UBBMP Bioquímica y Biología Molecular de Plantas

CICY

From the Philosopher Stone to the First Nobel Prize in Biochemistry

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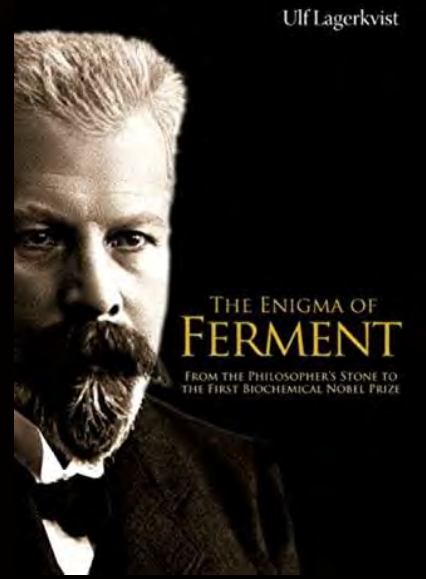
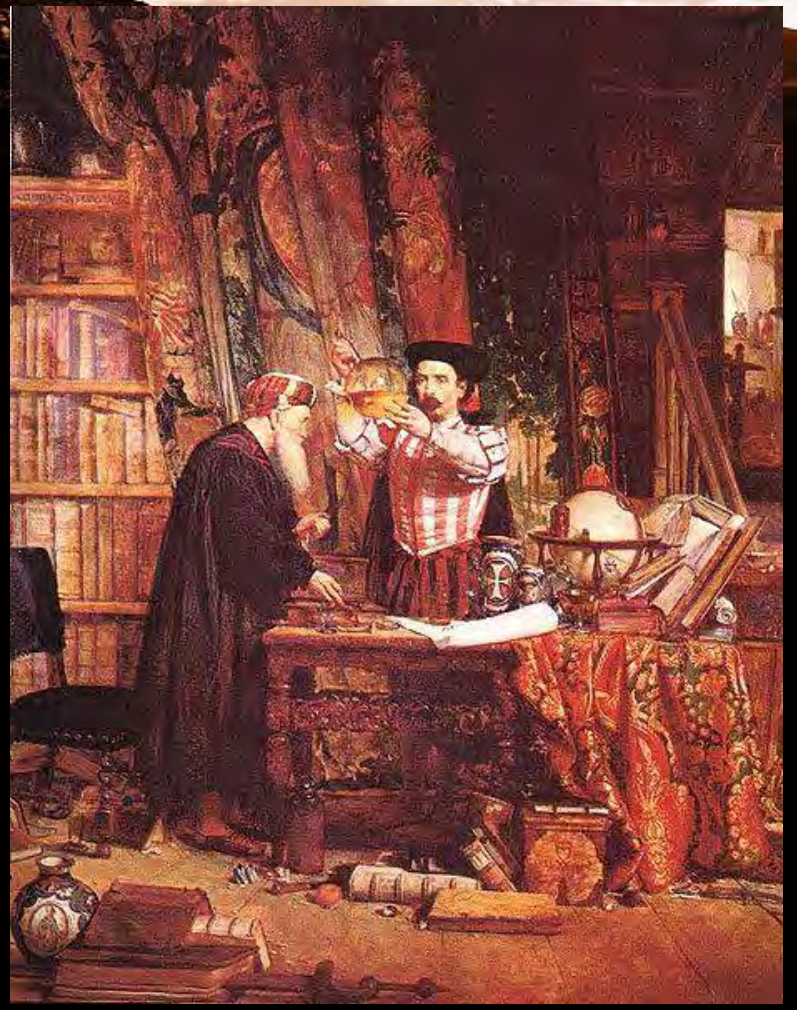


Outline

- Introduction.
- Alchemy and the dawn of Chemistry.
- Chemistry in the Scientific Revolution.
- A golden age of Chemistry.
- Ferment of vital force.
- A fortuitous observation.
- The Nobel Prize.



The alchemist, 1853. Sir William Fettes Douglas

Beginning

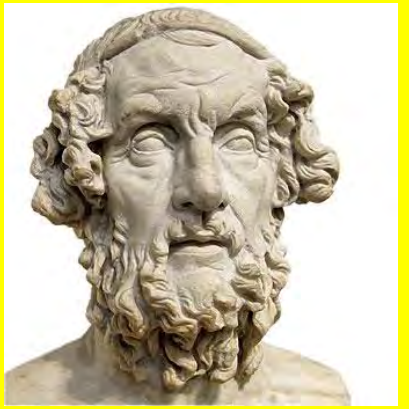
- The oldest known reference to the commercial use of enzymes (**ferment**) comes from a description of wine making in the Codex of Hammurabi (@ 4100 aPT).
- Vinegar, cheese, beer, bread, tanning of leather….

Manufacture of wine in Egypt, around 1500 b.C.

Appling et al. 2e – Biochemistry, (2019)

Old references to enzymes

- A reference to the enzymatic activity of the ficin (sulfidryl proteases) can be found in the Iliad (Book V):
  - As when the fig's press'd juice, infused in cream,
  - To curds coagulates the liquid stream,
  - Sudden the fluids fix the parts combined.

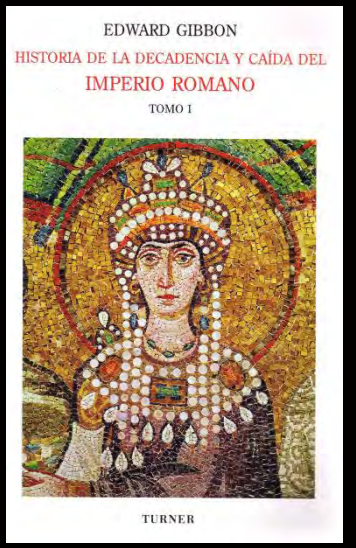


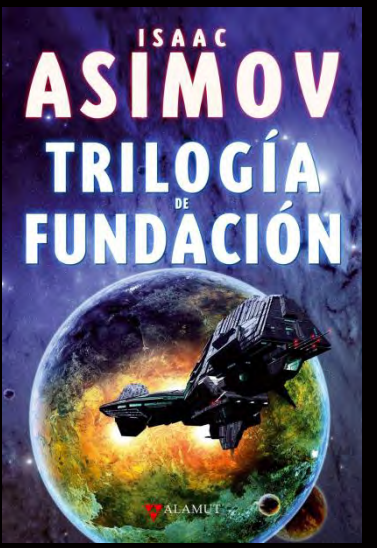
- Aristotle also wrote several times about the milk curdling process and offered the following hypothesis for the action of the renin extract.
  - Renin extract is a kind of milk formed in the stomach of young animals while they are still suckling. This extract is thus a milk that contains fire, which comes from the heat of the animals while the milk is being cooked.

The History

Fall of the Western Roman Empire

- In 476, the Germanic barbarian king Odoacer deposed the last emperor of the Western Roman Empire, Romulus Augustulus, and the Senate sent the imperial insignia to the Eastern Roman Emperor Flavius Zeno.





The Dark Ages end (29 May 1453)

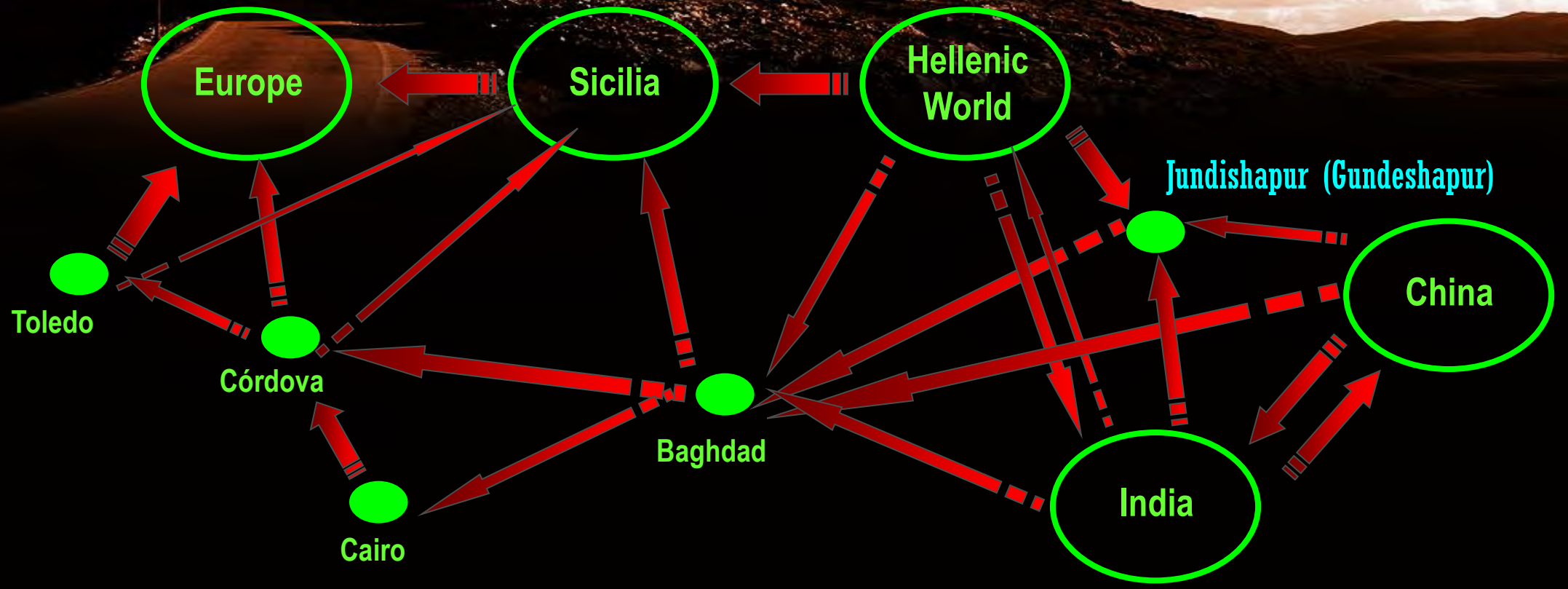
Steven Ruscinan

The siege of Constantinople (1453).
Jean Le Tavernier after 1455.

Mehmed the Conqueror enters Constantinople.
Fausto Zonaro

https://en.wikipedia.org/wiki/Fall_of_Constantinople

Illuminating the dark ages of Europe



Scientific knowledge that originated in India, China, and the Hellenic world was obtained by Arab and Muslim intellectuals, translated, refined, synthesized, and augmented in different centers of learning, beginning in Jundishapur in Persia (Iran) around the 6th century, from where it passed to Baghdad, Cairo and finally to Córdova and Toledo, from where it spread to Europe.

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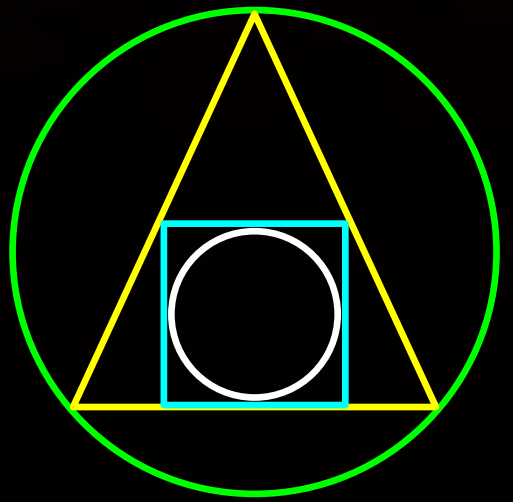
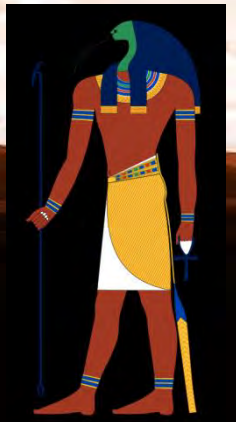
Alchemy



Alchemy origins



Alchemy is a theoretical discipline that performs interventions on substances and living organisms to make them reach a state of perfection. According to tradition, the origins of this discipline are very ancient and go back to the invention of science and the arts by the mythical Hermes Trismegisto.

Hermes Trismegistus is a legendary Hellenistic figure that originated as a syncretic combination of the Greek god Hermes (protector of human heralds, travelers, thieves, merchants, and orators) and the Egyptian god Thoth (the moon, wisdom, writing, hieroglyphs, science, magic, art, and judgment). He is the purported author of the *Hermetica*, a text that lay the basis of various philosophical systems known as Hermeticism.

