

## Opium before morphine: the elusive quest for the active principle of drugs

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### Abstract

The idea that the history of modern, essentially experimental, pharmacology began in the early years of the 19<sup>th</sup> century is widely shared by scholars. The emblematic milestone is the isolation of morphine by Friedrich Sertürner in 1805. Nevertheless, a closer look into 18<sup>th</sup> century pharmacology shows that contemporary scholars were utterly persuaded that there were principles of activity in matter, and that they could be isolated in the laboratory. In the present paper we show that disciplinary demarcation was one of the key elements defining the framework within which doctors, naturalists, chemists and pharmacists sought to answer one of the greatest medical enigmas of all times: how do narcotics act?

### Keywords

Experimental pharmacology; 18<sup>th</sup> century; opium; scientific communities

## O ópio antes da morfina: a procura elusiva pelo princípio ativo dos fármacos

### Resumo

De acordo com uma visão amplamente compartilhada, a história da farmacologia moderna, inerentemente experimental, começou no início do século XIX. A marca emblemática é a descoberta da morfina por Friedrich Sertürner em 1805. No entanto, um olhar mais próximo para a farmacologia do século XVIII mostra que os estudiosos da época estavam completamente persuadidos de que a matéria contém princípios ativos, passíveis de ser isolados no laboratório. No presente artigo mostramos como a demarcação entre disciplinas foi um dos elementos determinantes dos contextos nos quais médicos, naturalistas, químicos e farmacêuticos procuraram responder um dos maiores enigmas médicos de todos os tempos: como agem os narcóticos?

### Palavras-chave

Farmacologia experimental; século XVIII; ópio; comunidades científicas

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*Opium facit dormire [...]  
quia est in eo vertus dormitiva.*  
Molière, *Le malade imaginaire* (1673)

## Introduction

The standard view of scholars on the rise of the inherently experimental modern pharmacology holds that it first emerged at the beginning of the 19<sup>th</sup> century. Such feat is emblematically signaled by the isolation of morphine by Friedrich Sertürner (1783-1841) in the first decade of the 1800s, which, indeed, was the first organic plant alkali (alkaloid) to be identified.

A critical look into the standard view shows that with very few exceptions, most studies approached Sertürner's findings as if they would have been virtually preordained, i.e., as if the alkaloids were self-subsistent entities waiting to be 'discovered' since the beginning of times rather than scientific notions that must be constructed as all other. Focusing on the attribution of priorities, most such studies passed over the fact that the notion of the active principles of matter, albeit known by many other names and represented by quite variable concepts, has a much longer history. A very long history, indeed.

The present paper, addressing the period immediately predating the isolation of morphine, is a part of a wider-scoped project aiming at understanding the epistemological shifts in the notion of active principles of drugs at the turn of the 19<sup>th</sup> century. In this regard, the case of opium affords the modern scholar a privileged glimpse into the concerns, ideas, practices and methods of several scientific communities undergoing incipient, but fast specialization and institutionalization. As we show, disciplinary demarcation represents one of the key elements defining the framework within which doctors, naturalists, chemists and pharmacists sought to answer one of the greatest medical enigmas of all times, ironically immortalized by Molière: how do narcotics act?

## How to look for the active principle of plant drugs?

One of the offshoots of the so-called 'Scientific Revolution' was the explicit attempt to explain the phenomena of living matter on the grounds of physical and chemical notions and methods. Consistently, all throughout the 18<sup>th</sup> century doctors across Europe did not spare time and resources in the investigation of the chemical composition and properties of the human frame, and naturally also of the substances employed to heal its diseases. Within that particular context opium, together with

mercury and Peruvian bark were some of the main subjects of interest as a function of the current theoretical and practical concerns.<sup>1</sup>

On the grounds of the prevailing physiological notions, narcotics (also known as sedatives, anodynes or hypnotics) were universally understood as “medicines that decrease the sensitivity and irritability, relief pain and induce stupor and sleep”<sup>2</sup>. Some of the narcotics, including opium, were known since the remotest antiquity, and the main concern of clinical practitioners and authors of books on materia medica at the turn of the 19<sup>th</sup> century was to understand their physiological action and therapeutic effects. This choice of words is not arbitrary, as one of the topics widely discussed at that time and that bore direct influence on the notion of active principles of drugs, was the incipient distinction between the actions proper to drugs on the healthy human body and the effects that resulted from their interaction with the living human body in both health and disease.

