martin Wall (1747-1824), who had reported about his successes with opium in treating so-called low fevers or typhus (i.e. "putrid" fevers, characterized by debility) and synochus (i.e. an initially inflammatory fever changing to the debility of typhus).\(^{213}\) Moreover, Crumpe distinguished between "acute" and "passive" inflammations. The former, e.g. pneumonia, gastritis, and acute rheumatism, resulted from an increase in excitement, and the use of opium as a stimulant medicine was therefore harmful in them. However, the latter, "passive" forms, including scrophulous inflammations, chronic rheumatism, and certain species of tonsillitis and ophthalmia, were seen as connected with debility and therefore benefitting greatly from the drug's stimulant effect.\(^{216}\)

\(^{213}\) Crumpe, op. cit., note 143 above, p. 218. For the antispasmodic treatment of tetanus large and often repeated opium doses were given; see e.g. T. Conyns Cole, 'Case of tetanus successfully treated by the exhibition of opium', Medical and Physical Journal, 1802, 7: 55-57.

\(^{214}\) Crumpe, op. cit., note 143 above, pp. 225-226.

\(^{215}\) See Martin Wall, The use of opium in low fevers, and in the synochus; illustrated by cases, 2nd edn, Oxford, Clarendon Press, 1786, which contains 17 case histories, including three unsuccessful treatments. Though inspired by the "Pupils of Dr. Brown" to try opium in those fevers, Wall regarded the drug traditionally as a cordial and sedative rather than as a stimulant. Cf. ibid., pp. xiii, 12, 17, 37, 60-61.

\(^{216}\) Crumpe, op. cit., note 143 above, pp. 248-263.
Along these lines a considerable list of other diseases or pathological conditions was discussed by Crumpe. His usual rationale was to identify their nature or stages in terms of the Brownian doctrine of excitement and then to outline the use of opium on the new supposition that it was a stimulant. Sometimes this would confirm the drug's traditional use (e.g. in intermittent fevers, going back to Galen), sometimes it would suggest change (e.g. contraindication for opium in measles, against Sydenham) or differentiation (e.g. in smallpox depending on their stage, partly confirming, partly departing from Sydenham). Acute inflammations had largely been a contraindication for the use of opium on the basis of the "rarefaction theory". But now with opium as a stimulant, and acute inflammation as a state of excessive excitement or sthenia, there were new reasons for not allowing its use.

Very similar efforts to redefine opium therapy can be found some years later in Germany as well. In 1803 the Braunschweig doctor Adolph Henke (1775-1843) devoted a lengthy article to this subject, which was published in the Archiv für medizinische Erfahrung. The editor of this journal, Ernst Horn (1774-1848), formerly a medical professor in Braunschweig and now in Wittenberg, dealt with the same topic in a monograph in the following year. Both of them expressed their belief in the stimulant power of opium, yet were anxious to correct not only traditional therapy, but also therapeutic "misuse" or "abuse" of the drug by "crude Brownians". Henke quoted

217 See ibid., pp. 247-248, 265-300, for his discussion of the use of opium in intermittent fevers, gout, smallpox, measles, haemorrhages, phthisis, dysentery, tetanus, chorea, epilepsy, asthma, pyrosis, colic, cholera, diarrhoea, hysteria, hydrophobia, mania, and syphilis.

218 Ibid., pp. 247-248, 269-272, 276-277.

219 Adolph Christian Heinrich Henke, 'Abhandlung über die Wirkungsart und klinische Anwendung des Mohnsaftes, mit Hinsicht auf die Meinungen der älteren, neueren und neuesten Zeit über diesen Gegenstand', Archiv für
Alexander von Humboldt's animal experiments as proof of the view that opium was a stimulant, apart from the clinical experience of well-known Brownian physicians, such as Joseph Frank (1771-1832) and Andreas Röschlaub (1768-1835). Both Henke and Horn generally warned of giving the drug in "hypersthenic" states, advocating simultaneously its circumspect, critical use in asthenic diseases.

Seen as a whole, these examples point to the conclusion that pharmacological experiments with opium and the theories drawn from them, or at least connected with them, had in fact a distinct and considerable influence on therapeutics in the later eighteenth and early nineteenth centuries. Though this may be said in general, contemporary resistance and opposition of doctors to the new pharmacological approach must not be overlooked, however.

The perhaps most influential critic was the Edinburgh medical practitioner George Young (1691-1757), whose Treatise on opium, founded upon practical observations (1753) was very frequently quoted in the second half of the eighteenth century and also published in a German translation in 1760. Young rejected the chemical investigation of drugs, arguing that they revealed their medicinal properties in the human body, not in the retort or still. Likewise he did not accept in

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221 Young, op. cit, note 68 above; idem, Abhandlung vom Opio, oder Mohnsaft, auf Praktische Bemerkungen gegründet. Aus dem Englischen übersetzt, Bayreuth, Verlag Johann Andreas Lübecks, 1760.
vitro experiments with opium or other drugs on freshly
drawn blood, because such trials failed to consider that
the circulating blood was continually changed by
absorption and secretion. Neither would intravenous
injections in living animals teach anything about the
therapeutic effects of substances, since even harmless
milk had acted as a deadly poison, when applied in this
way. And the classic method of examining drugs by tasting
and smelling them could give no more than some first
hints. For Young the only valid method of finding out
their medicinal qualities was to study their effects in
the treatment of particular diseases and to deduce from
this "some general rules". In other words, Young's
approach was that of therapeutic empiricism. Accordingly
he discussed in detail the use of opium in a great
variety of symptoms, diseases, and conditions on the
basis of his own practical and therapeutic experiences.
It has already been mentioned above that similarly
dissimissive remarks about experimental evidence were made
by the contemporary German authority on opium therapy,
the Breslau physician Balthasar Ludwig Tralles (1708-
1797).

The resistance of medical men to accept experimental
results, especially if they did not conform with
conventional practice, can further be illustrated with the
question of external, topical use of opium. Opium-
containing plasters and ointments had already been used

222 Young, op. cit., note 68 above, pp. 4-13.

223 See ibid., pp. 28-168, for his discussion of opium use
in cough and catarrh (including observations on himself),
diarrhoea and vomiting, diarrhoea in weaning-illness of
infants, rickets, and scrofula, in dysentery, tenesmus,
nephritis, pregnancy, labour-pains, milk-fever, weed,
lochia, flux of the menses, spasms, haemorrhoids,
rheumatism, operations in surgery, fractures, phthisis
pulmonalis, lowness of spirits, melancholia and mania,
great fatigue, hysterics and nervous disorders, nervous
asthma, rickets and scrofula, toothache, cancer, kidney
stone, lethary and other sleepy diseases, asthma senile,
peripneumonia notha of old men, internal inflammations,
smallpox, measles, salivation, and fevers.
Yet since the seventeenth century doubts had been voiced concerning the analgesic efficacy of such preparations. As Alston noted, Wedel had stated that he had been unable to observe a stupefying effect of externally applied opium. Following his general plan of examining open questions experimentally, Alston made a test on himself, putting opium plasters over night on his arm and little finger. Since neither stupefaction, nor inflammation, nor any other effect occurred, he concluded: "Hence... Opium is not, properly speaking, narcotick externally; and there may be Pains which it cannot remove as a Topick." Alexander Monro secundus took up the question as well, comparing the effects of internally and externally applied opium solutions on frogs. The same symptoms of poisoning appeared in both cases, yet more slowly after external application, and Monro concluded that "in us, from the greater proportional hardness and compactness of the skin, the difference will probably be still more considerable than in the frog". Accordingly he suggested that it was better to take opium inwardly, even if pain or convulsions were local. John Leigh (before 1755-after 1792), an American physician, who in the 1780s did some experimental work on opium in Edinburgh, repeated Alston's experiment with opium plasters on two men, also without any noticeable effect. Consequently he concluded "that the common received opinion respecting the operation of opium, externally applied, must be erroneously founded".

224 See Scarborough, op. cit, note 6 above.
225 Alston, op. cit., note 18 above, p. 159.
226 Ibid.
227 Ibid., note 18 above, pp. 303-306.
228 Ibid., p. 308.
229 John Leigh, An experimental inquiry into the properties of opium, and its effects on living subjects: with
essay of 1789, on the other hand, reported that he had produced polyuria, sleepiness and typical changes of the pulse by rubbing dogs with an opium ointment and that he had killed a new-born rabbit by immersing its body in a strong solution of the drug.230 Yet, four years later Crumpe confirmed Alston's and Leigh's negative findings on his own skin.231

There was thus a considerable body of experimental knowledge on the efficacy of externally applied opium. It suggested that, while such efficacy could be found in some animal trials, there was no experimental proof that opium acted as an analgesic, narcotic, or in any other way through human skin. But external opium therapy continued, it seems, unabated. Characteristically a reader of Leigh's study commented in the Critical Review in 1786:

Dr. Leigh found the external application of opium had little effect; yet, whoever has tried it in spasmodic pains of the side, in hysteric affections of the stomach, or... in a locked-jaw, will probably find it an useful remedy.232

True, Michael Ward, as mentioned above, apparently produced a sedating effect with opium embrocactions in two experiments on his house pupil.233 And - encouraged by Percival - he had reported cases of delirious patients, in which such external treatment had produced good effects, a finding also described shortly before Ward by the Florence physician Vincenzio Chiarugi (1759-1820).234
But such evidence was probably not much needed to sustain the old practice of external opium treatments. Hufeland, in his authoritative and influential manual of therapy Enchiridion medicum, first published in 1836, still advocated this form of application. Likewise it continued to be mentioned in medical dictionaries and encyclopedias of the first half of the nineteenth century.

A certain lack of recognition of experimental studies in medical practice can also be traced in some other responses to the above-mentioned work of John Leigh. On the basis of chemical analysis and pharmacological trials - the latter made on animals, healthy test persons (including self-experimentation), and patients - Leigh had shown among others that the resin of opium was its most efficacious component, that a mixture of this resin with liquorice was most easily dissolved in the stomach, and that previous taking of acids lessened the drug's effects. Though his study had earned him the prize of the Edinburgh Harveian Society for the year 1785, reviewers were not impressed at all.


236 See ibid., pp. 110-115.

237 The Harveian Society had been founded in 1782 by Andrew Duncan sen. (1744-1828). On the history of the Harveian Society and its prize essays see Sir D'Arcy Power (ed.),
The critic of the *Monthly Review* thought that Leigh had not made any new observations and that his experiments, though numerous, merely confirmed "the opinions concerning the properties and effects of this powerful medicine, which most writers on the *materia medica* have formerly delivered." The above-mentioned reader writing in the *Critical Review* even characterized Leigh's experiments as "few, trifling, and inconclusive". Variations in the drug's effects on "different constitutions, and on the same at different times" required many more trials. But even this would only be a very first, small step. Diseases, argued this critic, changed the pharmacological effects. Accordingly he rather referred to the experiences of "the more attentive practitioners" - no doubt with authors like Trailes in mind, whose work he had quoted earlier with approval.

A more positive critique appeared in the German review journal *Medizinische Bibliothek*, edited by the Göttingen professor of medicine Johann Friedrich Blumenbach (1752-1840). It acknowledged that Leigh's animal and human experiments were "always interesting", but they were

... on the whole, and particularly in comparison with the almost innumerable, divergent and often contradictory trials of his many predecessors, still not yet sufficient to draw certain general conclusions. If only someone could be found, who had both the wit and knowledge and the full time to perform a truly pragmatic revision of all these hitherto published trials, to repeat himself the most decisive of them, to compare them etc., so that this until now largely dead capital might pay some practical interest at last.

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In other words, the considerable experimental knowledge on opium, which had been amassed until the late eighteenth century, still had not led to reliable guidelines for therapeutic practice, even in the assessment of a rather sympathetic reviewer.\textsuperscript{241}

It is quite possible that it was Blumenbach himself who had written these lines, for in the same year, 1788, he initiated and put a prize question on the effects of opium (compared with those of wine) to the medical students of Göttingen. It was specified in the question that the drug's effects had to be studied in warm-blooded animals and that the use of amphibians was permitted only for comparative purposes.\textsuperscript{242} Obviously there was concern about the transferability of results to man. Siebold's essay was the only work that came in, yet it won the prize not for this reason alone. In their opinions the professors of the medical faculty said they were pleased with the variety of carefully performed experiments and the conclusions drawn from them.\textsuperscript{243} Blumenbach wrote a very friendly review in the \textit{Göttingische Anzeigen von gelehrtten Sachen}, in which he emphasized Siebold's findings on dose-effect relations and stated that the "useful practical conclusions and applications" included

\textsuperscript{241} A similar tendency can be identified in a review of Leigh's study in the \textit{Allgemeine deutsche Bibliothek}, supplement to vols 53-86 [no year], part I, pp. 395-396. Its author acknowledged Leigh's chemical and pharmacological work, writing that it could provide useful knowledge for some doctors, who either over- or underestimated the powers of opium. But he criticized that "clearly too little" had been said by Leigh on the therapeutic use of the drug.

\textsuperscript{242} Universitätsarchiv Göttingen, Medizinische Fakultät. Dekanats- und Promotionsvorgänge und -urkunden for the year 1788, letters by J. F. Blumenbach dated 3 May and 9 May 1788.

\textsuperscript{243} Ibid., Dekanats- und Promotionsvorgänge und -urkunden for the year 1789, including opinions on Siebold's essay by the Dean Heinrich August Wrisberg (2 May 1789) and professors Johann Andreas Murray (3 May 1789) and Johann Friedrich Gmelin (5 May 1789), with notes of agreement by professors Richter and Blumenbach.
in this essay gave an example of the "important, immediate beneficial use" that practical medicine gained from theoretical inquiries of this kind. What he probably meant was Siebold's experimentally substantiated two-stages theory of the effects of opium and their relation to dosage (see above). In fact the latter had advised on these grounds giving small doses of opium, if a patient's pulse and other vital functions had to be increased, and to administer a larger quantity, if sedation was required.

As has been noted above, Crumpe later made a similar distinction after his own experiments, and it was also adopted by the moderate Brownian Adolph Henke. On the other hand, Crumpe's animal and human experiments were simply dismissed in the Critical Review as adding "little to our knowledge", and with reference to his chemical experiments with the drug the reviewer reminded that there were "facts not to be learned in the laboratory, but which must be obvious to every attentive practitioner".

Taken together, the examples of Leigh's and Siebold's prize essays, and the contemporary comments made on them and other experimental studies, allow three conclusions. Firstly they show that the medical elite of the time, in Edinburgh and Göttingen, were well aware of the potential of practical, therapeutic conclusions from pharmacological experimentation and consequently encouraged such work; secondly, however, that there was a view that the requirements of medical practice had so far not been sufficiently fulfilled in most experimental studies. Blumenbach's praise of Siebold's work, which did

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244 Göttingische Anzeigen von gelehrten Sachen, 1790, 29: 281-283.

245 Siebold, op. cit., note 140 above, p. 11.

246 Henke, op. cit., note 219 above.

fulfill these requirements to some extent, indirectly confirms this point; and thirdly (if we consider also the question of external opium treatments) they indicate that practitioners resisted accepting experimental evidence, when it tended to discredit traditional therapeutic practice. Basic arguments against any investigation of drugs in animal and human experiments were the problems of transferability from animal to man and from healthy test persons to patients. If the opinion was adopted that diseases actually changed the effects of drugs, then therapeutic empiricism as exercised by George Young was in fact the only way forward in pharmocotherapy.

Seen as a whole, it may be said from the case of opium that the connection between experimental pharmacology and therapeutics was strengthened in the course of the eighteenth century. But it was still a new and not yet well established relationship: experimentalists were often very rash in their conclusions, and practitioners may well be seen as having been rightly sceptical about this new approach.

10. Opium as a habit-forming drug

In exploring the relations of pharmacology and therapeutic practice, one further aspect of opium needs to be discussed, which, though much less important to the eighteenth century than to our times, did not go unmentioned: the drug's potential to cause addiction.

Detailed knowledge about habitual, non-medicinal taking of opium in Oriental countries had been made available through the reports of travellers since the sixteenth century. Such travel works were very popular throughout the seventeenth and eighteenth centuries, as their multiple editions and translations indicate. They

See also Sonnedecker, op. cit., note 1 above.
were also quoted in the pharmacological literature of the time, particularly as several of the travellers were medical men. The astonishingly high doses of the drug consumed and tolerated by habituated opium-eaters were especially pointed out in the accounts of sixteenth-century travel authors, such as the Portuguese physician Garcia da Orta and the Dutchman Jan Huygen van Linschoten, who both wrote on India, and the Italian doctor Prosper Alpin, who reported on Egypt. This phenomenon was seen as remarkable, because it was an impressive example of habituation to a substance that was essentially considered a poison. As Alpin noted, Galen had already mentioned habituation with respect to another dangerous drug, hemlock. Apart from interest in particular properties of opium, such as its alleged aphrodisiac effect (discussed in detail by da Orta) and its euphoric and dream-inducing powers (a central topic in Alpin), the craving of opium-eaters and their dangerous symptoms when failing to obtain a new dose were regularly described. Such drug dependence was not yet seen as a disease in the modern sense, however, as it was

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249 For recent studies into this literary genre see Kenneth Parker, 'Telling tales: early modern English voyagers and the Cape of Good Hope', *The Seventeenth Century*, 1995, 10: 121-149.

250 For the scientific reception of travellers' reports on opium see e.g. Alston, op. cit., note 18 above, pp. 112-116, 122-123, 163-164; Siebold, op. cit., note 140 above, pp. 9, 37, 63; Crumpe, op. cit., note 143 above, pp. 177-179.


252 Ibid., p. 333.
since the nineteenth century. Yet it was circumscribed both in physiological and moral terms.

Alpin, for example, understood habituation to opium as a process in which human nature, being stronger than the poisonous drug, made the latter "in some way into a foodstuff". This explained for him also the crisis in which opium-takers fell, if they were deprived of the drug. "Slavery" (servitus) was the term he used for the phenomenon of addiction. Yet not dependence as such was considered harmful by the travel authors - such concern emerged only, as Claudia Wiesemann has recently shown, in the early nineteenth century. The problem was rather seen in the acute danger to life in withdrawal situations and especially in the drug's long-term toxicity. Da Orta and van Linschoten related that habitual opium-eaters appeared always sleepy and drowsy, and were known to become impotent. Alpin emphasized that they turned "comatose, lethargic, like frozen", and that their personality changed: becoming inconstant, they would say "yes" in one moment and "no" in the next, so that people were on their guard against making deals with them.

Concerns about the harm to physical and mental health through habitual consumption of the drug became more prominent in the descriptions of later travellers, such as the French merchant Jean Chardin (on Persia) in the late seventeenth century, and the physicians Engelbert Kaempfer (Persia and India), Alexander Russell (Turkey), and Jakob Reinegg (Persia), and the Baron François de Tott (Turkey) in the eighteenth century.

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253 Ibid., p. 334.

254 See Wiesemann, 'Die heimliche Krankheit', note 7 above.

255 Alpin, op. cit., note 104 above, vol. 2, p. 341. See also Waldschmied, above.

Their accounts now went beyond the scientific or medical interest, revealing also their personal attitude to opium-eaters. It reached from pity in Chardin and de Tott to outright disgust and moral condemnation in Reinegg. Russell described them as "debauchees", who looked "old and besotted, like such as in Europe have ruined their constitutions by hard drinking". Kaempfer depicted them as emaciated, weakened, with gloomy and stupid minds, and he had been outraged by Indians who committed suicide by taking opium and then running amok. Reinegg described with abhorrence the initiation of a young man to habitual opium-eating as well as the physical and moral decline of the habituated. On the other hand it was acknowledged that some opium-takers, who suffered from their condition, made efforts to break their habit. Alpin had already observed that they tried to substitute the drug with plenty of seasoned Cretan wine, and Kaempfer reported that they had often presented themselves to him and offered a high reward, if he could cure their craving without endangering their lives or damaging their health. Reinegg claimed to have met opium-eaters "who had freed themselves from this plague by the frequent use of vinegar" and mentioned others who substituted the drug by the smoking of hashish.

This knowledge conveyed with the travel literature, about opium-induced euphoria and dreams, habituation to and tolerance of the drug, about dependence, withdrawal


259 Reinegg, op. cit., note 73 above, pp. 373-380.


261 Reinegg, op. cit., note 73 above, pp. 380-381.
symptoms, and long-term effects, has to be considered as a background to descriptions also of Western opium-eaters, that were given in medical works since the beginning of the eighteenth century. Detailed information both about the effects of habitual opium consumption and the acute symptoms in withdrawal was given for example by John Jones in his *Mysteries of opium reveal'd*. He not only listed effects or symptoms, but gave also pathophysiological explanations for them, based on his general understanding of opium as a substance causing a "pleasant Sensation" and general relaxation. Thus the physical weakness of chronic opium-users was seen as contracted by "habitual over-relaxing" of their bodily parts, and their lacking in drive caused by "habitual Pleasure, Comfort, Promptitude, and Euphory" which made the sensitive soul (i.e. the anima sensitiva in the Aristotelian sense) "lazy, listless, and averse to all Actions". Jones compared the latter phenomenon with a man who is used to dance to excellent music and is then required to perform without any music at all. Likewise, because the sensitive soul was deprived of its usual comfort and pleasure in the state of withdrawal, intolerable distress, anxiety, and depression would follow. In addition pain, contractions, and diarrhoea set in, perhaps leading to death, because the soul was no longer diverted through the opium-induced "pleasant Sensation" from the perception of irritations. Wine was recommended by Jones as a substitute to get free of the habit, combined with a very slow, gradual reduction of the daily opium dose.

It is not entirely clear how much Jones relied on the reports of the Orient travellers and to which extent

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262 See above.
263 *Jones, op. cit.*, note 63 above, pp. 31, 245-246.
he drew upon his knowledge of European opium-takers and possibly his own, personal experience with the drug. Yet he matched the travellers' usual accounts of Oriental opium-eaters tolerating high doses with an extreme example of his own, writing he had been told of someone in Banbury (Oxfordshire), who was thought to take the enormous dose of two ounces per day. Moreover he referred to several other English people who consumed daily doses between two and six drachms, some up to one ounce. It should be noted, however, that Jones did not mention such cases to point out the extent of the practice of opium-eating in England in his time. His interest in them had rather to do with physiology. He quoted these cases against the common opinion that Oriental people could generally stand larger doses of the drug, due to differences in climate and their physical nature. In Jones' view the opposite was true: Orientals, living in hot climates and having "soft and flaccid Flesh", actually tolerated less of the relaxing opium than "firm Fleshed Persons" in the cold north.  

This is not to say, however, that Jones had no moral concerns about the English opium-eaters. An indicator is his remark that he could give the names of these persons, but abstained from doing so, having "Reasons to the contrary". In fact Jones, though fascinated by the drug's powers, denounced its abuse in religious and moral terms, comparing it with immoderate drinking:

As an Excessive Dose of Opium is Intemperance for one time, so a long and lavish Use of it is an habitual Intemperance for a long time; therefore if you could not rationally expect good Effects in that Case, any more than from the best Wine taken suddenly in a vast Quantity, it follows, that you cannot expect good Effects from an habitual Intemperate Taking of it, any more than from a long and lavish Drinking of Wine... There is nothing so good, whereof an intemperate Use is not mischievous, God having so ordered it to deter from, and punish Intemperance, and the Abuse of his Creatures;

266 Ibid., pp. 32-33, 307-308.

267 Ibid., p. 307.
Therefore ill Effects are not always to be imputed to the viciousness of the Things used, but frequently of the Person that imprudently uses them.  

Despite this condemnation, it should be noted that Jones, like the travellers to the Orient, did not criticize habitual use and ensuing dependence as such, but the self-inflicted physical and mental harm through the misuse of a substance.

How Western people became habituated to the drug, and some further hints on moral and social responses to this, can be inferred from a number of case histories, which were published by George Young in his treatise on opium in the middle of the eighteenth century. In all cases, patients got accustomed to the drug through its therapeutic use, for instance as an antitussive in pulmonary phthisis, as an analgesic in cancer, or as a stimulant in states of weakness and melancholia. Young described habituation, tolerance, and dependence (becoming "slaves" to opium) rather as interesting pharmacological phenomena and therapeutic problems than as matters of moral or social concern. There was in fact in Young's time a simple mechanical explanation for the development of tolerance to opium and the need for increasing doses. As Etienne-François Geoffroy had speculated in his treatise on the materia medica, opium, by thinning the blood and inducing excessive sweating, eventually diminished the mass of blood. Therefore increasingly higher doses were necessary to reach the same degree of fluidity of the blood, which would (according to the rarefaction theory) distend the arteries and - via compression of neighbouring nerves - produce sleep. Though Young did not mention this aspect of the rarefaction theory, it is quite likely that he

268 Ibid., p. 245.

269 Young, op. cit., note 68 above, pp. 77-78, 97-105, 124-126.

knew of it, since he quoted Geoffroy in another context.\footnote{Young, op. cit., note 68 above, pp. 4-5, where he criticizes Geoffrey's approach of studying the properties of opium and other drugs with chemical analysis.}

Young was also aware that the habitual use of opium by patients with advanced phthisis or with breast cancer probably shortened their remaining lifespan. He pointed out that the drug, though the only effective palliative in such cases, was actually harmful in those conditions.\footnote{Ibid., pp. 94-103, 124-129.}

The moral and social dimension of the use of opium nevertheless becomes apparent from some brief remarks in Young's case histories. In part they stemmed from the patients themselves. In one case a woman, who had suffered from menorrhagia, weakness, and "a desponding mind", had benefited greatly from taking the drug. Yet, as Young noted:

All her friends advised her to lay aside the use of opium, lest it should by habit become necessary; but she whispered me privately, that she would rather lay aside her friends.\footnote{Ibid., p. 77.}

Even in a patient with incurable consumption:

Some advised her not to indulge herself in the use of opium. She answered, that she would take it, tho' she was certain it would hasten her death...\footnote{Ibid., p. 102.}

The former case may be seen as pointing towards some actual fear of drug dependence as such, which would be unusual for the time. Yet the friends' concerns might well have simply been about the financial burden imposed through habitual opium-eating. The latter case appears to indicate concern about the abuse of a drug leading to physical harm and an early death - which would be in line
with the comments of Jones and some of the travel authors.

Young's own position shines through in his discussion of the use of opium as a cough medicine and hypnotic in patients with phthisis. The poor, who could not afford to pay for the "sleepy draughts", died "with ease both of body and mind", whereas the "people of rank" became "slaves" to the medicine, got confused, lost their memory, and died "delirious". The common ideal to meet one's Creator with a clear and prepared mind may have influenced this observation of Young. But also in a secular sense, the fear to lose one's rationality could be a reason to abstain from opium even in painful and terminal conditions.

This worry was clearly expressed by Albrecht von Haller, who — as mentioned above — habitually took opium during his own final illness and published his personal experience with it. Initially he had been very reluctant to make use of the drug, fearing that his "intellectual power" might suffer. He referred to "the example of the Turks" and the "terrible weakness of mind through the use of opium, that was imposed on the Hindostan princes instead of death". Only after his correspondent Sir John Pringle had assured him that in England such a damage of intellect had not been described, Haller was ready to commence the regular taking of opium. Yet even then he was anxious to emphasize that it had so far not damaged his mental capacities, and that he would certainly give up the drug, if it showed this effect on him only in the

275 Ibid., pp. 98-99.

276 Haller, op. cit., note 170 above, p. 11. Haller's source here is not known, yet Chardin mentioned an infusion made from poppy seeds, hempseed, and nux vomica, and commented that the "Indians use it with their State-Criminals, when they wont take their Life away, in order to deprive them of their Senses; and with the King's Children, when they intend to Incapacitate them for Reigning." Cf. Chardin, op. cit., note 256 above, pp. 245-246.
slightest degree. Again, Haller did not show concern about the habitual taking of the drug as such, as long as no harmful effects were noted from it. But for a man of the Enlightenment, the "age of reason", the prospect of risking a loss of rationality through opium must have been a serious threat indeed.

As Claudia Wiesemann has recently argued, the modern concept of addiction emerged only at the end of the eighteenth and in the early nineteenth centuries, in connection with the debate on Brown's system. Since both opium and alcohol were understood as stimulants according to Brunonian doctrine, habitual consumers of these substances were seen as persons getting accustomed to stimuli, who fell into a state of weakness (debility) when deprived of their drug. The regular taking of stimulants allowed them for some time a state of "relative" or "deceptive health", before harm, caused by exhaustion of the body's excitability, became obvious.