Liber Hermetis de alchemia

Floor mosaic in the Cathedral of Siena

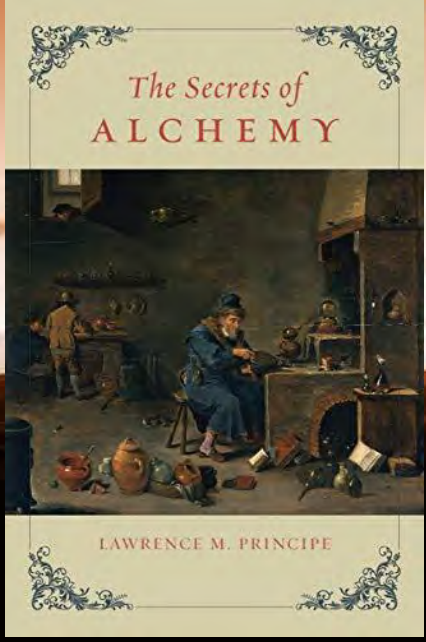
https://es.wikipedia.org/wiki/Hermes_Trismegisto

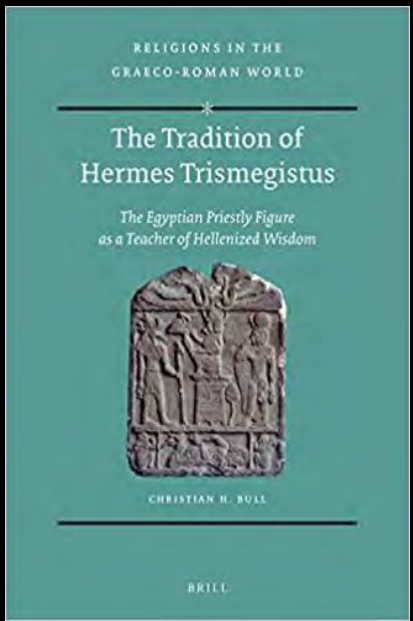
Eco U., La Edad Media. I. Bárbaros, Cristianos y Mulsumanes, Fondo de Cultura Económica, México D. F., pp 450-454, (2015).

Alchemy origins

- In addition to the *Corpus hermeticum*. He is also credited with writing the *Emerald Tablet*, which was considered by alchemists to be the foundational book of alchemy.
- The expression "hermetically sealed" comes from the alchemical procedure to make the Philosopher's Stone. This required a mixture of materials to be placed in a glass vessel which was sealed by fusing the neck closed, a procedure known as the Seal of Hermes. The vessel was then heated for 30 to 40 days.[1]

[1] Principe L. M., The Secrets of Alchemy, Univ. Chicago Press, p 123, (2013)





Christian H. Bull, The Tradition of Hermes Trismegistus: The Egyptian Priestly Figure as a Teacher of Hellenized Wisdom. Series Religions in the Graeco-Roman World. Vol. 186. Leiden and Boston: Brill Publishers. pp. 31–96. (2018)

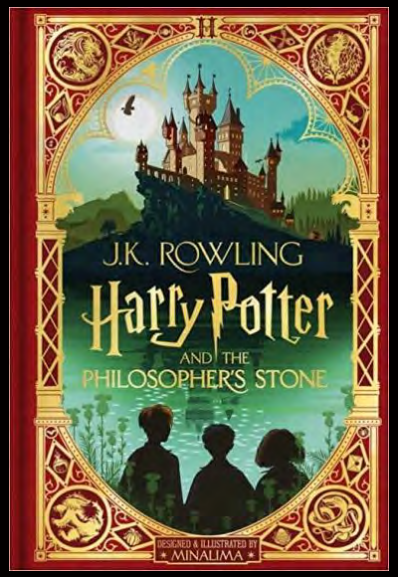
Alchemy

- The Arabic word *Kimiya* is derived from the Egyptian term *kmt* or *quem*, which refers to the "black earth" of the Nile valley.
- Other scholars think that *kem* would be an allusion to nigredo, "black work," a term with which alchemists designate the initial stage of the transmutation process. The other two states are *albedo* ("work in white"), when the substance is purified by sublimation, and "*rubedo*" ("work in red"), which represents the final phase of the process.
- Another interpretation, perhaps the most accurate, derives the term *Kimiya* from the Greek verb *keo*, which means "to melt and cast" metals.

Eco U., La Edad Media. I. Bárbaros, Cristianos y Mulsumanes, Fondo de Cultura Económica, México D. F., pp 450-454, (2015).

Alchemy

- The idea that they could be changed into each other (transmutation) by suitable procedures was therefore close at hand. It is here that we encounter the concept of the philosopher's stone, sometimes also envisaged as an elixir or potion, which acted as a FERMENT in the process, in the same way as leaven did in the making of bread or the brewing of ale.



Lagerkvist U., The Enigma of Ferment, World Scientificv, Singapore, pp 1-161, (2005).

The Philosopher's Stone

The philosopher's stone stone (Arabic: ḥajar al-falāsifa, Latin: *lapis philosophorum*), is a mythic alchemical substance capable of turning base metals (mercury) into gold (chrysopoeia, from the Greek χρυσός khrusos, "gold", and ποιεῖν poiēin, "to make") or silver. It is also called the elixir of life, useful for rejuvenation and for achieving immortality; for many centuries, it was the most sought goal in alchemy. Efforts to discover the philosopher's stone were known as the Magnum Opus ("Great Work").

The Alchymist, in Search of the Philosopher's Stone by Joseph Wright of Derby (1771)

The Philosopher's Stone

- The theoretical roots outlining the stone's creation can be traced to Greek philosophy.
- The earliest known written mention of the philosophers' stone is in the Cheirokmeta by Zosimos of Panopolis (c. 300 aC).
- According to Plato, the four elements are derived from a common source or prima materia (first matter), associated with chaos.
- Prima materia is also the name alchemists assign to the starting ingredient for the creation of the philosophers' stone.

Magnum Chaos, wooden in lay by Giovan Francesco Capoferri at the Basilica di Santa Maria Maggiore in Bergamo, based on a design by Lorenzo Lotto.
https://hmn.wiki/nn/Chaos_(cosmogony)

Chaos (Greek: χάος, Romanized: kháos) is the mythological void state before the creation of the universe (kosmos) in Greek creation myths. In Christian theology, the same term is used to refer to the gap created by the separation of heaven and earth.

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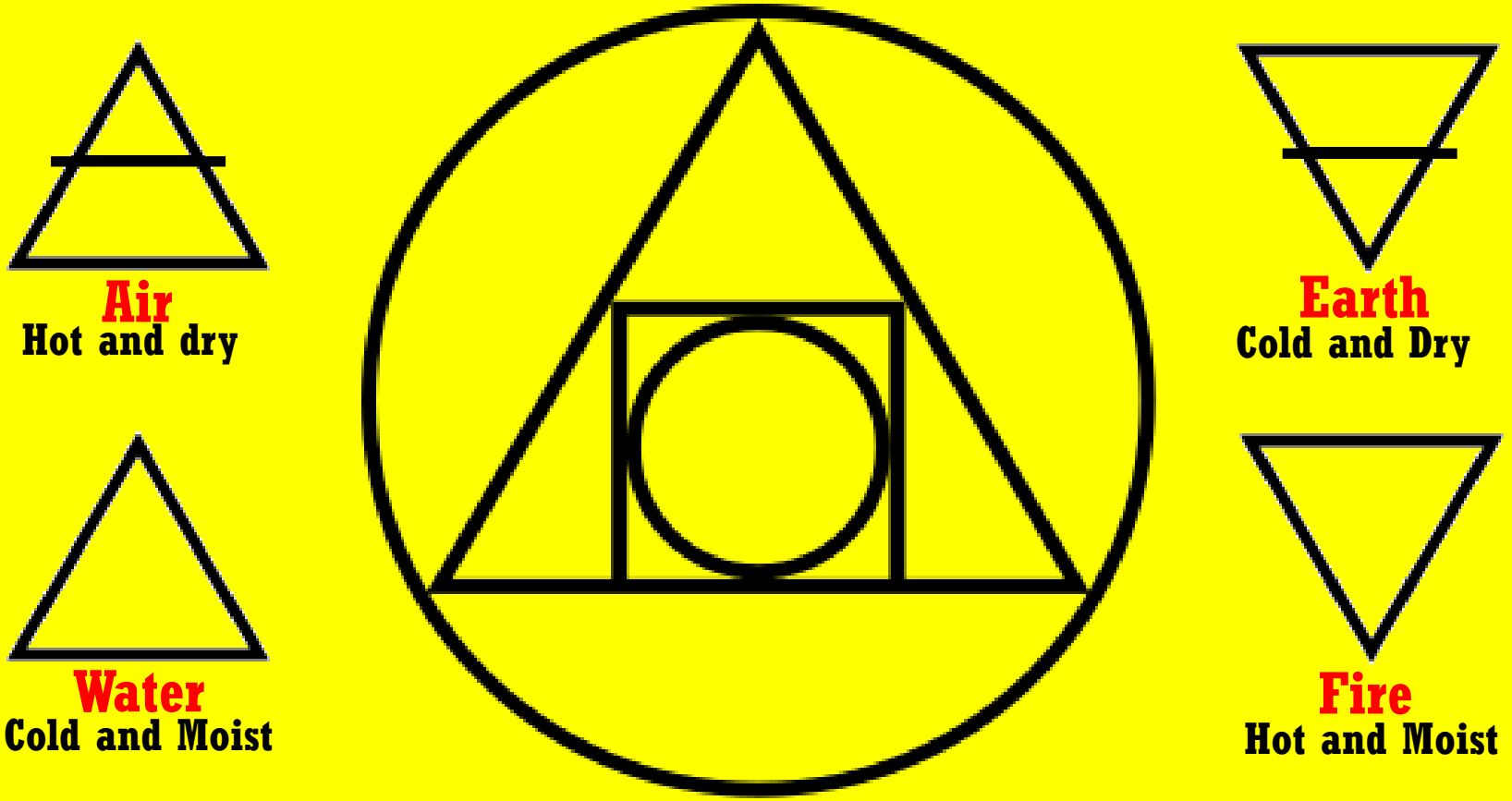
The Squared Circle



The Philosopher's Stone. Middle Age

- Byzantine and Arab alchemists were fascinated by the concept of metal transmutation and attempted to carry out the process.
- The 8th-century Muslim alchemist Jabir ibn Hayyan (Geber) analyzed each classical element in terms of the four basic qualities.

The Philosopher's Stone: Alchemy and Chemistry / حجر الفلاسفة في كيمياء العصور الوسطى
Author(s): Jehane Ragai and جيهان رجائي
Source: *Alif: Journal of Comparative Poetics*, No. 12, Metaphor and Allegory in the Middle Ages / المجاز والتمثيل في العصور الوسطى (1992), pp. 58-77

Alchemy

Jābir ibn Hayyān (Geber), Persian alchemist whose experimentation created the foundations of chemistry.

A central idea of alchemy was the notion that all metals can be transformed

S XV. Retrato de "Geber"

The Philosopher's Stone. Middle Age

- Geber theorized that every metal was a combination of these four principles. From this premise, it was reasoned that the transmutation of one metal into another could be effected by the rearrangement of its basic qualities.

- This change would be mediated by a substance, which came to be called xerion in Greek and al-iksir in Arabic (from which the word elixir is derived). It was often considered to exist as a dry red powder (also known as al-kibrit al-ahmar, red sulfur) made from a legendary stone—the Philosopher‘s Stone.

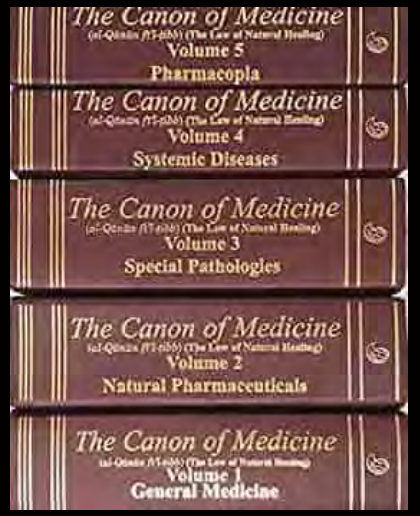
Ragai J., The philosopher's stone: Alchemy and chemistry, Alif: J. Comparative Poetics, 12:58-77, (1992).
Holmyard E. J., Maslama al= Majriti and the Rutbatu'l= Hakim, ISIS, 6(3):293-305, (1924).

Alchemy

- During the 11th century, Muslim world chemists asked on whether the transmutation of substances was possible. A leading opponent was the Persian physician and philospher Avicenna (Abū ʻAlī al-Husayn ibn ʻAbd Allāh ibn Sīnā) (Al afal wa al-infialat; On Actions and Passions).

980 - 1037

1025
(Al-qanun fi al-tibb)



→ 760 substances →

- → Mandrágora
- → Opium
- → Hemlock
- → Indian hemp

Eco U., La Edad Media. II. Catedrales, Caballeros y Ciudades, Fondo de Cultura Económica, México D. F., pp 340-377, (2018).
Ragai J., The philosopher's stone: Alchemy and chemistry, Alif: J. Comparative Poetics, 12:58-77, (1992). Holmyard E. J., Maslama al= Majriti and the Rutbatu'l= Hakim, ISIS, 6(3):293-305, (1924).
https://www.iqb.es/historiamedicina/personas/avicena.htm

Mandragora

Mandrágora

Mandragora officinarum

Genesis (XXX, 14) includes a curious reference to the generative virtues of the Mandragora.

Like the Borametz, the plant called Mandragora borders on the animal kingdom, because it screams when uprooted; that cry can drive those who hear it crazy (Romeo and Juliet, IV, 3).

Alberto Magno could write that the Mandragora figure humanity with the distinction of the sexes.

Plinio said that the white Mandragora is the male and the black is the female.

The root is black, but the flower is like milk. It is a difficult task for men to pull it out of the ground, but the gods are almighty.