Several theories were put forward to account for the action and effects of opium, which were thoroughly dealt with by A.-H. Maehle, in *Drugs on Trial*.<sup>3</sup> Our interest here, however, is mostly methodological. One of the main centers of drug research in the second half of the 18<sup>th</sup> century was the medical school of Edinburgh. A former student of Hermann Boerhaave’s (1668-1738) and Leyden graduate, starting 1738 Charles Alston (1683-1760) held the chair of materia medica and botany in Edinburgh; his lectures were published posthumously by John Hope in 1770.<sup>4</sup> The most remarkable fact about Alston’s pharmacological work is his critical assessment and systematization of the methods and techniques for the study of drugs, which he first applied to the study of opium in 1752.<sup>5</sup> This, indeed, was qualified by some scholars as the “first wide-scoped modern study on opium”<sup>6</sup>, the reason being that Alston systematically applied the following methods: 1) accurate botanical identification; 2) historical and etymologic analysis; 3) description of the medicinal virtues and therapeutic indications; 4) description of the sensory qualities; 5) chemical analysis; 6) animal experimentation; 7) human and self-experimentation by several routes of administration; 8) *in vitro* experiments on various organic fluids; and 9) literature review of clinical observations. Such thorough approach led them to the following significant conclusions:

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<sup>1</sup> The reason being that mercury and Peruvian bark were the exemplary models of the much sought for specific medicines against syphilis and intermittent fevers, respectively, while opium afforded universal relief of pain, see Silvia Waisse-Priven, *Hahnemann: Um Médico de Seu Tempo* (São Paulo: Educ; Fapesp, 2005) and the references cited there.

<sup>2</sup> Anonymous [a member of the London College of Physicians], *Thesaurus medicaminum: a new collection of medical prescriptions*, 3<sup>rd</sup> ed. (London: C. and R. Baldwin, John Murray & L. B. Seeley, 1804), 260.

<sup>3</sup> Andreas-Holger Maehle, *Drugs on Trial: Experimental Pharmacology and Therapeutic Innovation in the Eighteenth Century* (Amsterdam: Rodopi, 1999), 132 et seq.

<sup>4</sup> Charles Alston, *Lectures on the Materia Medica*, ed. John Hope (London: Edward and Charles Drelly; Edinburgh: A. Kincaid and J. Bell, 1770).

<sup>5</sup> Charles Alston, “A Dissertation on Opium,” *Medical Essays and Observations* 5, part 1 (1752): 93-146.

<sup>6</sup> Maehle, 148.

- In regard to its chemical composition, opium yielded mostly gum, resin, and an earthy component in ratio 5:4:3, whereas only the gum kept the taste and smell of the poppy juice. These findings allowed Alston conclude that the narcotic virtue of opium did not depend on a volatile sulfur, as Friedrich Hoffman (1660-1742) and Etienne F. Geoffroy (1672-1731) held.<sup>7</sup>
- Then, a most striking finding that seemingly was not taken into account by later chemists, as we shall show. According to Alston, opium was more **alkaline** than acid without, however, representing a ‘true alkali, whereas its essential salt had a definitely **ammoniac** nature.<sup>8</sup>
- On distillation, opium yielded phlegm, a **urinous spirit**, oil, volatile salt, fixed salt and earth. Nevertheless, Alston remarks that several simples ranging from foodstuffs like cabbage to poisons such as belladonna yielded exactly the same principles and thus distillation was useless as a method to investigate the virtues of opium.<sup>9</sup>

Alston concludes that the **active principles** (sic) of opium were not volatile, as the contemporary chemists believed, but highly fixed – having personally attested that they could be conserved for up to 40 years. More significantly, Alston found several hints pointing to the presence of alkaline substances, which he, however, dismissed, as it did not seem to him that chemical analysis could account for the action of opium.

