

## HOW CHEMICALS ENTERED THE OFFICIAL PHARMACOPOEIAS

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It is generally agreed upon that what we call modern therapy received its first authoritative recognition through the introduction of chemicals for internal use into the official standards of pharmacy. The question how and when this happened is, therefore, of historical importance.

The first representative of the European drug standards issued and legally enforced in the various political units and later generally called pharmacopoeias, was the Florentine *Nuovo Receptario Composito*, published in 1498. It took half a century and more until the next official pharmacopoeiae of general importance appeared, the Nuremberg *Dispensatorium Valerii Cordi* of 1546, the Augsburg *Enchiridion sive Dispensatorium* of 1564 and the *Dispensarium Reipublicae Coloniensis* of 1565. As pointed out by Husemann, all of these official formularies represented "the orthodox teaching of medicine as contrasted with that of Paracelsus and his followers, who raged against the teachings of Greek and Arabic medicine."<sup>1</sup>

The great past-medieval reformer of medicine, Theophrastus Bombastus Paracelsus of Hohenheim, had died in 1541. Only twelve years later, in 1553, an English Act of Parliament authorized the Royal College of Physicians of London "to survey and examine the stocks of apothecaries, druggists, distillers and sellers of waters and oils, and preparers of chemical medicines."<sup>2</sup> However, what was, in the middle of the sixteenth century, implied in the term chemical?

The situation has been greatly obscured because, in the modern sense, the term chemical processes has acquired a different meaning from that which is implied in the writings of Paracelsus. Modern pharmaceutical literature classifies aromatic waters, tinctures, and

extracts with galenicals, although they were unknown to Galen. According to Paracelsus, they were prepared by means of chemical processes as he understood the word. Paracelsus also advocated the use of inorganic chemicals for internal medication. It is this advocacy that primarily caused his and his followers' quarrels with the Galenists and Hippocratists.

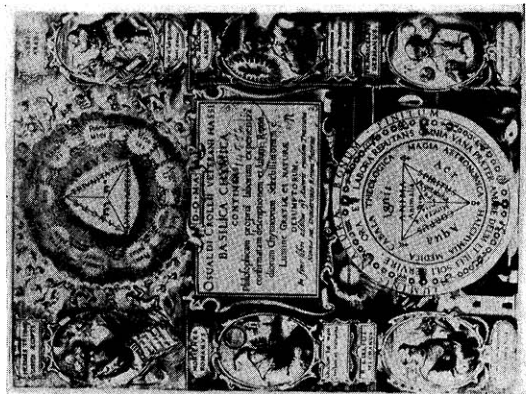
The chemical concept as indicated, greatly antedates Paracelsus. Thus the process of distillation was regarded as a chemical process. It was known to the ancients and developed by the Arabs during the Middle Ages. If any one individual were to be accredited therewith, this individual would not be Paracelsus but Arnaldus de Villanova who introduced, in the end of the thirteenth century, distilled waters into European therapy.

Not only heat, but destructive fire was employed in the preparation of empyreumatic oils and more particularly in the preparation of the so-called fixed salts resulting from the incineration of organic drugs and the lixiviation of the resulting ashes. The production of so-called "essential" forms from crude drugs was implied in the designation chemical, whether this was accomplished by separating the finer parts from the grosser parts by distillation or by boiling down the mother liquid concerned and allowing crystallization. In like manner the "essential," even "quintessential" parts were obtained by extraction, whether the product be termed a tincture or extract. To these methods of technique, there were added those now commonly regarded as distinctively chemical.

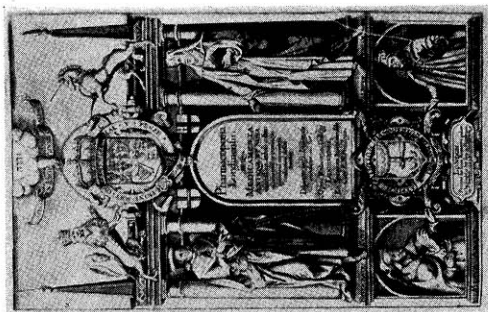
Have the early pharmacopoeias mentioned above indeed declined all chemical preparations? The interesting fact has to be noticed that the most progressive of these formularies, the Augsburg Enchiridion of 1564, contains several chemical preparations for external use known already before Paracelsus, namely, Aqua fortis, i.e., nitric acid, a solution of corrosive sublimate listed as Aqua cum Mercurio, and an aqueous suspension of lead sulfate and basic acetate called Lac Virgineum. Furthermore the book gives formulas for oil of turpentine to be obtained by direct distillation from the oleoresin and an oil of juniper to be prepared by destructive distillation of juniperwood. It finally lists a series of volatile oils and other preparations, among them oil of vitriol, i.e., sulfuric acid without, however, saying more about these products than that they "may be prepared by the experts by distillation." For the preparation of distilled waters, general directions are given.