This new understanding of habituation and dependancy was reflected both in the contemporary literature on the consumption of alcohol and pharmacology. The Erlangen doctor Carl Christian Heinrich Marc (1771-1841), for example, in a treatise on the effects of poisons based on Brunonian doctrine, explained the phenomenon of drug tolerance in the new way. Patients suffering from chronic diseases, who were treated with stimulants such as opium, benefited from this only for some time, noted Marc, before therapy became ineffective and they got worse again. The reason for this was that the patients' excitability became "blunt" through a uniform stimulus

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278 See also Wiesemann, 'Die heimliche Krankheit', note 7 above, pp. 107-109.
279 Cf. ibid., pp. 112-123.
280 Wiesemann, ibid., quotes among others Christoph Wilhelm Hufeland's Ueber die Vergiftung durch Branntwein (1802) and Thomas Trotter's Essay on drunkennes (1804).
over a long time, and that the then necessary higher doses eventually exhausted it.\footnote{Carl Christian Heinrich Marc, \textit{Allgemeine Bemerkungen über die Gifte und ihre Wirkungen im menschlichen Körper. Nach Brownischem Systeme dargestellt}, Erlangen, Johann Jacob Palm, 1795, p. 271.} Ernst Horn, as mentioned above a moderate Brownian, stressed the necessity of stimulation for habituated opium-eaters in order to enable themselves to cope with even simple demands of daily life. He mentioned from his own experience "not a few" medical colleagues, a noblewoman, and "several young men studying literature", who had come to this state, and he warned that the latter ruined their prospects in life through this "perpetual and excessive irritation and excitement of the vital flame".\footnote{Horn, op. cit., note 219 above, pp. 60-63.} As is well-known, the period's icon of the young, opium-consuming intellectual became the writer Thomas De Quincey (1785-1859). He actually started his life-long habit in London in the same year, 1804, in which Horn's work came out in Germany, and he later also characterized the drug in Brownian terms as a stimulant.\footnote{Thomas De Quincey, \textit{Confessions of an English opium-eater. Now first carefully revised by the author, and greatly enlarged}, 2nd edn, Edinburgh and London, James Hogg and R. Groombridge & Sons, 1856, p. 203: "... the primary effects of opium are always, and in the highest degree, to excite and stimulate the system." The \textit{Confessions} were first published in a shorter version in 1821, in the \textit{London Magazine}. On De Quincey's experience with the drug and its relevance for his literary work see Hayter, op. cit., note 3 above, and Lindop, op. cit., note 3 above.}

Comparisons between the effects of opium and alcohol (wine) had been for long a traditional topic of writers on the drug. Yet it was only in 1829 that Christoph Wilhelm Hufeland, who had strongly argued against the spreading consumption of spirits at the beginning of the century, first compared alcoholism ("Trunksucht") directly with addiction to opium, actually coining the German term for the latter: "Opiumsucht". Though he was
known as a critic of Brunonian therapeutics, Hufeland nevertheless used the idea of stimulation in this by now classic description:

Spoiling. - In chronic illness one can at last get so accustomed to the use of opium that it becomes a daily need, also if pains have been removed, in order to lift the general feeling to the point of well-being, of liveliness, of physical and mental usefulness, - just in the same way as the drinker of spirits finally gets accustomed to spirits and they become an indispensable need for him - but also with the same consequence, the need for ever higher doses, - addiction to opium - completely in analogy to addiction to alcohol and its effects, ever increasing weakening of the nerves, trembling, destruction of the digestive and reproductive powers, in the end Delirium tremens, bluntness of the senses and the mind, haemorrhages, dissolution of the blood, Tabes. 284

Opium addiction was thus eventually characterized as a disease of its own, as had been alcoholism a decade earlier by the Moscow physician Constantin von Brühl-Cramer. 285

As can be seen from this brief view on the early knowledge about the addictive property of opium, contemporary pharmacological theories were occasionally applied in order to understand the clinical phenomena. Jones' concept of the opium-induced "pleasant sensation" offered some understanding of habituation, of withdrawal symptoms, and of physical and mental changes in the habituated. The "rarefaction theory" of opium provided an


explanation for the need of ever higher doses to produce the desired effects. And Brownian ideas about opium as a stimulant eventually formed the matrix for the modern understanding of addiction as a disease. Yet, on the whole the impact of the large amount of experiment-based pharmacological knowledge, as described in detail above, was small. It may also seem striking at first sight that in the seventeenth and eighteenth centuries apparently no animal experiments were carried out with opium to study habituation and tolerance any further. Like most experiments with drugs and poisons in this period, opium was given in "acute trials" only. The drug was occasionally applied to the same experimental animal two or three times, yet this was done out of convenience for the researcher, or to increase the dose to the point of intoxication, not in order to study long-term effects.

The method of chronic drug testing as such, however, was not unknown in the eighteenth century. The London physician Browne Langrish, for example, had used it in the first half of the century in his study of lithontriptic solutions on dogs in order to estimate the effect of repeated injections into the bladder.²⁸⁶ Likewise he had made chronic trials with cherry laurel on dogs and a horse, giving it orally in small, yet slowly increasing doses for periods from one to over four months. His interest in these trials, however, had rather been in the drug's effects on the blood and circulation than in the phenomenon of habituation.²⁸⁷ Also in the well-known animal and self-experiments of the Viennese clinician Anton Störck (1731-1803) poisonous plants, such as hemlock and hyoscyamus, were tested in small doses for longer periods. Yet also here the potential for intoxication was the main concern - in view of possible therapeutic uses.²⁸⁸

²⁸⁶ See above, part A.

Habituation and tolerance became quite familiar phenomena, as has been shown above, both from reports on Oriental opium-eaters and from accounts of opium use by Western patients. But they did not constitute a specific field of experimental investigation. There were no attempts in the eighteenth century to produce addiction to the drug in animals, for instance. Only one study, from the beginning of the nineteenth century, has been found, in which the effects of longer periods of taking opium were described on the basis of self-experimentation. F. Weber, a young surgeon at the Foreign General Hospital at Lymington (Hantshire), mentioned his own tolerance to opium pills, which he constantly carried with him and took "at all times". He also described withdrawal symptoms on sudden discontinuation, such as exhaustion, stupor, lassitude, and violent pain in the knee and hip joints. Weber matched these self-observations with similar phenomena in hospital patients, who had been used to taking the drug for a long time. Yet, his observations in this area were only a small part of a general study of the effects of opium. Dealing mainly with dose-effect relations within a Brownian framework, it was not dissimilar to Crumpe's work. Indeed Weber's account may well have been provoked by Ward's critique of Crumpe, since it was published only a year later in the same periodical, the London Medical and Physical Journal.

Likewise, eighteenth-century experimental studies on opium displayed little interest in its psychopharmacological aspects. Certainly, the psychological effects of the drug were well-known from the accounts of the Oriental travellers. Moreover, John Jones had eulogized them in his book. Opium, he wrote,

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288 See Winau, 'Experimentelle Pharmakologie', General Introduction above, note 4, pp. 74-82.

causes a brisk, gay and good Humour... Promptitude, Serenity, Alacrity, and Expediteness in Dispatching and Managing Business... Assurance, Ovation of the Spirits, Courage, Contempt of Danger, and Magnanimity... prevents and takes away Grief, Fear, Anxieties, Peevishness, Fretfulness... causes Euphory, or easie undergoing all Labour, Journeys, &c.... lulls, soothes, and (as it were) charms the Mind with Satisfaction, Acquiescence, Contentation, Equanimity, &c.  

George Young, too, had noted such euphoric effects in some of his case histories. But, before De Quincey's (non-medical) introspection, self-observations by doctors included psychological effects only briefly, among a lot of physical phenomena. Moyse Charas in the late seventeenth century, for example, mentioned a strong tranquilizing effect and insomnia, yet his main interest was in the gastro-intestinal effects of the drug. Nearly a century later, Albrecht von Haller described this tranquillity as well, which, as he observed, was combined with cheerfulness and a strong motivation to work. But again, this was not his central scientific interest, which lay rather, as has been outlined above, in the effects on heart action and irritability. Psychopharmacological aspects were still mentioned rather briefly, when medical men took opium in deliberate self-experiments to explore its effects. John Leigh, for instance, in his prize-winning essay of 1786, quoted a report of such an experiment by his medical friend James Ramsay of Virginia. Similar to Haller, Ramsay first noted an enlivening effect, that enabled him to continue studying late at night but was followed by a state of exhilaration and carelessness. Eventually forced through vertigo to go to bed, he lay "almost motionless" for

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290 Jones, op. cit., note 63 above, pp. 21-22.
291 Young, op. cit., note 68 above, pp. 101-105
292 See Salomon-Bayet, op. cit., note 10 above.
293 Haller, op. cit., note 170 above, pp. 11-15.
several hours, while his "imagination was ... distressed by the appearances of horrid images". The author did not say, however, what these images showed, nor did he try to give a pharmacological explanation. Likewise Weber, who was very detailed in his account of the physical effects of the drug, just spoke of "a strange chaos of happy and disagreeable visions", among many other symptoms. Though exaggerating, De Quincey was therefore principally right when he criticized in his Confessions that, concerning opium, "most ... even of those who have written professionally on the materia medica, make it evident, by the horror they express of it, that their experimental knowledge of its action is none at all." Reasons for what may now appear as a relative lack of interest in, or even neglect of, the psychological effects and the addictive property of opium, can be found in contemporary modes of the drug's use, however. It was widely employed, it seems, for rather short periods as a medicine for acute symptoms, especially in strong pains and excessive diarrhoea. A danger of dependence developed mostly in cases of serious chronic disease, such as pulmonary phthisis and breast cancer, where opium was taken continuously as a palliative. Yet here prognosis was bleak anyway. The main concerns about opium in the seventeenth and eighteenth centuries were its potential for acute, dangerous intoxication through overdosage, and the risk of making symptoms worse, if it had been given in the wrong condition. Experimental research in this period, focusing on the intake of the substance into the body and its acute effects, reflected these concerns. For eighteenth-century authors, wide-spread habitual use of opium in the West was at most a conceivable danger. It

294 Leigh, op. cit., note 229 above, pp. 113-117.
296 De Quincey, op. cit., note 283 above, pp. 199-200.
297 See the cases of Young, above.
was only occasionally envisaged, for example by the Greenwich apothecary John Awsiter, in an essay on the toxicology of opium in 1763 (later quoted by De Quincey).\(^{298}\) Most contemporaries, it seems, regarded non-medicinal opium-eating as a specific Oriental problem that had its parallel in alcohol consumption in the Occident.

As for the psychic effects, it has been noted above that Alston and Whytt recommended opium in various "nervous disorders"; and Young actually reported cases in which he had tried it in "melancholia". But on the whole opium does not seem to have been much employed in mental illness during the eighteenth century. Young himself confessed his disappointment about the effectiveness of the drug in melancholia, and mentioned that it had "failed in other peoples hands" as well.\(^{299}\) The so-called "opium cures" for mental patients are largely a phenomenon of the nineteenth century.\(^{300}\) Considering this, the small psychopharmacological interest in the previous century becomes understandable. In addition, the lack of a methodological basis may have played a role here. Whereas eighteenth-century, vivisecional physiology provided such a basis for "somatic" experimentation with opium, there were no specific tools known yet to examine the drug's psychological effects. Only gradually the very basic method of taking a defined dose of the drug, careful self-observation and recording of symptoms was used in a more systematic manner. An early example for

\(^{298}\) John Awsiter, *An essay on the effects of opium. Considered as a poison. With the most rational method of cure, deduced from experience*, London, G. Kearly, 1763, p. 5: "... there are many Properties in it [i.e. opium], if universally known, that would habituate the Use, and make it more in Request with us than the Turks themselves, the Result of which Knowledge must prove a general Misfortune." See also De Quincey, op. cit., note 283 above, p. viii.

\(^{299}\) Young, op. cit., note 68 above, pp. 106-108.

\(^{300}\) See Weber, op. cit., note 6 above.
this approach is the work of the Grenoble physician Pierre-Alexandre Charvet (1799-1879), whose Paris dissertation of 1826, *De l'action comparée de l'opium, et de ses principes constituants sur l'économie animale*, has recently been suggested to have been "the first book on modern experimental psychopharmacology". Other historians of the subject have located its scientific beginnings only in Emil Kraepelin's experimental work of 1892 on "the influencing of simple psychological processes through some medicines". The substances studied in this way by Kraepelin were, among others, alcohol, paraldehyde, ether, amyl nitrite, and morphine.

It was in fact only after the isolation of morphine in the early nineteenth century, and its gradual introduction both as a medicine and a "recreational" drug, that habituation, tolerance, and opiate addiction became fields of scientific investigation. Hufeland's notion of "Opiumsucht" - published more than twenty years after Sertürner's discovery of "morphium", yet also about twenty years before subcutaneous injections of morphine and other substances were introduced - was apparently an early perception without much immediate impact. Only after Eduard Levinstein's clinical work on "morbid craving" for morphium had set the scene in the late 1870s, drug tolerance and withdrawal were studied experimentally, including trials with "dependent" animals.

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301 Siegel and Hirschman, op. cit., note 11 above.


304 See Kramer, op. cit., note 11 above.
11. The identification of morphine

For the present historical study, the isolation of morphine, and subsequently of other opium alkaloids, can form an end. Experimental work increasingly concentrated rather on the properties of these active constituents than on the whole drug. Yet in therapeutics the use of opium as a whole continued through the first half of the nineteenth century and beyond. Conservative practitioners, most notably Hufeland, argued that the whole drug was more than its parts, and thus therapeutically more valuable. But after the introduction of hypodermic injection in the 1850s, opium started to be replaced by morphine, at least as an analgesic. Though in psychiatry "cures" with Tinctura opii simplex kept their place into the 1950s (when they were quickly abandoned for the new tricyclic antidepressants), indications for opium were eventually narrowed down to its present, very limited medical use as a means to check hyperperistalsis.

Seen in this way, Sertürner's discovery of morphine marked a new departure, not only in the history of opium, but for the study of plant drugs and poisons in general. In 1817, François Magendie and Pierre Joseph Pelletier isolated emetine from ipecacuanha roots, and Pierre Robiquet extracted narcotine from opium. In 1818 Pelletier and Joseph Bienaimé Caventou found strychnine as the active principle of St. Ignatius beans and nux vomica. In the same year brucine was isolated from spurious angostura bark and veratrine from a species related to white hellebore. Codeine, the second therapeutically important opium alkaloid, was isolated in

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305 See ibid.
307 Weber, op. cit., note 6 above; Haller Jr., op. cit., note 6 above.
1832, followed by thebaine in 1833 and papaverine in 1848.  

In retrospect the isolation of morphine by the young Paderborn apothecary Friedrich Wilhelm Sertürner (1783-1841), first published by him in 1805 and with important additions in 1817, is often regarded as a "breakthrough" in the history of plant chemistry and pharmacology, that opened up the study of alkaloids. Though this view is on the whole right, it is more accurate to see Sertürner's contribution also as one more small, yet decisive step in the long search for the "true" nature of opium, which went back - as has been shown in this chapter - to the seventeenth century.

In 1804, the Berlin chemist Adolph Ferdinand Gehlen (1775-1815) published a review article on the "present state" of knowledge of opium in the Medical and Physical Journal. The problems which he identified were in principle not much different from those pointed out by Charles Alston more than sixty years earlier. It was still not sufficiently clear whether the Asian product "opium" was really the inspissated juice obtained by incisions of poppy capsules. Recent analyses by the French chemist Dubuc, confirmed by the Arnstadt apothecary Kuehn, had again raised doubts on this question. They suggested that the pure juice was mixed with a fermented mass of squeezed poppy heads and leaves.

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Furthermore, opium had turned out to be a "very compound substance" - a fact, which had made it increasingly difficult to answer the old question of its active principle. According to Gehlen's stock-taking, the drug contained a "volatile narcotic principle", extractive matter, mucilage, resin, oily matter, "a crystalline substance", a kind of gluten, kaoutshouc, and diverse vegetable particles. The quantitative proportions of these components appeared to vary, and it was not known whether all of them were actually present in all "sorts of opium".30

Opinions were divided as to what was the true "narcotic" principle. The "volatile narcotic principle", which was inferred from the drug's smell, had recently been challenged by the German apothecary Buchholz, because concentrated distilled water of opium had produced no deleterious effects on a dog. Earlier in the eighteenth century Caspar Neumann (1683-1737) of Berlin and Friedrich Hoffmann had held the view that an oily, non-volatile substance obtained from opium was its narcotic constituent, since it killed dogs already in doses of a few grains. But the French chemist Josse, on the basis of his new analyses, had suggested a glutinous matter as the carrier of the drug's narcotic and excitant qualities.31 The latest contribution in this field had been made in 1803 by the Paris pharmacist Charles Louis Derosne (1780-1846). By way of alcohol extraction from pure opium, addition of alkalies, and repeated washings, he had obtained a white, crystalline substance, later known as the "sel de Derosne" or Derosne's salt. It showed an alkaline reaction and could easily be dissolved in acids. These properties were, in Derosne's view, apt to explain why acids, especially vinegar, were known to


act as an "antidote" in opium poisoning. In fact he referred to experiments, in which he had "relieved and cured" dogs after six to eighteen grains of opium by giving them vinegar. This, however, was directly contrary to Jossé's opinion, who thought that acids, by dissolving the active components of the drug, made intoxications with opium even worse.

Though Sertürner, in a postscript to his first relevant publication of 1805, claimed not yet to have known about Derosne's work, his efforts have to be seen as part of those renewed efforts in the analysis of opium and the ongoing search for the "narcotic principle". He had first isolated an acid from opium, which he called "Mohnsäure" or "Opiumsäure". While this opium acid (meconic acid), like any other acid, coloured both blue Litmus paper and the blue tincture of violets red, an aqueous extract of opium showed a weaker reaction with the former and merely discoloured the latter. From this difference in the reaction with blue plant pigments Sertürner concluded "the presence of another substance" in the extract. In fact a greyish precipitate appeared,

312 Cf. Gehlen, op. cit., note 310 above, pp. 118-119. See also Krömeke, op. cit., note 309 above, pp. 5-6.

313 Gehlen, op. cit., note 310 above, pp. 43, 119. On acids, especially vinegar, as antidotes to opium and the treatment of opium poisoning in general see Awsiter, op. cit., note 298 above, pp. 38-52. See also idem, 'An account of the effects of opium as a poison; with the method of cure; and proper directions what to do, when medical assistance is not at hand', Gentleman's Magazine, 1763, 33: 51-54.


when he added kali or ammonia to the aqueous extract. This precipitate could be completely dissolved by heating it in concentrated acetic acid and made to fall out again by adding ammonia. Earlier researchers (e.g. Leigh, above) had assumed that the active principle was in the resin of opium, but Sertürner doubted this, since resin hardly dissolved in water and yet aqueous extracts of the drug were known to be effective. Instead he presumed that his greyish precipitate, obtained from an aqueous extract, was the substance which contained this "effective factor". Testing the substance on a dog, he actually found that the animal showed extreme sleepiness, followed by vomiting, trembling and convulsive movements. After various chemical procedures he subsequently obtained from this substance pure crystals. Given to a dog, they produced no vomiting, but to a greater degree sleepiness, trembling, and convulsions, ending in the animal's death. By contrast, when the precipitate was removed from the opium extract by way of filtration, and the remaining fluid given to a dog, those symptoms could not be observed. On this basis Sertürner was convinced that the narcotic effect of opium came from its content of the "crystallizable body" that he had isolated and which he named "sleep-producing substance" or "Principium somniferum".316

The young apothecary's conclusions were far-reaching. Not only would his "sleep-producing substance" act in the same way as, if not better than, the whole drug, doctors would at last be freed of the problem of variations in quality and strength, that they had always had to cope with in using the customary opium preparations. Moreover, Sertürner saw a new field opening up for the "practical chemist", who could now hope to isolate similarly the active substances from other plants and vegetable poisons.317 As outlined above, these

316 Cf. Sertürner, op. cit., note 314 above.
317 Ibid., pp. 55-56.
visionary statements of 1805 in the long run actually
became true, but for several years Sertürner's work was
little acknowledged. Johann Bartholomä Trommsdorf (1770-
1837), the editor of the *Journal der Pharmacie*, in which
Sertürner's article had been published, cautioned in a
note "not yet to regard the files as closed" in this
matter and suggested repeating the experiments with
larger quantities.\(^{318}\) Other researchers initially had
difficulties in duplicating Sertürner's results.\(^{319}\)

Naturally the question of priority arose in view of
Derosne's salt. There was, however, as Sertürner had
already noted in the postscript to his article of 1805,
an important difference in the understanding of the
alkaline quality of the crystalline substances that they
had both isolated. Derosne believed that it came from a
small amount of mineral alkali, added in the process of
isolation, which was inseparably bound to the salt.
Sertürner asserted that it was a property of the newly
found substance itself.\(^{320}\) It was actually this
interpretation in which the German apothecary was proved
"right" (plant alkaloids), and accordingly it was "pour
avoir reconnu la nature alkaline de la morphine" that he
was eventually awarded the Montyon prize of the Institut
de France in 1831.\(^{321}\)

Meanwhile Sertürner's nowadays famous morphine
article of 1817 had attracted wide attention to his
findings. He had further purified his crystalline
substance and renamed it "morphium" (after the god of
sleep, Morpheus). Here he described also the step from
animal to self- and human experimentation with the new

\(^{318}\) Ibid., p. 57.

\(^{319}\) F. W. Sertürner, 'Ueber das Opium und dessen
krystallisirbare Substanz', *Journal der Pharmacie*, 1811,
20, republ. in Krömeke, op. cit., note 309 above, pp. 58-
60.

\(^{320}\) Sertürner, op. cit., note 314 above, pp. 56-57.

\(^{321}\) Krömeke, op. cit., note 309 above, p. 19.
substance, that is often mentioned in the historiography of pharmacology and medicine in general. As a reason for this step he gave his opinion that "experiments with animals lead to no real results", probably alluding to the then widely held view that pharmacological findings from animal studies could not immediately be applied to the human body.

Besides Sertiirner, three young men - none of them older than 17 years - swallowed initially half a grain (ca. 30 mg) of morphium. Blushing, reddening of the eyes, and a sense of general stimulation were the first symptoms. Having taken 30 minutes later a further half grain, nausea and "dumb headache with a stunned feeling" followed. A third half grain, taken only 15 minutes later, brought quickly more intense symptoms: stomach pains and a heavily dazed state, bordering on faintings. Sertiirner remembered that he fell into a "dreamlike state", feeling twitches in his arms and legs accompanying his pulse beats. Fearing a serious intoxication, he gave vinegar, the known "antidote", to his three test persons, and took it himself. After vehement and lasting vomiting (which was then treated with magnesium carbonate) and "heavy sleep" in the night, all four recovered, though they continued to suffer from daze, headache and abdominal pains, constipation and loss of appetite over the next few days.


Sertiirner, op. cit., note 322 above, p. 68. On the problem of transferability in contemporary pharmacology see Maehle, Kritik, General Introduction above, note 16, pp. 37-44.

Sertiirner, op. cit., note 322 above, pp. 68-69.
Sertürner concluded from this experience that morphium acted as a "strong poison", but simultaneously he assumed that it was the component of opium, on which its important medical effects rested. In fact he was able to report from his own experience that severe toothache, which did not respond to opium, was immediately removed by taking a solution of morphium in alcohol.\footnote{Ibid., pp. 69-70. See also Andreas-Holger Maehle, 'Neue Mittel der Schmerzbekämpfung. Vom Morphium zur Narkose', in Heinz Schott (ed.), Meilensteine der Medizin, Dortmund, Harenberg Verlag, 1996, pp. 297-303.}

As indicated above, the discovery of morphine opened new paths of research on opium, as well as of the drug's use, in the nineteenth and twentieth centuries, on which the reader may consult the secondary literature quoted at the beginning of this survey. One issue, however, which becomes particularly apparent in Sertürner's rather dramatic account of his human trials remains to be discussed: the ethical implications of such experimental investigations.

12. Ethical aspects

As is obvious from this historical study, research on opium rested to a great extent on animal and human experimentation. It has been shown elsewhere by the present author that animal experiments became a moral issue already in the seventeenth and eighteenth centuries.\footnote{See Maehle, Kritik and 'The ethical discourse', General Introduction above, note 16.} The sources on opium experiments also reflect this beginning moral awareness, yet to a lesser extent than others, for one obvious reason: as a narcotic and analgesic opium mitigated the usual suffering of vivisected animals. One can actually find the occasional remark that an opiated experimental animal showed no or few signs of pain during vivisection.\footnote{Ibid., pp. 69-70. See also Andreas-Holger Maehle, 'Neue Mittel der Schmerzbekämpfung. Vom Morphium zur Narkose', in Heinz Schott (ed.), Meilensteine der Medizin, Dortmund, Harenberg Verlag, 1996, pp. 297-303.} Still, Haller's
pupil Sproegel, for example, included some utterances of compassion in the protocols of his experiments. He spoke of "the poor dog" that had been poisoned with the drug, vivisected, and finally strangled; or he remarked that another poisoned dog was "released" from its "tortures". But this releasing was actually death through vivisection. Siebold, in the preface to his prize essay, noted that it was only "just" that he had experimented on himself as well, since he had "tortured" so many animals for his study. Crumpe excused the "apparent inhumanity" of his animal experiments by assuring that they were necessary in order to investigate "many points among the most interesting to mankind". He abstained, however, from animal tests with highly concentrated extracts of opium, believing that such trials would have no therapeutic consequences. Remarks such as these were rather common among contemporary researchers. They reflected some compassion with experimental animals, and thus a degree of sensibility, yet no serious moral concern. In view of possible progress in medical knowledge and therapeutic improvements the suffering and death of animals were held to be easily excusable. Compassion was generally no major obstacle to experiments on living animals.

In the contemporary accounts of human experiments with opium there are likewise some hints at ethical considerations. Since opium was a widely prescribed medicine, the transition from its therapeutic to its experimental use was often smooth or blurred. Yet the trials made by Leigh, Crumpe, and Sertürner indicate a certain concern not to harm the test persons. The

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328 Sproegel, op. cit., note 106 above, pp. 31, 35.

329 Siebold, op. cit., note 140 above, p. 4.

330 Crumpe, op. cit., note 143 above, pp. 54, 77.
standards as to which effects were seen as tolerable for the subjects in these experiments seem to have been rather low, however. Leigh, for instance, wrote that he "got two patients in the same room", a circumstance that offered him the opportunity to compare directly the effects of high doses of resin and gum of opium. The patient who had received the resin, a thirty-year-old man, got into "a kind of raving", and the other, a twenty-five-year-old woman, who had been given the same amount of gum, was thrown into "violent convulsions". There is no indication that Leigh had a specific therapeutic reason to try these opium components in high doses (five grains, as compared to the usual one or two grains of whole opium) in these patients. In another protocol Leigh remarked that only with difficulty he prevailed on a healthy man to take some drops of a presumably very effective solution of oil of opium. It produced such vehement vomiting that Leigh was deterred from making any further trials of this kind.332

While such experiments may appear ethically questionable to the modern reader, one has to consider that most of those who experimented with opium on human beings included themselves among the subjects. This applied to Leigh, as it did to Bard, Wirtensohn, Crumpe, Weber, and Sertiirner, as mentioned above. The case of the latter indicates that at least some of the experimentalists were prepared to take the same risks as their subjects. The last quoted trial by Leigh moreover suggests that sometimes the benefits and dangers were discussed with the test person beforehand. Sertiirner similarly wrote that he "persuaded" his three test persons to take the morphium.333 Such apparent consent is questionable, however, in Leigh's experiment on the two

331 Leigh, op. cit., note 229 above, p. 57; Crumpe, op. cit., note 143, above, p. 77; Sertiirner, op. cit., note 322 above, p. 69.


333 Sertiirner, op. cit., note 322 above, p. 68.
patients, and one may also wonder how voluntary Ward's trial on his house pupil was. Contemporary sources discussing experiments on hospital patients in general, such as the Thoughts on hospitals by the Warrington surgeon John Aikin or the well-known Medical ethics of the latter's prominent physician-friend Thomas Percival, do not in fact mention information or consent of the test persons. Aikin assured his readers that all precautions were taken and that the subjects would be the first to benefit from new forms of treatment. Percival thought it necessary that a consultation with all physicians and surgeons of the hospital took place, before a trial was performed, suggesting thus a kind of peer review. The concept of informed consent in the modern sense was clearly formulated only in the late nineteenth century - after abuses in experimentation on hospital patients had become a public issue. On the whole it can be said that in both animal and human experimentation with opium ethical attitudes transpired. But neither compassion with experimental animals nor a certain concern not to harm the test persons prevented extensive and sometimes dangerous trials.

334 See above.


336 Thomas Percival, Medical ethics, or, a code of institutes and precepts, adapted to the professional conduct of physicians and surgeons, Bath, Richard Cruttwell, [1803], pp. 377-378.

13. **Conclusions**

The history of opium from the seventeenth to the early nineteenth century, as discussed in this chapter, elucidates a number of issues in contemporary pharmacology and therapeutics. Perhaps most striking is the change of theories of the drug's mode of action during this period. In the seventeenth century, the Galenic notion of a cooling effect of opium was challenged by adherents of chemiatric concepts, such as Thomas Willis, Georg Wolfgang Wedel, and Michael Ettmüller, who replaced it with the speculation that the drug's active chemical principle fixed or bound the spiritus animales in the nervous system. Around 1700 this view was questioned by iatromechanists, notably by Friedrich Hoffmann, Johann Gottfried Berger, John Freind, and Richard Mead. They concluded from clinical and pathological observations, as well as from animal experiments and *in vitro* trials, that opium acted by rarefying the blood. Effects on the nervous system were seen as indirect, following from distended blood vessels, which pressed on the "tubuli" of the brain and nerves and in this way obstructed the flow of the spiritus. About the same time a "vitalistic" interpretation, propagated by John Jones, assumed that the drug caused a "pleasant sensation" in the stomach, that led to general relaxation. Yet, this latter view gained less ground than the "rarefaction theory". In the middle of the eighteenth century, however, Charles Alston and Robert Whytt of the rising Edinburgh school of medicine, as well as Boerhaave's nephew Abraham Kaau, suggested that opium acted primarily and directly on nerves, its action being spread by "sympathy" from nerve ends in the stomach walls throughout the whole nervous system. Their arguments in support of this view came also from clinical observations and animal experimentation. But further animal experiments, both from within the Edinburgh school (Alexander Monro secundus) and from without (Felice
Fontana), pointed again to action via the blood, and a rival theory of opium's effect through the circulatory system was put forward at the beginning of the nineteenth century by Michael Ward.

These shifts in pharmacological theories of opium mirrored more general changes and issues in the theory of medicine. The giving up of an explanation with the primary quality "cold" (or as some early critics wanted it, "heat") was part of the general challenge of Galenic doctrines in the seventeenth century. The dispute over direct, chemical action on the spiritus animales or their mechanical obstruction by turgid blood vessels reflected the opposing concepts of the body held by iatrochemists and iatromechanists. And the known preoccupation with the nervous system of influential Edinburgh teachers, such as Whytt, found its expression in the theory of opium's direct effect on nerves. Fontana's criticism of this view, in turn, was part of a wider experimental project of his, in which he showed that also fast-acting and powerful poisons, such as viper venom, curare, and cherry laurel, acted only after absorption into the blood. Experiments with opium were further an integral part of the controversy between Whytt and Albrecht von Haller over the relation between sensibility and irritability. Here the drug was used as a tool for the study of an important problem of contemporary physiology.

The present "case study" on opium has moreover revealed a remarkable degree of methodological awareness in eighteenth-century pharmacology. For instance, the question of artificial conditions through vivisectional procedures within pharmacological experimentation was brought up by Haller against Whytt. That the latter was aware of this difficulty, is clear from his control experiments, which involved vivisection, but not application of the drug. Certainly, most researchers who performed trials with opium in vitro on blood, or in various species of animals, were rather quick to extrapolate their experimental results to the human body
and thus to the patient. Yet they did so amidst criticism by medical practitioners, such as George Young and Balthasar Ludwig Tralles, who denied the transferability of such results and insisted on the supremacy of therapeutic experience. Samuel Crumpe's negative view of examining the effect of opium on blood shows that methodical criticism of this kind could also come from the experimentalists' own camp. Self-experimentation was an answer to the problem of transferability, though subjective factors could distort findings - a problem, which was recognized by Samuel Bard and Carl Joseph Wirtensohn. For those, however, who believed that diseases changed drug effects, trials on one's own body, or on any other healthy person, was no valid solution either. Therapeutic empiricism in the style of Young and Tralles was then the only way to gain pharmacological knowledge.