That same mistrust of chemistry was expressed by most clinical practitioners at that time, as attested by a memoire presented by Naples medical professor Michel Attumonelli (1750-1802) to the *Société de Médecine de Paris* in 1802,<sup>10</sup> and that was read to, and unanimously approved by the *Classe des Sciences physiques et mathématiques* of the *Institut national des sciences et des arts* in its session of 3 Frimario XI. In that memoire, Attumonelli explicitly states that the action of opium could only be ascertained through the observation of the effects it induces and the analysis of the diseases where it is effective, while he criticizes some “highly reputed doctors who fruitlessly attempt to apply chemistry to the phenomena exhibited by the human body, by assimilating it to a laboratory where nature acts as if it were a chemist”<sup>11</sup>. It is worth to emphasize that Jean-Charles Desessartz (1729-1811), relator of the abovementioned session, declared the memoir “very useful, and deserving of the attention of doctors and the [*Institut’s*] Class”<sup>12</sup>.

An interesting glimpse into the relative weight attributed by the various scientific communities to the different approaches to the study of drugs is afforded by the work of John Murray (d. 1820), a professor of chemistry, materia medica, and pharmacy at Edinburgh, and author of widely read handbooks. The results of his

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<sup>7</sup> Alston, “Dissertation”, 115-6.

<sup>8</sup> Ibid, 119-22.

<sup>9</sup> Ibid, 123-8.

<sup>10</sup> Michel Attumonelli, *Mémoire sur l’opium* (Paris: chez la V<sup>e</sup> Panckoucke, An X).

<sup>11</sup> Ibid, 3; 69.

<sup>12</sup> Ibid, appendix, IV.

endeavors were initially published in 1804 as *Elements of Materia Medica and Pharmacy*,<sup>13</sup> and then reworked as a proper *System of Materia Medica and Pharmacy* (1810)<sup>14</sup> for reasons that we now discuss in detail.

In the introduction to *Elements*, Murray states that three different disciplines contribute to the investigation of the powers of drugs, namely natural history, chemical history, and medical history, following the prevailing Baconian approach that understood history as the proper process of science. Natural history supplies the characteristics that allow distinguishing among medicinal substances, whereby the ones that ground the natural classification of plants might also afford indications of their medicinal virtues. Chemical history, in turn, investigates the chemical composition and properties of drugs, and thus is allegedly able to lead to the knowledge of their healing virtues, which Murray does not consider to be a fully improbable enterprise, as “the medicinal powers of any compound body must result from its chemical composition”<sup>15</sup>. However, he warns that although analysis of substances might in time lead to the **proximal principles** where the virtues of the plant substances reside, such knowledge does not provide any information whatsoever on the virtues themselves. Neither the analysis of such principles is able to account for the source of the power attached to particular substances, as “it is too subtile [as] to be detected by chemical means”<sup>16</sup>. Finally, medical history comprises the investigation of the virtues and practical uses of drugs in the treatment of diseases, and thus informs on their action on the human frame, from which their application to the treatment of diseases is inferred, as well as on their mode of action on health and disease, which allows inferring their peculiar effects.<sup>17</sup>

Thus, at this point Murray fully agrees with the prevailing opinion among clinical practitioners and medical authors on materia medica. Six years later, however, his views exhibited a dramatic shift, whereby the chemical methods became the main road to the study of the powers of drugs,<sup>18</sup> to the point that now Murray qualifies the study of ‘pharmaceutical chemistry’ as having the propaedeutic role of introduction to the study of the materia medica and pharmacy.<sup>19</sup> The catalyzer of such epistemological upheaval was none other than the status of the plant alkalis.

This leads us to another subject of much controversy at that time, involving a different community of scholars, who focused their work on strictly chemical subjects.

As several scholars pointed out, the true explosion of newly found organic substances, parallel to the development of a rational classification and nomenclature for

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<sup>13</sup> John Murray, *Elements of Materia Medica and Pharmacy* (Philadelphia: B. and T. Kite, 1808).