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FIG. 1. Title page of Minderer's *Pharmacopoeia Londinensis*.

FIG. 2. Title Page of Croll's *Basilica Chymica*.

FIG. 3. Title page of the *Pharmacopoeia Augustana*.



Neither extracts nor vegetable salts, nor one of the new chemical compounds for internal use, however, can be found in the first edition of the Augsburg *Enchiridion* or the later editions of this *Pharmacopoeia* until 1613. Of these typical innovations introduced by Paracelsus and his followers there was not even an intimation in the early Augsburg *pharmacopoeias*.

All the early official *pharmacopoeias* were issued by one or the other Italian or German City Republics of this period and their legal authority was, naturally, restricted to the territories of these comparatively small political units. Thus it certainly electrified the physicians and pharmacists in the whole of Europe when, in 1585, it became known that the Royal College of Physicians of London intended to issue a *pharmacopoeia* with the view to have this standard made obligatory for all England. The question in everybody's mind was, naturally, whether and to what extent the authors of the English standard would recognize the claims of the new chemico-therapeutical movement. A decision one way or the other had to be reached.

Who were the members of the Royal College of Physicians of London who took upon themselves such a grave responsibility, and what kind of decision could be expected of them?

The principal places for the cultivation of the chemico-therapeutical movement were the universities of Basel (Switzerland), Leyden (Holland) and to a certain extent the Universities of Padua (Italy) and those of Montpellier and Nantes (France). The principal place of resistance, the bulwark of medical conservatism, was the University of Paris.

Although more than a third of the members of the *Pharmacopoeia* Committee established by the College in 1589 had graduated abroad, it is significant that not one of them had completed his studies in Paris. They had graduated in Nantes, Padua, Leyden, and three of them in Basel. A doctor of Basel was the prominent member of the College, Thomas Muffett, also spelled Moffett and Moufet (1553–1604) of whom his biographer said that he, "while on the continent, adopted with enthusiasm the Paracelsian system of medicine, and when he settled again in England he shared with John Hester<sup>3</sup> the chief burden of upholding the principles therein."<sup>4</sup>

However, Muffett wrote also a digest of Hippocrates. He was no fanatic, but decided to take the good wherever he found it.

It was undoubtedly this progressive eclectic, as we may call him, who was influential in the first English *pharmacopoeia* movement

and its direction. It corresponds with this assumption that the "order and classification" of the planned pharmacopoeia, as noticed in the Annals of the London College of Physicians under the date of October 10, 1589, lists all the old groups of remedies, the *Julapia*, *Tragemata*, *Eclegmata* and so forth, but also a group, the insertion of which in an official pharmacopoeia of this period would have meant a revolutionary step, namely "*Extracts, Sales, Chemica, Metallica*," i.e., the group of drugs connected with the name of Paracelsus and the very subjects of the Galenico-iatrochemical controversy.

Unfortunately, we do not know what chemicals had been proposed nor whether they were intended for internal or merely for external use. The plan of a London pharmacopoeia conceived in the late sixteenth century has never been realized. No explanation has been found why the work did not progress and why it finally was dropped. It may be that the political uncertainty which prevailed during the last decade of the reign of Queen Elizabeth was responsible. It is, however, by no means unlikely that there had developed sufficient opposition within the College against so progressive an undertaking as the one planned.

Soon after, in the early seventeenth century, there appeared two books written by ardent Paracelsists, which summarized the pharmacuetico-chemical experience of the early Paracelsic epoch: the *Pharmacopoea Dogmaticorum Restituta* . . . of the French physician Joseph Du Chesne, latinized Quercetanus (1601) and the *Basilica Chymica* of his German colleague Oswald Croll (1608). Both books, especially that of Croll, exerted an extraordinary influence.