This methodological awareness was matched by some degree of ethical concern, both in animal and human experimentation with opium. The suffering of experimental animals was mentioned by a number of the researchers discussed in this chapter. And the danger of poisoning was not concealed by those who performed human experiments with the drug or its preparations.

The example of opium has further shed light on the relations between pharmacological experimentation, theory, and therapy. It has become clear that experiments were rather "embedded" in speculation than used as crucial tests for hypotheses. Experimental observations also served only to a limited extent as a basis for pharmacological theory-building. They rather supplemented clinical experiences as additional "arguments" for a particular view of the drug's *modus operandi*. Likewise, there was not always a straightforward way from theory to therapy. Extensive therapeutic experiences with opium counted more to eighteenth-century medical practitioners than the latest interpretations and explanations of its actions. However, as the case of opium indicates,
therapeutical conclusions were increasingly drawn from pharmacological concepts. Johann Jakob Waldschmied in the late seventeenth century, believing in the chemiatric "spiritus animales theory" of the drug's action, deduced contraindications from it, such as apoplexia, epilepsy, lethargy, and paralysis. Alston, as a critic of the "rarefaction theory", was less concerned about the dangers of giving opium to plethoric patients than the followers of this view. Conversely, he feared that they might endanger patients by ordering venesection after an overdose on the wrong assumption that the blood had been thinned. Whytt, as an advocate of the theory of opium's direct action on nerves, used it consequently in the treatment of various nervous disorders. And Crumpe differentiated his therapy with the drug, giving it either traditionally as a painkiller or in the "new" way as a stimulant. In fact, as has been shown, Brunonians regarded his pharmacological characterization of opium as a stimulant as proof of John Brown's therapeutic system.

On the whole it can be concluded that - despite opposition of empiricist medical practitioners - the connection between the emerging experimental pharmacology and therapeutics was strengthened in the course of the eighteenth century.

The new theories of opium also contributed to the understanding of the phenomena of drug tolerance and habituation. The craving for ever increasing doses of opium was explained, for example, with habituation to the "pleasant sensation" (Jones) or the patient's excitability becoming "blunt" from perpetual stimulation (Carl Ch. H. Marc, Ernst Horn). As the comments by Jones, Young, Haller, and several Oriental travellers on habitual opium-taking indicate, however, not drug dependence as such, but the prospect of physical and mental harm through this habit caused concern. It has further been shown that interest in the psychopharmacological aspects of opium was rather limited during the seventeenth and eighteenth centuries.
"Somatic" experimentation with the drug, benefiting from the methodology of contemporary physiological research, was clearly predominant. By contrast, there was no specific methodology to assess the psychological effects of opium, which were merely mentioned by most experimentalists. This changed only with the considerable efforts in introspection by writers of the Romantic Period, especially Thomas De Quincey.

Finally, as in the study of lithontriptics, the case of opium illustrates the impact of improved chemical analysis with the beginning of the nineteenth century. Friedrich Wilhelm Sertürner's isolation of morphine not only permitted much more accurate dosage and effective treatment, but created the conceptual framework for the new research field of plant alkaloids.
C. PERUVIAN BARK: FROM SPECIFIC FEBRIFUGE TO UNIVERSAL REMEDY

1. Introduction

Most histories of therapeutics, and of medicine in general, mention the introduction of Peruvian bark in the seventeenth century as an important event.¹ There are chiefly three reasons for this attention. Firstly, Peruvian bark (Cinchona officinalis Lin.) was the predecessor and source of the therapeutically effective alkaloid quinine. Secondly, it was the prototype of a "specific" remedy (against intermittent fevers, i.e. malaria), which challenged the principles of traditional, Galenic therapy. And thirdly, it was an example of the transfer of medical knowledge and drugs from the New to the Old World.

Whereas the relevance of Peruvian bark for the history of medicine is thus widely acknowledged, only few scholarly studies have actually examined the subject in any detail. In 1941 Alec W. Haggis provided a careful analysis of the pertinent seventeenth- and early eighteenth-century sources.² He exposed "fundamental errors" in the early accounts of the bark, that had been perpetuated through the centuries. The probably most important of these "errors" concerned the confusion about the botanical origin of the drug. Haggis demonstrated that up until Charles Marie de La Condamine's description of the cinchona tree in 1740 (sent from his South American expedition), its bark was often

¹ Recent examples are Koelbing, op. cit., General Introduction above, note 12, p. 102; Weatherall, op. cit., General Introduction above, note 12, pp. 9-10; Stille, op. cit., General Introduction above, note 1, pp. 299-300.

mixed up with that of the Peruvian balsam tree (Myroxylon peruiferum Lin. fil.). The chances of confusion were especially great, because the bark of both trees was known under the same indigenous name, "Quina-Quina". Moreover, since the beginning of the seventeenth-century, Jesuit missionaries in South America had been sending the bark of the balsam tree as a febrifuge back home to Rome, as they did the cinchona bark from the 1630s. Haggis furthermore showed that the famous story of the "discovery" of the healing power of cinchona bark - through curing the wife of the Viceroy of Peru, the Countess of Chinchon, from a tertian fever - did not match authenticated events and must therefore be regarded as a fable. A few years after Haggis, Jaime Jaramillo-Arango examined many of the same sources and problems and confirmed the former's main conclusions. Around the same time M. L. Duran-Reynals published a popularly written history of Peruvian bark and quinine from the beginnings in the seventeenth century up to 1945. Not always accurate and reliable, and lacking exact references, this work is only of limited value to the historian.

This first group of relevant publications had in part been stimulated by the military importance of malaria control and quinine therapy during the Second World War. In the following four decades various aspects of the history of Peruvian bark found further attention, sometimes in studies of closely related areas, such as the history of malaria and of "fevers". But only in 1993, with Saul Jarcho's book

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3 Hence the name cinchona, given by Linnaeus in 1742.


6 See for example Rudolph E. Siegel and F. N. L. Poynter, 'Robert Talbor, Charles II, and cinchona. A contemporary
Quinine's predecessor, another major specialist study has come out. Based on an admirable amount of primary sources from the seventeenth and early eighteenth centuries, Jarcho traces the introduction of cinchona bark into European medicine and the controversies linked with this process. His account elucidates the crucial role that the Jesuit order played in the distribution of the drug (hence also called "Jesuits' bark"), and it gives many insights into how physicians used the new medicine in treating intermittent and other fevers. In particular, he analyses the *Therapeutice specialis* (1712) of the Modena professor of medicine Francesco Torti, an influential work, which classified fevers in view of their suitability for treatment with cinchona. As an appendix to his study, Jarcho summarizes a selection of concepts of intermittent fever from Galen to the beginning of the eighteenth century, providing thus a useful addition to the historical studies of theories of fevers edited by Bynum and Nutton in 1981.

The present chapter partly attempts to provide a follow-up to Jarcho's account of the use of Peruvian bark as
a febrifuge, by studying important developments in the late
seventeenth and in the eighteenth centuries, up to the
isolation of quinine in 1820, which forms a "natural" end.
As in the "cases" of opium and lithontriptics, contemporary
medical and scientific interest in the Peruvian bark are
reflected by the vast amount of literature that has been
produced on this drug: Edward John Waring's Bibliotheca
therapeutica lists (under the heading "Cinchona")
internationally 33 monographs from the seventeenth century,
followed by another 187 titles published between 1700 and
1820. While my discussion of works on the bark's febrifugal
powers will be selective, my focus will widen to include
literature on the drug's "new" therapeutic uses. For
example, the treatment of "gangrene" with cinchona, which
was introduced in the 1730s, will be studied in some detail.
In general, attention will be given to experimental
investigations of the bark and their consequences for
pharmacological theory and therapy. Experimental aspects do
not figure largely in Jarcho's book, Quinine's predecessor.
Yet in 1992 he edited a late seventeenth- or early
eighteenth-century manuscript on Peruvian bark, which among
others mentions some contemporary trials. This text forms

9 Edward John Waring, Bibliotheca therapeutica, or
bibliography of therapeutics, chiefly in reference to
articles of the materia medica, 2 vols, London, The New
earliest entry here, Pedro Barba's Vera praxis ad curationem
tertianae, etc. (Sevilla 1642) is misplaced, however, since
it is not a treatise on cinchona, as Jarcho, op. cit.,
General Introduction above, note 26 above, pp. 27-28, has
pointed out.

10 Saul Jarcho (ed. and transl.), Tractatus simplex de
cortice Peruuiano. A plain treatise on the Peruvian bark
("The Stanitz manuscript"): a late seventeenth or early
eighteenth century anonymous manuscript account of the
Jesuits' bark, Boston, The Francis A. Countway Library of
Medicine, 1992.
thus an interesting reference for my account of pharmacological experimentation with the drug around 1700.

2. Early controversy on the new febrifuge

Regular shipment of the bark from Peru to Rome was established by the Jesuit order during the 1640s. It was also a prominent member of this order, the Spanish-born Cardinal Juan de Lugo (1583-1660) in Rome, who is said to have initiated first "tests" of the drug in fever patients after 1645. At de Lugo's request, the personal physician to Pope Innocent X, Gabriele Fonseca (d. 1668), tried the bark in "own experiments" ("propriis experimentis") and found it "not only harmless, but most beneficial" ("non modo ... innoxium, sed etiam saluberrimum") - according to a later Jesuit defender of the medicine. No further details about the nature of these "experiments" are known. According to the same source, several thousand people in Rome had been treated with the bark, in 1653 alone, without harmful effects. De Lugo and the keeper of the apothecary's shop of the Jesuits' Collegium Romanum, Pietro Paolo Puccerini (1600-1661), seem to have been the main distributors of the remedy in these early years. A pharmaceutical handbill, the so-called Schedula Romana, advised about dosage and method of administration. In patients with tertian and quartan fevers two drachms of pulverised Peruvian bark, macerated in white wine, should be given at the beginning of the fever


12 Antimus Conygius [Honoré Fabri] (1655) as quoted in: Melippus Protimus [Vopiscus Fortunatus Plempius], Antimus Conygius, Peruviani pulveris febrifugi defensor, repulsus, [no place], 1655, p. 6.

13 Ibid.
paroxysm. "According to experience", it said here, "almost all" who took the powder were freed from their fever, if they had been well purged beforehand and abstained from other medicines during the following four days. However, the bark should not be taken, said a final warning, without previous consultation of a medical man, who judged about the right time and mode of administration.

By the early 1650s the use of Peruvian bark had spread to other European centres. Yet this was also the time when a first public dispute about the efficacy and harmlessness of the new drug flared up. Immediate cause was the case of the Archduke of Austria and Governor of the Spanish Netherlands, Leopold Wilhelm (1614-1662). In 1652 he was diagnosed with a "false" (impure) tertian fever, which turned into a "double" quartan. The physician in charge, Jean-Jacques Chiflet (1580-1660), reluctantly yielded to the pressure of bystanders and gave - as prescribed in the Schedula Romana - two drachms of powdered bark in white wine. The Archduke became subsequently free of fever, but thirty-three days later he had a relapse. Having received a letter from his brother, the Holy Roman Emperor Ferdinand III, which advised against the use of the bark, he further refused to take the bitter medicine again.

By order of his noble patient, Chiflet published, in 1653, a tract against Peruvian bark. All patients with quartan fever in Brussels who had taken the drug, he stated, had suffered relapses. The medicine merely extended the interval between the paroxysms. In Galenic fashion he further speculated that the humours might be thickened by the bark, giving thus rise to prolonged and fatal disease. Chiflet therefore recommended traditional European

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15 Ibid., p. 29.
febrifuges, such as gentian. The message of the Archduke's physician appears to have been well received among the conservatively minded medical élite of Paris, who had his text reprinted for "the benefit of the public". As the Paris professor of medicine and surgery René Moreau (1587-1656) wrote to a friend in Brussels in July 1655:

The reputation of the powder of Peru is so dead in this town, that one does not talk about it any more, and we do not prescribe it any longer.

In the same year, however, the Jesuit order countered with a defence of the bark, written by the priest Honoré Fabri (1606-1688) under the pseudonym "Antimus Conygius". Although he was not a medical man, as "Conygius" openly admitted, he had been encouraged to answer Chiflet by the approval of de Lugo and Fonseca. Fabri, the defender of the Peruvian bark referred to above, pointed to the many good experiences in Rome with the drug - including the treatment of his own intermittent fever. Yet later in 1655 a vitriolic response to "Conygius" was published by Vopiscus Fortunatus Plempius (1601-1671), professor of medicine at the University of Louvain. Though his pamphlet is a typical example of a seventeenth-century medical polemic - comparable to the better known contemporary attacks of Jean Riolan on Jean Pecquet's and Thomas Bartholinus' discovery of the lymphatics - it is worth looking at in some detail. Plempius defended Chiflet with strong words against

16 Ibid.
17 Cf. Protimus [Plempius], op. cit., note 12 above, p. 3.
18 Cf. ibid., pp. 4-5; Jarcho, op. cit., General Introduction above, note 26, pp. 30-32.
19 See also ibid., pp. 32-33.
20 On this controversy see Maehle, Kritik, General Introduction above, note 16, pp. 22-27.
"Conygius", yet he did this also in a very systematic way, quoting and "refuting" Fabri's arguments one after another, and thus highlighting the central issues involved in this dispute.

Addressing Archduke Leopold Wilhelm, who had received the writing of "Conygius" against Chiflet, the Louvain professor first of all emphasized the requirement of medical competence in order to be able to make a judgement in this question of therapeutics. "Conygius" (i.e. Fabri) had admitted that he lacked such expertise, and de Lugo was eminent in theology, not in medicine. Thus only Fonseca, the Pope's physician, had to be taken seriously.21

Nevertheless Plempius went into Fabri's arguments. One of Fabri's points had been that Chiflet's reference to the traditional medical authorities - Hippocrates, Galen, Celsus, Pliny, Avicenna - was irrelevant in this case: none of them knew of the Peruvian bark. Plempius disagreed. Of course they could not have known about this new remedy, but they had disapproved of quick "cures" without evacuation and had in general condemned empirical febrifuges which left the "febrile matter" in the patient's body. Since the bark was such a medicine, Chiflet's citation of the ancients was adequate and important.22 In other words: the fact that cinchona bark had no evacuant properties, which were required of a Galenic febrifuge, spoke against it. Galenist doctrine was the chief obstacle to the acceptance of the Peruvian drug - and remained so for many decades.

Fabri's next argument discussed by Plempius was that of experience. As mentioned above, Fabri pointed to Fonseca's "experiments" with the bark and its widespread beneficial use in Rome. The Louvain professor countered with negative experiences. Like Chiflet he claimed "our Brussels people",

21 Protimus [Plempius], op. cit., note 12 above, pp. 3-5.
22 Ibid., pp. 5-6.
who had been treated with the Peruvian powder, had all relapsed. Most of them had become cachectic, some of them had died. That similar outcomes could be observed in Rome as well, he claimed to have learned from letters of a Florentine nobleman. Moreover, in an attempt to oppose the authority of Fonseca, Plempius quoted the testimonies of two other eminent physicians against the bark: Johann Gregor Glantz in Regensburg, physician to the Emperor, testified to have seen relapses after initial improvement in nine cases; and Johann Guttierrius a Godoy, a doctor of the Spanish King, reported from Madrid about two cases of quartan fever that had become worse after use of the bark, one of them ending in death. Further examples, he added, could have been given. Plempius concluded that experience stood against experience, but that there was more evidence against the drug: "Conygius" referred to Rome, whereas he claimed to have negative reports not only from there, but also from other Italian towns as well as from Vienna, Paris, and Brussels.

A further point of contention were the Galenic primary and secondary qualities to be attributed to the Peruvian bark. Its bitter taste would normally have indicated a very warm quality. This view led, however, to the paradox that a hot medicine was supposed to remove the heat of fevers. Fabri had shown a way out by stating that the bark was actually cold, arguing that not all bitter substances were necessarily hot. Plempius partly accepted this, referring to the bitter tasting opium as another example: at least in ancient opinion it was a cooling medicine, though recent authors had attributed a warm quality to it. But he was not prepared to give up the Galenic rule that bitterness was a sign of warmth. Instead he suggested that the bark's not

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23 Ibid., pp. 6-8.
24 See also above, part B.
only bitter but sharp taste indicated an additional cold component. Peruvian bark had therefore both warming and cooling effects.25

In this context the central question arose, whether the drug was actually a safe medicine in intermittent fevers, as "Conygius" had assured. Plempius believed that it was pernicious. It merely suppressed the febrile fits without removing their cause. In this respect, he thought, it was similar to analgesics, which merely stupefied and left the morbid cause in the body, so that pain returned later with even more violence.26

Fabri had also tried to make the bark more acceptable to Galenists by stating that it actually did provoke sweating and increased urine and stools, thus removing the fever "not without method, solution, and good signs". In other words, he claimed that it was an evacuant. Plempius denied that such effects of the drug had ever been observed in his country. If sweating occurred, it was an effect of the disease, not of the remedy. Likewise, the "miraculous effects" of the bark in "Conygius'" own disease should rather be attributed to simultaneously taken evacuant remedies and to a robust constitution than to the new medicine. In his final onslaught on the Peruvian powder Plempius pointed to a statement of a "Father of the Society [of Jesus]", saying that "this powder was [like] the remedy of a quack", who promised a certain cure and left the town, before the patients relapsed and complained.27

The controversy surrounding the Archduke's case thus brought the main arguments against the new South American medicine to light: it could not be integrated into the concepts of Galenic fever therapy, and its effect seemed to

25 Protimus [Plempius], op. cit., note 12 above, pp. 9-10.
26 Ibid., pp. 10-11.
27 Ibid., pp. 11-12.
be only temporary, perhaps making fevers even worse in the long run. It has often been suggested in the secondary literature that Protestant resentment of the Jesuit order was at the bottom of the resistance against Peruvian bark, the "Jesuits' powder". Although this may generally be true to some extent, this religious aspect does not appear in Plempius' attack on "Conygius" (i.e. Fabri)\(^{28}\) — contrary to the (undocumented) view of Duran-Reynals. In her account Plempius, as a professor in Louvain, the centre of Jansenism, and as someone who had converted from Protestantism to Catholicism for professional rather than spiritual reasons, "naturally felt the greatest dislike for the theological subtleties of the Jesuits".\(^{29}\) But scrutiny of Plempius' pamphlet against "Conygius" does not reveal this. As a matter of fact he referred to the Jesuit Cardinal de Lugo as "most eminent" and acknowledged his status as a theologian.\(^{30}\) There is further no clear indication that Plempius suspected "Conygius" to have been a Jesuit. Within the broader context of the controversy, Archduke Leopold Wilhelm, the original "critic" of the Peruvian powder, does not fit into an anti-Jesuit pattern either. Just to the very contrary: as Bishop of Passau and Strasbourg (since 1626) Leopold Wilhelm is known to have extended the Jesuit College in the former town and to have supported the Jesuits and Counter-Reformation in the latter.\(^{31}\) Medical concerns about the safety of the new remedy seem thus to have been more important than religious scruples or prejudices.

\(^{28}\) I agree here with Jarcho, who makes the same point with reference to an account by the American historian A. R. Steele (1964). See Jarcho, op. cit., General Introduction above, note 26, p. 34.

\(^{29}\) Duran-Reynals, op. cit., note 5 above, pp. 58-60.

\(^{30}\) Protimus [Plempius], op. cit., note 12 above, p. 5.

In retrospect, poor quality and purity of the Peruvian bark, and insufficient dosage, seem reasonable explanations for the failure of the drug in some places and cases. Following Haggis, we may also doubt that the bark was always stemming from cinchona trees - it might well have come from the Peruvian balsam tree or even other sources. And finally, many "fevers" in which the bark was given may not have been malaria at all, and thus resisted treatment. Such considerations, however, emerge from the historian's perspective. They hardly played a role in the seventeenth-century dispute discussed above.

The memory of the controversy between Chiflet, Fabri, and Plempius stayed alive over the next years. In 1663 the Genoese physician Sebastianus Badus (also Baldus), in his work *Anastasis corticis Peruviae*, still defended the bark against Chiflet. He referred to successful, but not further explained, "trials" with the drug in local hospitals, and he produced testimonials confirming its efficacy in numerous cases.^{32} Like Fabri, Badus was well aware, however, of the difficulties in comprehending the medicine's action in terms of Galenic qualities and humoral theory. In particular it was hard to see how the supposedly hot and dry bark could cure a tertian fever, which was traditionally thought to arise from corrupted yellow bile - a hot and dry humour. In quartans, believed to be caused by cold humours, this was somewhat easier to understand, but the problem remained, how a hot substance healed a fever. Badus resorted to occult or hidden qualities in the Peruvian bark, comparing it in this respect with the guaiac wood, which was successfully used in the treatment of syphilis.^{33}


^{33} Badus (1663) as quoted by Jarcho, ibid., p. 19. For Hippocratic and Galenic ideas about the causes of intermittent fevers see Wesley D. Smith, 'Implicit fever
Contemporary iatrochemistry offered another answer. Thomas Willis (1621-1675) in Oxford developed a chemical rather than purely humoral theory of fever. It suggested that fevers generally originated from excessive fermentation of the blood, comparable to bubbling wine. Intermittent fevers in particular were thought to arise from alterations in the blood, that had been induced by changes in the seasons, local climate, or the individual's physical constitution. The patient's blood turned acid, bitter, or harsh and salty, so that it became unable to concoct, or assimilate to a sufficient degree, the nutrient humours which were being absorbed from the intestines. The nutrient juice thus acted as alien and morbific matter, causing unnatural fermentations in the blood. Depending on the blood's chemical state and remaining capacity to concoct, a crisis was reached either daily or after two or three days, resulting in the intermittent fever fits. In this way, Willis linked an acid state of the blood with quotidian fever, a bitter state with tertian, and a harsh and salty state with quartan fever. In order to bring the unnatural fermentation of the blood to an end, the morbific matter had either to be evacuated or its activity suppressed.34

The latter effect, thought Willis, could be obtained by giving powdered Peruvian bark in wine. He explained how suppression of the fits could be a useful practice, e.g. in order to keep patients relatively free of fever over the autumn and winter, until the "disposition" of their blood changed in the spring and successful treatment with other (evacuant) remedies became possible. On the other hand he


warned that, even if patients took the bark repeatedly and in high doses, "they retain within, the Enemy still, tho asleep". Willis was cautious in suggesting a pharmacological theory of the Peruvian bark, because one had "not found as yet in any Subject, besides, the like efficacy". Yet, via an analogy with animal poisons and antidotes, he did provide "some Theses". Particles of the bark, he speculated, entered the blood and effected a "new" fermentation. The particles of the blood, though "distempered with an evil disposition", were agitated and altered in such a way that they were enabled to concoct "in some measure" the nourishable juice and to evaporate its recrements. Consequently, the blood would not "heap up" any longer "Excrementitious matter, or enter Feaverish turgencies", that had caused the fits before. Willis compared this action with that of antidotes, which retained the venom of a mad dog's bite or of a poisonous sting in "another Fermentation", preventing it thus from producing harmful symptoms. But also, as the venom would act, as the antidote had worn off, so the fever would return, when the particles of the Peruvian bark had "wholly flown away" from the blood.36

Willis' theory of fever represented no radical departure from the traditional view. It applied new iatrochemical ideas to traditional concepts, or as Don G. Bates has put it, it was a "conservative transformation (almost translation) of Galenic doctrine into a 'modern' corpuscularian materialism".37 However, soon after Willis' 


36 Ibid., pp. 87-88. See also Jarcho, op. cit., General Introduction above, note 26, pp. 46-48.
death, Galenic explanations were uncompromisingly dismissed by Thomas Sydenham (1624-1689), when he described Peruvian bark as a specific remedy against intermittent fevers, and indeed as the only true specific known in medicine, in his influential Observationes medicae (1676) and Tractatus de podagra et hydrote (1683).

The notion of specific remedies against specific diseases had chiefly evolved with Paracelsus (1493/94-1541) and his followers. It has been suggested that the experience of the "new" disease syphilis, and the failure of Galenic medicines in curing it, formed an important background to this development. While Ulrich von Hutten and others hailed guaiac wood (introduced from Hispaniola to Europe in 1508) as a specific for syphilis, Paracelsus despised it for its commercial association with the wealthy Fuggers. But he extolled the arcane power or quinta essentia of mercury as the specific curative agent in this disease. In the course of the seventeenth century, chemiatric "specifica" became fashionable. Georg Sticker, in his historical account of specific therapy, quoted as examples Specificum purgans Paracelsi, Specificum ad vertiginem Quercetani, Specificum lithontripticum Agricolae, Specificum pleuriticum Agricolae, Specificum antifebrile Crollii, Specificum cephalicum Michaelis, and Specificum febrifugum Sylvii. It was this "inflation" of specifics, against which Sydenham asserted the unique power of Peruvian bark in intermittents. Moreover, the very existence of the bark as a specific remedy was a cornerstone of his concept of specific disease entities.

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Initially, Sydenham had been rather cautious in his comments on the new "Jesuits' powder". As he explained in 1666, in the first edition of his Methodus curandi febres, it might temporarily suppress the febrile fermentation, but leftovers would regain strength and soon start "a new war against nature". Evidently, he shared these concerns with Willis. Moreover, Sydenham quoted some fatal cases, in which the bark had been given in the traditional manner immediately before a fever fit. He therefore advocated its careful use in the decline of the febrile paroxysm and during the period of intermission - a topic, on which he elaborated in 1679 in his epistle to the Regius professor of medicine at Cambridge, Robert Brady. In the meantime, however, Sydenham had changed from a rather lukewarm to an enthusiastic supporter of the use of the bark in intermittent fevers. As he explained in his Observationes medicae, prolonged retention of the humours in the body, a certain constitution of the air, or some poisonous contagion caused specific "exaltations" (i.e. probably fermentations) of the humours, which produced specific diseases, such as quartan fever. A specific remedy would "destroy" and "extinguish" the "species" of the disease, not merely introduce one or the other primary or secondary quality, as conventional, Galenic medicines did. Only the Peruvian bark, asserted Sydenham, fulfilled the task of a specific remedy. The efficacy of other so-called specifics, for example mercury and sarsaparilla in syphilis, probably depended on their evacuant powers, such as salivation in the former, and sweating in the latter. They were therefore, concluded

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Sydenham, as little specific as a phlebotomy scalpel in the treatment of pleuritis.\textsuperscript{42}

In his tract on podagra (gout), he came back to this topic, calling the Peruvian bark "that greatest specific in intermittent fevers". It had shown that the "dogmatists" (i.e. Galenists) had been "hallucinating" about the essence and treatment of diseases. For centuries, said Sydenham, clever minds had tried to find the causes of those fevers and had in vain adapted their therapeutic practice to their theories, altering and evacuating the various humours that they believed to produce the different species of intermittents. Now, with the successful bark treatment, the kind of humour did not matter any longer, nor did the diet and regimen of the patient. If correctly administered, he assured, the bark even cured when mistakes in care were made, such as keeping the feverish patient too warm.\textsuperscript{43}

In view of the lasting respect for Sydenham throughout the following century and beyond, there can be little doubt that his praise of the Peruvian bark as the specific was instrumental to its propagation and adoption in medical practice. However, his dismissive comment on theories of fevers, and his rather simplistic notion that the bark eradicated the species of the disease (which was of course in line with his general empiricist approach) were not widely accepted. Towards the end of the seventeenth century, and at the beginning of the eighteenth, the old difficulties in understanding the bark's operation in fevers provoked a number of new answers. Some of them rested in part on


\textsuperscript{43} Cf. Sydenham, op. cit., note 42 above, pp. 453-454.
experimental evidence; others took off from clinical observations. Most were highly speculative.

3. **Experiment and speculation: efforts to explain the bark's action around 1700**

Among the experimental studies of cinchona in that period, the work of the Paris physician Jacques Minot, first published in 1684, stands out. With his colleague "Mr. de Monginot" (i.e. Francois de La Salle), who had written about the treatment of fevers with the bark five years earlier, he shared an iatrochemical view: fevers, such as the quartan, were caused by an excess of acids in the blood and chyle, and cinchona (or "quinquina", as they called it) healed by destroying these acids. In order to convince himself perfectly of this ("pour estre pleinement convaincu"), Minot had made experiments with the bark on blood, and on milk, as a fluid "analogous to chyle". Yet this was not the only reason. He also declared that he wanted to "exculpate" the remedy from its alleged harmful effects, in which the public and "some medical men" still believed, assuming that it "fixed" the fever-producing humours. Without doubt, Minot meant the Galenic criticism of Peruvian bark, which had been prominent in the early debates outlined above. Fevers were


46. Minot, op. cit., note 44 above, p. 320.
traditionally deemed to be the effects of accumulated and corrupted humours (yellow bile in tertian, black bile in quartan, phlegm in continuous fever), and because cinchona did not lead to evacuation through stool, vomiting, or sweating, it was thought to fix the deleterious "febrile matter" in the body, making thus the disease worse in the long run.

Minot's experiments were meant to show that this was not true. They comprised three comparative in vitro trials, and one animal experiment. In his first trial Minot filled two pre-warmed phials with 4 or 5 ounces of freshly let venous pig's blood. To one phial he added two spoons of vinegar (i.e. an acid), to the other about the same amount of "quinquina wine", as commonly given to fever patients. Both phials were then immersed in a water bath of approximately blood temperature. Minot observed that within a short time the blood with vinegar coagulated completely, assuming a brownish red to black colour. By contrast, the blood with the Peruvian bark wine stayed fluid and showed a "nicely red" colour, coming close to that of arterial blood. Minot affirmed that he had repeated this trial several times on the blood of other animals and human blood - always with the same result.

In his second experiment he filled two bowls with fresh cow's milk, adding quinquina wine to one of them. In a third bowl solely the medicine was poured. Minot then applied a cheese press to the bowls and put them on medium heat. Shortly after he found in the first bowl white and soft cheese with a bit of residual milk ("petit-lait"). The second bowl (with added quinquina) contained less and rather firm and dry cheese, with a greater amount of "petit-lait". And the pure cinchona wine in the third vessel showed no sign of coagulation.