The Odyssey, Book Ten

The mandragora in The Book of Imaginary Beings by Borges

The Mandrake in Waiting for Godot by Samuel Barclay Beckett.

Other plants

Opium

Papaver somniferum

Hemlock

Conium maculatum

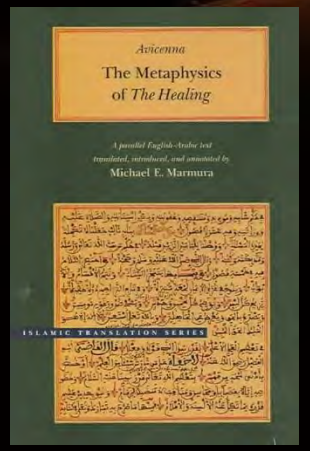
Alkaloids derived from piperidine:
Coniine or cicutin,
methylcicutin,
conhydrin,
pseudoconhydrin

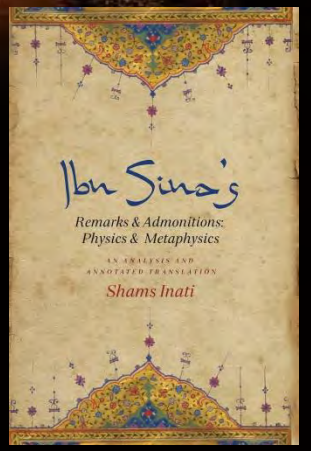
Indian hemp

Cannabis sativa

Cannabinoids

Books (Avicena)





Al-Isharat wal-Tanbihat
(Remarks and Admonitions)

The Online Books Page

Online Books by

Avicena

Bookdepository

Project Gutenberg books

Al Afal wa al-infialat (On Actions and Passions)

The philosopher's stone. Middle Age

- According to legend, the 13th-century scientist and philosopher, Albertus Magnus, is said to have discovered the Philosopher‘s Stone. Magnus does not confirm he discovered the stone in his writings, but he did record that he witnessed the creation of gold by "transmutation."

c. 1200, - 1280

https://www.britannica.com/biography/Saint-Albertus-Magnus

Ragai J., The philosopher's stone: Alchemy and chemistry, Alif: J. Comparative Poetics, 12:58-77, (1992).
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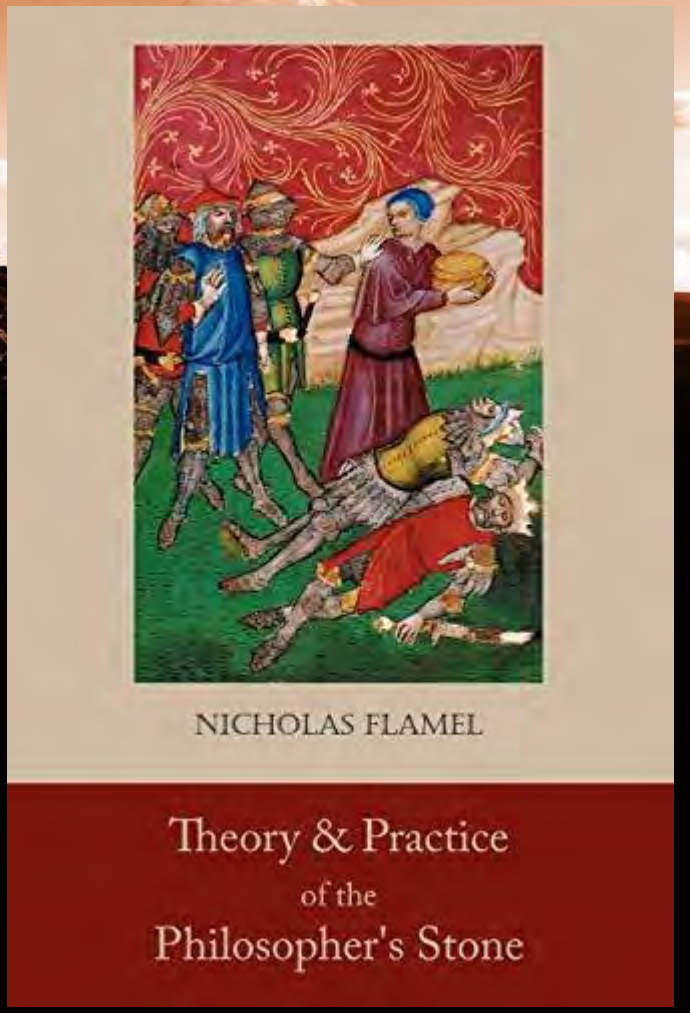
Nicholas Flamel



Tombstone of Nicolas Flamel, 1418.
Musée de Cluny, Paris.

Nicolas Flamel c. 1330 – 22 March 1418) was a French scribe and manuscript-seller.

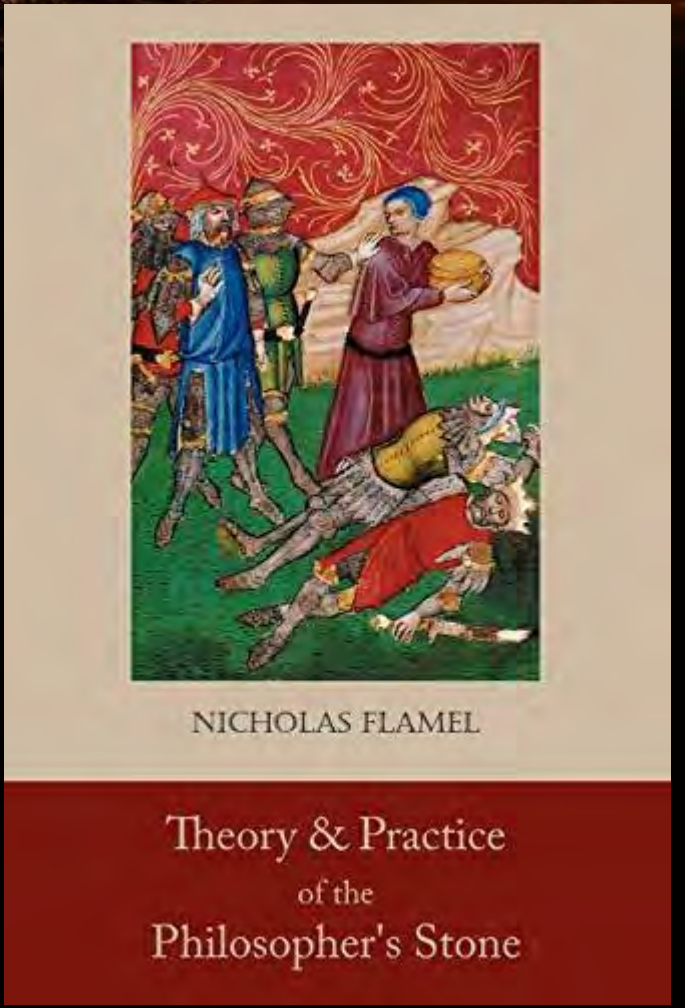
Nicholas Flamel

This imaginative portrait of Nicholas Flamel dates from the 19th century.

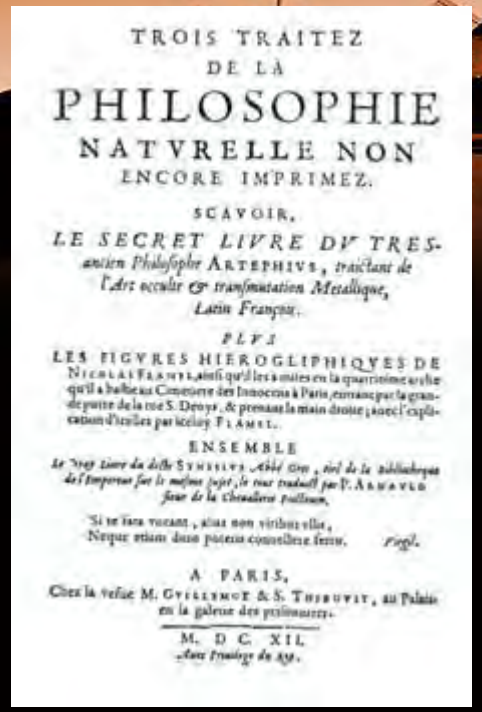
https://commons.wikimedia.org/w/index.php?curid=1512935

Nicholas Flamel

- Legendary accounts of Flamel's life are based on 17th-century works, primarily Livre des figures hiéroglyphiques. The essence of his reputation are claims that he succeeded at the two goals of alchemy: that he made the Philosopher's Stone, which turns base metals into gold, and that he and his wife, Perenelle, achieved immortality through the "Elixir of Life".



Nicholas Flamel



TROIS TRAITEZ
DE LA
PHILOSOPHIE
NATVRELLE NON
ENCORE IMPRIMEZ.

SCAVOIR,

LE SECRET LIVRE DV TRES-ancien Philosophe ARTEPHIVS, *traictant de l'Art occulte & transmutation Metallique, Latin François.*

PLVS

LES FIGVRES HIEROGLIPHIQVES DE NICOLAS FLAMEL, *ainsi qu'il les a mises en la quatrieme arche qu'il a bastie au Cimetiere des Innocens à Paris, entrant par la grande porte de la rue S. Denys, & prenant la main droite, auec l'explication d'icelles par icelluy* FLAMEL.

ENSEMBLE

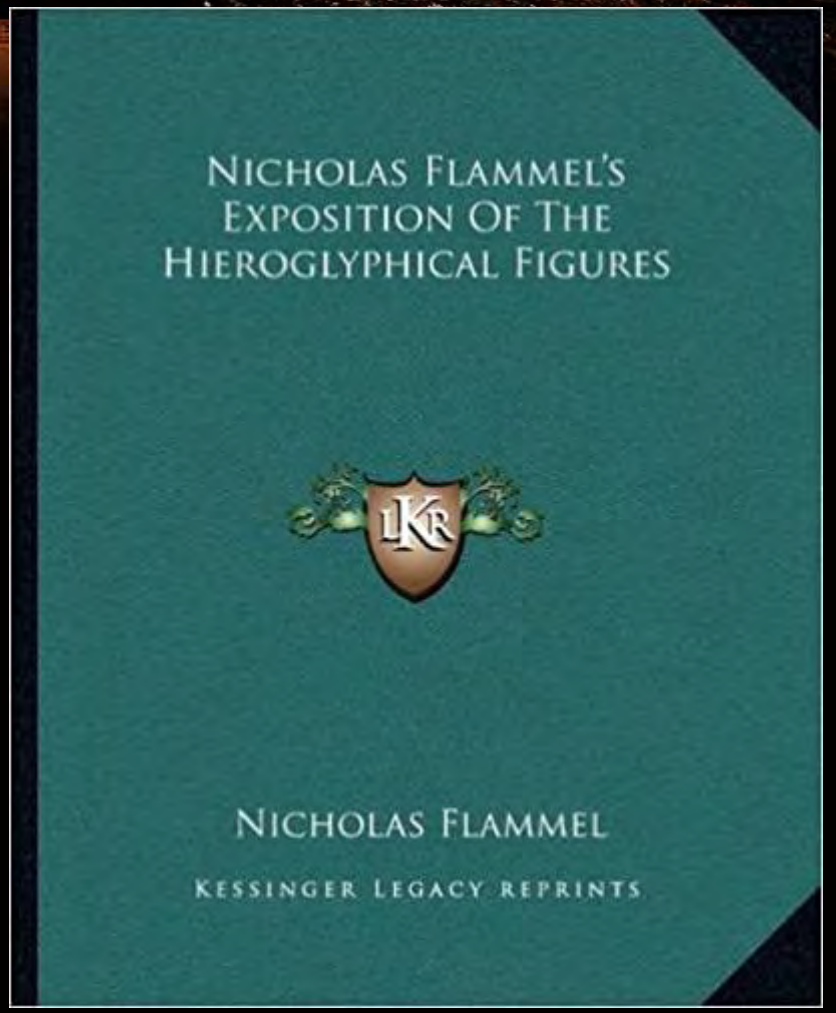
Le Vray Liure dudit SYNESIVS *Abbé Grec, tiré de la bibliotheque de l'Empereur sur le mesme sujet, le tout traduict par* P. ARNAVLD *sieur de la Chevalerie poitevin.*

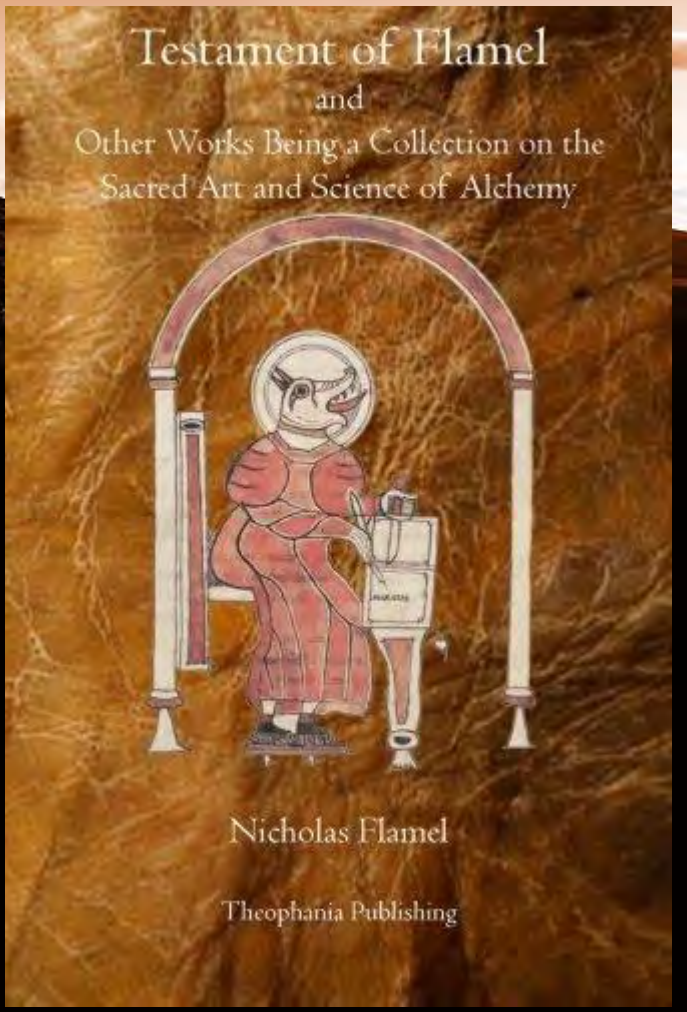
Si te fata vocant, aias non viribus ullis,
Neque etiam deus potens consilium fretus. *Virgil.*

A PARIS,
Chez la veufue M. GVILLEMOT & S. THIBOVST, au Palais en la galerie des prisonniers.