<sup>14</sup> John Murray, *System of Materia Medica and Pharmacy* (Edinburgh: William Laing, J. Anderson, J. Bathgate, Brown & Crombie, and A. Black; London: Longman, Hurst, Rees & Orme, 1810).

<sup>15</sup> Murray, *Elements*, I: 14.

<sup>16</sup> *Ibid.*

<sup>17</sup> *Ibid.*, I: 15.

<sup>18</sup> Murray, *System*, I: 1-3

<sup>19</sup> *Ibid.*, I: 6.

the inorganic compounds at the turn of the 19<sup>th</sup> century, drew the attention of chemists to the classification and nomenclature of the organic compounds.<sup>20</sup> Within that context, one particular class of substances strikingly misses when one has in mind the pivotal role it would play starting just a few years later, namely the plant organic alkalis, or alkaloids.<sup>21</sup> According to some scholars such as J.E. Lesch and J. Fournier, the failure, indeed, to acknowledge the existence of plant organic alkalis represented a kind of epistemological obstacle to the identification of the active principles of plant drugs. As we have already shown, Alston had pointed as early as 1752 to an **alkaline, ammoniac-like, urinous component in opium**, which was completely passed over by past chemists and doctors, as well as by contemporary historians of science.

To illustrate this discussion let us come back to Murray. Upon listing and describing in the *Elements* what he then designated as 'simple substances', he vaguely characterizes the alkalis as bearing properties very similar to the earths, with penetrating acrid taste, the ability to turn plant dyes green, strong affinity for water and combination with acids forming neutral salts.<sup>22</sup> Following the ideas prevailing at that time, Murray lists only three substances in this category, to wit, ammonia, potash, and soda. In 1804, only the chemical composition of ammonia had been established, whereby it was presumed on analogical grounds that also potash and soda could also consist of nitrogen and hydrogen only.<sup>23</sup> In addition, although both potash and soda were mainly obtained from the combustion of wood, their actual organic origin was highly disputed, whereas the prevailing opinion stated that they were products of combustion, rather than actual components of plants.<sup>24</sup> Moreover, at that time nitrogen was held to be a typical component of animal matter, thus allowing distinguishing it from plant matter.<sup>25</sup> Murray finally calls the attention to an additional analogy that would prove crucial to his shift of opinion on the relative significance of chemical analysis: the alkalis behaved exactly as the earths and metallic oxides in that their combination with acids gave rise to neutral salts bearing properties different from the ones of the constituent acid and base.<sup>26</sup>

Indeed, a major feat mediated between the publication of *Elements*, in 1804, and *System*, in 1810: the isolation of potassium and sodium from potash and soda, respectively, by Humphry Davy (1778-1829) in 1807. In his later work, Murray thus

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<sup>20</sup> See, e.g., John E. Lesch, "Conceptual Change in an Empirical Science: The Discovery of the First Alkaloids," *Historical Studies in the Physical Sciences* 11, no. 2 (1981): 305-28; and Josette Fournier, "Découverte des alcaloïdes: des marqueurs pour l'histoire de la chimie organique," *Revue d'histoire de la pharmacie* 89, no. 331 (2001): 315-32.

<sup>21</sup> Both Lesch and Fournier show how this class missed in all the main chemical books of the second half of the 18<sup>th</sup> and first decades of the 19<sup>th</sup> century, from P.-J. Macquer's, *Dictionnaire de chimie* to A.F. Fourcroy's *Système des connaissances chimiques* and L.J. Thénard's *Traité de chimie*, among several others.

<sup>22</sup> Murray, *Elements*, I: 42.

<sup>23</sup> *Ibid.*, I: 43-4.

<sup>24</sup> *Ibid.*, I: 43.

<sup>25</sup> *Ibid.*, I: 34.