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47 Cf. ibid., pp. 321-325, 337-338.
Minot concluded from these first two in vitro experiments that Peruvian bark impeded the coagulation both of blood and milk. But he wished to go further to see whether the remedy was able to dissolve already coagulated matter. To this end he performed a third trial. Adding cinchona wine to the cheese of the first bowl of the previous experiment, he noted that the cheese was partly dissolved. When he poured the medicine, however, in the phial containing the blood which had coagulated through vinegar in the first trial, he could not recognize any changes. Yet, when quinquina wine was added to blood which had coagulated at the open air (i.e. without admixture of another substance), it lost some of its taste and appeared to become more cloudy than the wine of the previous experiment.

On this basis Minot felt confident to conclude that Peruvian bark not only kept blood and milk fluid, and should therefore do the same to the humours in the human body; it also healed fevers by rarefying the blood, by dissolving coagulations produced through excessive acid, and by correcting and destroying acid ferments wherever it found them. The bark was therefore in his view not only an excellent remedy against fevers, but also useful against other "indispositions" arising from an excess of acid and acrid humours, such as "canine hunger" (i.e. probably bulimia), rheumatism, and gout. On the other hand, Minot qualified his belief in the bark's efficacy with respect to acid-induced coagulations that led to obstructions, as in "hydrops accompanied by inveterate scirrhi of the spleen" (i.e. probably splenomegaly in malaria). Here he took the medicine's lacking or poor effect on already coagulated blood into account, that he had seen in his last in vitro experiments.

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48 Ibid., pp. 325-326.
Minot's experimentally supported theory of the mode of action of cinchona provided him further with an explanation of the drug's "more specific" effect in intermittent as compared to continuous fevers. In the latter, he argued, the harmful acids were all too dissipated, and the humours in great movement, so that a remedy dissolving and rarefying the blood, such as the bark, may not be suitable. In intermittent, however, cinchona was the medicine of choice:

...because in the intermittent fevers there are always acid ferments that condense the chyle and the blood, and form an obstacle to their movement; that is why the Quinquina is a very sure remedy for these sorts of fevers.\(^50\)

Finally, the supposed antacid effect of Peruvian bark was a reason for Minot to prescribe it alone and not to mix it with acids such as lemon or orange juice, as some doctors did. Obviously such admixtures would reduce its efficacy.\(^51\)

Though Minot had "demonstrated" in his in vitro trials that cinchona rather impeded than caused coagulation of bodily fluids, it remained his ultimate task to defend the drug against the Galenists' charge that it led to condensation and fixation of humours within the body. To this purpose he injected the quinquina wine intravenously in a dog. The animal showed no signs of discomfort. As Minot pointed out, this stood in contrast to known injection trials with vinegar and other acid and coagulant fluids, which led immediately to the animals' death, their heart and veins being filled with coagulated blood.\(^52\) "One has thus to

\(^{49}\) Ibid., pp. 326-331.

\(^{50}\) Cf. ibid., pp. 332-333.

\(^{51}\) Ibid., pp. 334-335.

\(^{52}\) For accounts of the first intravenous injections in the seventeenth century see Scheel, op. cit., part B above, note 39; and Buess, op. cit., part B above, note 37. From the early 1690s, Giorgio Baglivi performed intravenous injection trials on dogs and in vitro experiments on blood with a
conclude...in conformity with our experiments", the Paris physician ended his discussion, "that the Quinquina neither coagulates nor fixes the humours; that on the contrary it rarefies and purifies the blood and reestablishes its free and natural movement."

From a modern perspective, both the achievements and the shortcomings of Minot's experimental approach are remarkable. As we have seen, he used control experiments in his first two in vitro trials, he was careful to keep his experiments with fresh animal blood at body temperature, he repeated them with human blood, and he did make the transition from the phial to animal experimentation. On the other hand one may be surprised by his direct conclusions from the effects of the bark in the phial to those in patients, by his bold equating of milk with chyle, and by the obvious lack of control experiments with pure wine (to assess the specific efficacy of his "quinquina wine"). Of course such critical observations would be purely presentist and ahistorical, if there was not evidence that in Minot's own time commentators recognized difficulties in his experimental method.

The late seventeenth- or early eighteenth-century manuscript on Peruvian bark recently edited by Jarcho, which probably reflects contemporary medical teaching at Naples, includes a brief summary of Minot's work, followed by criticism. Its anonymous author questioned the clinical variety of chemical substances, also concluding that "acids are inimical to the blood and change its composition". Baglivi does not seem to have experimented with Peruvian bark, however, and was in fact known as an opponent of the drug. Cf. G. Baglivi, Opera omnia medico-practica, et anatomica, 6th edn, Leyden, Sumptibus Anisson, & Joannis Posuel, 1704, pp. 463-465, 613-615. For Baglivi's attitude to Peruvian bark, cf. Jarcho, op. cit., General Introduction above, note 26, p. 167.


transferability of Minot's "externally" made experiments on animal blood. In therapy, the argument ran, the bark was administered internally, and thus dissolved in the stomach and pervaded by ferments from other places, before it entered the blood. It might therefore act differently from its effect on freshly drawn animal blood. The critic added examples of differences in the effects of substances depending on their mode of administration: aloe was applied externally by surgeons to control bleeding, but is opened the orifices of veins when given internally; sugar killed worms outside the body, but it was not an internal anthelmintic; and vinegar clotted blood externally, as shown by Minot, yet the ancients gave oxycratum (i.e. a mixture including vinegar and water) internally to remove blood clots from the chest. Similarly, the anonymous commentator doubted the significance of Minot's intravenous injection experiment on the dog. As he pointed out, the Italian physician Giorgio Baglivi (1668-1707) had found coagulated blood in the lungs after injecting spirit of wine in such an animal experiment. Yet nobody thought that spirit of wine produced coagulation when applied externally.\(^55\)

On the whole this critique of Minot's work indicates that the new experimental approach to the pharmacology of Peruvian bark was by no means readily accepted. Indeed more characteristic of the period were largely speculative accounts of the drug's action, based on some clinical observations or on iatromechanical ideas. Prominent examples for such concepts were those of Minot's English colleagues Richard Morton (1637-1698) and William Cole (1635-1716).

In his work *Exercitationes de morbis universalibus acutis* (1692) Richard Morton, a fellow and censor of the Royal College of Physicians of London, developed the theory that intermittent and continuous fevers were produced by

poisonous ferments. Peruvian bark, he claimed, acted as an "antidote" to these poisons. The arguments to support this interpretation were derived from his clinical experiences (of which he gave some examples): the bark acted fast, independently of the patient's humours and temperament, and it was effective already in small doses. In other words, his theory of the drug's antidotal action was able to leave aside the controversial questions of the bark's Galenic qualities and its effects on the humours. The disadvantage of Morton's concept was that it smacked of empiricism, and accordingly its learned author stressed repeatedly that his "hypothesis" was rational, philosophical, and aetiological. It is known that Morton admired Sydenham, whom he called a "Prince of Physicians" and "a noble example for the most experienced Practitioner to walk by". It was thus obviously not the latter's neo-Hippocratic, empirical approach, from which Morton wanted to distance himself. His defensive attitude probably had another reason. In the early 1680s it had been revealed that the active ingredient of Sir Robert Talbor's (c. 1642-1681) famous and secret "English Remedy" against the ague had simply been cinchona bark. Morton


58 Cf. Morton, op. cit., note 56 above, vol. 2, "Ad Lectorem" [pp. 15-17]. There is some similarity to Willis' ideas, yet Morton did not acknowledge his influence in this context.

despised Talbor as a "quack" and "vagabond", and it seems very likely that the London physician was anxious to avoid any impression that he advocated this empiric's medicine.\(^60\)

In 1693 the Worcester physician William Cole, a former correspondent of Sydenham, published "new hypotheses" on intermittent fevers and the Peruvian bark's mode of action, which were even more speculative than those of Morton. Assuming that intermittents were produced by affections of the nervous system, he developed corpuscular and mechanical explanations of the bark's efficacy.\(^61\) Absorbed into the circulating blood the drug's particles, he thought, were carried into the small "glands" of the cerebral cortex. Partly they were deposited here, partly they moved with the nervous fluid or "succus nervosus" (which the glands secreted) into the brain's medulla and further into the roots of the nerves. The particles of the bark acted in three ways. Firstly, sticking in the ducts of the cerebral glands and medulla, they made the neighbouring parts contract and thus relaxed the tone of those ducts. Secondly, they prevented the thicker and heterogeneous particles of the blood - which in Cole's view constituted the "materia morbifica" - from entering the ducts. At the same time they allowed the finer parts in, which were converted into the nervous fluid. And thirdly, they joined the particles of the nervous fluid, preventing cohesions and making it flow evenly.


\(^{61}\) William Cole, Novae hypotheseos, ad explicanda febrium intermittentium symptomata et typos excogitatae hypothyposis. Una cum aetiologya remediorum; speciatim vero de curatione per corticem Peruvianum [1st edn 1693], Amsterdam, Apud Georgium Gallet, 1698. See also Jarcho, op. cit., General Introduction above, note 26, p. 253.
For a good number of years Cole's "new hypotheses" seem to have found wide attention - to judge from the repeated editions of his work until the early eighteenth century. It certainly illustrated the "explanatory power" of iatrophysics at the time. In fact one of the leading representatives of iatrophysics and iatromathematics, Archibald Pitcairne (1652-1713) of Edinburgh, in his *Dissertationes medicae* (1701) attacked a chemical interpretation of remedies, including the Peruvian bark. If its efficacy in fevers was caused by an acid or alkaline property, he argued, other barks with "Acid or Alkalic Powers" should equally act as febrifuges - which they did not. Pitcairne had observed that an infusion of the "Cortex Peruvianus" in water tinged a solution of turnsole juice red, which was a sign of acidity. But a decoction of Sassafras wood produced this reaction to a greater degree, and still the Peruvian bark was greatly superior in curing intermittent fevers. Moreover, an "Acid Spirit drawn from Jesuit's Bark" was ineffective as a febrifuge, as were spirits of this kind gained from other barks. Having thus discarded the iatrochemical view on cinchona, Pitcairne did not proceed, however, to provide an alternative, mechanical (or other) explanation. He only warned that to assume now "hidden Properties" in the drug's salts meant to "fly off again from the boasted Powers of Acids and Alkalies, and fall back shamefully to occult Qualities, and such Trifles".

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63 Sassafras albidum was introduced as a medicinal drug from North America in the late 16th century. See Estes, op. cit., General Introduction above, note 74, p. 173.

64 Cf. Archibald Pitcairne, 'Dissertatio brevis de opera quam praeestant corpora saliave acida dicta vel alcalica, in
Despite such arguments, in the eighteenth century Cole's mechanical and corpuscular interpretation appears to have had eventually the same fate as Morton's antidote-theory of the Peruvian bark: it became a mere item of historical reviews and was eventually forgotten. Characteristic are probably the judgements of the Göttingen professor of medicine Ernst Gottfried Baldinger (1738-1804) in his 'Geschichte der Chinarinde' (History of the cinchona bark) of 1778. He valued Morton for his historical account of the introduction of the bark, and as "one of the bravest defenders" of the drug, but thought that "his theories were otherwise, however, not the best, especially on the proximate causes of fevers, and the way in which the bark heals with its properties". Cole's "nervous" theory was not even mentioned by Baldinger, who noted only that "William Cole, was also a great friend of the cinchona bark in cold fevers."65 Waring's Bibliotheca therapeutica, a century later, lists neither Morton's nor Cole's work.


65 Cf. Ernst Gottfried Baldinger, 'Geschichte der Chinarinde und ihrer Wirkungen', in idem (ed.), Magazin vor Ärzte, 1778, 2: 993-1030, 1049-1067, on pp. 995-996, 1001, 1027. See also Thomas Molyneux's early criticism of Morton's work, in a letter to John Locke of 20 December 1692, where he calls Morton's theory of fevers "a sort of mere waking Dream". Locke, in his answer of 20 January 1693, wondered
In the shadow of theoretical controversy, however, some further experimental work on the Peruvian bark had been carried out, which also arrived at an iatromechanical explanation. At the newly founded University of Halle, the medical student Johann Balthasar Schondorff in 1694 defended a thesis on the "mode of operation, use and abuse of cinchona bark" under his soon famous teacher Friedrich Hoffmann (1660-1742). Schondorff and Hoffmann provided not only a critical review of current opinions on the bark's pharmacology, but reported observations and experiments of their own, resulting in a pharmacological theory and therapeutic conclusions. Among the recent theories which they rejected was the iatrochemical concept in the sense of Minot, and Morton's antidote theory.

In view of the former, they mixed powdered Peruvian bark with aqua fortis (nitric acid), which caused some bubbles when heated. While this indicated some alkaline quality of the bark, its powder was not dissolved in the acid, nor did the latter lose its "corrosive" property. Schondorff and Hoffmann concluded that it was wrong to assume that the alkalinity of cinchona destroyed the acid ferments in fevers (as Minot had suggested). Morton was also wrong, they argued, because if the bark was a real "alexipharmacon" or antidote, it should be a very useful medicine in other "poisonings", such as plague, malignant fevers, and in bites of vipers and rabid dogs. But there were no cases or observations that showed such efficacy. Moreover, they said, it was simply not true that Peruvian.

"that after the Pattern Dr. Sydenham has set them of a better Way, Men should return again to that Romance Way of Physick". Cf. Dewhurst, op. cit., note 59 above, pp. 178-179.

66 Johann Balthasar Schondorff and Friedrich Hoffmann (Praeses), Disputatio inauguralis de Chinae Chinae modo operandi, usu et abusu (24.6.1694), Halle, Christoph Andreas Zeitler, 1704.
bark helped every person and in a very small dose, as Morton had written in support of his theory.  

Schondorff examined the powdered bark with a microscope, observing that it consisted of "long and rough filaments and particles with innumerable pores". He burned it in a pipe, noting that the smoke slightly constricted the mouth and throat. And he distilled it, finding that it lost its bitterness and that its components - spirit, oil, and caput mortuum (precipitate) - had no febrifugal power of their own, even if joined together again. From a number of simple chemical tests, he further concluded that the bark contained a resinous and balsamic principle together with earthy particles. Finally, he added a warm decoction of the bark to freshly let venous blood, which immediately formed a blackish clot. When the same experiment was made with milk, it started to turn to cheese.

From all this, Schondorff and his teacher Hoffmann drew two pharmacological conclusions: firstly, that the Peruvian bark did not act through one single component, but through a combination of all of them, resulting in a "peculiar power against fevers". This was conveniently backed up with the authority of Galen, who had taught that many poisons and remedies acted "tota substantia" (i.e. through their whole substance). Secondly, they assumed that the beneficial  

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67 Ibid., pp. 5-7. Similarly, the contemporary author of the Tractatus simplex de cortice Peruviano, ed. by Jarcho, note 10 above, pp. 46-47, argued against Morton that practitioners viewed the bark with suspicion in malignant fevers (which they should not, if it was an antidote). He also pointed out that the best known antidotes were not efficient in intermittent fevers, whereas the bark was.

68 Schondorff and Hoffmann, op. cit., note 66 above, pp. 9-11, 13-14.

effects of the bark in fevers came mostly from an astringent and tonic power: it gave a firmer texture to the blood, made the fibres more vigorous, strengthened the "tubuli" of the skin, and - by constricting also the nervous "tubuli" - concentrated the animal spirits. Blood, animal spirits and all fluids moved evenly, fulfilled their functions, and became thus more able to eliminate the "morbific matter" from the body. Moreover, the blood having obtained a stronger texture, the "febrile ferment" could less easily excite it to tumultuous movements.\textsuperscript{70} It was like in a thermometer, Schondorff and Hoffmann explained. If filled with a thin and spirituous fluid, warmth caused greater extension than in a thicker liquor.

In the same way, the blood in the tubules of our body, which represent a true thermometer, when made thicker by the bark, cannot so [easily] be expanded and rarefied by warmth, and therefore the warmth cannot excite such grave symptoms.\textsuperscript{71}

Schondorff and his professor had thus ultimately arrived at a iatromechanical interpretation of the Peruvian bark’s "modus operandi" - which was in keeping with Hoffmann's overall conception of physiology and medicine. They had worked chemically as well, but the results in this area were rather used to discard iatrochemical claims about the bark than to build their own theory.

Hoffmann and Schondorff finally tried to draw therapeutic conclusions from their theory of an astringent qualitate, nempe aut calefaciendo, aut refrigerando, aut humectando, aut siccando, aut dictorum conjugatione quapiam, aut tota sua substantia, sicuti complura deleteriorum, seu lethalium medicamentorum, nec paucu alexeteriorum, seu amuletorum, tum purgantia omnia, ac pleraque eorum quae attrahentia nuncupant.

\textsuperscript{70} Schondorff and Hoffmann, op. cit., note 66 above, pp. 12-13.

\textsuperscript{71} Cf. ibid., p. 14.
and tonic action of cinchona bark. But here, it seems, their arguments became contradictory and confused. Contrary to common practice in intermittent fevers (which was based on the *Schedula Romana*), they strongly advised *not* to give the bark shortly before the next fever fit, but to start with the remedy in the decline of a paroxysm. Their comprehensible reason for the latter was that the blood would be more "calm and contracted" in the decline of a fit and thus yield more easily to the constrictive power of the bark. But against the administration of the bark before the fit, they argued that, since the remedy constricted the texture of the blood, the disturbing febrile ferment would find "greater resistance" and "punish" this with even "greater tumult, heat, and impetus".\(^72\) As outlined above, however, in their comparison with the thermometer, the very same increase of the texture of the blood (through the bark) had been cited as an explanation of the remedy's beneficial, febrifugal effect! Of course the reason for such an inner contradiction in argument may simply be sought in the limited academic experience of Schondorff, or in an oversight of Hoffmann. Yet, there may be another, more important explanation. With reference to giving the bark before or in a fit, they had stated: "Many times we have observed an unhappy outcome, and that always grave symptoms were excited, such as spastic contractions, and that praecordial anxieties were increased..."; and in the same context they quoted Sydenham's observation that the bark given in this way had actually cost some patients' lives.\(^73\) Obviously there had been clinical evidence that cinchona might be harmful, if administered before the paroxysm. Schondorff and Hoffmann thus seem to have tried afterwards to fit their pharmacological theory to the clinical "facts"

\(^72\) Ibid., pp. 17, 19.

\(^73\) Ibid., p. 19. Cf. Sydenham above.
- and it was here, where their efforts seem to have gone wrong.

It is also remarkable, that the in vitro trials with Peruvian bark on blood, performed independently by Schondorff in Halle and Minot in Paris, had quite opposite results: coagulation in the former, rarefaction of the blood in the latter. Minot's experimentation, it seems, was more carefully planned. Yet their experiments are not directly comparable, because they used different "solvents" for the bark: in Minot it had been wine, in Schondorff water (decoction). Subsequent researchers, as will be shown in the following, did consider the question of solvents in such experiments - but still the results remained contradictory. 

John Freind's (1675-1728) study of 1703 on various substances that would either promote or diminish menstruation ("emmenagoga" and "astringentia") included not only opiates (as discussed above), but also Peruvian bark.° His experiments with the bark were quite similar to those of Minot, whom he did not quote, however - despite the fact that the French doctor's work had just gone through its third edition.°° Admixing Tinctura Corticis Peruviani (i.e. an extract of the bark made with spirit of wine) with fresh arterial blood from a dog, Freind noted that the blood became thick and dark. The next day it appeared brighter, but even more firmly coagulated. By contrast, an infusion of the bark in wine made the same dog's blood very fluid and gave it "a most elegant colour". The same discrepancy was observed, when Freind experimented on human blood "serum" (i.e. plasma): a decoction of the cinchona bark (in water) increased its fluidity, while the tincture coagulated it to some extent. Having seen the same difference with other

° Freind, op. cit., part B above, note 57.

°° Jacques Minot, De la nature, et des causes de la fièvre...revue et augmentée de quelques remarques sur l'opium, Paris, Laurent d'Houry, 1701.
substances, he concluded that it was the spirit of wine in the tincture, which caused coagulation. The Peruvian bark itself, when dissolved in water or wine, could be seen as a substance attenuating and rarefying the blood. Its mode of action was in this respect similar to that of opium, with which it also shared an "acrid and bitter" taste, indicating a "volatile salt" as the active principle.\(^7\)

Interestingly, Minot in the third edition of his book (mentioned above) had added a part on opium, in which he too pointed out that this drug rarefied the blood as well. On this assumption he even suggested the combination of Peruvian bark and opium in the treatment of fevers. Other than Freind after him, however, Minot did not report here about experiments with opium.\(^7\) Perhaps he was influenced in this point by Pitcairne, who in 1693 had suggested on theoretical grounds that opium acted by rarefaction of the blood and subsequent distension of the arteries.\(^7\)

Similarly to Schondorff and Pitcairne before him, Freind also tested the Peruvian bark for its acidity or alkalinity, mixing its tincture with syrup of violets. This mixture assumed a watery colour, as opposed to the change from blue to green that an alkaline substance would have effected in the syrup. Since Freind's other tests suggested that his "emmenagoga" were alkaline substances, this result did not easily fit. In fact he hesitated to actually count the bark among the "emmenagoga", but saw it as a substance very close to them, "because of its excellent power in

\(^6\) Freind, op. cit, part B above, note 57, pp. 173-181.

\(^7\) Minot, op. cit., note 75 above, dedication to Guy Crescent Fagon, First Physician of the King [pp. 2-3], pp. 223-232.

attenuating the blood". This property was finally "confirmed" by Freind - as Minot had done it - in a living animal. Having injected one and a half ounces of a decoction of Peruvian bark into a dog's jugular vein, he found the animal's heart beat initially strong and frequent. But after a quarter of an hour the dog began to show frequent spasms, and following injection of a further half ounce, it died in a kind of tetanus. The postmortem examination revealed the bark's supposed rarefying effect on the blood: bright red and liquid it left the crural and axillary veins. When the chest was opened on the next day, the lungs were very red and distended; and while blood was found in a compact mass in the right ventricle of the heart, it was still fluid in the left ventricle, and flowed out being "liquid" and "thinner than in the natural state", as the portal and jugular veins were cut.

Besides in vitro and animal experimentation, and speculation based on some clinical observations, microscopy was used in the early efforts to understand the Peruvian bark's action, as briefly mentioned in Schondorff and Hoffmann above. In 1707 one of the pioneers of microscopy, Anthony van Leeuwenhoek (1632-1723), reported his observations on the cinchona bark to the Royal Society. He had become interested in the remedy through a physician acquainted with him, Angelus van Wikhuysen of Middleburgh in Zealand, who had told him that the powdered bark infused in wine cured fever patients with great success ("...hardly one in a hundred have failed of [sic] being cured"). The famous

80 Ibid., pp. 186-187. In today's perspective, fluid blood in the corpse would probably be interpreted as a sign of death by suffocation.
Dutch microscopist observed that this "Bark called China China" consisted of long, round, yellowish, and somewhat transparent particles, with both ends running to a point. In addition he saw vessels in the bark, which originated from the wood and at first glance appeared to nourish the long particles. However, despite various sections through these vessels, Leeuwenhoek could not find one that was actually joined to those particles. Accordingly he assumed that the latter were "Coagulated Salts". With this hypothesis, he immersed a piece of the Peruvian bark into brandy for 24 hours, expecting that some of the salts had "gone over" to the alcohol after that time. When he subsequently put a drop of this brandy under the microscope, however, he noted to his surprise that the fluid coagulated to a white substance, which consisted of "an unconceivably vast Number of small Particles". In other words, he found a suspension of minute bark particles, not a solution of its supposed "salts". The same phenomenon could be observed, when he used wine - the common "solvent" for the bark.

So far, Leeuwenhoek's observations and experiments had been rather botanical and pharmaceutical than pharmacological. Yet, like Minot, Schondorff, and Freind - to none of whom he referred - he also tested the bark on blood. Having pricked one of his fingers with a needle, he mixed some drops of his blood with about the same quantity of the Peruvian bark brandy, and examined it with his microscope:

...with great Amazement [I] observed the Operation of this mingled Stuff, in which there was such a fermenting and running about of the Parts, that it is impossible for me to express to you; and in these Commotions I observed that most of the Globules of the Blood (which are the occasion of its redness) were dissolved, and I judged that this fermentation

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82 Ibid., pp. 2446-2447.
83 Cf. ibid., pp. 2447-2452.
lasted about a quarter of a Minute; and because it was very diverting, I repeated the Experiment several times.®

No such "fermentation" could be seen when this experiment was repeated with an infusion of the bark in wine, but also here he observed "in some few places the Globules of Blood Coagulated after such manner, that it appeared like a very thin Membrane torn to pieces, and several thin Fibres or Threads thereof lay about".®

From a modern perspective, Leeuwenhoek obviously described haemolytic reactions, which we would now rather ascribe to the alcohol content of his cinchona preparations than to the bark itself. In his own understanding, however, these reactions signified that the usual coagulation of the blood was impeded. In fact, with respect to the last experiment, he emphasized that he "never saw so little Coagulation of the Globules of the Blood when mingled with any Liquid as I perceived with this mixture". On this basis Leeuwenhoek ultimately arrived at a theory of the Peruvian bark's mode of action, which - like that of Minot and Freind - regarded the drug's rarefying effect on the blood as central. The digested and absorbed bark had "such an Affinity with the Serum of the Blood, as to hinder its Separation, and so keeps the Blood in such a Fluid state, that the Distemper which we call a Fever is thereby prevented."®

In 1712, five years after Leeuwenhoek's article on Peruvian bark appeared in the Philosophical Transactions of the Royal Society, Francesco Torti (1658-1741) of Modena published the first edition of his comprehensive book on the treatment of fevers, the Therapeutice specialis. As Jarcho

® Ibid., pp. 2453-2454.
® Ibid., p. 2454.
® Ibid.
has shown in his detailed discussion of this "classic", Torti's work was differentiated and critical, both in diagnostics and therapeutics. It was largely based on its author's clinical experience. Pharmacological experimentation did not play a great role in it, but the Modena professor did perform a number of in vitro trials with cinchona bark to explore its action, and in their interpretation he also showed circumspection and a critical mind.

In a first series he added the bark to a variety of fluids of vegetable and animal origin, both separately and together: to lemon and orange juice, to vinegar, freshwater and salt water, oil, bovine bile, canine lymph, human urine, saliva, and others. The taste of these fluids appeared slightly bitter and styptic from the bark, but so little, as Torti noted, that no febrifugal power would have been transmitted to them. Likewise the bark, having absorbed these fluids and dried again, obtained to some extent their tastes. But this would have happened, he thought, to any bitter and styptic, non-febrifugal bark as well.

Not satisfied with these results, Torti proceeded to experiment on human blood and bile. Having filled four glass vessels with blood from a healthy person (obtained in one phlebotomy), he added powdered Peruvian bark to one and pulverised bark of an apple tree to another. Nothing was added to the remaining two vessels; they obviously served as controls. Compared to the pure blood in these vessels, coagulation was slightly delayed in the blood with Peruvian bark, but equally so in the blood with apple tree bark. Moreover, both blood portions with bark adhered less firmly

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87 See Jarcho, op. cit., General Introduction above, note 26, chapters 9-11.

88 Francesco Torti, Therapeutice specialis ad febres periodicas perniciosas, 3rd, enl. edn, Venice, Apud Laurentium Basilium, 1732, p. 23.
to the walls of their vessels than the two portions of pure blood. Torti concluded that it was merely the mechanical effect of the powder that caused these effects, since shaking and mixing pulverised bark and blood had led to "rupture" and "distraction" of the latter's "fibres''. He was therefore not prepared to follow "other" authors (he gave no names), who had reported that Peruvian bark impeded the coagulation of venous blood. Neither did his experiments with human bile elucidate the drug's mode of action. The bile was absorbed by the bark, but this was, as he declared, a simple physical phenomenon, which occurred in other barks and fluids as well. Ultimately therefore, Torti admitted that he had made these experiments in vain: "nothing beyond what I have told could be deduced from them".  

Seen as a whole, the early efforts to explain the Peruvian bark's efficacy in fevers may appear rather heterogeneous. There had been a variety of methods, partly contradictory results, and marked differences in interpretation. But this should not make us overlook the fact that they converged on two basic points. Firstly, fevers, especially the intermittents, were thought to be produced by a pathological condition of the blood: this condition could be due to unnatural fermentation (Willis), febrile ferments (Schondorff and Hoffmann), or poisonous ferments (Morton), to thick and heterogeneous particles (Cole), or to excessive acids (Minot). Secondly, particles of the bark were believed to act on the changed blood, counteracting the "morbid matter": by producing a "new fermentation" (Willis), by acting as an antidote (Morton), as a filter when the nervous fluid was produced from the blood (Cole), as an antacid (Minot), by "rarefying" the blood (Minot, Freind, Leeuwenhoek), or (to the opposite) by giving the blood a "firmer texture" (Schondorff and

89 Cf. ibid., pp. 23-25.
Hoffmann). As in the case of opium, around 1700 a general pharmacological conception emerged: the Peruvian bark was a substance that acted via the blood, rather than through the nerves.  

4. The Stahlian critique of cinchona treatment

Another "common denominator" of the experimentalists and theorists discussed above, was their conviction of the therapeutic benefits of the Peruvian bark, particularly in tertian and quartan fevers, the so-called "simple" or "pure" forms of intermittents. As also Jarcho's extensive study suggests, the bark was widely accepted in European medicine at the beginning of the eighteenth century. However, there was still resistance from one influential "school" of physicians: that of Hoffmann's colleague and intellectual rival at Halle, Georg Ernst Stahl (1659-1734).

For Stahlians, fever - like pain - was a natural response of the soul-guided body in its fight against the peccant matter. As it was therefore wrong simply to numb pain with opium, so it was wrong to administer Peruvian bark to suppress fevers. In 1706 Stahl had this view publicly defended in a disputation on tertian fever by one of his students, R. Gottfried Meyer. For Meyer and his Praeses Stahl the cause of this disease lay in some damage of the stomach, and vomiting and other symptoms were seen as

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90 This is even true for Cole, who emphasized the role of the nervous system in fevers and their cure (see above).