M. D C. XII.
Auec Priuilege du Roy.

First-edition cover of the book of The Hieroglyphic Figures, not published until 1612



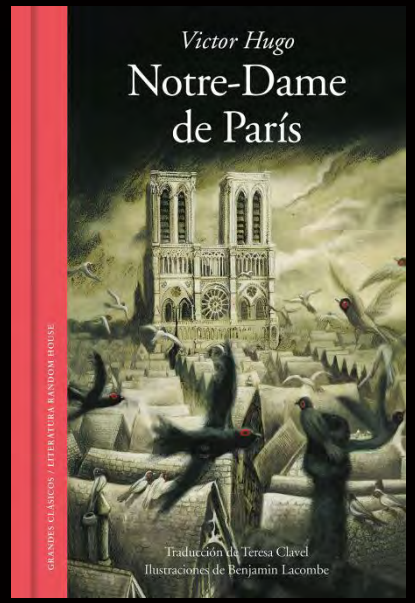


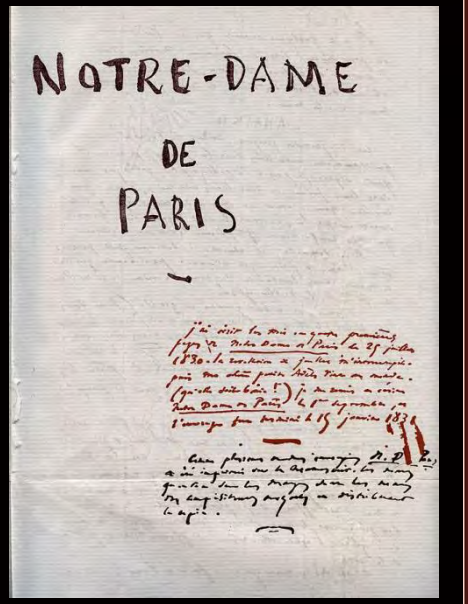
Nicholas Flamel

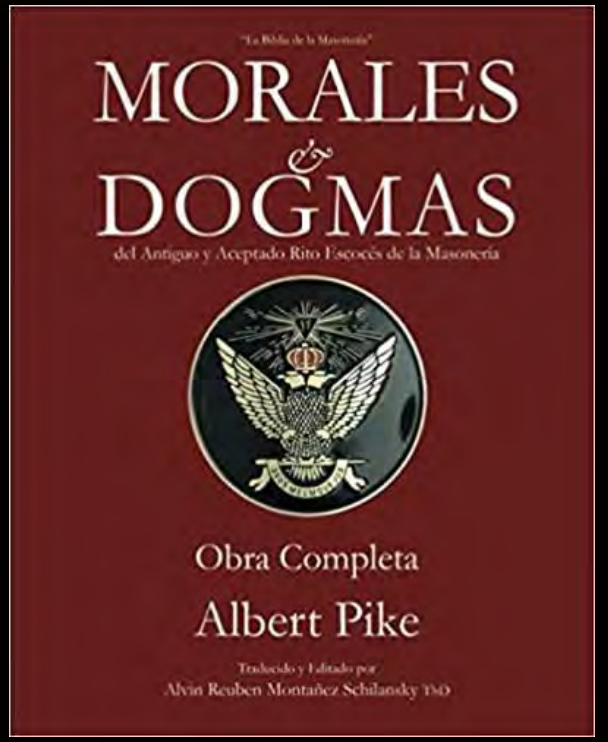
- Flamel had achieved legendary status within the circles of alchemy by the mid 17th century, with references in Isaac Newton's journals to "The Caduceus, the Dragons of Flammel."
- Victor Hugo mentioned him in The Hunchback of Notre Dame.
- Éric Alfred Leslie Satie was intrigued by Flamel.
- Albert Pike refers to Nicholas Flamel in his book Morals and Dogma of the Scottish Rite of Freemasonry.
- Harry Potter and the Philosopher's Stone.
- Fantastic Beasts: The Crimes of Grindelwald.

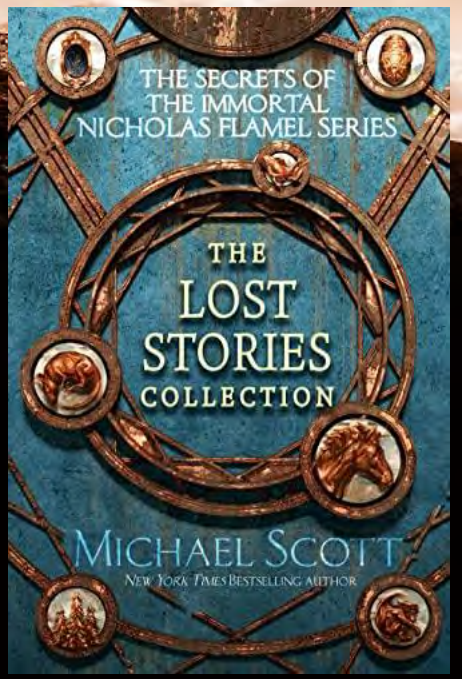
Nicholas Flamel

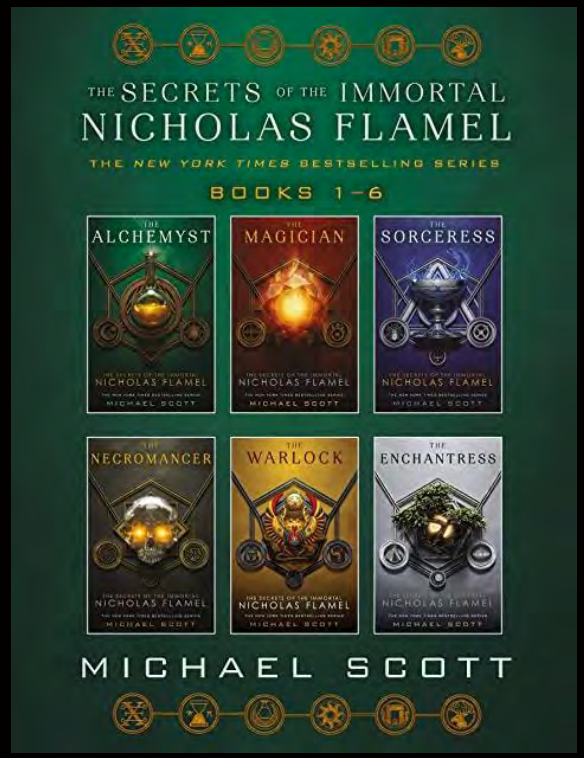
In Victor Hugo's 1831 novel Notre Dame de Paris, the tragic main character Claude Frollo is a young priest and alchemist who spends much of his time studying the carvings in Les Innocents, trying to fathom Flamel's secrets











Dante and the alchemists

We alchemists are in the eighth circle of hell.
According to Dante.

The Alchemist's Room
Pieter I Bruehel (1525 – 1569)

1465 Dante Illuminating Florence with his Poem
Domenico di Michelino.
Museo dell'Opera del Duomo, Firenze.

As always….

- The growing interest in alchemy in various spheres of society prompts the interventions of the ecclesiastical authorities.
  - In 1380 Carlos V of France prohibited the practice of alchemy.
  - John XXII prohibited alchemy in 1399 (Spondent decretal).
  - Aragón Nicolas Eymerich. Treaty against the alchemists.
  - In 1403, Henry IV condemned the transmutation of metals in England.
  - In 1468. the Senate of Venice prohibited alchemy.

The alchemist (16??). Van Ostade Adriaen

Hugo de Payns, Godofredo de Saint-Omer, (1307; 1312); Felipe IV y Clemente V; Jacques de Molay (18/mzo/1314

Eco U., La edad media. IV. Exploraciones, comercio y utopías, Fondo de Cultura Económica, México D. F., pp 395-396, (2019).

Appearance

- According to alchemical texts, the stone of the philosophers came in two varieties, prepared by an almost identical method: white (for the purpose of making silver), and red (for the purpose of making gold), the white stone being a less matured version of the red stone.
- In a solid form, an intermediate between red and purple, transparent and glass-like. The weight is spoken of as being heavier than gold, and it is soluble in any liquid, and incombustible in fire.

Appearance

Philosopher's stone as pictured in Atalanta Fugiens Emblem 21
Michael Maier

"Make of a man and woman a circle; then a quadrangle; out of this a triangle; make again a circle, and you will have the Stone of the Wise. Thus is made the stone, which thou canst not discover, unless you, through diligence, learn to understand this geometrical teaching."

Michael Maier, Atalanta Fugiens, (1617)

https://en.wikipedia.org/wiki/Philosopher%27s_stone

Appearance

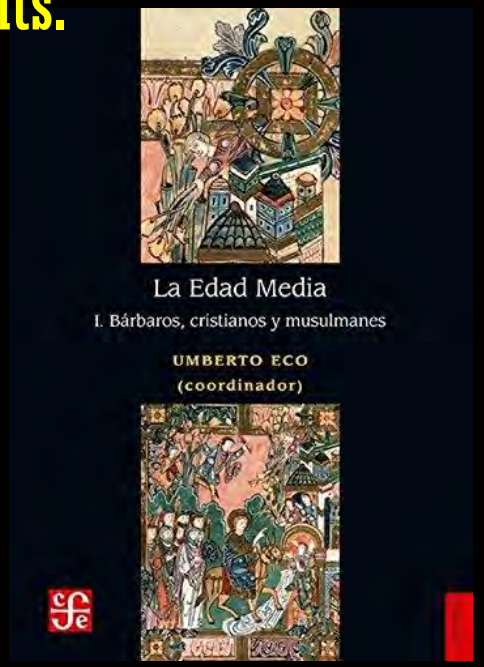
The first key of Basil Valentine, emblem associated with the 'Great Work' of obtaining the Philosopher's stone (Twelve Keys of Basil Valentine).

The Explosion in the Alchemist's Laboratory
Justus Gustav van Bentum (1670–1727)

https://en.wikipedia.org/wiki/Philosopher%27s_stone

From Alchemy

- Conceptual framework.
- Metallurgy.
- Distillation.
- New elements.



And then everything changed I

- Chemistry was first introduced as an academic discipline in medical faculties, academies, botanical gardens, and museums in the late 17th century.
- The distillation vessels used in 18th-century apothecaries' laboratories originated in the late medieval alchemical tradition.
- Pharmacopoeias and other apothecary books of the 18th century included recipes for hundreds of chemical medicines originally introduced by the Paracelsian medical-chemical movement.
- Johann Friedrich Henckel (1678–1744) in Freiberg, done the first experiments for the extraction of sugar from beets.
- In the 1740s, the Prussian king Frederick II commissioned three chemists to study the manufacture of porcelain.

Klein U., Not a pure science: Chemistry in the 18th and 19th centuries, Science, 306(5698):981-982, (2004).

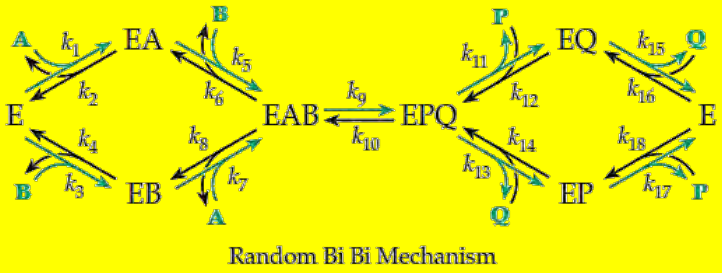
And then everything changed II

- The extraction of sugar from beets, for example, which had been initiated by Marggraf in the 1840s, was pursued by German chemists. Most successful was Franz Carl Achard.
- In the early 18th century, chemists began to develop areas of inquiry that were largely unfamiliar outside of academia. They refined techniques of chemical analysis, restructured the relations between chemical analysis and theories of chemical composition, explored cycles of analysis and resynthesis of substances in the laboratory, and analyzed experimental results to establish **laws of chemical affinity between substances**.
- Substances extracted from plants and animals were largely excluded from these developments.
- Between the late 1820s and the 1840s, this changed fundamentally when, spurred in particular by the work of French and German chemists, a new form of organic or "carbon chemistry" emerged.