The title page of Croll's *Basilica Chymica* (Figure 1) pictures the mysterious symbolism of alchemy rather than the undeniable endeavor of the author towards scientific clarity. There is the celestial and the terrestrial sphere, and within the latter the four Aristotelian elements, fire, air, earth and water, have found their place quite as well as the symbols of the Paracelsic three essential substances, sulfur, mercury and salt. Of the six men portrayed three, i.e., Hermes Trismegistos, Morienes Romanus and Geber, are mystical figures whose writings are apocryphal. Of the writings of Raimundus Lullus and Roger Bacon, just the alchemical ones are likewise considered as apocryphal. It is the figure of Paracelsus with the accompanying motto "separate and lead to maturity (perfection)" that actually symbolizes the spirit of Croll's *Basilica Chymica*.

It was not until 1614, twenty years after the first plan of an official English pharmacopoeia had been mentioned in the Annals of the Royal College of Physicians of London for the last time, that the members of the College took up the idea again, and this time they succeeded. For the revival of the plan as well as for its success apparently two men were primarily responsible: Dr. Henry Atkins (1558–1635) who had received his Doctor's degree at the University of Nantes (France) and who had participated in the earlier attempt, and the famous Theodore de Mayerne (1573–1665).

Sir Theodore Turquet de Mayerne, Baron D'Aubonne and Dr. of Medicine of the University of Montpellier, knew what it meant about 1600 to adhere to the doctrines of Paracelsus. Born in Mayerne (near Geneva), Switzerland, in 1573, he began his medical career in Paris, but spent his later life in England. He was the first of several French physicians and pharmacists who, being Protestants and Paracelsists, sought refuge in Great Britain. After being anonymously attacked because of his public recommendation of chemical remedies, Mayerne published in 1603 a pamphlet proving that the use of chemicals in therapy does not contradict the teachings of Hippocrates and Galen. At once an anonymous reply appeared which was filled with abuse, and shortly later, still in 1603, the College of Physicians in the University of Paris condemned Mayerne by a unanimous vote, ordered physicians not to meet him in consultation, and recommended that he should be deprived of his office.<sup>5</sup>

It is very likely that the idea of reviving the plan to create an official London Pharmacopoeia originated with Atkins. In the realization of this plan, however, Mayerne was certainly very instrumental. Being, as far as we know, the only one of the members of the College of Physicians of London, doing his own and successful chemical research, he was undoubtedly responsible for the chemical part of the first issue of the London Pharmacopoeia, 1618, and may even have prepared it. Thus Theodore de Mayerne may well have been the first one to have given the Paracelsistic movement the first adequate recognition within official European pharmacy if there would not have appeared, in 1613, the sixth issue of the Augsburg Pharmacopoeia, edited by Raymund Minderer (1570–1621).

While the father of the first attempt at an official London Pharmacopoeia, Thomas Muffet, as well as the man who helped the second attempt to become a success, Theodore Mayerne, grew Paracelsist during their studies, Raymund Minderer, the son and grandson of

"chymici" was born with Paracelsism. Nevertheless, like the men mentioned before, he was eclectic and very anxious not to hurt too much the feelings of the Galenists. In his introduction to a treatise which he wrote on vitriol (1617), Minderer explained his point of view as follows:

Even though, having been born among chemical vapors, and having been brought up amidst spagyric furnaces, I not infrequently adhere to their vaults — being derived from two excellent and illustrious chemists of their times, as I may state without boasting, my grandfather on my mother's side being Laurentius Danus, and my father Balthasar Minderer — I have as physician always followed the Hippocratic and Galenical method. Even now I esteem it and adhere to it and shall not deviate therefrom by the breadth of a finger. If I do not always use remedies from the animal and vegetable kingdoms, but occasionally employ metallic and mineral remedies, I do this that they may supplement vegetables pure and simple to which new and graver, or inveterate diseases will not yield. This I do that medicine may not despair.<sup>6</sup>

Minderer went rather far in his attempt to prevent medicine from despair by putting at its disposal the preparations recommended by Paracelsus and his followers. Here they are, the simple extracts (33) and the more compounded ones (9), the *sales artificiosi* from plants (14) and furthermore *Sal Saturni* (lead acetate), *Sal Vitrioli* (ferrous sulfate), *Nitrum Sulfure purgatum* (a mixture of potassium nitrate and sulfate), *Crocus Martis* (ferric oxide), *Flores Sulfuris* (sublimed sulfur), *Flores ac Vitrum Antimonii* ( $S_2O_3$  with small amounts of  $Sb_2S_3$ ), *Antimonium diaphoreticum* (mixture of antimony oxide and potassium antimoniate) and *Turbethum minerale* (mercuric sulfate). Finally formulae are given for *Lapis septicus* (caustic potash) and *Lapis Philosophorum* (fusion of alum, vitriol, bolus, cerussa, camphor and vinegar), and there is a large increase in the number of items listed in the chapter on distilled waters.