"efforts of nature in protecting herself". Accordingly, cinchona bark was rejected by Stahl and his pupil, since it acted as a kind of "oppressor of rising nature". Instead they put their therapeutic hopes in measures to assist nature, with digestive salts and absorbent medicines.\(^2\)

Not surprisingly, the Stahlian opinion of the bark caused some controversy. Johann Gottfried Berger (1659-1736) of the nearby University of Wittenberg defended the drug in a disputation of one of his students, arguing in agreement with Torti that it was a safe and effective medicine, if given in sufficiently high and frequent doses, and if administered as the pure powder rather than as some extract.\(^3\) Similary Hoffmann responded with a dissertation, which repeated his theory of the beneficial roborating and tonic effects of the bark. He admitted that Peruvian bark, when "promiscuously and empirically" used, had done harm through severe relapses and other diseases, such as hydrops after a quartan fever and hypochondriacal disorders after a tertian. But he strictly disagreed with the view that the bark was absolutely and always noxious. If harm was done, he assured, this had not to be attributed to the remedy as such, but to its wrong use.\(^4\)


\(^3\) Johann Gottfried Berger and Heinrich David Stieler, 'De Chinchina ab iniquis judiciis vindicata' (Wittenberg 1711), in Haller, op. cit., General Introduction above, note 32, vol. 5, pp. 41-59; and Haller's short review, ibid., vol. 6, p. 836.

\(^4\) Friedrich Hoffmann, 'De recto corticis chinae usu in febribus intermittentibus' (Halle 1728), in idem, Opuscula medico-practica seu dissertationes selectiores ante diversis temporibus editae nunc revisae et auctiores, Halle, Officina Rengeriana, 1736, pp. 372-403, on pp. 377-378, 403.
This seems to have been the general view of the bark's advocates, also outside the German territories. For example, a dissertation of 1727 on tertian and quartan fevers, defended in Boerhaave's Leyden by a Dutch student named Johann Anton Kloek, explained the circumstances, in which it was appropriate to administer Peruvian bark. The drug being astringent, he argued, it was only safe to give it after the morbific matter had been evacuated and intermission had set in, in order to stop febrile movements which continued "out of simple habit". With their method of giving the bark at the beginning of a fever paroxysm, "the Jesuits" had killed many, he thought. But the (moderate) advocates of cinchona were matched by supporters of Stahl's opinion, such as the medical professors Heinrich Heinrici in Halle and Andreas Ottomar Goelicke (1671-1744) in Frankfurt/Oder, who stated that the bark was harmful in any circumstances. Hoffmann's view that it had astringent powers, was turned against the drug by Stahlians. Fever was a healing method of nature, they argued, in which the cause of the disease was expelled from the body by way of secretion and excretion. Therefore the humours should be fluid and the ways open. Peruvian bark, however, as an astringent, thickened the fluids and narrowed or shut the small "excretory channels". The

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95 Johann Anton Kloek, *Dissertatio medica inauguralis de usu et abusu corticis Peruviani in febris intermittentibus tertiana et quartana*, Leyden, Apud Conradum Wishoff, 1727, pp. 3-4, 16-18. See also Jarcho, op. cit., General Introduction above, note 26, p. 87, who quotes the view of the Paris physician Jean Baptiste Sénac (c. 1693-1770) that charges against the bark by the Dutch and Germans had to be attributed "to an improper method of using it". Sénac also thought that the patient should be purged and bled, before the bark was given in small doses in the phase of intermission. Cf. [J. B. Sénac], *De recondita febrium intermittentium, tum remittentium natura, et de earum curatione*, 2nd rev. and enl. edn, Geneva, Fratres de Tournes, 1769, pp. 324-347.

96 See Baldinger, op. cit., note 65 above, p. 1055.
morbific matter was consequently locked inside the body, producing relapses and other serious conditions. In essence, the Stahlian critics thus used the old, seventeenth-century argumentation against the bark in a new, partly animist, partly mechanist framework.

As Baldinger observed in 1778 in his history of cinchona, the advocates of the bark had ultimately been victorious, but it had been a struggle. His account suggests that the acceptance of the remedy was delayed by Stahlian opposition in the German lands, compared to other European countries. The latest German defence of Peruvian bark had only been published in 1769. Baldinger quoted examples from the 1770s, where the bark was given in extremely small (and probably ineffective) doses, or was abhorred as "poison". And he had still been an eye-witness of the "hatred against the bark in Halle".

The "victory of truth" that Baldinger wanted to document with his historical account of the cinchona bark not only referred to the drug's eventual acceptance as a febrifuge. He also meant the discovery of other therapeutic uses of the bark, most of which, he said, had been made by "the English". In fact, the probably most important new indication for cinchona, "gangrene", had been introduced empirically by British surgeons during the 1730s. This development can serve as a "case study" into the Peruvian bark's way from a specific febrifuge to an universal remedy,

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98 Baldinger, op. cit., note 65 above.


100 Baldinger, op. cit, note 65 above, pp. 1054, 1059-1060.

101 Ibid., p. 1027.
and it will therefore be discussed in some detail in the following sections.

5. A surgeons' matter: the bark in "gangrene"

When we refer to "gangrene" as a new indication for the use of Peruvian bark, we have to consider that in the eighteenth century this diagnosis seems to have encompassed a variety of conditions, including some complicated forms of leg ulcers. As Irvine Loudon has shown, leg ulcers were very common in Britain during the eighteenth and early nineteenth centuries, possibly due to widespread ascorbic acid deficiency, not only in the navy and army, but also among the civilian population. The "gangrenous ulcer" can be found in current classifications of ulcers in that period. Moreover, as for example John Douglas, a leading London surgeon of the early eighteenth century, explained, "gangrene", as a "superficial mortification", had to be distinguished from "sphacelus", in which the mortification reached deeply into the flesh and bone. In contemporary understanding, gangrene and ulcers had also a partially common aetiology. Both could be due to "external causes", such as wounds, but more importantly, faulty, acrid humours in the blood were thought to be the "internal cause" of both conditions. Accordingly, treatment was also similar: diverse externally applied medicines; incisions and scarifications

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103 Loudon, op. cit, note 102 above, p. 266.

104 John Douglas, *A short account of mortifications, and of the surprising effect of the bark, in putting a stop to their progress, etc.*, London, John Nourse, 1732.
to drain the harmful humour; and finally, as *ultima ratio*, amputation of the limb.\(^{105}\) Often, it seems, ulcers and gangrene were regarded as rather gradually than essentially different conditions. A "grey area" between the two diagnoses should therefore be kept in mind, when one reads about the successes with cinchona bark in "gangrene", which will be discussed in the following.

At the beginning of the "story" stood the otherwise little known Northampton surgeon John Rushworth (1669-1736). In October 1731 he wrote a letter to the "Masters or Governors of the Mystery and Commonalty of Barbers and Chirurgeons of London", reporting a case which he claimed to have communicated earlier to "some Physicians and Surgeons" and to Sir Hans Sloane. The case, actually dating back to 1715, was that of a man with a "mortification" on the foot "from an internal Cause". The patient had high fever and an irregular pulse. Without success Rushworth had tried the usual treatment: incisions into the gangrenous part, scarifications in the inflamed neighbouring areas, and "common Applications" (i.e. fomentations and topic treatment with various medicines). Suspecting that the fault lay "in the Blood and Juices", he was reluctant to amputate, since the gangrene might return in the stump. In common judgement, this was a lost case. As Douglas later commented, "Mortifications from an internal Cause, are given up by Physicians as Incurable".\(^{106}\) When the patient's fever went into a remission, Rushworth gave him Peruvian bark, apparently to mitigate the next febrile attack. To his surprise the fever did not return. He amputated the leg, and the patient recovered completely. "I have since several times had the Experience of the good Effects of it [i.e. the


\(^{106}\) Douglas, op. cit., note 104 above, p. 6.
bark] in the like Case", added Rushworth, "which has been no small Satisfaction to me."\(^{107}\)

Despite the rather obscure origins of this case report, it met a positive response by the then acting Master of the Barber-Surgeons' Company and Sergeant Surgeon to King George II, Claudius Amyand. Not only was Rushworth's letter read out in February 1732 before the Company's court of assistants, but Amyand himself tried the Peruvian bark treatment of patients with gangrene. By the end of July of the same year, when he wrote back to his Northampton colleague, he claimed to have had seven successful cases. Among them was that of a 78-year-old man suffering from "a Gangreen after a Phlegmon", in whom (as Amyand claimed) the progress of the gangrene was stopped after he had been given the bark.\(^{108}\) Full of optimism the Royal surgeon concluded:

... I think it evident that we may be as sure of getting the Better of, or at least of stopping a Mortification, from any internal Cause, by the Bark, as conquering an Ague thereby.\(^{109}\)

Rushworth, understandably pleased with this positive assessment, answered immediately, reporting the case of a 50-year-old woman, whose gangrene returned after leaving off the bark, but who "perfectly recover'd" after treatment had been resumed.\(^{110}\)

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\(^{109}\) Ibid., p. 16. Also in Douglas, op. cit., note 104 above, p. 36.

\(^{110}\) Letter of Rushworth to Amyand, 5 August 1732, in Rushworth, op. cit., note 107 above, pp. 22-23.
Amyand had also shown Rushworth's initial letter to John Douglas (d. 1743), surgeon to the Westminster Infirmary and Fellow of the Royal Society, who was well-known as one of London's foremost lithotomists. Having also made good experiences with the new treatment for gangrene in a patient of his own, Douglas congratulated the Northampton surgeon:

"I think this new Use of the Bark (for which we are more oblig'd to you, than to him who first shewed the Use of it in Intermitting Fevers) is of too much Consequence, not to be communicated to the Fraternity..."

Not surprisingly, and as customary in his day, Rushworth in 1732 published the whole correspondence in a pamphlet, advertising the "Great Advantage" of his new method.

Initially, the apparently beneficial effect of Peruvian bark in patients with gangrene had been little more than a "chance observation" made by a country surgeon. Rushworth had used the drug as a febrifuge in a clinical condition, in which it would normally not have been applied. The span of more than fifteen years until publication indicates that at first little attention was paid to his "discovery", which might soon have sunk again into oblivion. It obviously gained momentum, however, through the support of two leading surgeons, and it is this circumstance which made this new development historically remarkable. Certainly, if we trust Amyand's and Douglas' printed words, they had confirmed Rushworth's observation in cases of their own and were impressed by therapeutic success. As became very soon clear, however, the new treatment also involved an important professional issue.

In the same year, 1732, Douglas published his successful case in full detail in a pamphlet of his own. The motto on the title page reflected the enthusiasm that he and Amyand had also expressed in their letters to Rushworth:

\[\text{\textsuperscript{11}} \text{Ibid., p. 32.}\]
Douglas narrated, almost day by day, the case history of an about 50-year-old "gentleman", who suffered from spreading gangrene at the back of his right foot. The patient, being "the last Branch of a very ancient and considerable Family", was not only treated by the surgeon Douglas, but also by the physician Dr Newington of Greenwich and the surgeon-apothecary Mr Wade of Bromley. In addition, the Royal Sergeant Surgeon Ambrose Dickins and the eminent London surgeon and lithotomist William Cheselden (1688-1752) acted as consultants. There was general agreement that the gangrene had an "internal" cause in the "poorness" of the patient's blood. Amputation was therefore regarded as useless. The other common forms of treatment, externally with fomentations, dressings, scarifications, and cautery, and internally with Confectio Raleigh as a cordial and theriac as an "antidote", had all failed. The patient had high fever. His death was expected very soon.

In this situation Dickins suggested Peruvian bark, having learnt about the new method from his colleague Amyand. Powdered bark was made into boles, which the patient was asked to swallow every four hours. After four to five doses the patient started to feel better, and his foot soon began to suppurate. The cinchona bark treatment was continued, and within the next four months Douglas successively amputated toes, metatarsal and tarsal bones, until the whole foot was taken off. The stump healed, and eventually a prosthesis was fitted.

112 "What medicine does not cure, the steel cures; what the steel does not cure, fire cures; what fire does not cure, the bark cures; what the bark does not cure, is incurable." Douglas, op. cit., note 104 above, title page.
If one considers just these "facts", this case was probably not much different from those of Rushworth or Amyand, apart from the patient's social status and (therefore) the number of healers involved. But Douglas' lengthy account was interspersed with revealing remarks, which belittled the role of the physician, while elevating that of the surgeon. When it came to try the Peruvian bark in this case, he noted, Dr Newington refused to write the prescription, "alleging it to be a Practice so much out of the Way, that he would not have it seen under his Hand".\textsuperscript{113} With sarcasm Douglas added:

\textit{Which is not at all strange, considering it was a Medicine cook'd up by a Parcel of Surgeons, who had no Authority (except Experience) to alter the establish'd Practice.}\textsuperscript{114}

The morning after the patient had been given the remedy, "The Doctor, supposing him to be dead, did not come", Douglas laconically remarked in his entry for this day.\textsuperscript{115} And in a postscript to the case history, he reported a further case of the same kind, in which the doctor in charge likewise refused to follow Douglas' advice to give the bark. Left without it, this patient died within twenty-four hours.\textsuperscript{116}

By contrast, in the comments on his successful case, Douglas used Rushworth's therapeutic "discovery" as a showpiece of the surgeon's role in medical progress. The success of surgical empiricism was pitched against the alleged inefficiency of the learned speculations of physicians. Referring to Rushworth he wrote:

\textsuperscript{113} Ibid., p. 14.
\textsuperscript{114} Ibid. Emphasis in the original text.
\textsuperscript{115} Ibid., p. 15.
\textsuperscript{116} Ibid., pp. 44-48.
Query, Whither a Surgeon, thus directed by Providence, had not as good an Authority to prescribe internal Medicines as any Alma-Mater House in Europe could give him? Nay, the Success was extraordinary as well as his Authority; for though he order'd a Common Medicine in an Uncommon Case, yet he saved his Patient, who would infallibly have drop'd through his Fingers, had he persisted in the Method established by Law... Physicians have for many Years, not to say Ages, settled by their Hypotheses and Theories of Mortifications, that the best Method of putting a Stop to their Progress, was to give Sudorific and Alexipharmick Medicines; yet now a Plain, Plodding, Country Surgeon, has overthrown, with one simple Medicine, without any Preparation, all the Hypotheses and Theories as well as Practice in Mortifications, which had been established for so many Years, and were supported by so many Scores, not to say Hundreds of Volumes, and, it is plain, did Mischief.\textsuperscript{117}

Criticizing in general the poor state of pathological and pharmacological knowledge in medicine, Douglas reminded doctors that only if this changed there would be "no more Danger of Indians or Surgeons encroaching, as it is call'd, on their Province."\textsuperscript{118} In other words, medicine had to be empirical, as long as medical theory failed to give therapeutically successful advice.

Douglas thus indicated a number of issues involved in the new treatment of gangrene. Peruvian bark, as an internally administered remedy, belonged to the realm of the physician. But to treat gangrenes (and ulcers) was mainly a surgeon's job. What made things even more difficult: a "plain" country surgeon had made a "discovery" in this internal medicine. Or, put in more positive terms: Rushworth's finding demonstrated that surgeons contributed empirically to therapeutic innovation. In fact, Douglas was keen to emphasize the surgeon's role as experimentalist, especially since in his own patient's case there had been some lay criticism on that point. An "old Gentleman" had

\textsuperscript{117} Ibid., pp. 33, 41.

\textsuperscript{118} Ibid., pp. 41-42.
visited his patient, telling him that "he heard his Surgeons had been making Experiments upon him, which might as well have killed him as cured him".¹¹⁹ Not surprisingly therefore, Douglas finished his pamphlet with a plea for clinical experimentation:

From all which I may conclude, that Experience is the only sure Guide in the Practice of both Physick and Surgery; and that until industrious, prudent, and knowing Men are allowed to make feasible Experiments, and are rewarded, instead of being roasted, when they discover any Thing really Useful, little Improvement can be expected either in PHYSICK or SURGERY.¹²⁰

Douglas' linking of a primarily therapeutic question with epistemological and professional aspects matches with what is known about the situation of English surgeons in his time. The London élite of surgeons, often associated with the hospitals, resented the old association with their lowly "brethren", the barbers, and "scientific" work was certainly a way to emphasize the difference. In 1745 the London surgeons eventually achieved formal separation from the barbers by creating a single Company of Surgeons. As Philip Wilson has recently shown, since the 1720s surgeons increasingly contributed to the Philosophical Transactions of the Royal Society - mostly case histories, but also articles on improved techniques and experimental work - in an effort to elevate their personal and professional status.¹²¹

It is therefore no surprise that also Rushworth's and Douglas' observations on Peruvian bark quickly entered the pages of this leading scientific journal. Douglas' pamphlet was immediately, extensively, and favourably reviewed by his

¹¹⁹ Ibid., p. 21.

¹²⁰ Ibid., p. 43.

¹²¹ Wilson, op. cit., General Introduction above, note 64.
brother James Douglas (1675-1742), M.D., Physician to the Queen, and F.R.S. In the same issue, the prominent London surgeon John Shipton (1680-1748) summarized Rushworth's, Amyand's, and Douglas' cases and reported two of his own, plus one from his colleague Mr Bradley. Writing in Latin, Shipton not only imitated the learned style of the doctors, but obviously aimed also at educated readers on the European Continent (with success, as will be shown below). In one of Shipton's cases, a diabetic gangrene of the foot, the bark had not helped, and the patient had died within two weeks. But since the other cases were "successes", he concluded that the remedy was generally effective in gangrenes. And not only here. The London surgeon asserted that Peruvian bark acted also as a styptic in internal and external bleedings, and that it generally stopped excessive evacuations. Perhaps warned by John Douglas' case, Shipton assured that he did not belong to those who wanted to turn their speculations into "experiments on the life and health of others". Yet, on the basis of analogy, he suggested trying the bark as well in phagedaenic (i.e. probably syphilitic) ulcers - though not without additional general treatment by a physician.

Shipton evidently wanted to confer respectability upon Rushworth's discovery. There was no theory behind the use of Peruvian bark in gangrene, except John Douglas' brief explanation that it worked by "taking off" the concomitant fever, thus allowing "nature" to form abscesses, and

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123 John Shipton, 'De usu corticis Peruviani ad gangrenam et sphacelum', ibid., pp. 434-443.

124 Cf. ibid., p. 442.

125 Ibid., pp. 442-443.
stopping mortification in this way. It was therefore all the more important to confirm the new method of treatment with new case histories, or as Douglas had put it, "one Swallow makes no Summer".

This empirical approach did in fact characterize the further history of the bark treatment in gangrene. In the next few years the Medical Essays and Observations of the Edinburgh Medical Society became a forum for experiences with this new therapeutic method. In 1735 the Shropshire surgeon Samuel Goolden and his Glasgow colleague John Paisley (c. 1698-1740) each reported one successful case. Two years later the periodical published a collection of a further eight relevant case histories, that had been communicated by the surgeons Paisley and James Calder jun. from Glasgow, by their Edinburgh fellow-surgeons William Wood, Gibson, John Douglas (d. 1751), and Alexander Monro primus (1697-1767), and by the St. Andrews professor of medicine, Thomas Simson (1696-1764). The idea was, as the editor's preface stated, to ascertain the bark's efficacy in gangrenes from different causes "by a sufficient Number of well vouched Histories". The editor, Alexander Monro primus himself, was obviously satisfied, since he concluded from the ten relevant cases so far published in his periodical that they were "sufficient to convince the most incredulous how valuable a Discovery has been made by Mr. Rushworth".

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127 Douglas, op. cit., note 104 above, p. 31; Shipton, op. cit., note 123 above, p. 443.


129 Not identical with the London surgeon and F.R.S. John Douglas, discussed above.
Nethertheless he added a further case in an article of his own in 1742, which also discussed the bark's good effects in ulcers and smallpox. 131 And the Philosophical Transactions thought the topic still important enough in 1757 to publish a report on yet another "remarkable" success with the bark in a mortification. 132

As Shipton seemed to have intended, the news about cinchona's "efficacy in gangrene" also spread to the Continent. At least four French authors - Bagieu, Boucher, Bouvart, and Marchand - soon discussed the remedy's new use. 133 For the German educated public, the Wittenberg professor of anatomy Abraham Vater (1684-1751) provided a Latin dissertation "on the admirable efficacy of cinchona in stopping gangrene" in 1735, which summarized the first English experiences. 134 His Rostock colleague Georg Christoph Detharding (1671-1747), however, who had earlier voiced criticism of lithontriptics through a student's dissertation, 135 also had doubts in this new matter. In 1746 his doctoral student J. Daniel Schäffer defended the view that there were "still doubts on the cinchona bark's efficacy in gangrene and sphacelus". 136 In two of their cases

130 'Histories of gangrenes cured by the Peruvian bark; by several hands', Med. Ess. Obs., 1737, 4: 47-65.
133 Baldinger, op. cit., note 65 above, p. 1052.
134 Abraham Vater, 'De efficacia admiranda Chinae ad gangraenam sistendam' (Wittenberg 1735), quoted in Baldinger, op. cit., note 65 above, pp. 1007, 1028.
135 See above, part A.
136 Georg Christoph Detharding and J. Daniel Schäffer, 'De corticis Chineae efficacia in gangraena et sphacelo adhuc
the bark had been given entirely in vain, in another the patient had died of a relapse. Yet in one case use of the bark seemed to have deferred death for six months, and one patient recovered. The otherwise critical Albrecht von Haller (1708-1777), commenting on Schaffer's dissertation in the late 1750s, thought that these results were not as bad as the title of the latter's work suggested. Haller's rather positive assessment of the bark's use in gangrene was matched by that of the Nuremberg physician Georg Leonhart Huth (1705-1761), who in 1760 published a collection of English and French treatises on the Peruvian bark in German translation, which included the two writings of the London surgeons John Douglas and Shipton. Referring also to the Edinburgh Medical Essays and Observations, he stated with confidence that "the fever bark, which shows such a special and reliable power in intermittents, has now found to be an equally effective remedy in gangrene from an internal cause".

However, other than the initial cases of Rushworth, Amyand, and Douglas, the later case histories, from Shipton to Monro and beyond, also included a variety of gangrenous conditions that followed from "external causes", such as diverse injuries, fractures, and gunshot wounds. Moreover, the new therapy was extended to various ulcers or "sores",

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137 Ibid., p. 845.

138 Georg Leonhart Huth (ed. and transl.), Sammlung verschiedener die Fieberrinde betreffender Abhandlungen und Nachrichten, Nuremberg, Johann Michael Seligmann, 1760. The collection further includes translations of La Condamine's account of the fever bark tree (originally in Mémoires de l'Académie Royale des Sciences, for the year 1738, publ. 1740) and of letters or articles on the bark in the Philosophical Transactions by William Oliver (1704/05), John Gray (1737/38), and John Wall (1747). See on these below.

and to smallpox, especially when no regular suppuration (as the step to healing) occurred, or the development of gangrene was feared. The idea was, as Monro explained, to assist nature "in what the Ancients called the Concoction and Maturation of the morbid Matter". Yet Monro himself, though generally positive about the new treatment, had already warned that the bark did not work in all cases of gangrene and smallpox, or might even be harmful in some of them. Well-established treatments, such as blood-letting, emetics, baths, and blisters, should therefore not be neglected. The diversity of "gangrenous" and "ulcerous" conditions in which cinchona bark was soon administered - not only orally as in the beginning, but also by clyster and externally as a topic medicine - inevitably led to the experience of therapeutic failures. The Worcester physician John Wall (1708-1776), for example, had two fatal cases among the seven smallpox patients he reported to have treated with Peruvian bark. Both of the failures he blamed on the patients' nurses or an omission of the patient herself - not on a lack of efficacy of the remedy. Another

140 Monro, op. cit., note 131 above, p. 105. See also John Wall, 'A letter...to Eward Wilmot M.D. F.R.S. and Physician to His Majesty, concerning the use of the Peruvian bark in the small pox', Phil. Trans., 1747, 44: 583-595 (also German transl. in Huth, op. cit., note 138 above); George Bayly, 'A letter...to Henry Pemberton M.D. F.R.S. etc. of the use of the bark in the small-pox', Phil. Trans., 1751/52, 47: 27-31. The use of Peruvian bark in smallpox had already been recommended by Richard Morton, but seems to have caught on only after the "discovery" of the effect in gangrenes, and especially after Monro's article of 1742. See R. Morton, Pyretologia, pars altera: sive exercitatio de febribus inflammatiis universalibus, London, Sam. Smith and Benj. Walford, 1694 ('De Variolis', cap. 10), who also in this context stressed the bark's power as an "antidote".

141 Monro, op. cit., note 131 above, pp. 104-105.

142 Wall, op. cit., note 140 above, pp. 586, 592. For more "successes" see Nicolaus Rosen and Peter Jonas Bergius, 'De variolis curandis dissertatio' (Uppsala 1754), in Haller,
response to failures, however, was to differentiate empirically between those conditions, in which the bark was probably helpful, and those where little or no success could be expected.

This approach was taken in 1754 by the British surgeon Thomas Kirkland (1722-1798). He generally distinguished between spreading and local gangrene, each of which might have been either externally or internally caused. For each of the four types of gangrene he gave some case histories, which came mostly from his own practice. In the two internal forms the bark treatment was apparently beneficial. But he had one death from the externally caused, spreading form of gangrene: a 3 5-year-old carpenter, thought to have a "scorbutic" disposition of his humours, had developed an "ascending gangrene" after an open fracture of his lower leg, and the Peruvian bark did not save him. Kirkland suspected that in this rather young man, with strong fibres, the astringent and tonic effect of cinchona might have made his condition even worse. In otherwise comparable patients with weak fibres, he assured, the bark had produced good effects. He therefore started to combine the bark with saltpetre in risky cases like the one above, assuming that this would increase the "antiseptic" effect (i.e. the action against "putridity" of the humours). In six cases, he claimed, this had been successful. In local, externally caused gangrene Kirkland saw merely a supportive role for oral treatment with Peruvian bark, in order to prevent spreading. The main treatment here was local, as usual with scarifications, fomentations, and dressings. This local treatment was also applied in internally caused gangrene, in addition to the orally administered bark. In old people,

with "weak arteries" and insufficient flow of the humours, he further recommended supporting the bark's effect by the traditional treatment with cordials. On the basis of case histories, Kirkland's study of gangrenes had thus arrived at a quite differentiated scheme of therapy. Cinchona bark played an important role in it, but conventional treatments continued to have their place. Huth in Nuremberg regarded the British surgeon's work as so important that he prepared a German translation and, in 1761, published it as a continuation of his collection of treatises on the bark.143

In fact, also on the Continent the so-called "surgical" use of Peruvian bark in gangrene continued to be discussed, for example at the universities of Halle144 and Vienna. At the latter, opinions were divided: Heinrich Johann Nepomuk von Crantz (1722-1797), the teacher of materia medica, doubted that the bark had been useful in dry gangrene and gangrenous angina, while the renowned clinician Anton de Haen (1704-1776) administered it in large quantities both internally and externally in the treatment of gangrene and sphacelus.145

In Britain efforts went on to extend the use of cinchona beyond that in gangrene to related conditions. In 1751 John Wall had reported in the Gentleman's Magazine about successes with the bark in "sore Throat attended with Ulcers", explaining them with an "antiseptic" power of the

143 Georg Leonhart Huth (ed. and transl.), Thomas Kirklandes eines englischen Wundarztes Abhandlung von den Brandschäden, Nuremberg, Johann Michael Seligmann, 1761.

144 Carl Ernst Kronecker and Andreas Elias Büchner (Praeses), Dissertatio inauguralis medica de usu corticis Peruvian chirurgico, Halle, Typis Io. Christ. Hendelii Viduae, 1765.

drug. He claimed to have treated in this way more than 50 patients, two of whom died; and an apothecary named Cooper, using Wall's method, was said to have had experience in 242 such cases, of which 7 ended with death. Huth duly published a German translation of this account, which may have alerted Crantz to the use of the bark in "Angina gangraenosa".\textsuperscript{146} The Medical and Philosophical Commentaries, edited by Andrew Duncan senior, in 1774 carried a case history on the "successful" use of cinchona in a pre-gangrenous swelling of the arm.\textsuperscript{147} Its author was the Warrington surgeon John Aikin (1747-1822), now better remembered for his Thoughts on hospitals (1771). And in the same periodical, ten years later, surgeon William Rait reported the drug's good effects in a soldier with an obstinate ulcer of the leg, stemming from an earlier accident. Under treatment with the bark, the patient's general condition improved, allowing the surgeon to amputate with success (i.e. without "relapse" in the stump).\textsuperscript{148} Obviously Rushworth's "discovery", now more than half a century old, was still a basis for further "trials" in surgical treatment. As late as 1807 the Edinburgh medical and physical dictionary, published by the physician Robert Morris and the surgeon James Kendrick, was convinced that cinchona was beneficial in smallpox, and was being used

\textsuperscript{146} Huth (ed.), 'Doctor Walls Nachricht von einer glücklichen Methode die schwürige Bräune zu heilen', in Huth, op. cit., note 143 above, appendix, pp. 186-221. Wall's cases of "putrid sore throat" seem to have been scarlet fever and diphtheria, which were not distinguished at his time.

\textsuperscript{147} John Aikin, 'The history of an uncommon swelling of the arm, which, after threatening a general gangrene, terminated favourably', Med. Phil. Comm., 1774, 2: 417-419.

"with extraordinary success" in ulcerated sore throats and "externally and internally, in every species of gangrene".¹⁴⁹

From a modern perspective, it is hard to see how Peruvian bark (respectively quinine) could have produced the "successes" in "gangrene" claimed in the eighteenth century and beyond - except perhaps through its antipyretic effect and thus some improvement of the patients' general condition. One might also speculate that the bark’s content of quinidine, having a good effect in certain forms of cardiac arrhythmia, may have helped some of those gangrene patients who had an "irregular pulse" and circulatory problems. What is probably more important, the ambiguities of the historical diagnosis "gangrene", as discussed above, need to be taken into account: not every case of "gangrene" was one in our understanding of the term. It is unlikely, however, that the taking of Peruvian bark did much to improve the vitamin C deficiency in patients with scorbutic ulcers. The bark did not arrive fresh in Europe (see below), it was often processed to decoctions and tinctures, and it was generally prescribed in rather small doses. From our historical analysis, it seems that professional interests of surgeons played an important role in the propagation of the new indication "gangrene" for the bark. It was an excellent opportunity for surgeons to practise internal medicine, otherwise the domain of the physicians. Yet physicians accepted the new method of treatment as well - after all Peruvian bark had become an accepted febrifuge in their hands.