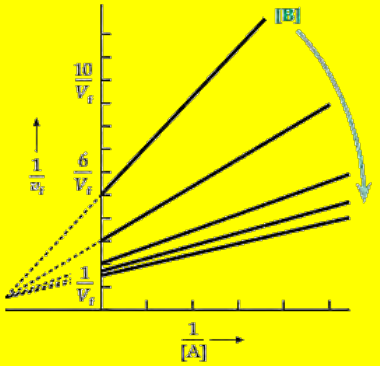
Klein U., Not a pure science: Chemistry in the 18th and 19th centuries, Science, 306(5698):981-982, (2004).

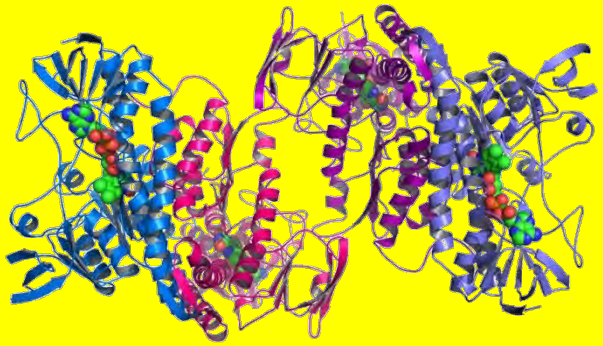
Introduction to enzymes

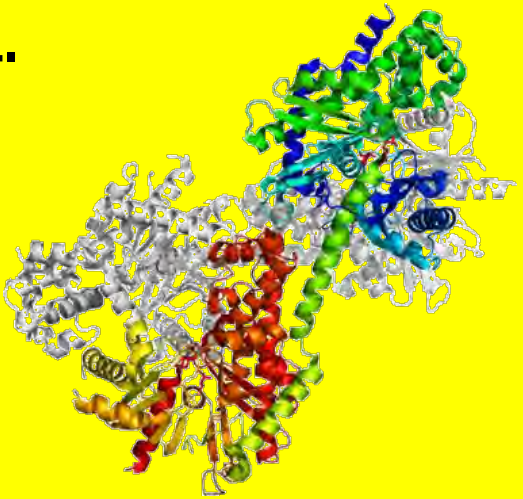
- While the ancients made practical use of enzymes, these applications were based purely on empirical use and tradition rather than systematic study or chemical appreciation of the processes employed.
- In the 18th and 19th centuries, scientists began to study the actions of enzymes' actions more systematically. Digestive processes became a popular research object during the Enlightenment years.
- Scientists wondered how predatory birds digested meat without a gizzard.



Random Bi Bi Mechanism







Beginning

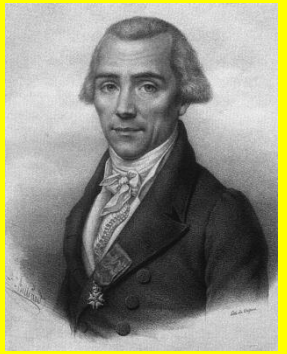
- In 1752, René Antoine Ferchault de Réamur (thermometer) demonstrated the solvent power of the gastric juice of birds and by 1783 Abbé Lazzaro Spallanzani had extended the studies to humans and other species and showed that the process of digestion is temperature dependent and is related to the amount of gastric juices applied to the meat.
- Ferchault determined that while the meat was digested and the bone softened by the action of gastric juices, the plant material was insensitive to the action of the "solvent"; this was probably the first experimental demonstration of the specificity of enzymes.
- In 1777, Edward Stevens isolated human gastric juice and performed the first successful *in vitro* digestion.

Richmond C., Two and a quarter centuries of digestive juices, Trends Biochem. Sci., 11(12): 528-530, (1986).

Beginning

- In 1780 Abbé Lazzaro Spallanzani, confirmed earlier doctrines of the solvent properties of the gastric juice. He also discovered the action of saliva in digestion (ptyalin, amylase from saliva).
- In 1814 Gustav Kirchhoff observed that a "glutinous" (i.e. proteinaceous) component of wheat was capable of converting starch to sugar.
- In 1830 Pierre Jean Robiquet, and Antoine Boutron-Chaland discovered the hydrolysis of amygdalin by bitter almonds (*Prunus dulcis* var. amara).
- In 1833 Anselme Payen & Jean-Framois Berzon prepared a catalyst from germinating barley in the form of a white powder, which they called diastase (now α-amylase)[Paycn A. & Persoz J., Ann. Chim., 53, 73-108, (1833).]






Segel I. H., Enzyme Kinetics. Behavior and Analysis of Rapid Equilibrium and Steady-State Enzyme Systems, John Wiley & Sons, New York, pp 1-957, (1975).

Fruton J. S., A history of pepsin and related enzymes, Quat. Rev. Biol., 77(2): 127-147, (2002).

Hoffmann-Ostenhof O., 100 Years ago: The origin of the term enzyme, Trends Biochem. Sci., 3(3): 186-188, (1978).

Beginning

1810-1882

- In 1836 Theodor Schwann isolated the enzyme pepsin (EC 3.4.23.1) from gastric juice. Was the first enzyme prepared from an animal tissue.
- In 1836 Jöns Jacob Berzelius introduced the concept of catalyst (from the Greek καταλυσις catalysis meaning dissolution)[Iahres-Ber, 15: 237-245, (1836)].
- In 18489 Claude Bernard isolated lipase (EC 3.1.1.3) from pancreas[Pharm. Chim. (Paris) 15, 336-357].
- In 1860, Marcelline Berthelot, invertase (3.2.1.26) from yeast[Compt. Rend. 50, 980-984].
- In 1862 Aleksandr Danilevsky discovered trypsin (ES 3.4.21.4) and was isolated 15 years later by Friedrich Wilhelm 'Willy' Kühne .
- In 1877 Wilhelm Kühne suggested the term "enzyme." [Neue Folge [new series] (Heidelberg) 1: 190–193].

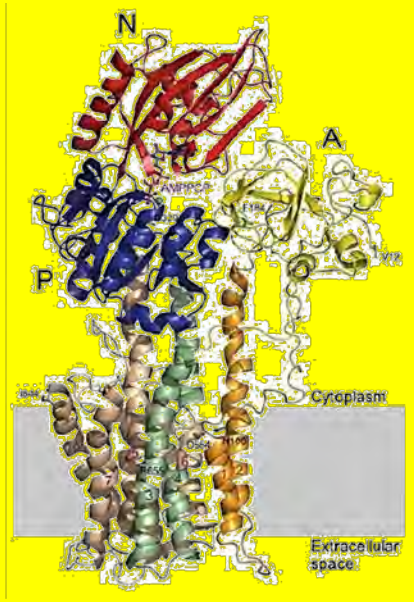
Segel I. H., Enzyme Kinetics. Behavior and Analysis of Rapid Equilibrium and Steady-State Enzyme Systems, John Wiley & Sons, New York, pp 1-957, (1975).

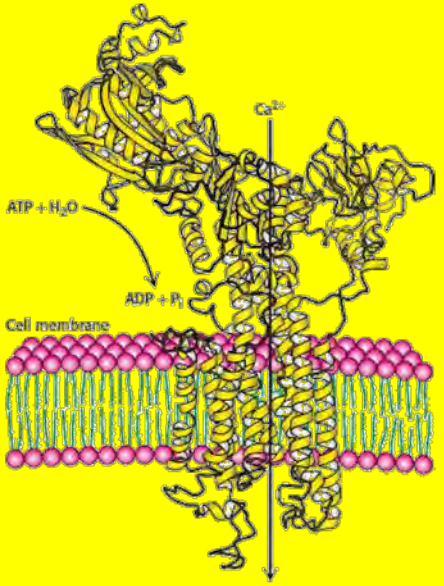
Fruton J. S., A history of pepsin and related enzymes, Quat. Rev. Biol., 77(2): 127-147, (2002).

Hoffmann-Ostenhof O., 100 Years ago: The origin of the term enzyme, Trends Biochem. Sci., 3(3): 186-188, (1978).

Beginning

- Jöns Jacob Berzelius & Iahres-Ber recognize that a natural catalyst, an α-amylase that causes the hydrolysis of starch, had already been isolated from germinating barley in 1833 and that "in living plants and animals thousands of catalytic process take place".





Berzelius J. J., Iahres-Ber, 15: 237-245, (1836).
Paycn A. & Persoz J., Ann. Chim., 53, 73-108, (1833).

The discovery of enzymes

- In 1833 α-amylase, that causes the hydrolysis of starch, was isolated from germinating barley. This discovery was made by Anselme Payen (1795-1871) and Jean-Francois Persoz (1805-1868) and is considered the "discovery" of the enzymes. They treated an aqueous extract of malt with ethanol and precipitated a heat-labile substance (diastase from greek separation) which promote the hydrolysis of starch.

> This substance that we have managed to isolate... has the following properties: it is solid, white, amorphous, insoluble in alcohol, soluble in water and weak alcohol, its aqueous solution is neutral and has no marked taste, does not precipitate with lead subacetate; by itself, it changes more or less quickly depending on the atmospheric temperature and becomes acidic; heated between 65° and 75° with starch, it has the admirable power of promptly separating the pods from the modified inner substance, the dextrin, which dissolves easily in water while the insoluble teguments in that liquid supernatant or precipitate according to the movements of the liquid. This particular property of separation decided us to give the substance that possesses it the name of diastase, which precisely expresses this fact. This well-done operation produces the purest dextrin ever prepared.

Payen A. y J. F. Persoz, Mémoire sur la diastase, les principaux produits de ses réactions, et leurs applications aux arts industriels, Ann. Chim. Phys., 53:73-92, (1833).

Armstrong E. F., Enzymes: A Discovery and its Consequences, Nature, 131(3311):535-537, (1933).

Segel I. H., Enzyme Kinetics. Behavior and Analysis of Rapid Equilibrium and Steady-State Enzyme Systems, John Wiley & Sons, New York, pp 1-957, (1975).

Fruton J. S., A history of pepsin and related enzymes, Quat. Rev. Biol., 77(2): 127-147, (2002).

Hoffmann-Ostenhof O., 100 Years ago: The origin of the term enzyme, Trends Biochem. Sci., 3(3): 186-188, (1978).

The discovery of enzymes

MÉMOIRE *sur la Diastase, les principaux Produits de ses Réactions, et leurs applications aux arts industriels;*

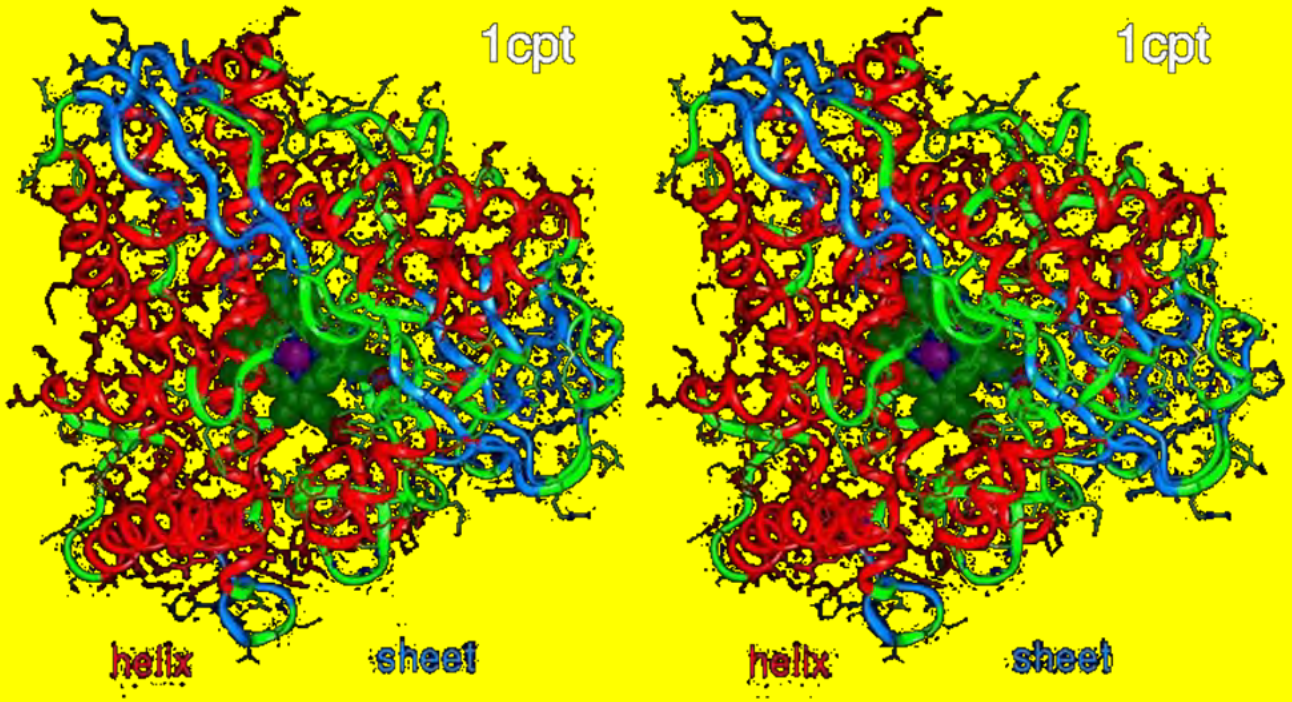
PAR MM. PAYEN ET PERSOZ.