In a decree of the Augsburg Senate, issued in 1582 and appended to the fifth edition of the Augsburg Pharmacopoeia published in 1597, the apothecaries were still admonished not to prepare or offer for sale "substances which are known to be detrimental or poisonous, such as *Labdanum minerale*, the so-called antimony, also *Turpethum minerale* and other purging mercurials."

In view of the fact that the Augsburg Pharmacopoeia of 1613 listed these banned chemicals, this decree naturally had to be changed. Thus the authorities concerned published on September 3, 1613, another edict which authorized the sale and use of "spagyric"



remedies when "prepared according to directions and prescribed by very experienced physicians who know how to combine rationality and experiment."<sup>7</sup>

Nothing in the beautiful title page of the, in every respect, new book, however, betrays the change of therapeutic principle which it augurs. It is still King Salomon of Bible fame and King Mithridates of Pontus (132 — 63 B.C.), the inventor of the time honored panacea theriac who are presented as the Patron Saints of this, in the opinion of the Galenists, certainly extremely unholy sixth edition of the *Pharmacopoeia Augustana* (Figure 2).

Succeeding and not preceding Minderer's *Pharmacopoeia Augustana*, 1613, the London Pharmacopoeia, 1618, did not offer anything revolutionary. However, being the first official drug formulary to be made obligatory not for the comparatively small territory of a city republic but for a great country, for all England, its recognition of the chemico-therapeutical movement was of highest general importance. Furthermore the book of Minderer only listed the *Vitrum Antimonii*, the *Turpethum minerale*, the *Nitrum Sulphure purgatum*, etc., and referred the reader to the authors of the formulae concerned, i.e., to "*Andernacum, Osvaldum Crollium, Quercetanum et alios*," while the London Pharmacopoeia, 1618, put the formulas, selected with knowledge and discrimination, directly at the disposal of its readers. Finally the London Pharmacopoeia, 1618, contained three real chemicals not listed in the *Pharmacopoeia Augustana*, 1613, i.e., *Tartarus vitriolatus* (potassium sulfate) *Mercurius Vitae* (a mixture of  $\text{SbOCl}$  and  $\text{Sb}_2\text{O}_3$ ) and, above all, *Mercurius dulcis*, i.e., mercurous chloride or, as it was commonly called since the end of the eighteenth century, calomel.

Theodore de Mayerne has generally been accredited with the introduction of calomel into therapy. This is correct if we restrict this claim to official therapy. The London Pharmacopoeia, 1618, was indeed the first official formulary to include a formula for the preparation of this drug which for centuries was the most popular chemical to be taken internally. Mayerne did not come to his formula, however, quite on his own. It was already preconceived by somebody else, although in somewhat uncertain terms. The British Museum owns the copy of the second issue of the London Pharmacopoeia, 1618, which once was in the possession of Mayerne. It is replete with annotations written in Mayerne's own hand. The anno-

tation penned to the directions for the preparation of calomel by precipitation reads: "Croilly in *Basil, chym.* p. 130." Thus we know from Mayerne himself where he took his formula from or at least got his inspiration.

On page 130 of Oswald Croll's *Basilica Chymica* the following "*duo secretissimi modi tractandi Mercurium pro medicina corporis*" (two very secret methods of treating mercury for being used for bodily relief) are given, not in a special monograph, but at the end of that dealing with *Arcanum corallinum Paracelsi, seu Mercurius sublimatus rubeus non corrosivus* (HgO).

In the first case mercury may by itself change back into a very red cinnabar without any admixture merely by means of certain implements.