¹⁴⁹ Robert Morris and James Kendrick, The Edinburgh medical and physical dictionary, containing an explanation of the terms of art...and also, a copious account of diseases and their treatment, agreeably to the doctrines of Cullen, Monro, Hunter, Fordyce, Gregory, Denham, Saunders, Home, and other modern teachers in Edinburgh and London, 2 vols, Edinburgh, Bell and Bradfute, 1807, vol. 1, article 'Cinchona'.
In addition to these peculiarities of the bark's "surgical use", one needs to consider that indications for cinchona were generally broadened during the eighteenth century. To give just a few further examples from articles in the leading scientific and medical periodicals in London and Edinburgh: the use of Peruvian bark was recommended, on the basis of cases, as a remedy in febrile delirium, dysentery, hoarseness after the measles, ophthalmia, and to prevent catching cold. Moreover, cinchona was tried and recommended at some stage in almost every kind of fever - not only the intermittents and remittents, for which it had been introduced in the seventeenth century. Baldinger, in his 1778 history of cinchona, made the effort to list indications for the bark recommended by British authors since Sydenham. They included, besides "gangrene" and "fevers", dropsy, periodic haemoptysis, hypochondriasis, pertussis, haematemesis, menorrhagia, mania, dysentery, slow fevers, amenorrhoea and constipation "from debility".


anuria, ischuria, scrophulosis, malignant and epidemic fevers, putrid bilious fevers, putrid sore throat, malignant smallpox, measles, scurvy, puerperal fever, night blindness, obstinate ophthalmia, asthma, periodic cough, gunshot wounds, and epilepsy.\textsuperscript{152} For many of these indications "histories", like those for intermittent fevers and gangrene, might be reconstructed. Also in those other uses of the bark some special reasons would probably be identified - beyond therapeautic experience. Yet it is unlikely that the overall picture would be much altered. Evidently the Peruvian bark changed from a specific to an universal remedy.

6. New pharmacological experiments: the bark as astringent and antiseptic

From the above account it seems that this broadening of indications for cinchona was largely an empirical matter: often far-reaching therapeutic conclusions were drawn from very few case histories. What then was the role of the experimental, pharmacological approach in this transformation of the bark's medical perception? As will be suggested in the following sections, new pharmacological trials with the bark from the 1730s acted synergistically in creating a picture of Peruvian bark as a general remedy, eroding the old idea of the drug's specificity.

It has been described above how towards the end of the seventeenth century Friedrich Hoffmann and his pupil Schondorff arrived at the theory that cinchona acted through its astringent and tonic properties. It has further been mentioned that in the early eighteenth century both advocates of the bark (such as Kloek in Leyden) and its

\textsuperscript{152} Ibid., p. 1029.
adversaries (such as Stahl and his followers), accepted this pharmacological interpretation - obviously with opposite therapeutic conclusions. This was the state of knowledge, when the Reverend Stephen Hales (1677-1761) - whose experiments on lithotriptics have been discussed earlier - conducted further pharmacological experiments on drugs which were being used in the treatment of fevers, including Peruvian bark.

These trials were a kind of appendix to Hales' famous experiments on blood pressure and the circulation. As he wrote in 1733, he wanted to demonstrate "what Effect different Liquors have on the finer Vessels of the Body, viz. when they are either hot or cold, or have different Degrees of restringent or other Qualities."\textsuperscript{153} Probably with Hoffmann and the like in mind (whom he did not quote here, however), Hales said that he was aware that the contracting, respectively relaxing, effects of certain liquors were known by "long Experience" to "the skilful Physician".\textsuperscript{154} Yet, he still thought that his experiments would be useful, through either confirmation or clarification.

A rather sophisticated "animal model" (in our current terminology) was used in these trials. Dogs were exsanguinated, and their intestines slit lengthways, opposite the insertion of the mesenteric arteries. A long tube was then inserted in the descending aorta. Hales poured defined quantities of his various test liquors through this tube, counting the seconds it took for each of them to be emptied through the edges of the cut intestinal wall. Warm water served as a standard. A delay in the emptying of the fluid was taken as a sign of constriction of the arteries, an increased speed as indicating vasodilatation. In this way Hales tested, besides hot and cold water, brandy, warm milk,

\textsuperscript{153} Hales, op. cit., part A above, note 8, vol. 2, p. 126.

\textsuperscript{154} Ibid., p. 127.
Pyrmont mineral water, and decoctions of Peruvian bark, oak bark, cinnamon, and camomile flowers. According to his measurements, all four decoctions and Pyrmont water, as expected, constricted the vessels, as did brandy and cold water, whereas hot water and warm milk dilated them.  

In Hales' view, constriction of the small arterial vessels meant that the blood passed through them with greater force, acquired "a greater Degree of Heat" and was "more attenuated and digested". Since he assumed that in fevers the blood was in a "viscid State", this interpretation helped to understand the Peruvian bark's febrifuge effect. The bark, he thought, not only attenuated the blood in this indirect way as an astringent, but also directly by diluting it. The diluting effect, he stated, was well-known from experiments on extravasated blood. Though he did not quote any authors here, Hales was probably familiar with Freind's trials, perhaps also with those of Leeuwenhoek and Minot. Hales' theory of the Peruvian bark's mode of action allowed him further to explain, why fevers had been observed to be increased and prolonged, when the drug was given in a paroxysm. The constriction of the vessels and the consequently more rapid flow of the blood, he thought, would necessarily increase its temperature.  

Yet, the cinchona bark was not unique in acting as a "stiptic Attenuator", as he described it. Camomile flowers and chalybeate waters (i.e. mineral waters rich in iron,

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155 Ibid., pp. 48-49, 126-139. For a good summary of these trials see also J. Worth Estes, 'Quantitative observations of fever and its treatment before the advent of short clinical thermometers', Med. Hist., 1991, 35: 189-216. Estes attributes the Peruvian bark's astringent effect on blood vessels to "the irritant action of its quinine content". Ibid., p. 195.  


157 Ibid., p. 138.
such as that from Pyrmont) produced in Hales' opinion the same kind of effects on the vessels and the blood as the bark. And their action also lasted about the same time, all three of them being "Restringents" whose effects on the solid parts of the body had "a more permanent Duration". Furthermore, in his conclusions Hales did not really make quantitative comparisons of the vasoconstrictive powers of his test substances. To judge from his measurements, he should have regarded hot decoction of cinnamon as the strongest astringent. Seen in this perspective, the results of Hales' trials meant that a current theory of the Peruvian bark's febrifugal powers - namely that of Hoffmann - had been confirmed; but they also meant that the bark did not in principle act differently from some other medicinal substances used in fevers.

J. Worth Estes has recently commented of these trials and conclusions of Hales that they were "seldom, if ever, cited in medical texts, although they probably were known to British physicians". The latter should indeed be assumed, given Hales' status as a Fellow of the Royal Society, his acquaintance with physicians and surgeons (e.g. as a member of the committee on Mrs Stephens's medicines), and not least the place of publication of these trials - the soon well-known, and internationally translated, Haemastaticks. Moreover, this assumption is supported by the fact (not mentioned by Estes) that Hales' "animal model" for those experiments was soon copied by a medical researcher. In 1746 Browne Langrish (before 1700-1759), a member of the London College of Physicians and F.R.S., described how "in Imitation of my very ingenious Friend, the Rev. Dr. Hales" he had prepared a foxhound in the same way, in order to test

158 Ibid., pp. 136-138.

159 Estes, op. cit., note 155 above, p. 196.

160 See above, part A.
the effect of cherry laurel water. He found that this solution also acted as a vasoconstrictor. Estes has suggested, as a possible explanation for the relative silence on the above experiments of Hales, that "readers merely agreed with him and read on", since his findings were consistent with the medical theories of the time. It might be added to this interpretation that the concept of the Peruvian bark's astringent and tonic action was already linked with Hoffmann's name, and that it became later (as will be shown below) a characteristic feature of William Cullen's teaching.

Yet astringency was not the only property of the bark that was examined experimentally. When authors such as Thomas Kirkland and John Wall wrote of an "antiseptic" effect of the bark in gangrene and related conditions, they had more than their clinical experience in mind. They also referred to a series of in vitro experiments, which had recently been performed by the Physician-General to His Majesty's Forces, John Pringle (1707-1782), F.R.S. In seven papers, read to the Royal Society between June 1750 and February 1752, Pringle had communicated extensive trials on putridity and substances that would either promote or impede putrefaction, the so-called "septics" and "antiseptics", respectively. According to the renowned military physician himself, he had made these experiments because of the "uncommon number of putrid distempers under my care in the hospitals of the army", i.e. the various "putrid" fevers and dysenteries. Appropriately, he published his experimental studies not only as scientific papers in the Philosophical Transactions, but also as an appendix to his successful

161 Langrish, op. cit., part A above, note 118, pp. 115-116. For Langrish's experiments with lithontriptics see above, part A.

162 Estes, op. cit., note 155 above, pp. 196-197.
handbook of military medicine, the Observations on the
diseases of the army, in camp and garrison (1st edn 1752).\textsuperscript{163}

On small pieces of meat, or on yolks of eggs, Pringle
examined the ability of added substances to either delay or
to speed up putrefaction, which he identified visually or by
the unpleasant smell. Testing against a standard of 60
grains of sea salt in water, he found that infusions of
Peruvian bark, Virginian snakeroot\textsuperscript{164}, and camomile flowers
were considerably more powerful antiseptics than the saline
solution. This was also the case with their decoctions, as
well as with one of wormwood.\textsuperscript{165} Moreover, powdered Peruvian
bark, snakeroot, and camomile flowers, rubbed into pieces of
meat, all kept them quite fresh for several days. And even
corrupted flesh was "sweetened" again by repeated affusions
of a strong decoction of the bark. Not only "the corrupted
smell was removed", noted Pringle, "but a firmness restored
to the fibres".\textsuperscript{166} He finally extended his trials to human
blood serum, observing that it was "preserved by a decoction
of the Bark, and an infusion of snake-root; nor with less
efficacy than flesh".\textsuperscript{167}

\textsuperscript{163} See Pringle, op. cit., General Introduction above, note
72. I refer in the following to the appendix of \textit{idem},
Observations on the diseases of the army, in camp and
garrison, 2nd enl. edn, London, A. Millar & D. Wilson and T.
Durham & T. Payne, 1753, pp. 309-403. For Pringle's life and
achievements see Sydney Selwyn, 'Sir John Pringle: hospital
reformer, moral philosopher and pioneer of antiseptics',

\textsuperscript{164} Snakeroot, Aristolochia serpentaria, had been introduced
from Virginia to England by the early 17th century and
became known, among others, as a tonic and alexipharmic. See
177.

\textsuperscript{165} Common wormwood, Artemisia absinthum, was known, among
others, as a bitter, tonic, febrifuge, and narcotic. See
ibid., pp. 1-2.

\textsuperscript{166} Pringle, op. cit., note 163 above, pp. 319-333.
Pringle's obvious conclusion was that Peruvian bark was strongly antiseptic - a property, which in his view explained both its efficacy in intermittent fevers, malignant putrid fevers, and in gangrene. As for intermittents, he noted that they could be linked with marshy regions, hot and moist air, and putrid "effluvia" from stagnant waters. The effluvia, he speculated, acted as "ferments" on the humours of the body, causing them to putrify and thus to produce fever. This was why Peruvian bark, as a powerful antiseptic, was "most specific" in these kinds of fever. However, he emphasized that other medicines had also proved useful in intermittents, among them myrrh, camphor, camomile flowers, and wormwood, all of which were "highly antiseptic". In other words: although Pringle still used the term "specific" for cinchona bark, he explained its efficacy as a febrifuge through a more general property, which could be found in other drugs as well.

Similarly differentiated were his views on the bark's action in gangrenes. It was only beneficial here, he thought, when the blood was "dissolved" and disposed to putridity, and the blood vessels relaxed. If the vessels were overfilled, or the blood was thick, cinchona would do harm by "increasing the tension of the fibres, and siziness of the blood". It should therefore also be avoided in the inflammatory state of wounds. Pringle's direct experimental evidence for an astringent effect of the bark, as a basis for this view, was rather weak compared with that of Hales. He had merely seen that the fibres of meat put in a decoction of the bark appeared to become firmer. However, he believed to have an indirect proof. Pringle attributed the experimentally established antiseptic power of Peruvian

167 Ibid., p. 334.

168 Ibid., pp. 330-332.

169 Ibid., p. 336.
bark to its astringency, because "the very nature of putrefaction consists in a separation or disunion of the parts". All antiseptics, he concluded, were to some extent astringent; and all astringents were strong antiseptics. Implicitly, Pringle thus established different levels, on which the pharmacological effect of cinchona could be described. On the clinical level, it was a "specific"; on the experimental level it acted as an "antiseptic"; and on the level of theoretical analysis it was essentially an "astringent".

Pringle's work on putrefaction and antiseptics was soon taken up by the Dublin physician David Macbride (1726-1778), who extended and modified the former's experiments. Among others he poured a decoction from a mixture of Peruvian bark, valerian, and camomile flowers on putrid meat, which, however, was not "sweetened" by this within 36 hours. Macbride concluded that the antiseptic decoction needed time to "ferment", before it would unfold its efficacy on the meat. In his next trial he therefore mixed powdered Peruvian bark with saliva and added it to a putrid solution of ox gall in water. After 24 hours, as "fermentation" began, the unpleasant smell of the mixture abated. Macbride now put a piece of putrid meat in the neck of the phial, and a further 24 hours later he found that both the foetor had gone and the meat had been sweetened.

From these results Macbride formed the hypothesis that some "antiseptic vapour" had been produced. In this way, he imagined, the bark acted for example in intermittent fevers. The swallowed drug would meet the "morbific matter" in the duodenum, ferment, and emit vapours, which made the matter "mild and sweet" and so prevented the next febrile fit.

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170 Ibid.

171 Macbride, op. cit., General Introduction above, note 72, pp. 128-129, 138-139.
vapour would further reach the blood, "restore its consistence, and correct its sharpness".  

But what was this vapour? Macbride thought that it was "fixed air", released through fermentation and identical with the "gas sylvestre" (i.e. carbon dioxide) that suffocated animals. In support of this view he quoted other experiments of his, in which "fermenting" (i.e effervescing) mixtures of acids and alkalis, as well as their emitted "air", had shown antiseptic effects on putrid meat. Fixed air, he explained, restored the "cementing principle", which prevented putrefaction of animal matter.

Macbride anticipated objections to conclusions from his in vitro trials to the ill human body, such as the critical question, how the "antiseptic vapour" or "fixed air" could sufficiently penetrate the humours to produce its beneficial effects. Nevertheless he was confident to draw such conclusions. Like Pringle, for example, he warned against giving Peruvian bark in inflammatory diseases. Not only would its astringency increase the tension of the blood vessels' fibres (as Pringle thought), but it would throw "much air" into the vessels, which were already overfilled with thick and "sizey" blood. Or, since vegetables produced much "antiseptic air", a vegetable diet prevented and cured putrid diseases, such as scurvy. Thomas Percival, in 1778, claimed to have stopped the mortification of a leg by

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172 Ibid., p. 141.

173 Ibid., pp. xi, 143-147. On contemporary experiments with fixed air see above, part A.

174 Macbride, op. cit., General Introduction above, note 72, pp. 142, 147, 157-162. On Macbride's experiments on antiseptics, his recommendation of malt as an antiscorbutic, and its tests in the navy, see Carpenter, op. cit., General Introduction above, note 9, pp. 76-88. Peruvian bark was only occasionally tried against scurvy; see ibid., pp. 70, 96. See further McBride, op. cit., General Introduction above, note 9, and Lawrence, op. cit., General Introduction above, note 9.
internal application of fixed air. And attaching bladders filled with fixed air became known as a method for the local treatment of leg ulcers. Yet, it was dismissed already in 1801 by the Edinburgh surgeon John Bell (1763-1820) as belonging to the "farrago of empiricism" in this area. As for the Peruvian bark, however, Macbride's experiments — like Hales' and Pringle's — had further reduced its "specific" power to yet another principle which was not unique.

The new experimental knowledge about the bark as an antiseptic was also adopted on the Continent. Together with the other properties that had been demonstrated in trials or were obvious from sensual perception, such as bitterness, astringency, and attenuation of blood, it provoked the question of the drug's specificity. Thus in 1765 a medical dissertation at the University of Göttingen discussed the "true specific power of the Peruvian bark". Although those "faculties" could be "considered separately", argued its author, Johann Friedrich Moller, they were always united in the drug. No single power in it could "rest" or be suppressed without affecting and moderating the others. From this, he wrote, came the "specific power" of the bark, which distinguished it from all other drugs sharing its properties, and which enabled it to produce certain effects "in another way, more potently and better than other bitters, astringents, roborants, incidents, antiseptics etc." Cinchona should therefore be regarded, he concluded, as a "Tonicum Specificum".

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Moller's use of the term "specific" thus referred to the drug's special mode of action. It did not mean that the Peruvian bark was a remedy specifically for one kind of disease, such as intermittent fever (malaria), as the term had been understood in the seventeenth century. Like other authors of his day, Moller believed that cinchona was effective in many types of fevers - "intermittent, remittent, semitertian, bilious, verminous, nervous, soporous, hysteric" - as well as in other diseases, such as dysentery, gangrene, and smallpox. The common features of these conditions were thought to be debility of the fibres and putridity, both of which were "cured" by the corroborant effect of the bark on both solids and fluids.\textsuperscript{177} Similar views, based largely on Hoffmann's and Pringle's doctrines, were soon disseminated through Edinburgh's influential professor of the practice of medicine, William Cullen (1710-1790).\textsuperscript{178}

7. Clinical inferences: the bark as a tonic

The question of "specificity" was also briefly touched upon by Cullen. Introducing his discussion of cinchona in his widely read \textit{First lines of the practice of physic}, he stated:

\begin{quote}
This bark has been commonly considered as a specific, or as a remedy of which the operation was not understood. But it is certainly allowable to inquire into this matter; and I apprehend it may be explained.\textsuperscript{179}
\end{quote}

\textsuperscript{177} Cf. \textit{ibid.}, pp. 13-18.

\textsuperscript{178} See for example Cullen's pupil John Warren, \textit{Dissertatio medica inauguralis de cortice Peruviano}, Edinburgh, Balfour, Auld, and Smellie, 1770, pp. 5-8, who reduced the barks "virtues" to a "vis tonica" and a "vis antiseptica".
Not surprisingly in view of his general "nervous" physiology and pathology, Cullen also explained the effects of the Peruvian bark with an action on the nervous system. Since the effects appeared so soon after ingestion of the drug that it could not yet have reached the blood, he argued, these effects could not arise from "its operating on the fluids". Instead the bark acted on the nerves of the stomach, and the effect was quickly communicated by sympathy to the rest of the nervous system. The bark's efficacy consisted in its "tonic power", which explained why it was a remedy in diseases stemming from "debility", such as gangrene, or from periodically recurrent "atony", such as the fits of intermittent fevers. This interpretation further permitted him to determine when cinchona could safely be used in continuous fevers: either during remissions, when - as in intermittents - atony had to be treated to prevent the return of fever, or in an advanced state of fever, when "general debility" had set in. By contrast, the bark was not indicated - because of its tonic effect - in inflammatory states.


Of course the idea of drug effects on the nervous system as such was not new. As has been mentioned above, Wepfer had elaborated this concept in the seventeenth century, and in Edinburgh Charles Alston, Cullen's predecessor as teacher of the materia medica, had argued for it in detail in the case of opium.\(^{182}\) Still, as for Peruvian bark, it conflicted with the current opinion that this drug acted on the blood - a view, which had been supported by a good number of \textit{in vitro} experiments since Minot. As one would expect, contemporary dissertations of Edinburgh medical students reflected Cullen's teaching also on this particular matter. In 1779, two students, Gabriel Wynne and George Brown, defended their professor's doctrine of the bark's direct effect on the nervous system. Both took Pringle's and Macbride's concept of the antiseptic power of the bark as their point of attack, because it represented the view that the remedy acted primarily on the humours. Wynne and Brown employed two main arguments. Since Pringle and Macbride relied on \textit{in vitro} trials, both Edinburgh students first of all doubted the transferability of those experimental results to the clinical situation: the nature of the humours in the gastro-intestinal canal, the amount extracted from the bark by them, and the absorbed quantity were all largely unknown.\(^{183}\) Secondly, they reiterated Cullen's "time argument" that the onset of the bark's effects was too soon for sufficient absorption to have taken

\footnote{\text{See above, part B.}}

\footnote{\text{Wynne, op. cit., note 151 above, p. 22; George Brown, \textit{Tentamen medicum inaugurale de usu corticis Peruviani in febribus intermittentibus}, Edinburgh, Balfour and Smellie, 1779, p. 9.}}
place. Wynne, by grossly exaggerating this point, made it also perfectly clear:

If finally the question should be asked: on which part of the human system does [the bark] act? I do not hesitate to answer: on the nerves and the living solids. For in a moment, and like an electric shock, a tiny dose of it often takes away diseases, before it would have been able to pervade the simple solids, enter the humours, and change them.\textsuperscript{184}

In addition to these general arguments, the two students made some more special points. Brown argued, for example, that the bark's efficacy in gangrene supported the view that it did not act via the humours, because only a very small amount of the drug, disseminated through the circulation, could come near the affected part, which was cut off from the blood supply. Instead he suggested that the bark's tonic power increased the "benign inflammation" in the parts adjacent to the gangrenous area, and thus helped "nature" in her efforts to demarcate and separate the latter.\textsuperscript{185} Or, Wynne argued that in some diseases which were cured by the bark, such as vernal intermittents, there was no putridity; therefore the antiseptic power would have no target.\textsuperscript{186}

Certainly, the two Cullen pupils somewhat overemphasized the differences between the view of Pringle and Macbride and that of their professor. After all, the former two also believed in the bark's astringent effect on


\textsuperscript{186} Wynne, op. cit., note 151 above, p. 23.
fibres; and as Cullen taught, tonics gave "firmness and strength to the whole system, and thereby to particular parts", having "an effect analogous and similar to that of astringents." Pringle and Macbride as well as Cullen therefore warned against the use of the bark in inflammatory fevers.  

However, those student defences highlighted the fact that Cullen had suggested a pharmacological theory for cinchona, which indicated a shift from a humoral to a nervous theory of its mode of action. In other words, Cullen took the same step concerning Peruvian bark, that - a generation earlier - Alston and Whytt had taken with respect to opium. In his successful Treatise of the materia medica, published in 1789, Cullen further elaborated on his nervous theory of the effects of cinchona. Regarding the bark as "one of the most considerable articles of the materia medica" and "the most frequently employed", he described its effects as that of a powerful tonic. He saw, as he put it, "no foundation for referring it to any mysterious and unexplained specific power". Peruvian bark just fitted into his general ideas about the action of medicines:

Upon the whole, it is sufficiently probable, that the peculiar action of medicines depends upon the sensibility and irritability of the human body; or, in other words, that it universally depends upon motions excited and propagated in the nervous system.


188 See above, part B.


190 Ibid., p. 91.

191 Ibid., vol. 1, p. 58.
While Cullen's interpretation of cinchona as a tonic was doubtlessly influential,¹⁹² it did not rest on experimental evidence. His conclusions were partly derived from clinical observations, such as the rather quick efficacy of the drug, partly they were a continuation of Hoffmann's ideas. However, a few years after Cullen's death, Alexander von Humboldt (1769-1859) did provide at least a small piece of experimental "proof", when he studied the effects of various substances on irritability. Working on nerve-muscle preparations (often of frogs), Humboldt had produced muscular weakness by application of opium, carbonic acid gas (carbon dioxide), and other substances. As astringents he then applied extract of cinchona and tincture of gall nuts. Though the muscles treated in this way did not contract when galvanized, their previously flabby and soft fibres now appeared firm and hard. When muscles which had only been weakened by warmth or the time of exposure were immersed into the astringents, their contractility returned - provided the whole muscle had been covered by the fluid. If the astringents were applied only to the end of the nerve, this effect could not be observed. In Humboldt's view these results demonstrated that cinchona and gall nuts restored the tone and irritability of muscle fibres, and he explicitly noted that this confirmed Cullen's doctrine of "the tone of the fibre" as formulated in the latter's Treatise of the materia medica.¹⁹³

Despite the prevailing theory of the Peruvian bark's tonic effect on fibres, research into its action on the

¹⁹² Doig et al., op. cit., note 180 above, p. 39, point out that Cullen's Treatise on the materia medica was "widely used throughout Europe and North America", was translated into German and French, and "remained a standard work for about forty years".

¹⁹³ Humboldt, op. cit., part B above, note 188, vol. 2, pp. 421-422.
blood was not entirely given up in the late eighteenth century. Although Torti had admitted that he had been unable to conclude anything from his in vitro trials with the bark, and in the meantime also Albrecht von Haller had questioned the pharmacological meaningfulness of such experiments more generally, the renowned John Hunter (1728-1793) took up the method again. In his *Treatise on the blood, inflammation, and gun-shot wounds* (1st edn 1793) he described a number of experiments with drugs on freshly let blood, including trials with a decoction of cinchona bark. The background to these experiments was Hunter's idea of a "living principle" in the blood, which kept it fluid in the vessels and made it coagulate outside. In this sense he actually compared coagulation of the blood's "lymph" with muscular contraction.

Hunter tested the effect of the decoction of the bark on fresh blood against two controls: pure blood (from the same source) and blood with water (to exclude an effect of the solvent). Repeated trials indicated that cinchona delayed coagulation and led to a less firm clot. The same effect was observed with a watery solution of opium. These experiments thus confirmed the observations made by Freind and others at the beginning of the century - none of whom were quoted by Hunter, however. In fact he abstained from drawing therapeutic conclusions, pointing out that the drugs were merely dissolved in the blood and did not combine with it chemically. If the latter happened, argued Hunter, the blood would be altered and the medicines' effects

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194 See Lindenberger, op. cit., General Introduction above, note 4, p. 38.


Moreover, in his discussion of drug treatment of inflammations, later in the same work, he presented Peruvian bark as a vasoconstrictor and tonic, that was appropriate in inflammatory states linked with weakness, but contraindicated in those "attented with too much strength and considerable irritation". Likewise, in his section on mortifications he stated that the bark was here "the principal medicine, as yet known, that we depend upon, as it increases the powers and lessens the degree of action". In neither of these contexts did he refer to his in vitro experiments, although they could have been regarded as relevant: the bark's effect on the blood could well have been taken as an argument against its use in inflammations - analogous to the contemporary opinion that opium was contraindicated here.

8. Early "clinical trials"

It has been discussed so far, how from the late seventeenth century onwards in vitro and animal experimentation, chemical tests and microscopical observation, and the analysis of single case histories were used to understand the pharmacology and therapeutic properties of the Peruvian bark. As Ulrich Tröhler has shown, simple clinical statistics or "arithmetic observations" to evaluate treatments began to be applied in British medicine in the second half of the eighteenth century. In particular, he demonstrated how the novel method

\(^{197}\) Ibid., p. 174.
\(^{198}\) Ibid., vol. 2, p. 126.
\(^{199}\) Ibid., vol. 1, p. 15.
\(^{200}\) See above, part B.
of analyzing clinical mass observations was developed in the new dispensaries and hospitals, and in the medical and surgical services of the armed forces.\textsuperscript{201} The following will show that this was also true for our special case of the therapeutic use of cinchona. Four examples will illustrate how "clinical experiments" with the bark were made during the last third of the eighteenth century: in a hospital, the army, the navy, and finally in private practice.

The first example is that of the Edinburgh professor of materia medica, Francis Home (1719-1813), who tested various medicines on patients of the Royal Infirmary.\textsuperscript{202} In words partly reminiscent of John Aikin's Thoughts on hospitals (1771), he explained why he regarded patients in this charitable institution as particularly suitable: their complaints originated from the body rather than the mind or habits; compared to patients in "higher life", their "theories and caprices" were less troublesome; they usually had no long history of previous treatments; and their diet was under absolute control.\textsuperscript{203} Furthermore, since simple medicines were prescribed in hospital practice, the effects of single drugs could be observed in rather pure form. More specifically, in the clinical (teaching) ward of the Edinburgh Royal Infirmary trials were witnessed and discussed by other doctors and students; and the cases were carefully documented, both in the Infirmary's records and the students' "report-books".\textsuperscript{204} Home was aware of the

\textsuperscript{201} Tröhler, 'Quantification' and "To Improve the Evidence'", General Introduction above, note 10. See also more generally Rusnock, 'The quantification', part A above, note 94.

\textsuperscript{202} See also Risse, op. cit., General Introduction above, note 15, pp. 190-191.

ethical implications of his therapeutic experiments. The physician, he stated, was "responsible to his own conscience alone" and could try new treatments, provided he had "a probability of success" and proceeded with caution. Indeed clinical experimentation was criticized by Home's colleague James Gregory, who described it as "corio humano ludere", i.e. as playing with the human hide. Not dissimilar to Home, he demanded that the patients themselves should benefit from the trials to which they were subjected, and that they must not be put in danger for the sake of scientific curiosity.

In such a climate of ethical awareness it was certainly important for Home to be clear about his intentions. These were, as he declared in the summary of his trials, "to ascertain the effects and value of several remedies in general use, and to discover new relations in others". Both aspects did in fact play a role in his studies of Peruvian bark.

Home's main study of the bark was concerned with the question whether it should be given either shortly before or just after a fit in intermittent fevers. The former method was the traditional one, going back to the Schedula Romana; yet, it was also the most up-to-date one, being taught by his colleague Cullen, because the drug's supposed nervous

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207 As Aikin, op. cit., part B above, note 335, p. 76, observed with regard to trials on hospital patients: "I am aware that the very name of experiment occasions great outcries and prejudices among the vulgar; and that it is apt to startle some well-disposed persons of a superior class..."

208 Home, op. cit., part A above, note 161, pp. vii-viii.
action was thought not to last very long. The second method, on the other hand, had been advocated by authorities on fevers, such as Sydenham and Torti.  

In fourteen patients with various intermittents (tertian, "double tertian", and quotidian fever), who were treated in the Royal Infirmary at different times between 1769 and 1779, Home evaluated the two methods. In eight cases, where the bark was administered shortly before the next expected fit, this fit could not be stopped, and only in three cases the succeeding one was prevented. By contrast, in six cases, where the drug was given after a paroxysm, there were no further febrile attacks. Being aware that his cases were not entirely comparable, Home tried in three patients both methods at different times in their course of treatment. Also the outcome of these experiments indicated that the bark given after a fit stopped further ones, whereas administration just before a paroxysm failed to do so. Moreover, in two cases the last method had made patients worse by exciting vomiting.