Depuis les savantes recherches et les travaux laborieux de Luwenhoeck, Saussure, Kirschoff, Vauquelin; des brasseurs anglais, de MM Dubrunfaut, Raspail, Guibourt, Couverchel, etc., on connaissait la conformation physiologique de l'amidon; on savait qu'une en-

Payen A. y J. F. Persoz, Mémoire sur la diastase, les principaux produits de ses réactions, et leurs applications aux arts industriels, Ann. Chim. Phys., 53:73-92, (1833).

The discovery of enzymes

- Frederick W. Kühne called these molecules **enzymes (from the Greek ἔνζυμον "*enzymos*, (in yeast or leavened)").** As vitalistic notions of life were disproved, the isolation of new enzymes and the investigation of their properties advanced the science of biochemistry.



Nelson D. L. y M. M. Cox, Lehninger Principles of Biochemistry, Worth Publishers, New York, pp 1-1198, (2017).

Enzyme (1877)

Ueber das Verhalten verschiedener organisirter und sog. ungeformter Fermente.

Sitzung am 4. Februar 1876.

Hr. W. Kühne berichtet über das Verhalten verschiedener organisirter
vorzubeugen
tragender vo
deren Wirk
derselben er
untersucht
Pankreas, f
veranlasst, d
Vortr. zuers
daulichen un
neutraler,
wird durch nicht zu kleine Mengen Salicylsäure, welche das Enzym in bedeutenden Quantitäten löst, bei 40° C. gefällt, ohne dabei seine specifische Wirksamkeit zu verlieren. Wird die Fällung in Sodalösung von 1 pCt. gelöst, so verdaut sie höchst energisch unter Bildung von Pepton, Leucin, Tyrosin u. s. w. Nur übermässiger Zusatz von Salicylsäure bis zur Bildung eines dicken Krystallbreies vernichtet die enzymotischen Eigenschaften. Dies Verhalten war kaum zu erwarten, seit Kolbe und J. v. Meyer die hemmende, selbst vernichtende Wirkung kleiner Mengen Salicylsäure auf einige Enzyme hervorgehoben hatten. Die Beobachtungen des Vortr., der ausser dem Trypsin noch das Pepsin eingehender untersuchte, stehen jedoch mit den Angaben von J. v. Meyer, nach welchen Salicylsäure bei einem Gehalte der

Hr. W. Kühne berichtet über das Verhalten verschiedener organisirter und sog. ungeformter Fermente. Um Missverständnissen vorzubeugen und lästige Umschreibungen zu vermeiden schlägt Vortragender vor, die ungeformten oder nicht organisirten Fermente, deren Wirkung ohne Anwesenheit von Organismen und ausserhalb derselben erfolgen kann, als *Enzyme* zu bezeichnen. — Genauer

Lösung von 1 : 250 die Pepsinwirkung in künstlichem Magensafte so verzögern soll, dass man sie als aufgehoben betrachten müsse, im Widerspruch. Vortr. fand, dass künstlicher Magensaft oder durch Dialyse gereinigte, neutrale oder saure Pepsinlösungen mit überschüssigem Krystallbrei von Salicylsäure tagelang bei 40° digerirt werden können ohne das Verdauungsvermögen zu verlieren.

Dass die Salicylsäure ein vortreffliches Mittel zur Abtödtung oder Aufhebung der zymotischen Wirkung vieler organisirter, echter Fermente sei, wie Kolbe entdeckte, vor Allen der Fäulniss bedingenden Bacterien, konnte der Vortr. bestätigen. Die Behandlung enzymhaltiger Flüssigkeiten und Gewebe mit Salicylsäure ist ein
cterienfäulniss
e zu isoliren.
800 grm.
Wasser bei
en geruchlos,
nach einigen
weisser Tyro-
uten kräftig.
felsäure oder
h 20 Stunden
von alkalischer Reaction, mit zahllosen Bacterien durchsetzt, der ausser Co_2 viel brennbare Gase entwickelte. Ueberraschender Weise ergaben Versuche mit Essigsäure ähnlich günstige Resultate, wie mit der Salicylsäure. Nach Digestion mit dem gleichen Volumen 1proc. Essigsäure waren die Drüsen in 24 Stunden schon sehr zerfallen und ausser den bekannten Verdauungsprodukten des Drüsenalbumins waren weder Bacterien, noch Indol, noch Gasentwicklung zu entdecken. Gleicher Erfolg wurde beobachtet bei absichtlicher Impfung der Masse mit kleinen Mengen gefaulten Pankreas'.

Bei der Bearbeitung thierischer Gewebe ist kein Ferment störender als die fast überall schon in gesunden lebenden Organismen vorhandenen Fäulniss erregenden Bacterien, welche sich bekanntlich in

Kühne, Wilhelm (1877). "Über das Verhalten verschiedener organisirter und sog. ungeformter Fermente" [On the behavior of various organized and so-called unformed ferments]. Verhandlungen des naturhistorisch-medicinischen Vereins zu Heidelberg. Neue Folge [new series] (Heidelberg) **1**: 190–193.

The discovery of enzymes

- Kühne (1877), p. 190: "Um Missverständnissen vorzubeugen und lästige Umschreibungen zu vermeiden schlägt Vortragender vor, die ungeformten oder nicht organisirten Fermente, deren Wirkung ohne Anwesenheit von Organismen und ausserhalb derselben erfolgen kann, als Enzyme zu bezeichnen."

- **In order to avoid misunderstandings and cumbersome circumlocutions, the presenter proposes to designate as "enzymes" the unformed or not organized ferments, whose action can occur without the presence of organisms and outside of the same.**

Kühne, Wilhelm (1877). "Über das Verhalten verschiedener organisirter und sog. ungeformter Fermente" [On the behavior of various organized and so-called unformed ferments]. Verhandlungen des naturhistorisch-medicinischen Vereins zu Heidelberg. Neue Folge [new series] (Heidelberg) **1**: 190–193.

The Meaning of Ferment

- The word ferment had a very different meaning to the alchemists. Even in the beginning of the 19th century, ferment was still an enigma that admitted of many alternative interpretations.
- In the year 1800 the French Academy of Sciences announced a competition to submit an essay in answer to the question of what distinguished the ferment from the substance being fermented.
- At that time the scientific community still entertained the hypothesis that a sugar molecule being fermented to alcohol and CO_2 could transmit this process to other sugar molecules.

Lagerkvist U., The Enigma of Ferment, World Scientificv, Singapore, pp 1-161, (2005).

The discovery of enzymes

- Kühne, suggested the term '**enzyme**' for those catalytically active substances that hitherto had been called '**ferments**' or, more specifically, '**unorganized ferments**.'
- The difficulty was that the term '**ferment**' was used in two different meanings:
  - To indicate a **microorganism** bringing about a fermentative process (e.g. alcoholic fermentation, lactic acid fermentation).
  - To indicate a **catalyst** causing a biochemical reaction *in vitro*, (e.g. the hydrolysis of sucrose to glucose and fructose, or the digestion of a protein). In the latter case the term 'unorganized ferment' was sometimes used.

Hoffmann-Ostenhof O., 100 Years ago: The origin of the term enzyme, Trends Biochem. Sci., 3(3): 186-188, (1978).

The origin of the word “Enzyme”

Although they do not tell in detail how they created the word, it gives the impression that they asked some philologist Greek to tell them how to say "separation" in Greek, and he replied that διάστασις diastasis, which they wrote in French diastase. It is interesting to observe the phonetic process from Greek to French and then to Spanish. In Greek, the word has a suffix in -sis characteristic to make abstract nouns from Spanish verbs that suffix remains as is. It is not surprising, therefore, that Persoz y Payen's word "diastasis" can be documented in nineteenth-century Spanish chemical publications as early as 1839.

Mayer A., Die Lehre yon den Chemischen Fermenten oder Enzymologie, Winter, Heidelberg, (1882) **The theory of chemical ferments or enzymology**

Cortés Gabaudan F., El sufijo 'asa' y la química francesa de los siglos XVIII y XIX, Panace, XIV: 341-342, (2013).

The origin of the word “Enzyme”

In French, words that use the suffix -sis end in -se; Since the Greek word from which it comes is feminine, it is also feminine in French, which is why the ending is '-a' in Spanish. "Diastase," as opposed to the primitive "diastasis," is a Gallicism. Note also where the accent falls; If it were not for the influence of French, Spanish would accentuate it as esdrújula.

However, the interest in the word does not end much less in itself; the most important thing is that it gave rise to a suffix -ase in English or French and '-asa' in Spanish, with the meaning of 'enzyme.' Nevertheless, it took time to get there because before, it was necessary to establish the concept of the enzyme.

Cortés Gabaudan F., El sufijo 'asa' y la química francesa de los siglos XVIII y XIX, Panace, XIV: 341-342, (2013).

The bird of the battle among vitalists & chemists

- **Charles Cagniard-Larour** suggested in 1837 that the vegetatite process gave rise to the fermentation of sugar to alcohol.
- **Theodor Schwann** discovered that that it was enough to heat the air that came in contact with a sterile solution of sugar to prevent fermentation. He concluded that fermentation was caused by some living organism that was present in the air.
- **Friedrich Kützing**. He made his observations of budding yeast cells and pick a fight with Jacob Berselius. In the annual report of 1839 on the origress of chemistry, he wrote "I pass over his philosophy regarding the organic and inorganic, which belongs to philosophical ideas that have long ceased to exert a harmful effect of the development of sciences."

Lagerkvist U., The Enigma of Ferment, World Scientificv, Singapore, pp 1-161, (2005).

Vitalism

- In the 1860s, **Louis Pasteur** concluded that fermentation of sugar into alcohol by yeast is catalyzed by "**ferments**." He postulated that these ferments were inseparable from the structure of living yeast cells, a view called **vitalism** (*vis vitalis*) that prevailed for many years.

Pasteur became increasingly convinced that real fermentation always required the presence of living microorganisms and that chemical reactions catalyzed by soluble ferments such as the splitting of protein by pepsin in carbohydrate by diastase were in reality entirely different phenomena.

Pasteur L., Amr. Chim. 3e série 58: 323426, (1860)
Lagerkvist U., The Enigma of Ferment, World Scientificv, Singapore, pp 1-161, (2005).

"Vital Force"

- The concept of "vital force" was introduced at the end of the 18th century by the German anatomist Johann Reil.

No chemist on earth can make out of the earth a piede of sugar, but a vegetable can do it

John Hunter (1786)

"…a word to which we can affix no idea…"

Berzelius (1813)

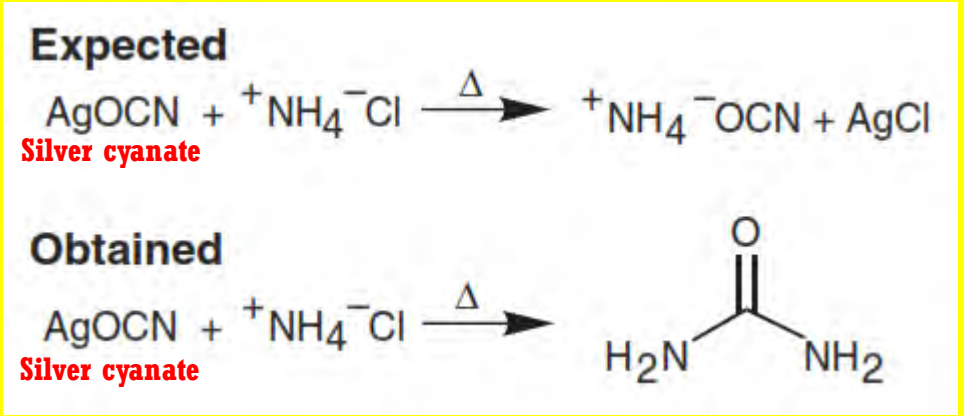
"…urea could scarcely be "considered as organic matter, being rather an excretion than a component of the animal body"…"

Johann Müller

Lagerkvist U., The Enigma of Ferment, World Scientificv, Singapore, pp 1-161, (2005).

Beginning of Biochemistry

- Many science historians set this *in vitro synthesis* of urea by Wöhler (1828) as the starting point of Biochemistry.



Synthesis of urea. Yielding a chemical previously isolated only from man or dog, the synthesis of urea represents a landmark achievement in organic synthesis and chemical biology.

Friedrich Wöhler (1800-1882)

During an attempt to synthesize ammonium cyanate, Wöhler heated a solution of silver cyanate and ammonium chloride. Separately, he also heated lead cyanate and aqueous ammonia. In both cases, he obtained not the expected product, but urea.