In the second case there may be killed the destructive spirits of vitriol and salt in mercury sublimate by which wonderful and simple adequate artifice there results a crystalline, completely tasteless powder: One of the most outstanding cathartics, by itself as well as combined with other drugs for internal medical use, it radically expels from the body everything harmful. This will not appear miraculous to those who know that mercury is nature's balsam in which is the virtue of incarnation and regeneration mysteriously renewed and freed from all impurities.<sup>8</sup>

It is undoubtedly the second of these two "very secret methods" to which the note of Mayerne refers and it cannot be said that Croll tries to reveal the secret. Clandestine ("*versteckt*") calls the historian of Chemistry, Hermann Kopp, the way in which "Oswald Croll described the preparation of Calomel in his *Basilica Chymica* in 1808."<sup>9</sup> As a matter of fact, he did not "describe" it at all. Only one very familiar with the occult language of alchemy could interpret the allusion given as meaning to use salt in order to achieve, by the way of precipitation, a mild and tasteless cathartic out of an acid (vitriol) solution of mercury. Theodore de Mayerne apparently was such a highly versed interpreter. What was even more, he was an excellent chemical experimenter himself. He did not simply take over what he found in the books of other authors. He checked and, if thought necessary, modified it.

According to the Mayerne formula in the first issue of the London Pharmacopoeia, 1618, dated May 7th, the mercurous chloride was obtained by precipitation from a solution of mercury in *Aqua fortis*, i.e., nitric acid, with an aqueous solution of *Sal marinus*, i.e., sea salt, whereby the mercury solution had to be poured into the salt solution, not the reverse. The precipitate was deprived of its acrimony by

washing. In addition to this formula, in the second issue of the London Pharmacopoeia, 1618, dated December 7th, another one directing the preparation of mercurous chloride by sublimation of mercury chloride and mercury was introduced. This latter formula soon became the one generally used and superceded the older one almost entirely until the method of precipitation, somewhat modified, was revived by the great apothecary Scheele who presented it before the Royal Swedish Academy of Science in 1777.

Although calomel is undoubtedly the most interesting and most important of the three chemicals introduced by the London Pharmacopoeia, 1618, into official internal therapy, the two other ones are likewise worthy of some consideration. For the formula of *Tartarus vitriolatus*, i.e., potassium sulfate, Oswald Croll's *Basilica Chymica*, had likewise served as source. In this case some literal conformity offers evidence. Prescribing the saturation of *Sal Tartari*, i.e., potassium carbonate, with *Oleum Vitrioli*, i.e., sulfuric acid, the formula was, for this period, extremely rational. The name of the preparation, *Tartarus vitriolatus*, likewise given to it by Oswald Croll, represents one of the few early attempts to intimate in the designation of a product its chemical nature. It is, however, characteristic of the mistakes to which even the great chemists of this period were subject that the same author thought the same substance, when prepared by the double decomposition of potassium carbonate and ferrous sulfate, to be a different product which he called *Specificum Purgans Paracelsi*, thereby accrediting Paracelsus with this process of manufacture.

The so-called *Mercurius Vitae* offers an even more striking example of the unsecure ground on which the chemists of this period were working. The preparation was obtained by pouring *Butyrum Antimonii*, i.e., antimony trichloride, into water. Because antimony trichloride on its part was obtained by distilling a mixture of antimony and bichloride of mercury, Paracelsus thought that it contained mercury. It was for this reason that he called the precipitate obtained by pouring the antimony trichloride into water, *Mercurius Vitae*. It took centuries until it was definitely stated that *Mercurius Vitae* does not contain even a trace of mercury and the mistake of Paracelsus was corrected.

It is understood that like the book of Minderer, the *Pharmacopoeia Londinensis* too avoided any display of its tolerant attitude towards the new chemical therapy which could be provocative. The title page of the issue of December 7, 1618, which was to be official (with slight modification in later reprints) until 1650, refrains from any hint at

the innovation (Figure 3). It is the figures of the Greek Hippocrates, the Graeco-Roman Galen, the Arab Avicenna and the apocryphical pseudo-Arab, Mesue Jr., i.e., the pronounced representatives of pre-Paracelsic therapy, who were chosen to symbolize the spirit of this pharmacopoeia.