Home's conclusion from this trial was not merely the obvious therapeutical one above. He also modified Cullen's theory of the bark's action (without naming him). In Home's view, the rather long period of time until the drug became effective showed that it did not act solely via the stomach and nervous system, but that its chief effect depended on its absorption into the circulating blood. In addition he pointed out that cinchona preparations applied to the skin were effective, which demonstrated that action on the stomach was not necessary. Though Home explicitly conceded that the bark probably did act on the nerves, he thus

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209 Ibid., pp. 2-6. For Cullen's view, with reference to his lectures, see Brown, op. cit., note 183 above, p. 12.

210 Home, op. cit., part A above, note 161, pp. 8-11.
concluded that it would find "a much greater field" and "greater sensibility" in the vascular system. The reason why Home had experimented with the bark was not only to find the best form of treatment in a given clinical condition. Besides this therapeutic aim, economical

Home's remaining experiments explored the efficacy of Peruvian bark in other diseases, without the comparative method used in his first trial. In four cases the drug had been given in typhus nervosus, or low fever, with varying results. While it appeared inappropriate when the disease was linked with respiratory problems, it seemed recommendable if there was "general symptomatic sweating", tremor, or "little or no drought". In two cases of phthisis pulmonalis (one of which was from Home's private practice) the bark seemed to make symptoms worse through its property "to bind the breast". Finally, in eight cases where cinchona was given as an antispasmodic (in epilepsy, hysteria, Saint Vitus's dance, catalepsy, and hiccup), most patients were "much relieved" or "cured" (except in hiccup). Home concluded that the bark was an excellent remedy in "pure spasmodic diseases", but - since it was generally known that it was harmful in inflammatory states - care had to be taken to avoid it in spasms accompanying inflammation.

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211 Ibid., p. 12.


213 Home, op. cit., part A above, note 161, pp. 119-120. Home had published cases from his private practice separately in his Medical facts and experiments, London and Edinburgh, A. Millar and A. Kincaid & J. Bell, 1759.

considerations played a role as well. As he explained with reference to his first trial:

It is often necessary to save the bark, as much as possible, in the army and navy. It may become scarce during war, or fail us from other accidents. Less will do, when given in the proper time; more will be required in a less proper time.  

This was precisely the background to our next two examples of "clinical trials" with cinchona, performed by two surgeons in the British army and navy, respectively, during the American War of Independence. The first of the two, Richard McCausland, had been stationed at Niagara since 1774 with the King's or 8th Regiment of Foot. The frequency of intermittent fevers among the troops, seamen, and "persons dependent on the post" had led to a shortage of Peruvian bark, making it necessary for him to try other remedies. Between 1775 and 1781 McCausland treated these patients with tartar emetic (i.e. antimony potassium tartrate) in the form of pills or solution. In his report, published in Duncan's Medical Commentaries, he claimed to have had a success rate of two in three cases with this medicine, and to have "removed" on the whole three hundred "agues" in this way.

In statistical tables he gave details of a part of these cases, which indicated that the pills were more successful than the solution. Overall McCausland recorded of his fever patients treated with tartar emetic (in either form) 84 as "cured", 19 as "relapsed", and 49 as "not cured". This he compared with his results with Peruvian bark, where 60 fever patients were registered as "cured" and

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215 Ibid., pp. 1-2.

34 as "relapsed". In other words, the ratio of cures to relapses was about 4:1 for tartar emetic, and about 2:1 for cinchona. Accordingly McCausland commented that there had been "much fewer relapses after the tartar emetic than after the Peruvian bark". However, he interpreted and weighed his evidence very carefully. In favour of the bark treatment went the fact that in 15 of its cases tartar emetic had been "inadmissible" (because of vomiting), and that in a further 15 cases the same had been given without success before. On the other hand, the trials with tartar emetic had been conducted in the summer, when the rate of relapses was usually high, whereas those with the bark had been made later in the year, when cold weather put a natural end to the epidemic of intermittent fever. Moreover, a "considerable number" of those treated with the bark left Niagara immediately afterwards, so that possible relapses could not be noted. These circumstances spoke indirectly for the tartar emetic. All in all McCausland concluded that "the arguments on both sides seem so nearly balanced, that we may venture to take the table as it stands."

Similarly careful were his judgements on other comparative trials, which he had likewise made at Niagara. They included, in intermittent fevers, tartar emetic combined with liquid laudanum (i.e. opium in wine) and sal ammoniac (i.e. ammonium chloride), and tartar emetic together with crude opium; in syphilis, various mercury sublimate preparations, with and without "decoction of the woods" (i.e. probably guaiac wood) and warm baths, mercurial ointments plus warm baths, and Plummer's Pills (i.e. sulfides of antimony, sublimated sulfur, calomel, and gentian) together with "decoction of the woods"; and in

217 Ibid., p. 256.
218 Ibid., p. 257.
dysentery, various combinations of emetic and cathartic salts, astringents, ipecacuanha, rhubarb and calomel, and vitrum ceratum antimonii (i.e. glass of antimony with beeswax).\footnote{McCausland, op. cit., note 216 above. On the last remedy see John Pringle, 'Vitrum antimonii ceratum, a specific medicine in the dysentery', Med. Ess. Obs., 1742, 5/I: 194-219, with reference to tests by several surgeons and physicians in numerous cases.}

The comparative design of McCausland's therapeutic trials - as well as that of Home's experiment on the bark in intermittents - are certainly reminiscent of James Lind's (1716-1794) famous pioneer "controlled" trial on the therapy of scurvy in 1747.\footnote{See on this Carpender, op. cit., General Introduction above, note 9, pp. 51-54; Tröhler, 'Quantification', General Introduction above, note 10; Rolf Winau, 'Vom kasuistischen Behandlungsversuch zum kontrollierten klinischen Versuch', in Hanfried Helmchen and R. Winau (eds), Versuche mit Menschen in Medizin, Humanwissenschaft und Politik, Berlin and New York, Walter de Gruyter, 1986, pp. 83-107.} Yet, there was an important difference. Lind's study of various treatments for scurvy (leading to the conclusion that oranges and lemons were most effective) had been carefully planned and performed at one time on a selected group of comparable patients under the same conditions.\footnote{Cf. James Lind, Abhandlung vom Scharbock, transl. from the 2nd English edn by Johann Nathanael Pezold, Riga and Leipzig, Johann Friedrich Hartknoch, 1775, pp. 230-236.} In this respect it is rightly regarded as a precursor to our modern controlled clinical trials. McCausland's and Home's studies, by contrast, were retrospective analyses of past cases in which various treatments had been tried rather on an ad hoc basis -

\footnote{On "Plummer's Pill" see Plummer, op. cit., General Introduction above, note 40. He tested it first on himself and subsequently in five cases (comprising "porrigo capitis", "red Spots and Pimples" in the face, and gonorrhoea).}
sometimes deliberately, sometimes out of necessity - during a period of many years.

Still, the methodical awareness, especially in McCausland (a figure unknown in the historiography of medicine), is remarkable. The army surgeon, who asked his readers for forbearance, since he had been cut off from the literary world "for these last thirteen years, and ever since he left the schools of medicine", discussed in detail "the fallacy of observation". Errors arose, he argued, when "decisive conclusions" were drawn from a very limited number of experiments. Individual factors could influence single cases. The patient might hide the cause of his complaints from his physician (e.g. in venereal diseases), or, disgusted with a nauseous remedy, he might unjustly ascribe bad effects to it. Diet, air, and other diseases could determine the outcome. Or the "effort of nature" and "lucky circumstances" might bring success, leading the practitioner to the false belief that this was due to the remedy. Moreover, medical practice could be influenced by motives of "prejudice", "obstinacy", and "caprice". To avoid errors through such individual influences, concluded McCausland, high numbers of observations were necessary, which had to be documented and published:

As long as there is no public repository of facts, nor any channel by which they might be conveyed to the world, so long will medicine probably labour under the imperfections we have been endeavouring to describe; for I believe it will readily be acknowledged, that in the proportion that experiments increase in number, in the same proportion are they set out of the reach and influence of the above mentioned casualties. It follows, therefore, that solid and invariable conclusions upon any subject, can only be drawn from a very large number of experiments and observations.  

223 McCausland, op. cit., note 216 above, pp. 280-283.

224 Ibid., pp. 281-282.
Obviously unaware of the work of Home and others, he therefore suggested that tabulated registers of cases were kept in military and public hospitals and dispensaries, and that private practitioners did the same. The colleges of physicians, he imagined, could organize clinical trials in the hospitals, and as a result, the pharmacopoeias would quickly be "weeded of their useless articles, whilst the virtues of every truly valuable remedy would be publicly known, and established upon the most incontestible footing".

As in McCausland, scarcity of the Peruvian bark during the American War - not some doubt about its efficacy - was the reason behind our third example of "arithmetic observations" in this medicine, carried out in the Royal Navy by the surgeon Robert Robertson (1742-1829). In 1776, when these observations started, Robertson had served for over fifteen years with the navy and was surgeon on His Majesty's Ship Juno. From his long experience he had been convinced that the bark was the "only" reliable cure of fever in hot climates. Accordingly he had used the drug also for the treatment of ship fever (i.e. the equivalent to "typhus" or hospital fever), when it broke out on board the Juno in America. Towards the end of the year 1776, however, he was running out of stock. When the ship arrived at New York, Robertson later recalled, "Peruvian bark was sold a guinea per pound: a price sufficient to tempt the sellers of that valuable drug to adulterate it; and to prevent surgeons of his majesty's ships from purchasing it". He could therefore use the bark "in particular cases only",

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226 From a modern perspective, the more severe form of "typhus", or hospital, ship, and jail fever, was probably louse-born typhus or relapsing fever, often together with typhoid fever. Cf. Risse, op. cit., note 212 above, pp. 177, 191.
a fact, which became the basis of a therapeutic comparison.\(^{227}\)

Most of his fever patients now had to be treated with antimony preparations, camphor, and blisters. Robertson recorded six deaths among the 296 patients of this group, and he contrasted this mortality of 1:49 (2.03%) with only one death in 216 fever patients (0.46%) that had been given Peruvian bark. These figures referred to cases treated on board the Juno. A number of the ship's fever patients were sent to the New York Hospital and Rhode Island Hospital, where they were treated with camphor and antimonials. In both these institutions the death rate for these patients was about 1:7 (5 of 36, and 4 of 26, respectively).\(^ {228}\) In Robertson's view these results — which he presented in tables — demonstrated how justified his preference for the cinchona treatment had been.\(^ {229}\) In fact he became later known as a staunch advocate of a generous and early administration of the bark in any kind of fever (except those originating from "actual inflammation, or topical affection").\(^ {230}\) Or as Robertson put it full of confidence in 1789, now being physician to the Royal Hospital in Greenwich:

\(^{227}\) Robert Robertson, Observations on fevers which arise from marsh miasmata, and from other causes, in Europe, Africa, the West Indies, and Newfoundland; with occasional remarks on the principal diseases incident to seamen, 4 vols, London, T. Cadell and W. Davies, 1807, vol. 2, pp. 176-177.

\(^{228}\) Ibid., p. 233.

\(^{229}\) Ibid., p. 177. If one applies present statistical criteria, the difference in mortality between Robertson's patients treated with bark and with other medicines on board the Juno is not significant. I thank Dr John Forrester, Edinburgh, for pointing this out to me.

\(^{230}\) See Robert Robertson, Observations on jail, hospital, or ship fever, from the 4th April, 1776, until 30th April, 1789, made in various parts of Europe and America, and on the intermediate sea, new, enl. edn, London, Printed for the Author and sold by G. G. and J. Robinson, 1789, pp. 368-377.
The danger which theorists threaten us with, from an early and liberal use of bark in fever, strikes me with the same idea as if they told me, I should possibly fall, if they saw me running out of a magazine of powder, which I knew was immediately to blow up by a train leading to it being lighted.  

That the enthusiasm both for Peruvian bark and for arithmetic observations of its effects reached also private practice, is illustrated by our fourth and last example. As mentioned above, Home had seen the "theories" and "caprices" of patients in "higher life", i.e. of private patients, as an obstacle to therapeutic experimentation. And John Aikin had stressed in the same context that outside the hospital practitioners had to be too much concerned about their reputation and were therefore reluctant to try new methods of treatment. Yet in 1785, Duncan's Medical Commentaries published a report of the otherwise unknown Alnwick surgeon T. Colingwood, which included a good amount of quantitative information about his various therapeutic experiences with the bark.

Colingwood's observations were less organized and less coherently presented than those of Home or of the military surgeons McCausland and Robertson; and they also represented the result of retrospective analysis of cases rather than a true therapeutic trial (in the sense of Lind's experiment). But he had clearly followed two approaches. First he

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231 Ibid., pp. 371-372. The copy of the first edition of Robert Robertson, Observations on the jail, hospital, or ship fever, London, J. Murray, 1783, in Edinburgh University Library (G.3.24), has at the end, on p. 318, humorous sketches scribbled in (probably by nineteenth-century hands), which show two heads in profile saying: "Give me a dose of Bark-", and "Give me a Pinch of [?]Bark".

232 Aikin, op. cit., part B above, note 335, p. 80.

explored the therapeutic spectrum of Peruvian bark. In 1778, Colingwood reported, he had "cured" with it 22 out of 25 cases of intermittent fever. In the same year he had given the bark to 80 smallpox patients, five of whom died, whereas out of six, who had not been treated with it, two died. In the following year he had seen 25 cases of confluent smallpox, and 21 of them recovered after the cinchona therapy. Also in 1779, he had tried the bark in cases of dysentery, where five out of nine patients recovered, who had previously been treated with ipecacuanha, vitrum antimonii ceratum, and blood-letting. Colingwood further mentioned that he had used the bark successfully in whooping cough, remittent fevers, mortification in cachectic patients, slow and nervous fevers, and periodic pain in the face and temples, which he regarded as "a species of rheumatism". On the other hand, cinchona had proved "hurtful", if a "topical inflammation" or an "obstruction of the viscera" existed, and it had increased the hectic fever of phthisis pulmonalis. In other words: Colingwood's (more or less) quantitative observations largely supported the therapeutic indications for the bark, that had been suggested by more prominent authors of his time, such as Pringle, Cullen, and Home.

Colingwood's second approach concerned the therapeutic efficacy of different "species" of cinchona bark, which were then on the British market. His above experiences had been made with the commonly used "quill bark". In 1779, however, so-called "red Peruvian bark" had become available (see below). Colingwood, regarding "experiments tried on human bodies preferable to pharmaceutical investigation", reported his observations with the new sort of bark: of eight patients with intermittent fever in 1782 he had "cured" four with the "red" and two with the "quilled" sort. Moreover, he claimed to have successfully used the red bark in nervous fevers, in two cases each of "chronic rheumatism" and "obstructed menses", and without any failure in dysentery.
On the whole he thought the new cinchona bark was more certain, and curative in smaller doses, than the conventional sort; and it rarely caused gripes, which had been a common problem with the quill bark. In fact in the mid-1760s the young Thomas Percival (1740-1804), then practising in Warrington, had made numerous pharmaceutical trials to find a preparation of the bark that was not only "elegant" and "sufficiently efficacious", but also "palatable".

9. Which bark is best?

This second part of Colingwood's observations leads us thus to a further - and in this account last - issue surrounding the pharmacology and therapeutic use of cinchona bark in the eighteenth century: the question of quality assessment. It was particularly discussed towards the end of the century in view of new "sorts" of bark, but it was not an entirely new problem. Richard Morton, in the late seventeenth century, had already lamented the fact that the valuable drug was being adulterated, so that he had to increase dosage from the usual two drachms prescribed in the Schedula Romana to two or three ounces. And as Robertson's

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234 Cf. ibid., pp. 273-275. The problem that Peruvian bark "sat" badly on the stomach was reflected, for example, in the case histories of patients in the Edinburgh Royal Infirmary; cf. Risse, op. cit., General Introduction above, note 15, p. 198.


236 Jarcho, op. cit., General Introduction above, note 26, p. 56.
experience in the American War, mentioned above, indicates, this was still a problem almost a century later. Moreover, deterioration of the bark on its long journey from South America seems to have been a common problem. As Jarcho has estimated, the original kind of Peruvian bark, which was harvested in the Andes mountains around the town of Loxa (now belonging to Ecuador), needed at least one year to reach a European apothecary. Jarcho also quotes Spanish official records of the late eighteenth century, which often referred to spoilage of the bark, in particular when it had been packed in damp bags.\(^{237}\)

These general problems of adulteration and deterioration were further complicated by the variety of "sorts" of Peruvian bark and, well into the eighteenth century, rather poor knowledge about the precise botanical origin of the drug. Early reports on this matter were characteristically made at second hand, rather vague, and partly contradictory. In 1705, for example, the physician William Oliver (1659-1716), F.R.S. communicated a piece of information in the Philosophical Transactions, according to which the Peruvian bark came "from a Tree about the bigness of a Plumb Tree, with Leaves like Ivy, but not quite so big, and...always green" and "Fruit not unlike a Chestnut".\(^{238}\) Being taken from the trees in autumn, Oliver continued, the bark grew again in four months - like cork. He had received this information about ten years earlier, when serving with the Red Squadron in the Mediterranean, from an apothecary in Cadiz, Spain, who had lived in Peru.\(^{239}\) Another article on

\(^{237}\) Ibid., pp. 203-204.

\(^{238}\) William Oliver, 'A letter...to Mr James Petiver, F.R.S. concerning the Jesuits bark', Phil. Trans., 1704/05, 24: 1596. Haggis, op. cit., note 2 above, p. 453, assumed that Oliver's description actually referred to the Peruvian balsam tree.

\(^{239}\) Cf. Oliver, op. cit., note 238 above.
the same topic, published some thirty years later in the
same periodical, had been written by John Gray, F.R.S., who
then lived in Cartagena in the Spanish West Indies. His
account, however, was not first hand either. He had compiled
it from papers given to him by a Scottish surgeon, William
Arrot, who was said to have collected the bark "at the Place
where it grows in Peru". According to this account, the bark
came from tall trees with leaves like that of a plum tree,
and - contrary to Oliver - it required at least 18 or 20
years to regenerate.\textsuperscript{240}

Arrot (respectively Gray) was quite specific, however,
about the various locations in Peru, where those trees could
be found, and the different sorts of bark that the Spanish
had harvested by Indian workmen. He distinguished a reddish
and a yellowish sort (Cascarilla colorada and C. amarylla),
which constituted "the true and genuine fine Jesuits Bark";
a whitish variety (C. blanca), which he said was bitter and
efficacious in intermittent fevers like the other two sorts,
if it was fresh, but turned insipid, when it became dry and
had been kept for long; and a curling bark (C. crespilla),
which was cut from the trunks of young trees and was much
esteemed in England on the wrong assumption that it came
from the branches. Arrot, obviously not free of anti-Spanish
sentiment, expressed concern that the best trees around Loxa
would soon become extinct, since they were now entirely cut
down to facilitate slicing off their bark, as would the
Indian cutters themselves, "by the Spaniards hard Usage and
Cruelty".\textsuperscript{241} Very little of the "fine", yellow and red bark,
he noted, was sent to Panama and from there to Europe. The
bulk of the exported bark was the weaker whitish sort.\textsuperscript{242}

\textsuperscript{240} John Gray, 'An account of the Peruvian or Jesuits bark',
\textit{Phil. Trans.}, 1737/38, \textbf{40}: 81-86.

\textsuperscript{241} Ibid., pp. 83, 85-86.

\textsuperscript{242} Ibid., p. 82.
The basic points of Arrot's account matched those of the French naturalist Charles Marie de la Condamine, who had witnessed the harvesting of the Peruvian bark near Loxa in February 1737, in the course of his astronomical expedition to South America. In his report, published three years later in the Mémoires of the Paris Royal Academy of Sciences, he also distinguished efficacious red and yellow sorts from a white bark, which he described as "powerless". The red bark, La Condamine observed, was regarded as the best. Having talked to a representative of the British Pacific Company at Panama, he had also learned that the thin bark (i.e. the curling or "quilled" bark from younger trees) was now preferred in Europe. Allegedly, chemical and other "tests" in England had been responsible for this, as well as the fact that thicker bark dried less easily and was therefore more in danger of rotting during the long transport. La Condamine further provided a botanical distinction between the Peruvian balsam tree and the genuine Peruvian bark tree, helping thus to bring eventually some clarity into the confusion that had existed on this point during the seventeenth century and beyond.²⁴³

As can be inferred from the above reports, in the early eighteenth century some general quality criteria for the assessment of Peruvian bark became known, based on colour, consistency, and taste. Yet, increasing scarcity of the "fine" barks, and no doubt greed for profit, led to exports of low-quality or adulterated bark, which in addition might have spoiled on transport.²⁴⁴ In the end, the true quality of


the drug was only revealed through the required dosage during treatment.

In this situation, other drugs, especially other barks, were occasionally tried as substitutes. Partly they were indigenous (thus promising lower cost), partly they came from other parts of the New World. William Cullen, for example, said to have successfully treated intermittent fevers with a combination of gentian (as a bitter) and gallnuts (as an astringent), with oak bark, and particularly with willow bark. Concerning the latter he referred, among others, to the now well-known study of the Reverend Edmund Stone on this bark's efficacy in agues. 245 Caribbean cinchona bark, from a local tree called "sea-side beech", was suggested in 1777 as a substitute for Peruvian bark by the physician and botanist William Wright (1735-1819). Being surgeon-general in Jamaica, he had tried it there with "success" in many cases of remittent fever. In fact, following its use in the army and navy during the American War, it was for some time imported into Britain from St. Lucia. 246 Another suggestion around that time was cinchona bark from the Kingdom of Santa Fé, which had been sent in


246 William Wright, 'Description of the Jesuits bark tree of Jamaica and the Caribbees', Phil. Trans., 1777, 67: 504-506; George Davidson, 'An account of a new species of the bark-tree, found in the island of St. Lucia', Phil. Trans., 1784, 74: 452-456; Morris and Kendrick, op. cit., note 149 above, vol. 1, article 'Cinchona'.
two varieties, as Sir George Baker (1722-1809) remembered, by the Madrid professor of botany, Casimiro Gómez Ortega. However, a committee set up by the Royal Society to test the quality of these barks found them "far inferior" to the commonly used Peruvian cinchona.  

The above-mentioned interest in other "sorts" of bark and their therapeutic potential had so far been rather sporadic. But strong interest into this matter was sparked off by a "fortune" in the American War. In 1779 the Hussar frigate captured a Spanish ship coming from Lima, whose cargo consisted mainly of red Peruvian bark. The vessel was carried into the port of Lisbon, from where the bark was either sent directly to Britain or imported by London druggists via Ostend. Since this red bark did not only differ in colour, but came also in larger and thicker pieces, it did not sell very well initially. As mentioned above, the British market preferred the finer, whitish or pale "quilled" bark. Druggists therefore first offered the red cinchona to apothecaries "by way of trial", and it was also early introduced into charitable institutions, such as St. Bartholomew's, St. Thomas's, Guy's, and London Hospital. Its superior efficacy, however, became soon obvious, and regular imports were made through a Spanish merchant.  

The first detailed tests of the "new" red bark were performed by William Saunders (1743-1817) of Guy's hospital, whose chemical and pharmacological interests have been

247 Sir George Baker, 'Observations on the late intermittent fevers; to which is added a short history of the Peruvian bark', Medical Transactions, 1785, 3: 141-216, on pp. 154-155.

discussed earlier on with regard to lithotriptics.\textsuperscript{249} Saunders examined the red bark in comparison with the common Peruvian bark in a series of chemical and pharmaceutical experiments. All results were in favour of the red variety: it was more soluble, both in water and alcohol; it contained a much larger proportion of "active and resinous parts"; and it longer retained its "sensible qualities", such as its bitterness, when diluted or boiled. Astringency was tested by adding Tinctura florum martialium (i.e. a solution of ferric chloride) to infusions of the barks, which turned them black and led to precipitation of a black powder. Again, the reaction was stronger with the red bark. Finally, a student of Saunders at Guy's Hospital, Thomas Skeete from Barbados, compared the antiseptic power by performing in vitro trials of the type that Pringle had introduced, and also here the red bark proved superior.\textsuperscript{250}

Saunders further reported his experiences with the new bark in the treatment of intermittent fevers. About half the usual quantity of bark was required, when the red sort was used, and it prevented the next fit with greater reliability. He also provided some case histories to show that patients resistant to common bark were "cured" by the red. Moreover, the new bark appeared to be effective in typhus and other fevers as well.\textsuperscript{251} Saunders supplemented his account by several letters from surgeons and doctors (among them William Withering of Birmingham), confirming this therapeutic experience and sometimes citing cases of their own practice.\textsuperscript{252} By 1783 four editions of Saunders' study had been published. As its author proudly stated in this year,

\textsuperscript{249} See above, part A.

\textsuperscript{250} Saunders, op. cit., note 248 above, pp. 21-36.

\textsuperscript{251} Ibid., pp. 41-78.

\textsuperscript{252} Ibid., pp. 78-174.
he had meanwhile received letters from all parts of England, the West Indies, and many parts of the European Continent, all testifying to the superior efficacy of the red bark - not only in intermittents, but also in "other febrile disorders", as well as in cases of gangrene and scrofula "accompanied with a defective tone in the system". In fact Saunders interpreted the action also of this new bark as a tonic (in the sense of Cullen), which opened for it the same wide therapeutic spectrum as for the common sort.

In the same year one of Saunders' correspondents, the Norwich surgeon Edward Rigby (1747-1821), published a booklet of his own in support of the red bark, based on his therapeutic experiences. His intention was, as he claimed, to convince those practitioners who were still sceptical because it was a "new" medicine. Rigby pointed out that so far no negative reports had been published on it, although such would certainly have been promoted by druggists who wanted to sell their old stocks of common bark. Already in the following year 1784, however, a study by the Edinburgh trained physician Richard Kentish qualified Saunders' results. Using the same chemical and pharmaceutical methods, he had compared cinchona officinalis (i.e. the common, quilled sort), red Peruvian bark, and Caribbean bark. His results indicated that the red bark was less astringent and antiseptic than the common sort, and that the Caribbean bark surpassed both in bitterness and astringency. A problem with the latter, however, was its known emetic (side) effect. Kentish gave examples of failures of the red bark, from


254 Saunders, op. cit., note 248 above, pp. 36-41.

Edinburgh, London, Leyden, and Haarlem, concluding that the quilled bark appeared to him "unjustly using ground". In fact there were indications that the quality, and thus the reputation, of the red variety began to sink. In an address to the Royal College of Physicians of London in 1785, the Royal physician Sir George Baker noted that it had caused nausea and vomiting, and that he had begun to avoid it. Moreover, he voiced the suspicion that now that the original stocks (from the captured Spanish ship) were exhausted, "a spurious drug, under the title of the red bark" had recently been imported from Ostend. Scepticism was also expressed on the Continent. A Göttingen medical dissertation of 1791 reviewed the botanical and pharmaceutical characteristics of all the known cinchona barks and doubted that practitioners were justified in preferring the red sort. And in the late 1790s John Fawssett, an Edinburgh medical student, was able to confirm Saunders' findings on a preserved sample from the original shipload, but found that the red bark currently on the market was inferior to that first imported.

Meanwhile, in 1794, another physician from Guy's Hospital, John Relph, had propagated yet another new import, the so-called "yellow bark". Assisted by the hospital's

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256 Richard Kentish, *Experiments and observations on a new species of bark, shewing its great efficacy in very small doses: also a comparative view of the powers of the red and quilled bark; being an attempt towards a general analysis and compendious history of the valuable genus of cinchona, or the Peruvian bark*, London, J. Johnson, 1784.


258 Johannes Andreas Christophorus Gravenhorst, *Dissertatio inauguralis medico-pharmaceutica de cinchonae corticibus*, Göttingen, Typis Barmeierianis, 1791.

259 John Fawssett, *Dissertatio medica inauguralis de febribus intermittentibus medendis*, Edinburgh, Adamus Neill et Socii, 1798, p. 32.
teacher of chemistry, William Babington, and applying Saunders' methods of investigation, he found that this new bark was more bitter and astringent, and provided more extract, than the common and the red bark. Since in his view chemical analysis provided only "collateral evidence", however, he emphasized his clinical success with the yellow bark, quoting Saunders as a witness. Relph had tried it, as he reported, "on the poorer orders of the community", such as "labourers employed in the fenny parts of Essex, and the hop-gatherers in Kent", who were treated for intermittent fevers at Guy's. And he had extended his trials, also with "success", to patients suffering from remittent fever, typhus, and other continuous fevers, rheumatism, scarlatina, and erysipelas. Like Saunders, Relph concluded the superiority of the new kind of bark from its efficacy in smaller doses. Although the rather low social status of his patients might well have permitted it, neither he, nor Saunders, seem to have conducted "controlled" clinical trials in the sense of Lind's scurvy

260 John Relph, *An inquiry into the medical efficacy of a new species of Peruvian bark, lately imported into this country under the name of yellow bark: including practical observations respecting the choice of bark in general*, London, James Phillips, 1794, pp. vii-viii, 80-120.

261 Ibid., p. 122. Relph left actually the whole chemical and pharmaceutical part of the study to Babington. Cf. ibid., pp. 80-81. A further chemical analysis of the yellow bark was performed by Francis Marabelli, apothecary at the Hospital of Pavia and "public repeater" of chemistry, materia medica and pharmacy at Pavia University. He considered resinous extractive matter and gallic acid to be the "most active parts" of this bark, and observed that its efficacy in intermittent fevers and some other diseases surpassed that of common Peruvian bark. Cf. the review 'Analysi chimica della china gialla...by Francis Marabelli...Pavia, 1795', *Ann. Med.*, 1798, 2: 197-207.


263 Cf. ibid., pp. 129-130.
experiment. Their work, like that of Kentish, was strictly comparative only in its pharmaceutical and chemical part. Clinically they relied, as had their contemporaries Robertson and Home, on retrospective summaries and analyses of case histories. Accordingly, "voluntary written testimonies" by other doctors and surgeons were also added as an appendix to Relph's account.