<sup>26</sup> *Ibid.*, I: 44.



celebrates “one among the most splendid discoveries made by modern chemistry”<sup>27</sup>, i.e., the composition of the fixed alkalis. Just as potash and soda were previously presumed to be composed of nitrogen and hydrogen by analogy with ammonia (the volatile alkali), following the isolation of sodium and potassium, now it could be presumed that also ammonia yielded a metallic matter, as “Berzelius and Pontin have shown”, according to Murray.<sup>28</sup> More important than that, the analogy linking the chemical composition of all three kinds of bases together was complete, as also the alkalis were metallic,<sup>29</sup> which had paramount importance in the explanation of their chemical behavior in the formation of neutral salts. It goes without saying that this path led further away from the notion of plant organic alkalis.

Due to his early mistrust of chemical analysis, in the *Elements*, Murray states that the most proper and useful approach to the classification of the items included in the materia medica is the one grounded on the effects they induce on the living system.<sup>30</sup> His classification is, indeed, quite simple: he holds all medicinal substances to cause stimulant effects on the living body, which only vary as to their ‘diffusibility’ (extension), i.e., general or local, and duration, i.e., transient or permanent.<sup>31</sup> As inducers of general and transient stimulation, the narcotics are the first class described.<sup>32</sup> In regard to opium,<sup>33</sup> Murray reproduces the ideas prevailing at that time and that do not differ substantially from Alston’s, except for the adoption of the Linnean classification, and is unable to point to the chemical component where its virtue resides. He is rather more intent in establishing its nature as primary stimulant, whereby its depressant action was secondary.

In *System*, Murray still considers that the most rational and useful classification of medicines is the one based on their operations, and consistently presents the items of the materia medica in the traditional order. Nevertheless, upon acknowledging the difficulty and vagueness of that classification, he adds a tentative classification of drugs according to their chemical and natural historical properties.<sup>34</sup> Consistently, the main two headings are “unorganised substances” and “products of organisation”, the latter subdivided into vegetal and animal. Whereas the unorganized substances are subdivided according to their chemical nature (salts, earths, inflammables, metals, waters, and airs), the products of organization are subdivided according to their ‘natural affinities’, most accurately represented by the Linnean system.

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<sup>27</sup> Murray, *System*, I: 36.

<sup>28</sup> Ibid, I: 29.

<sup>29</sup> Ibid, I: 27.

<sup>30</sup> Murray, *Elements*, I: 61.

<sup>31</sup> Murray also admits purely mechanical or chemical effects of drugs, corresponding to the classes of diluents, demulcents, emollients (and probably also the anthelmintics), and the antacids, lithontriptics (stone remedies), escharotics (and possibly also the refrigerants), respectively, *ibid*, I: 64-5).

<sup>32</sup> Ibid, I: 66 et seq.

<sup>33</sup> Ibid, I: 74 et seq.

<sup>34</sup> Murray, *System*, I: 512 et seq.

The section on opium now includes a thorough discussion of its chemical analysis, evidently triggered by Murray's newfound faith in this approach.<sup>35</sup> Indeed, he reminds of Alston's conclusions on the impossibility of ascertaining the active matter of opium on the grounds of its proximate principles, which Murray qualifies as "past beliefs". Although he acknowledges that modern chemistry has not yet succeeded in identifying the proximal principles of drugs, he makes explicit mention of Charles Derosne's (1780-1846) isolation (1804) of a peculiar principle in opium on which its narcotic property allegedly depended. According to Murray, that finding differed dramatically from the traditional ideas, and thus required careful confirmation before any conclusion could be drawn. Thus, Murray illustrates an incipient shift in the views on the relative importance of chemical analysis and the putative active principles isolatable from plant matter.