Dr. Theodore de Mayerne dared to publish in an official pharmacopoeia formulas for chemical preparations to be used as internal remedies. He did not, however, dare to openly explain what that in reality meant. On the contrary, he took the utmost care in concealing the importance of his venture. Wherever possible the authorship of the formulas is indicated in the London Pharmacopoeia, 1618. The only groups wherein the individual formulae are not supplied with references to either author or place of origin are the *Olea Chymica* and the *Praeparationes Chymica*. In his personal copy Dr. de Mayerne had added the name of Oswald Croll to the formula for mercurous chloride, but apparently it had not seemed expedient to give a Paracelsist official recognition.

True the name of Paracelsus appears once. It is quoted, however, not in connection with any chemical preparation but after his famous wound plaster. In other words the old line surgeon, the author of the *Grosse Wundtarzney*, not the medical reformer and chemist was thus recognized in the London Pharmacopoeia. Minderer, in the Augsburg Pharmacopoeia, 1613, concealed the formulas of the dangerous chemicals but referred to the Paracelsistic authors concerned. Mayerne, in the London Pharmacopoeia, 1618, apparently thought it less dangerous to reveal the formulas concerned than the names of their authors.

The England of the early seventeenth century was, in every respect, less orthodox than the European continent, and especially France. However, Mayerne was a burnt child. He adhered to his principles, but he tried to console the adversaries of the chemico-therapeutical movement by utmost modesty. The preface to the London Pharmacopoeia, 1618, which was written by Mayerne, refers to the chemical drugs as follows:

Although we revere the wisdom of the old masters and have arrayed their preparations, so to speak, in the first line of battle, nevertheless we have not rejected or disdained in this book the auxiliary troops of the new chemistry, but have granted them a place, a corner in the rear guard, so as to have them at the disposal of dogmatic medicine, i.e., ready for service, like auxiliaries.<sup>10</sup>

This statement is doubtless much more apologetic than that of

Minderer, quoted before.

In another passage of the same preface Mayerne explains why the authors of the London Pharmacopoeia have not followed the custom of other formularies to describe the use and the medical attributes of the drugs listed.

It is said: From this quiver, the itinerant drug peddlers and the quacks, being as ignorant as they are unscrupulous, equip themselves for their medical practice, and seizing our weapons, are responsible for the death of the sick, to the great detriment of the state. We, therefore, do not add anything about the efficacy of the medicines. We write this book only for the learned, for the disciples of Apollo, and for the welfare, not for the information of the common people.<sup>11</sup>

It is not necessary to set forth at length what part chemicals play in modern therapy, hence, in the pharmacopoeias of today. From the modest role of "auxiliary troops" hidden in a corner of the rear guard, they have advanced to the very front and represent the most important armament of modern medicine in the eternal fight against disease and premature death.

The story of the relations between scientific chemistry and pharmacy is long and intricate, but always enjoyable. The contributions of pharmacy to chemistry have been so large and important and the work done in the fields concerned has been so intimately correlated that the famous historian of chemistry, Hermann Kopp, even called pharmacy the mother of chemistry and Paul Walden called them twin sisters.<sup>12</sup> The very nature of chemistry and pharmacy makes it sure, that these intimate relations, which have proved so beneficial to society, will never change.

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<sup>1</sup> A Facsimile of The First Edition of the Pharmacopoeia Augustana With Introductory Essays by Theodor Husemann, Edited by Edward Kremers, Madison, Wis., 1927, p. X.

<sup>2</sup> Kremers-Urdang, *History of Pharmacy*, Philadelphia, 1940. p. 90.

<sup>3</sup> John Hester (d. 1593) was a distiller, or, as he styled himself, a "practitioner in the Spagercall Arte." He published several translations of excerpts from the books of Paracelsus and other "spagerick" authors.

<sup>4</sup> *Dictionary of (English) National Biography*, 38:101, (London 1894).

<sup>5</sup> *Ibid.*, 37:150, (London 1894).

<sup>6</sup> *Facsimile of Pharmacopoeia Augustana*, 1 c., p. XXXIV.

<sup>7</sup> *Facsimile of Pharmacopoeia Augustana*, 1 c., p. XXXIV.

<sup>8</sup> The author's translation from the Latin original.

<sup>9</sup> Hermann Kopp, *Geschichte der Chemie*, v. 4, Leipzig, 1847, p. 192.

<sup>10</sup> The author's translation from the Latin original.

<sup>11</sup> The author's translation from the Latin original.

<sup>12</sup> Paul Walden, *Der Apotheker als Kulturtrager*, Pharm. Zeit. 76:1311, 1930.