Relph's work, however, was relevant in another respect. In order to illustrate the economic importance of the cinchona trade for Britain and her colonies in the West and East Indies, he compiled import and export figures of the bark during the past five years, 1789 to 1793. His figures were evidently incomplete, and he did not quote his sources, but they indicated that London, the outer ports, and Scotland together imported on average nearly 127,000 pounds, and exported less than 25,000 pounds, of cinchona bark per year.\(^{264}\) Relph's point in giving such figures had been a call for a better quality control of imported bark. This task, he thought, could not be left to the druggists, who determined the value of a given bark merely from its greater or lesser external resemblance with the kind currently regarded as the best. Instead tests by physicians, like Saunders', were necessary.\(^{265}\) But such figures could also be read - and were read - as a call for less expensive cinchona substitutes, either indigenous or from the British colonies. Interest in the willow bark, as well as in Wright's Jamaican cinchona, had doubtlessly been fuelled by economic considerations.

Now William Roxburgh (1751-1815), surgeon of the East India Company and superintendent of the botanic garden of Calcutta, suggested the bark of an Indian mahogany tree, Swietenia soymida, as a substitute. Again Saunders' methods of comparative testing had been applied, and Roxburgh had

\(^{264}\) Cf. ibid., p. 2.

\(^{265}\) Cf. ibid., pp. 3-6.
found this bark more bitter, astringent, and antiseptic, as well as better soluble and stable than the common, pale and quilled Peruvian bark. In addition to sixteen "successes" in various fever cases from his own practice, he could refer to "trials" with the soymida bark made by Andrew Duncan senior at the Edinburgh Royal Infirmary. In ten of twelve cases, including intermittent fevers and typhus, where Duncan had given this new bark, it was said to have been successful.

Soymida bark, however, never gained acceptance in Western medicine. Instead calls for treatment with indigenous medicines were made again. Fawssett in Edinburgh, for example, referring to Relph's import figures and financial reasons, advocated a combination of the astringent bistorta (i.e. root of snakeweed) and the bitter calamus aromaticus (i.e. root of sweetflag), which he said to have been successful in "almost a hundred cases" of intermittent fever in Horncastle Hospital, Lincoln. Not surprisingly, Fawssett's pharmaceutical experiments "demonstrated" that this combination produced a better, i.e. more astringent and bitter, decoction and tincture than even the yellow bark.

More trials, and more claims to have found the best bark, or a powerful substitute, could be quoted. Behind

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266 William Roxburgh, 'An account of a new species of Swietenia (mahogany); and of experiments and observations on its bark, and to compare them with those of Peruvian bark, for which it is proposed as a substitute', Medical Facts and Observations, 1795, 6: 127-161, on pp. 142-143.

267 Ibid., pp. 144-152. On some of Duncan's treatments with soymida bark, alongside many other medicines, see Estes, 'Drug usage', General Introduction above, note 15.

268 Ibid., p. 381.

269 Fawssett, note 259 above, pp. 43-50.

270 For a short bibliography on cinchona substitutes from 1747 to 1854, which does not contain the works discussed
the many chemical experiments and clinical "trials", personal ambitions and commercial pressures were barely hidden. Nor was the debate limited to Britain. Around the turn to the nineteenth century it had its Spanish counterpart in a controversy between the botanists Hipólito Ruiz (1754-1816) and José Celestino Mutis (1732-1808), who had studied cinchona trees in the viceroyalties of Peru and New Granada, respectively. While Ruiz, backed by Mutis' enemy Ortega, acted as a spokesman for the Peruvian cinchona barks, Mutis insisted that some varieties from Granada were equally effective in intermittent fevers. With ever more "sorts" of cinchona being described, the confusion was likely to increase. Until today 150 varieties of cinchona in 38 species have been made known.272

However, as in the case of opium, strong efforts were made around 1800 to identify the "active principle" of Peruvian bark. While commercial pressures continued, leading to the first plantations of cinchona in Dutch Java and British India in the 1860s,273 a new criterion for the above, see Waring, op. cit., note 9 above, vol. 1, pp. 358-360.


272 Glick, op. cit., note 271 above. See also Jarcho, op. cit., General Introduction above, note 26, p. 194.

quality of the bark was eventually found: its content of quinine.

10. The isolation of quinine

Among the works immediately preceding the discovery of quinine, a study by the Lisbon physician Bernardino Antonio Gomès (1769-1823) proved to be of particular importance. At the beginning of the nineteenth century Andrew Duncan junior of Edinburgh had identified a chemical "principle" in solutions of Peruvian bark, that formed a precipitate with infusion of galls or tannin and was soluble in alcohol. Duncan, regarding this principle as a distinct and hitherto unknown vegetable substance, had named it "cinchonin", although he claimed to have found it in other drugs as well, among them ipecacuanha and opium. Gomès doubted that Duncan had isolated a pure substance and took the Scottish physician's findings as the starting point for an investigation of his own.274

Having analyzed the so-called grey cinchona or "huanuco bark" described by La Condamine (Cinchona Condaminea), Gomès reported in 1811 to have obtained purified "cinchonin" in the form of silver bright, very fine, filiform crystals. He isolated this crystalline substance also from several other sorts of cinchona bark, but in two barks imported from Rio de Janeiro, Cinchona pubescens and Cinchona macrocarpa, it seemed to be lacking. Since these two barks were hardly effective against fevers,

he concluded that "cinchonin is the principle which renders cinchona, and the other vegetable substances containing it, eminently febrifuge". Accordingly he suggested determining the "cinchonin" content of barks to assess their quality.

Like Duncan, Gomès emphasized the solubility of "cinchonin" in alcohol (but not in water), but did not clearly characterize it either as an acid or an alkali. This, however, did not match the knowledge about active plant principles, that was emerging with Sertürner's isolation of morphine, a salifiable base. In 1818, shortly after Sertürner's discovery had been made known in France, the Paris pharmacist-chemists Pierre Joseph Pelletier (1788-1842) and Joseph Bienaimé Caventou (1795-1877) obtained strychnine as another salifiable base from St. Ignatius bean and nux vomica. And a year earlier, Francois Magendie and Pelletier had described emetine as the active principle of ipecacuanha, which in retrospect appeared also to be a plant base. Therefore, when Pelletier and Caventou turned their attention to cinchona, they strongly suspected that Gomès had made a mistake in his chemical characterization of "cinchonin" and that actually a salifiable base would be found in cinchona as well. In fact, as they reported in 1820 to the Académie des Sciences, they obtained two of them. From grey cinchona, i.e. the species used by Gomès,

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275 Ibid., p. 429.
276 Ibid., p. 431.
277 See also Lesch, op. cit., General Introduction above, note 27, pp. 313-314.
they isolated cinchonine, thus basically confirming the Lisbon doctor's result. From yellow cinchona bark (Cinchona cordifolia), however, they obtained a substance which was also alkaline and bitter, but in some other properties differed from cinchonine. Whereas cinchonine formed crystals, the other substance was an amorphous mass, and there was also a marked difference in their solubility in ether. They therefore coined a name of its own for this new substance found in the yellow cinchona: quinine. These results were corroborated by their analysis of red cinchona (Cinchona oblongifolia), i.e. the sort of Peruvian bark, which was still regarded by many physicians as the best. It contained about four times as much cinchonine as the grey bark, and nearly double of the amount of quinine that had been found in the yellow cinchona. In view of this result the two chemists were convinced that the active, febrifuge principle had to consist in a salifiable base: cinchonine in the grey bark, quinine in the yellow, and both in the red.

Pelletier and Caventou anticipated the argument that not one or two components of the Peruvian bark, but the combination of all its constituents made it an effective remedy. In fact this view was held as late as 1826 by Jean Alibert, physician to the Saint-Louis Hospital in Paris - as it was expressed concerning opium and morphine by Hufeland still in 1836. But Pelletier and Caventou insisted that the

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280 Horst Real and Wolfgang Schneider have repeated Gomes' procedures on authentic huanuco bark and concluded that his "cinchonin" was pure cinchonine; see their article 'Wer entdeckte Chinin und Cinchonin?', Beiträge zur Geschichte der Pharmazie, 1970, 22/3: 17-19.

281 Pelletier and Caventou, op. cit., note 279 above. See also François Magendie, Vorschriften für die Bereitung und Anwendung einiger neuen Arzneimittel als der Krähenauge, des Morphins, der Blausäure, des Strychnins, des Veratrins, der China-Alkalien, der Jodine u. m. a., transl. from the French, Leipzig, Leopold Voß, 1822, pp. 38-40. The first edition of this Formulaire of Magendie was published in 1821.
other components of cinchona at most "modified" the active organic base. To question the value of searching for active principles in remedies, they argued, meant "to banish the chemical sciences from the sanctuary of medicine" and to revert to "empiric, absurd, and often dangerous" preparations.\textsuperscript{282}

The future, as we know now, proved the two Paris chemists right. As soon as they had isolated cinchonine and quinine, Pelletier sent samples to Magendie, who tested them for toxicity in animals. Since no sudden or extraordinary effects were observed, the transition to clinical "trials" was quickly made by physicians, among the first by Magendie himself, Pelletier's brother-in-law Francois Double, Louis Villermé, and Auguste Chomel. Of the various salts of quinine and cinchonine that Pelletier and Caventou had prepared in the course of their original investigation, sulfate of quinine proved most suitable for the treatment of intermittent fevers and other diseases.\textsuperscript{283} Numerous studies of both the pharmacology and the therapeutic properties of quinine (and initially also of cinchonine) were carried out during the nineteenth century, which would furnish enough material for a comprehensive "history" of its own.\textsuperscript{284} As in

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\textsuperscript{283} Magendie, op. cit., note 281 above, pp. 43-46; Smith, op. cit., note 6 above, pp. 349-352; Lesch, op. cit., General Introduction above, note 1, p. 143.

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the case of opium, also in the Peruvian bark the alkaloid eventually superseded the drug as the therapeutic agent.

11. Conclusions

This study of Peruvian bark has brought out some features which are similar to those in the histories of opium and lithontriptics, and others which are peculiar to this drug. Since both opium and the bark were no evacuant medicines (i.e. had no purgative, emetic, or diuretic properties), but were very effective in a number of conditions, they did not conform with the principles of traditional, Galenic humoral therapy. Neither did Galen's doctrine of primary and secondary qualities seem to fit. The two drugs' bitter taste pointed to heat as a primary quality. But in opium this was inconsistent with its analgesic and narcotic effects, which were thought to originate from a cooling action; and in the bark it led to the paradox that a hot medicine removed the heat of fevers. Non-conformity with Galenic doctrine seems to have been a greater problem, however, in the case of Peruvian bark, probably because it was a new drug in the seventeenth century, whereas opium had already been used by the ancients. Most serious - and surely more important than anti-Jesuit sentiment - was the objection of Galenists against the bark that it did not eliminate the "morbific, febrile matter" from the humours. As has been shown, this charge survived in the new guise of Georg Ernst Stahl's system well into the eighteenth century. According to Stahlians, Peruvian bark, by its astringency, trapped the materia peccans in the body and thus oppressed nature's efforts to eject it. This again had its counterpart in their criticism of opium, which was thought to hinder the soul-guided movements of the body in eliminating the cause of pain, suppressing merely the symptom. In fact, Stahl and his
followers are known to have avoided both drugs in their treatments.285

The seventeenth-century criticism of Galenic qualities led to the view that Peruvian bark had an occult property, which acted specifically in intermittent fevers, as guaiac wood did in syphilis. Influential was Thomas Sydenham's praise of the bark as the only true specific in medicine, that was able to eradicate the "species of disease". This notion of the bark as a specific began to be undermined, however, already in the late seventeenth and early eighteenth centuries, when various theories of the drug's mode of action were formulated. Though some of them had a basis in pharmacological experimentation and clinical observation, they were largely speculations within the then current concepts of iatrochemistry (e.g. Jacques Minot, Richard Morton) and iatromechanics (e.g. William Cole, Friedrich Hoffmann).

The further development of theories of the bark's modus operandi showed remarkable parallels with those of opium. As in the latter, the common view in the early eighteenth century was that cinchona acted on the blood. The experimental work of Stephen Hales, which demonstrated the bark's astringent effect on blood vessels, and of John Pringle and David Macbride, which pointed to an antiseptic power, expanded this view, but did not principally change it. As in opium, the shift to seeing the bark as acting directly on the nervous system (rather than on the blood and vascular system) was linked with the Edinburgh school of medicine. The "nerve theory" of opium, propagated by Charles Alston and Robert Whytt around 1750, had its later equivalent in William Cullen's doctrine of the bark as a general tonic. The preoccupation of the Edinburgh school with the nervous system286 was doubtlessly the background to

both these pharmacological interpretations. Yet in both cases criticism came from within. Concerning opium it was Alexander Monro secundus, who emphasized an additional effect via absorption into the blood, and Francis Home asserted the same for Peruvian bark. These similarities support Earles' thesis of a general change in experimental pharmacology from nervous theories in the eighteenth to theories of absorption in the nineteenth century. Yet, it has also become evident that the idea of drug action via the blood was - as such - by no means new.

The various pharmacological explanations of the bark's efficacy "eroded" its special status as a specific in the course of the eighteenth century. There was little doubt any longer that it was a most powerful remedy, especially in intermittent fevers, but other bitters, such as gentian and wormwood, and other astringents, such as camomile flowers and chalybeate waters, appeared also to be effective as febrifuges, tonics, or antiseptics. The search for substitutes, which arose chiefly from economic constraints, pointed in the same direction.

Acting synergistically in this "erosion" of the specificity of Peruvian bark was the tendency to widen the drug's therapeutic indications. Already in the seventeenth century the bark had been tried in other than purely intermittent fevers. The eighteenth century brought "gangrene" as a new and important, "surgical" indication. Often on the basis of reasoning by analogy, the spectrum was subsequently extended to include various ulcers, "putrid sore throat", smallpox, and many other conditions. The perception of Peruvian bark as a general tonic eventually "opened the floodgates" and made it a universal remedy. It

286 See Lawrence, 'Medicine as culture', part B above, note 98.

formed also the background to Samuel Hahnemann's famous self-experiment with cinchona, which led him to his "principle of similarity", the centrepiece of homoeopathy. Ackerknecht has traced the development from specific to panacea (and back to specific) in short, exemplary studies of the therapeutic uses of digitalis, iodine, and quinine in the nineteenth century. Our study of Peruvian bark has shown that such a development can already be observed a century earlier, and it thus lends further support to Ackerknecht's thesis that "the phenomenon seems by no means rare in the history of therapeutics". In fact he noted that quinine "inherited the glory and prejudices and the aura of controversy surrounding its predecessor", the bark, which "had already become a panacea".

However, Ackerknecht seemed to underestimate the role of pharmacological theories in this process, regarding them as mere "rationalizations" of empirical practice. The latter, he thought, was motivated by the fact that physicians were "under terrific pressure to do something against disease". Yet therapeutic scepticism and nihilism in the early nineteenth century do not easily fit this interpretation. And as for the present case study of Peruvian bark in the eighteenth century, the theories (partly experiment-based) of its astringent, antiseptic, and tonic effect seem at least to have facilitated its therapeutic use in a wide variety of conditions other than

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290 Ibid., pp. 402, 410.

291 Ibid., p. 408.
intermittent fever and "gangrene" (which were indeed empirically gained indications).

As a consequence of this "erosion", the definition of "specifics" changed around the turn to the nineteenth century. A specific was no longer, as Sydenham had taught, a remedy that extinguished the species morbi, regardless of the patient's individual condition. As the Edinburgh medical and physical dictionary put it in 1807, specifics were merely "such medicines as are more infallible than any other in any particular disorder". The extensive pharmacological knowledge, which had been gained in the past hundred years about the various effects of the bark on the body, precluded Sydenham's idea that the specific remedy simply targeted and destroyed the specific disease. The relevant article in the above dictionary made it clear that specifics could not "infallibly and in all patients" produce salutary effects, because these depended "upon the mutual action and reaction of the body and medicine upon each other". Or, as a medical critic had expressed it in 1797:

...as to specifics, if their idea be explicable by supposing an admiral sent down channel, across the Bay of Biscay, and up the Mediterranean, with express orders to attack the Maltese, but with the strictest charge not to molest any other state whatever; I cannot conceive any medicine such a specific as to conform most punctually with such orders, to act vigorously against one particular gland or humour of the body, without in the least affecting or disturbing any other, or, like a sheriff's officer, serve his writ upon the individual person it was intended for, and on no other person, in a mistake.

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292 Morris and Kendrick, op. cit., note 149 above, vol. 2, article 'Specifics'.

293 Ibid.

Nevertheless, the term "specific" continued to be used in conjunction with the bark. The at first glance contradictory notion of "Tonicum Specificum", used in Johann Friedrich Moller's Göttingen dissertation of 1765 on "the true specific power of the Peruvian bark", indicated a new definition. A "specific" became a drug which united its known pharmacological properties (such as astringency, antiseptic power etc.) in such a peculiar and inimitable way, that it was superior to all other drugs sharing those properties. The Edinburgh dictionary clearly reflected this new perception of specifics:

...although it be admitted that the Peruvian bark acts powerfully as an astringent, as a tonic, and as an antiseptic; yet these principles will by no means explain all the effects derived from it in the cure of diseases. And accordingly, from no artificial composition in which these powers are combined, or in which they exist even in a higher degree, can the good consequences resulting from Peruvian bark be obtained. Many practitioners, therefore, are disposed to view it as a specific. If by a specific we mean an infallible remedy, it cannot indeed be considered as intitled to that appellation; but in as far as it is a very powerful remedy, of the operation of which no satisfactory explanation has yet been given, it may with great propriety be denominated a specific.295

In other words: a specific remedy was no longer defined through its single target, such as intermittent fever in the bark, but through its uniquely powerful and not fully understood mode of action, which was beneficial in a number of diseases. In this way the change in the use of the bark "from specific febrifuge to universal remedy", as studied in this chapter, became manifest.

A further issue emerging from this study, as in the previous on opium, is the relation of experimental pharmacology and therapeutic practice. Also in this example

295 Morris and Kendrick, op. cit., note 149 above, vol. 1, article 'Cinchona'.
some direct conclusions from theory to therapy could be
identified, such as Minot's recommendation not to give the
bark together with fruit acids, since it acted as an
antacid; or Pringle's and Macbride's warning that its
astringency would make inflammatory conditions worse. On the
other hand, some experimentally gained knowledge about the
bark's action rather explained certain aspects of
therapeutic practice than determined them. Johann Balthasar
Schondorff's and Friedrich Hoffmann's conclusion, for
example, that the bark should be administered towards the
end of a febrile paroxysm, because its astringency was more
effective in calm and "contracted" blood, merely legitimized
the empirical practice of Sydenham. The same can be said
about Hales' view that the bark's vasoconstrictive power
increased the speed of flow and thus the temperature of the
blood. Yet it would be going too far to see such
pharmacological confirmations of medical practice as mere
"rationalizations" in the sense of Ackerknecht. The new,
"scientific" approach to therapy became further manifest in
the "clinical experiments" of Home on the best timing for
giving Peruvian bark in intermittents, and in Richard
McCausland's and Robert Robertson's protostatistical
comparisons of the bark with other fever medicines. And it
was fully developed in the comparative assessments of the
various "sorts" of cinchona by men like William Saunders,
Richard Kentish, John Relph, and William Roxburgh, who
combined physical, chemical, pharmaceutical, physiological,
and clinical criteria. These examples also illustrate how
economic pressures - scarcity of the drug in war and general
dependency on imports - stimulated pharmacological research.

This evolution of the pharmacological approach to the
bark was linked - as in the cases of opium and
lithotriptics - with both a notable methodological and
ethical awareness. The comparative and controlled in vitro
trials of Minot, Francesco Torti, and John Hunter, the
discussion of the transferability of such trials by Macbride
and Cullen's pupils Gabriel Wynne and George Brown, and the search for confirmation in experimental animals by Minot, John Freind, and Hales, all testify to the emergence of the former. It can also be recognized in the changing use of case histories as a means of proof. In the middle of the seventeenth century one prominent case, such as that of Archduke Leopold Wilhelm, could be sufficient to fuel a long debate on the bark's efficacy and safety. Less than a hundred years later, Alexander Monro primus strived to ascertain the drug's efficacy in gangrenes "by a sufficient number of well vouched Histories"; and towards the end of the eighteenth century even a minor figure like the army surgeon McCausland demanded "a very large number of experiments and observations" in order to counteract the fallacies of therapeutic judgements. Case histories served also, as has been shown in the work of Thomas Kirkland on gangrene treatment, as a means to develop differentiated schemes of therapy, based on a differentiated diagnosis. Some ethical awareness has been identified in the remarks of the London surgeons John Douglas and John Shipton in the early eighteenth century concerning the legitimacy of new forms of treatment with the bark. Yet such awareness was fully spelled out only later in the century by John Aikin, James Gregory, and Francis Home, who called for a cautious and responsible medical researcher in the new context of experimentation in hospitals and required that the patients subjected to a trial benefited from it personally. That the new indication of "gangrene" for bark treatment created problems of professional ethics between surgeons and physicians, has been brought out by an analysis of Douglas' first case of this kind.

Finally, as in the "case studies" on lithontriptics and opium, the impact of analytical chemistry on pharmacological knowledge after 1800 has also become evident from this study of the Peruvian bark. Pelletier's and Caventou's discovery of its alkaloid quinine was closely linked with Sertürner's
previous isolation of morphine from opium and the ensuing concept of salifiable bases as the active principles of plant drugs. The content of quinine became eventually the quality criterion of the various cinchona barks, as did the morphine content of the different cargos of imported crude opium. And like morphine and the new "chemical" lithontriptics, quinine permitted more accurate dosage and more efficient treatment.
GENERAL CONCLUSIONS

At the end of each of the three "case studies" - into lithotriptics, opium, and Peruvian bark - specific conclusions have been drawn, and some comparisons have been made. In this final section the more general characteristics of eighteenth-century pharmacology and therapeutics, as they have emerged from my investigation, will be highlighted.

It had been an open question to which extent experimental approaches to the study of drugs and remedies played a role in contemporary medicine. My quantitative survey of relevant articles in selected Edinburgh periodicals, covering the years 1733-1800, had suggested that experimental methods were considerably less often applied than clinical observation, which was usually summarized in case histories. All three of my detailed studies have confirmed the importance of this "case history approach". It could also be shown that there was a conscious tendency in the course of the eighteenth century to increase the numbers of case reports concerning a particular therapeutic issue, such as Mrs Stephens's medicines against bladder stones or Peruvian bark in "gangrene", in order to obtain more reliable overall results. Towards the end of the century, the numbers and ratios of "cures", relapses, or deaths after different treatments were sometimes retrospectively compared with each other, as has been illustrated with Richard McCausland's and Robert Robertson's inquiries into the therapy of fevers.

On the other hand, my three "case studies" have unearthed a previously unknown wealth of pharmacological experiments of different types. Besides chemical characterizations of the drugs and medicines in question, in vitro trials on body substances were a major approach. Alone

1 See General Introduction above.
my investigation into eighteenth-century pharmacotherapy of urinary stones has identified more than twenty authors who tested the "dissolving power" of supposed lithontriptics directly on the concrements. We have further seen that experiments on blood and other body fluids with opium and cinchona were performed by several researchers. Usually these in vitro experiments were comparative and controlled. Animal experimentation played a lesser role in the work on lithontriptics, where it was chiefly employed to assess the tolerance for the substances in intravesical injection. Likewise it was only occasionally used in studying the effect of Peruvian bark on the blood or the vascular system. But it was a major research method within inquiries into the mode of action of opium, the experiments being performed both on cold- and warm-blooded animals, and on isolated organs. Also control experiments were carried out in this area. Testing on human subjects, including self-experiments of the researchers, was a quite common method in studies of opium. The boundaries to self-observation during treatment were sometimes blurred, as Albrecht von Haller's account of his taking of the drug during his final illness illustrates. Experimental self-treatment with new lithontriptics has further been noted in David Hartley, James Jurin, Charles Alston, and Benjamin Colborne, who all suffered from symptoms of urinary stones. Finally, trials on patients, both therapeutic and non-therapeutic, have been described. The former involved either one particular treatment for different groups of patients (e.g. Sauveur-François Morand's trial with Mrs Stephens's remedy on patients with various bladder and kidney diseases) or different forms of treatment for patients with the same kind of illness (e.g. Francis Home's exploration of the best timing in giving Peruvian bark in intermittent fevers). No therapeutic effects could realistically be expected from the single intravesical injections of lime-water, performed under the direction of Robert Whytt, on patients of the Royal Infirmary of
Edinburgh. They were rather tolerance tests, as they had been made by Stephen Hales, and were subsequently performed by Browne Langrish and Michele Girardi, on dogs. Likewise the experiments on patients with opium extracts by the Edinburgh student and Harvey-prize winner John Leigh had no recognizable immediate therapeutic aim.

The amount and variety of trials alone, however, does not yet fully prove their importance for the development of modern pharmacology and therapeutics. A serious qualification of the value of eighteenth-century experimentation, that has been made for example concerning Anton Störck's therapeutic trials with poisonous plants, is that its results were often uncritically interpreted and generalized. Although our investigation has also revealed examples of this "weakness", particularly in pharmacological in vitro trials on blood, it has been shown that there was a considerable critical discourse about the validity of the experimental methods. It dealt especially with the problem of transferability of observations made with substances in the phial and in animals to ill human beings. Some medical critics went so far to accept only actual therapeutic experiences as evidence of a substance's efficacy.

In addition to such methodological awareness, found also among the experimentalists themselves, we have traced ethical considerations. They concerned the suffering of the experimental animals and the safety of the test persons. While the former caused little more than compunction in the researchers, the latter led to the exhortation regarding clinical trials that the individual patient should forseeably benefit from the experimental treatment. Consent was obviously not a major issue in tests on patients, though refusals have been documented in Morand's trial, when a

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second catheter examination of the bladder was suggested to ascertain the lithotriptic's efficacy for the "benefit of the public" (rather than that of the ill person concerned). It remains a moot point how voluntary experiments on healthy subjects were. Some of the "young men", on whom pharmacological tests were typically performed, may have been dependents of the experimentalist (e.g. the house pupil of the surgeon Michael Ward). The ethical "framework" changed to some extent, when the researcher included himself among the test persons, as for instance Samuel Bard, Carl Joseph Wirtensohn, Samuel Crumpe, and Friedrich Wilhelm Sertürner did in their experiments with opium, respectively morphine.

Yet, while methodical and ethical awareness certainly reflect an "advanced" state of pharmacological experimentation in the eighteenth century, they might still leave some doubt about the field's theoretical and practical relevance. It has been shown, however, in all three "case studies", that experimentation did contribute considerably to the theoretical understanding of drugs. It is true that experiments were not used in a modern way as rigid tests for the verification or falsification of specific hypotheses. But they were employed as "arguments" towards theories of a drug's mode of action - in addition to conclusions from clinical observations and sometimes postmortem findings. The questions which can be recognized behind eighteenth-century pharmacological trials were often fairly general (but not vague), for instance, whether a substance acted more on the blood or on the nervous system, whether it diluted or coagulated the blood, whether it stimulated or sedated, whether it might be classified among astringent, tonic, and antiseptic medicines, or to which extent it might dissolve and expel urinary calculi. The (partly) experiment-based theories of the modus operandi of a drug in turn narrowed or broadened its medical indications. In this way pharmacology
influenced and supplemented the therapeutic knowledge that was gained empirically in the treatment of patients.

My studies have further identified a number of key figures in the emerging field of experimental pharmacology. Robert Whytt and Charles Alston were prominent both in contemporary research on opium and lithontriptics, a finding which underlines the importance of the Edinburgh medical school in the eighteenth century. While Whytt's contributions have been historically appreciated in the past, Alston has been a very much neglected figure in the history of medicine, to whose pharmacological work full attention has been given here almost for the first time. Among the London researchers, William Saunders of Guy's Hospital stands out through his work both on fixed air as a lithontriptic and on the properties of the red Peruvian bark, as does the Reverend Stephen Hales with his studies of Mrs Stephen's medicines, lime-water, and vasoconstrictive substances. On the Continent, Friedrich Hoffmann with his doctoral students at the University of Halle contributed considerably to the knowledge of opium and Peruvian bark, as did Albrecht von Haller and his Göttingen pupil Johann Adrian Theodor Sproegel concerning opium. Finally it should be pointed out that Claude Joseph Geoffroy of the Paris Academy of Sciences was involved in the critical assessment of both Mrs Stephens's medicines and William Oliver's "antidote" against viper bites, and that Felice Fontana's experiments were influential in understanding the action of the viper venom as well as that of opium. However, besides these key figures, who were usually associated with eighteenth-century "centres of medical science", my investigation has brought to light a multitude of contributions by much less known, or virtually unknown, researchers. This shows how widespread the enterprise of

3 French, op. cit., part A above, note 5.
examining and testing drugs, medicines, and poisons actually was, both in Britain and in Continental Europe.

Eighteenth-century pharmacology was hampered for long by the difficulty of determining the nature and amount of active principles in the drugs or remedies. Though doses were usually carefully recorded, they had little meaning as long as the purity of a substance remained largely unknown. Yet intense efforts to determine chemically the active components of medicines have been observed in all three of my examples. The isolation of morphine from opium and of quinine from cinchona, as well as the new chemical therapy of urinary stone disease, were culminations of long developments as well as new starts.

Taking all this into account, it seems justified to speak of "experimental pharmacology and therapeutic innovation" already in the eighteenth century, and not to reserve these terms for the nineteenth and twentieth centuries, i.e. for the age of the natural sciences in medicine. Close examination has shown that the materia medica of the eighteenth century was less "chaotic" than Erwin Ackerknecht portrayed it.⁴ Experimentation with drugs was not unusual, and their assessment in case histories was very widespread. Pharmacological theories were not mere "rationalizations" of empirical practice, as he saw it,⁵ but steps towards rational therapeutics. In this sense the described experimental pharmacology can be seen as part of the wider efforts to transform medicine in the Enlightenment. Galenic, iatrochemical, iatromechanical, and vitalistic concepts did all play a role in contemporary pharmacology and therapeutics. But my analysis shows them rather as parts of a powerfully developing area of medicine.

⁵ Cf. idem, 'Aspects', General Introduction above, note 13, p. 408.
than as divergent forces or speculative excesses. If one wishes to continue to speak, with Chauncey D. Leake, of a "protopharmacology" in the eighteenth century, one should therefore imply with this term rather the field's historical strengths than its limitations.

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