One further approach to the study of the actions of drugs deserving of mention is the one of the botanists, then known as naturalists. In this regard, it is worth to pay close attention to the views of Augustin P. de Candolle (1778-1841), who devoted his doctoral dissertation to the correlation of the botanical classification with the medicinal properties of drugs.<sup>36</sup>

His *Essay on the Medical Properties of Plants* is particularly relevant for our purposes, as it was explicitly written for the chemists to pay particular attention to the possible correlations among the *matériaux immédiats* (immediate matters) of plants belonging to same natural orders.<sup>37</sup> The reason is that de Candolle acknowledges that the study of the plant immediate matters is the basis of the knowledge on their intimate structure, which is indispensable for their use, but that the recent developments in the study of organization allowed for the traditional natural history to attain the status of a proper science and make accurate predictions.<sup>38</sup> Thus, just as several morphological traits of plants were shown to exhibit correlation with their properties, also their chemical composition and medicinal use ought to bear some relationship with the morphological characteristics that based the natural classification of plants.<sup>39</sup> Consistently, the section on family *Papaveraceae* is not devoted to the description of the plants it includes, but to the search of similarities between poppy and plants from other families also bearing narcotic properties.<sup>40</sup>

A similar attempt at elaborating a 'medical botany' was published between 1790 and 1794 by William Woodwille (1752-1805), a former student of William Cullen's (1710-

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<sup>35</sup> Ibid, I: 159 et seq.

<sup>36</sup> Here we used the 2<sup>nd</sup> edition of his *Essai sur les propriétés médicales des plantes, comparés avec leur formed extérieures et leur classification naturelle* (Paris: Crochard, 1816), as according to the author it bears his more mature views on the subject.

<sup>37</sup> Ibid, viii-ix.

<sup>38</sup> Ibid, 2.

<sup>39</sup> Ibid, 10-11.

<sup>40</sup> Ibid, 116 et seq.



1790).<sup>41</sup> Different from de Candolle, in this case the targeted readership is the medical practitioners, who despite their thorough acquaintance with the effects and pharmaceutical uses of the medicinal plants were not equally familiar with the botanical characteristics that allowed distinguishing one from another. The book's structure, thus, follows the order of the Linnean classification, and the emphasis falls on the botanical description of plants, with a short mention of their hypothetical physiological action following Cullen's notions, while no mention is made of putative proximate principles or chemical aspects. Thus, Woodwille merely observes that opium acts directly on the nervous power decreasing the sensitivity, irritability, and mobility of the system to and from the brain, and thus induces sleep, this sedative action of opium explaining its power to allay pain.<sup>42</sup>

### Final remarks

The idea that particular principles explain the action of matter, the matter of drugs in particular, is no 19<sup>th</sup> century original formulation, but a quite older one. All throughout the 18<sup>th</sup> century, medical practitioners, chemists, naturalists, and pharmacists zealously sought for such principles by means of chemical analysis, among other means. Some lack of communication among the communities involved transpires in the literature of the period, which might be the reason that led de Candolle to state, "natural history, chemistry, and medicine are depicted as separate branches of the tree of science", whereas the records of all three of them ought to be placed together in order to infer general conclusions on the *materia medica*,<sup>43</sup> "the most useful kind of human knowledge".<sup>44</sup>

In the specific case of opium, although signs hinting at a peculiar matter of crystalline, alkaline, and nitrogenous nature had been detected, the current chemical theoretical models had no room for organic plant alkalis, whereas the practical doctors and writers on *materia medica* were highly mistrustful of the ability of the known principles of plant matter to account for the effects of drugs.

Thus, a frustrated pharmacist teaching at Montpellier, following a thorough review of the literature on opium and his own experiences with it, wondered in 1816: "What else one must do to convince doctors, pharmacists, chemists, and naturalists on

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<sup>41</sup> William Woodwille, *Medical Botany: containing systematic and general descriptions, with plates of all the medicinal plants [...] comprehended in the catalogues of the materia medica as published by the Colleges of Physicians of London and Edinburgh [...] 2<sup>nd</sup> ed* (London: William Phillips, George Yard, 1810).

<sup>42</sup> *Ibid*, 381.

<sup>43</sup> De Candolle, 7.

<sup>44</sup> *Ibid*, 2.

that the [crystalline] acid [found in opium] is [that which bears] its sedative [properties]?"<sup>45</sup>

The answer was given the following year. But this is another story.

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<sup>45</sup> Pierre-S. Montaignier, *Essai sur l' extract gommeux d'opium* (Lyon: Cabin et Compagnie, 1816), on 45.