Wöhler F., Poggendorff's Ann., 12: 253-256. (1828)

Wöhler F., Sur la formation artificielle de l'urée, Ann. Chim. Phys., 37: 330-333, (1828)

Horton H. R. et al., Principles of Biochemistry, Prentice Hall, Upper Saddle River, pp 1-862, (2002).

Morrison K. L. y G. A. Weiss, The origins of chemical biology, *Nat. Chem. Biol.*, 2(1):3-6, (2006).

V. *Ueber künstliche Bildung des Harnstoffs; von F. Wöhler.*

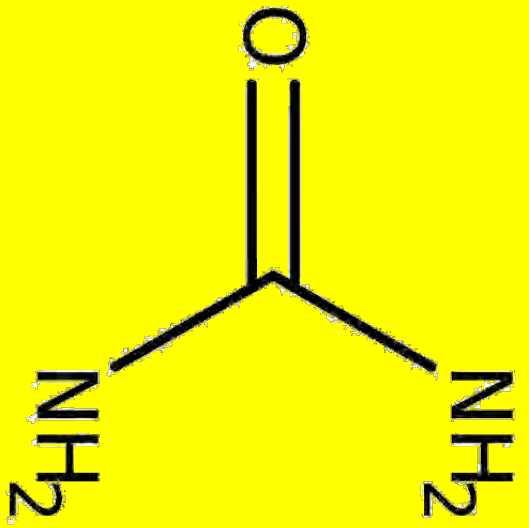
In einer früheren kleinen Notiz, die in dem III. Bande dieser Annalen abgedruckt ist, habe ich angegeben, dafs beim Einwirken von Cyan auf flüssiges Ammoniak, aufser mehreren anderen Producten, auch Oxalsäure und eine krystallisirbare weifse Substanz entstehe, welche letztere bestimmt kein cyansaures Ammoniak sey, welche man aber dessen ungeachtet immer erhalte, so oft man versuche, z. B. durch sogenannte doppelte Zersetzung, Cyansäure mit Ammoniak zu verbinden. Der Umstand, dafs bei der Vereinigung dieser Stoffe dieselben ihre Natur zu verändern schienen und dadurch ein neuer Körper entstände, lenkte von Neuem meine Aufmerksamkeit auf diesen Gegenstand, und diese Untersuchung hat das unerwartete Resultat gegeben, dafs bei der Vereinigung von Cyansäure mit Ammoniak Harnstoff entsteht, eine auch in sofern merkwürdige Thatsache, als sie ein Beispiel von der künstlichen Erzeugung eines organischen, und zwar sogenannten animalischen, Stoffes aus unorganischen Stoffen darbietet.

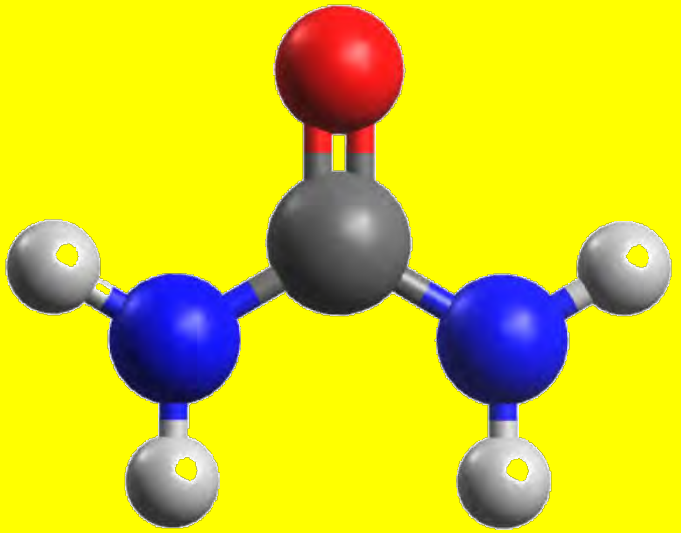
Ich habe schon früher angegeben, dafs man die oben erwähnte krystallisirte, weifse Substanz am besten erhält, wenn man cyansaures Silberoxyd durch Salmiak-Auflösung, oder cyansaures Bleioxyd durch flüssiges Ammoniak zersetzt. Auf die letztere Art habe ich mir die, zu dieser Untersuchung angewendete, nicht unbedeutende Menge davon bereitet. Ich bekam sie in farblosen, klaren, oft mehr als zolllangen Krystallen angeschossen, die schmale rechtwinklige, vierseitige Säulen, ohne bestimmte Zuspitzung, bildeten.

Mit kaustischem Kali oder mit Kalk entwickelte dieser Körper keine Spur von Ammoniak, mit Säuren zeigte er durchaus nicht die so leicht eintretenden Zersetzungs-

Wöhler F., Poggendorff's Ann., 12: 253-256. (1928)

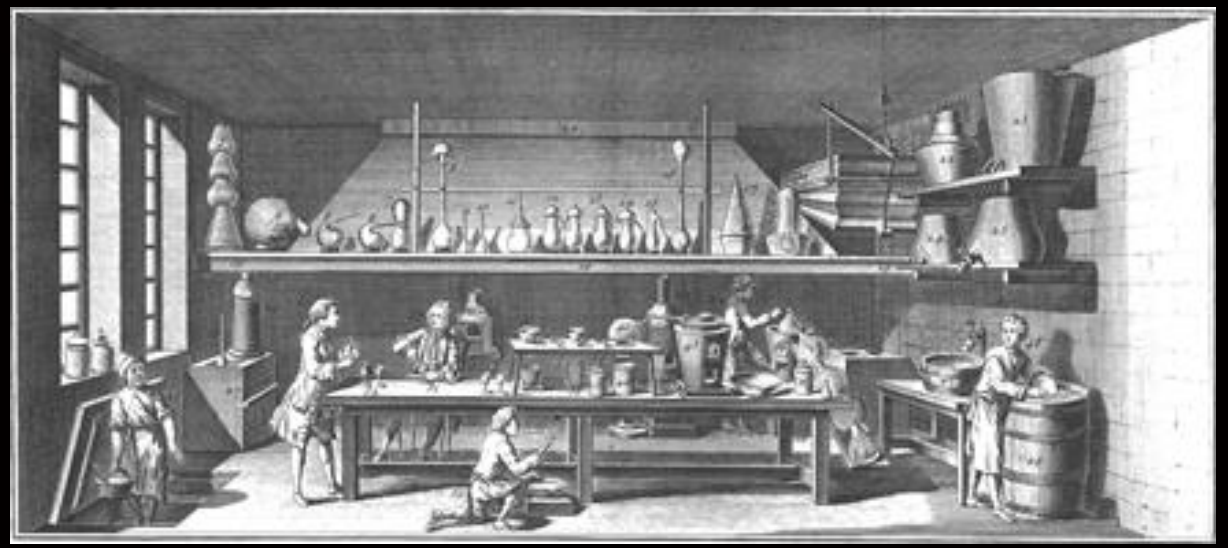
On the artificial formation of urea





Carbon Chemistry

- Most chemists involved in the emerging subdiscipline of carbon chemistry—such as Justus Liebig and Friedrich Wöhler in Germany and Jean Dumas and Auguste Laurent (in France—maintained their connections with pharmacy and industry in areas other than carbon chemistry. However, the applicability of substitution products and the usefulness of investigations into the structure of organic compounds were not on their agenda.



Klein U., Not a pure science: Chemistry in the 18th and 19th centuries, Science, 306(5698):981-982, (2004).

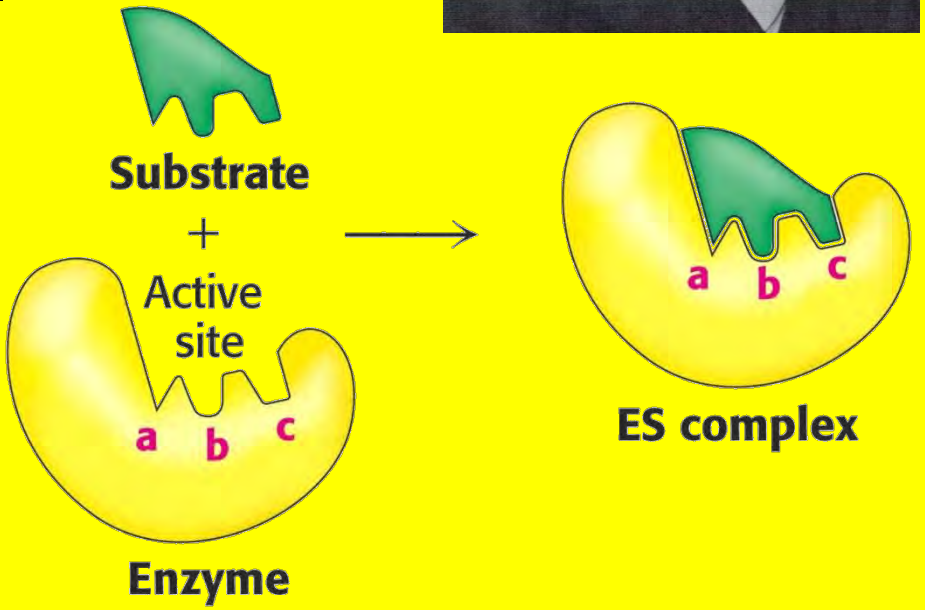
The Chemical View

- Pasteur lost no time in pointing out that (invertase reaction) was brought about by a great many other substances besides invertase.
- Claude Bernard discovered that fermentation could be carried out in a cell-free preparation from the juice of rotting fruit. He died before the publication of the discovery.
- At the time of Pasteur's quarrel with Berthelot over the publication of Bernard's´ posthumous manuscript, the number of the controversial **soluble ferments** approached 20. The German biochemist **Willy Kühne** suggested that such ferments should be called **enzymes**.

Lagerkvist U., The Enigma of Ferment, World Scientificv, Singapore, pp 1-161, (2005).

Lock-and-key-hypothesis

- The German physical-chemist **Eilhard Mitscherlic** thought more in terms of contact between the ferment and what we call its substrate, as prerequisite for fermentation.
- In a famous paper with the title "*Bedeutung der Stereochemie für die Physiologie*" ("The importance of Stereochemistry for Physiology") **Emil Fisher** put forward in 1898 the first full-fledged model for the mechanism of enzyme action.



Fischer E., Bedeutung der Stereochemie für die Physiologie, en: Untersuchungen Über Kohlenhydrate und Fermente (1884-1908), (Fischer E., ed.), Springer, Berlin, Heidelberg, 116-137, (1909).

Fischer E., Einfluss der Configuration auf die Wirkung den Enzyme, Ber. Dtsch. Chem. Ges., 27: 2985-2993, (1894).

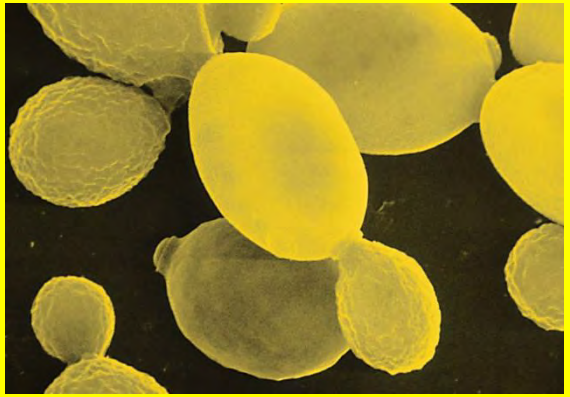
Influence of the configuration on the action of the enzymes

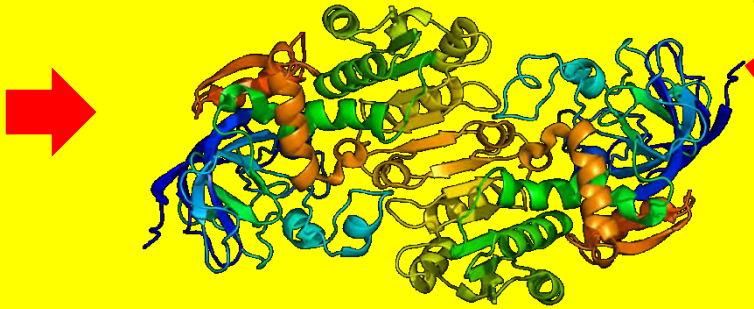
Berg J. M. et al., Biochemistry, W. H. Freeman and Company, New York, pp 1-1026, (2007).

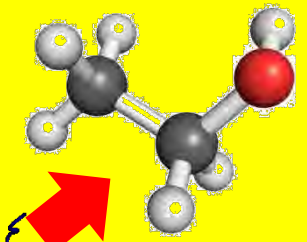
Lagerkvist U., The Enigma of Ferment, World Scientificv, Singapore, pp 1-161, (2005).

The track to the discovery

- In 1846 Friedrich Wilhelm Lüdersdorff had ground a small amount of yeast, until no yeast was observed in the microscope. However, he was no able to demonstrate any alcoholic fermentation. Same results from Carl Schmidt's laboratory.
- In 1872 & 1897 Marie von Manassein claimed that she had observed cell-free alcoholic fermentation in a yeast extract obtained by extensive grinding with fine fine sand. Her results were no generally accepted.







Lagerkvist U., The Enigma of Ferment, World Scientificv, Singapore, pp 1-161, (2005).

A Fortuitous Observation

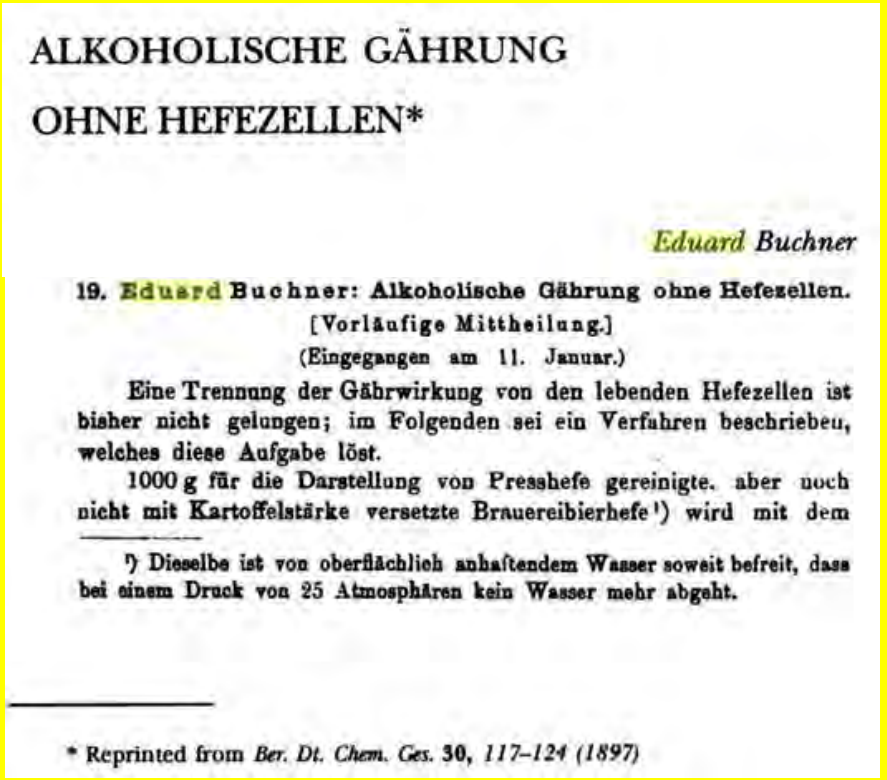
- Eduard joined Hans laboratory in 1896 in a project looking for an effective method to produce a yeast extract.
- Martin Hahn suggested they ground yeast in a mortar with one part of pulverized quartz and one-fifth of diatomaceous so as to obtain a paste that was the rapped in canvas and subjected to a pressure of 90 kg cm^{-2}. In this was, one kilogram of yeast yielded approximately 500 mL of fluid.
- For the preservation of the fluid, Hahn then thought of the classical method of preserving fruits by adding a high concentration of sucrose.
- Eduard made the observation that after the adding of sucrose there was a lively formation of gas in the fluid.

Lagerkvist U., The Enigma of Ferment, World Scientificv, Singapore, pp 1-161, (2005).

A Fortuitous Observation

- His brother must have notice a similar phenomenon in earlier experiments of the same kind, but apparently had paid no attention to it. However, it would seen that Eduard immediately drew the correct conclusion.

Eduard called his yeast extract "zymase."



ALKOHOLISCHE GÄHRUNG

OHNE HEFEZELLEN*

Eduard Buchner

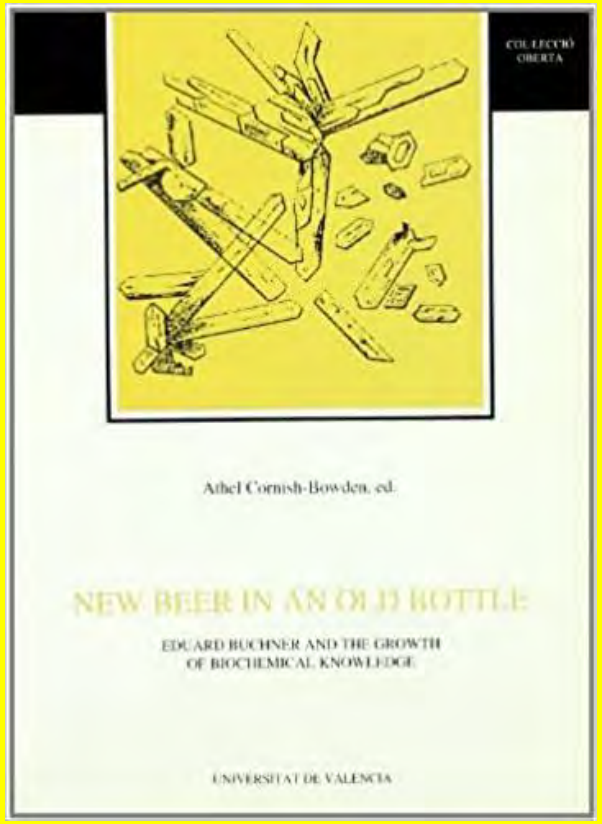
19. Eduard Buchner: Alkoholische Gährung ohne Hefezellen.
[Vorläufige Mittheilung.]
(Eingegangen am 11. Januar.)

Eine Trennung der Gährwirkung von den lebenden Hefezellen ist bisher nicht gelungen; im Folgenden sei ein Verfahren beschrieben, welches diese Aufgabe löst.

1000 g für die Darstellung von Presshefe gereinigte, aber noch nicht mit Kartoffelstärke versetzte Brauereibierhefe[1]) wird mit dem

[1]) Dieselbe ist von oberflächlich anhaftendem Wasser soweit befreit, dass bei einem Druck von 25 Atmosphären kein Wasser mehr abgeht.

* Reprinted from *Ber. Dt. Chem. Ges.* **30**, *117–124 (1897)*



Büchner E., Alkoholische Gährung ohne Hefezellen, Ber. Dt. Chem. Ges., 30:117-124, (1897).

Lagerkvist U., The Enigma of Ferment, World Scientificv, Singapore, pp 1-161, (2005).

A new science is born

Alcoholic Fermentation Without Yeast Cells

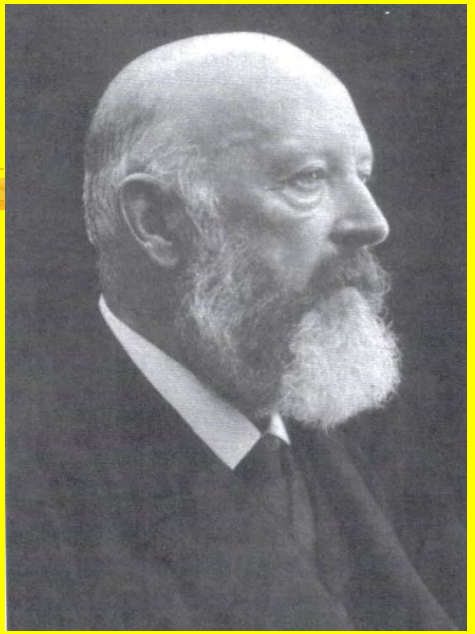
This page contains an English translation by Herbert C. Friedmann of the following paper: Eduard Buchner (1897) Alkoholische Gährung ohne Hefezellen, originally published in *Ber. Dt. Chem. Ges.* **30,** 117-124. The translation takes account of corrections published on pp. 335 and 1110 of the original journal. A facsimile of the original paper was published in pp. 17–24 and the translation in pp. 25–31 of *New Beer in an Old Bottle: Eduard Buchner and the Growth of Biochemical Knowledge* (ed. A. Cornish-Bowden), Universitat de València, Valencia, Spain. A PDF file is also available.

Preliminary Note, received 11 January

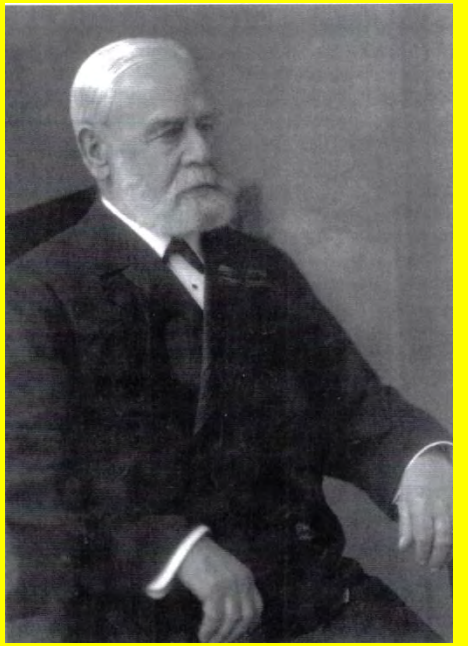
Until now it has not been possible to separate fermenting activity from living yeast cells; the following describes a procedure that solves this problem.

Buchner E., Berichte der deutschen chemischen Gesellschaft (Ber. Dt. Chem. Ges.,) 30: 117-124 (1897).

The nomination



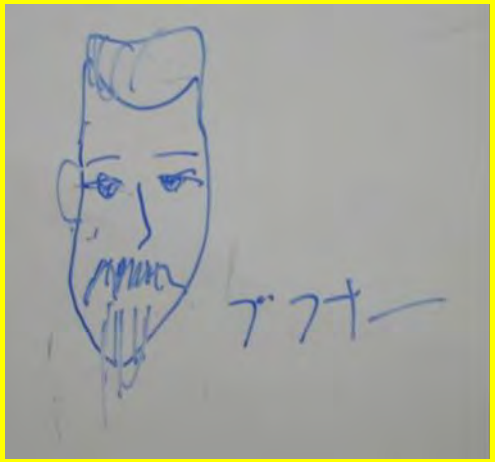
- First nomination, 1905 by Volhard at the University of Halle (2nd choice). Adolf von Baeyer.
- Second nomination in 1907 by Carl Harries professor at the University of Kiel and the Swedish biochemist, Hans von Euler. He competed against other 20 scientists; Ernest Rutherford, Walther Nernst.



Olof Hammarsten was the Committee appointed to evaluate the merits of Eduard Büchner. Hammarsten emphasizes that Büchner's demonstration of cell-free alcoholic fermentation once and for all puts an end to vitalism and its belief in a mystical "vital force" that did not exist outside the living cell.

Lagerkvist U., The Enigma of Ferment, World Scientificv, Singapore, pp 1-161, (2005).

The Prize



Eduard Büchner (1860 – 1917)

Nobel Prize in Chemistry 1907:"For his biochemical researches and his discovery of cell-free fermentation".

There were two dissenters, one of them Svante Arrhenius. He did not do his job properly. He tries to belittle the importance of Büchner's discovery for the demise of vitalism. He was right when at the end of his letter, he points out that Büchner has not really contributed anything to our understanding of the chemical process involved in the alcoholic fermentation.

"I therefore believe that Büchne's work is mainly of physiological interest and ought to have been judged by Medica Nobel Committee."

His letter shows a complete lack of understanding of the importance of Büchner's discovery for the development of biochemistry.

Nelson D. L. y M. M. Cox, Lehninger Principles of Biochemistry, Worth Publishers, New York, pp 1-1198, (2017).

Nobel Lecture 1907

EDUARD BUCHNER

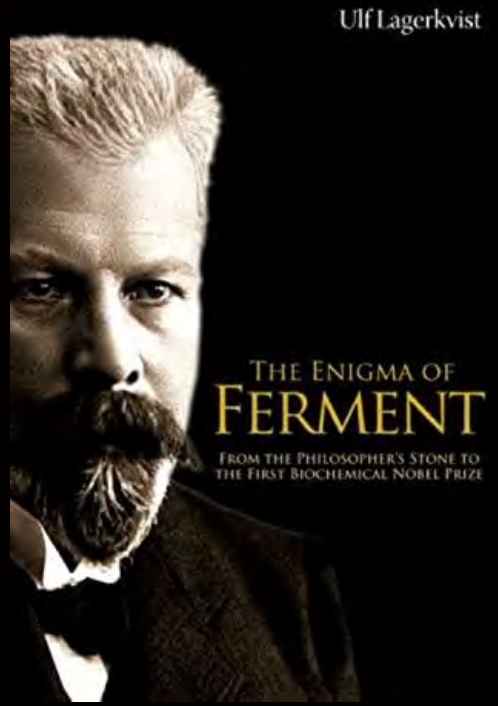
Cell-free fermentation

Nobel Lecture, December 11, 1907

I would first ask the assembled company to allow me to express my sincere gratitude for having been so highly honoured with the distinction of speaking today before the Royal Swedish Academy of Sciences, to which at one time a Scheele and a Berzelius belonged and which at the present time counts Arrhenius among its members, all men whose achievements fill every chemist with admiration. The work on which I have to report lies on the boundary between animate and inanimate nature. I therefore have reason to hope that I can interest not only the chemists but also the wide circles of all those who follow the advance of biological science with close attention. It is difficult, however, for a person to be comprehensible and at the same time remain scientific, so I must ask you to bear with me.

Conclusion

- Empirical knowledge has been the basis for the development of science.
- Alchemy laid the foundations for the development of chemistry.
- Even the brightest people have their downfalls.
- Serendipity is always up to mischief in our labs.




YUUMBO'TIK