

Gonorrhea Treatment along the Centuries: Terebinth, Cubeb and Copaiba

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Abstract

Among the oldest therapeutic approaches for venereal diseases, going back to Ptolemaic times or even earlier, is administration of the essence of terebinth (turpentine). Turpentine dominated such treatment for centuries, only gradually being complemented or replaced by cubeb powder from Java and copaiba essence from Brazil. The common denominator of all these cures was a limited therapeutic value and poor tolerability complemented by a horrible taste that inspired French pharmacists to improve on the ingestion experience. French pharmacist **Stanislas Limousin** (1831-1887) is credited with the introduction of *cachets* enclosing medicine and thus greatly facilitating their administration. In fact, such *cachets* were developed and used much earlier by the parish priest of the village of Pérols (*curé of Pérols*), **Joseph Lambert Arnal** (1798-1867), albeit not for venereal diseases but for malarial intermittent fever.

Keywords

Gonorrhea, Cachets a Pain, Turpentine, Cubeb, Copaiba

1. The Disease

Venereal diseases are as old as mankind and the associated sexual activity, possibly even older. The urethral discharge described by many authors of Antiquity is likely gonorrhea. It would take a lot of debate and time until the major sexually transmitted infections (STD), gonorrhea and syphilis, would be recognized as separate entities. The Edinburgh surgeon **Benjamin Bell** (1749-1806) was apparently the first to clearly differentiate between the two (Bell, 1792; Sinclair, 1889). Gonorrhea, is caused by infection with the Gram-negative diplococci first described by **Ernst Hallier** (1831-1904), and later, using a Zeiss microscope in much more detail, by **Albert Neisser** (1855-1916) (Hallier, 1869; Neisser, 1879). Neisser refers to diplococci as resembling German bread rolls (*Semmeln*), while others prefer

the analogy to coffee beans (**Figure 1**). One year later, **Arpad von Bokai** (1856-1919) (**Figure 2**) managed to culture the micro-organism, opening the way for attempts at rationale pharmacotherapy (**Bokai, 1880**).

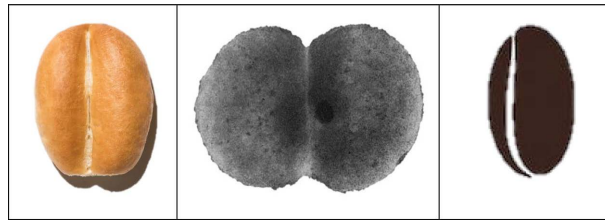


Figure 1. Neisser refers to diplococci as resembling German bread rolls (Semmeln), while others prefer the analogy to coffee beans. In the middle *Neisseria gonorrhea* diplococci.



Figure 2. Arpad von Bokai (1856-1919), Professor of Pharmacology in Budapest (nobilitated 1896 by the Emperor of Austria & King of Hungary) managed to culture the micro-organism.

2. The Name

It is apparently the Greek physician **Galen** (131 - 200 AD) that coined the term gonorrhea. The word is from the Greek words *gonos* meaning *seed* or *semen* and *rhein*, meaning *flow*. As such the name is a misnomer, since what flows out of the urethra of affected individuals is not semen but a whitish-yellowish, more or less purulent discharge, rich in polymorph nuclear monocytes. **François** (Franz Xaver) **Swediaur** (1748-1824) introduced the terms blennorrhagia and blennorrhea (*blénna* = *mucous discharge*) for acute and chronic gonorrhea, respectively (**Swediaur, 1815**). Blennorrhea is flow of mucous while blennorrhagia is an excess of such discharge. The terms are rarely used nowadays. Colorful colloquial designations, alluding to the symptoms or the mode of acquisition of the disease exist in most languages (**Figure 3**).

The French term *chaude pisse* (urina ardente) is inspired by the burning sensation associated with urination in those affected. The term was widely used in the French literature; among the more famous sufferers are **Pantagruel**, Gargantua's son, and **Sieur Gaulard**, noble of the Burgundian Franche-Comté (**Rabelais, 1596**; **Tabourot, 1614**). Of interest is also the attempt by **Ambroise Paré** (1510-1590) to

Gonorrhea				
				
Tripper	Clap(p)	Chaude-pisse	Gota matinal	Zivah
Bonjour-Tropfen	The whites	Goute militaire	Gota militar	
Hussaren-Tripper	A weakness	Les fleurs blanches	Purgaciones	
	Arçure/ arsure Mal de l'arsure	Clapiers purulents		
		Perte en blanc		

Figure 3. Colorful colloquial designations, alluding to the symptoms or the mode of acquisition of the disease exist in most languages.

differentiate between gonorrhea and chaude-pisse, not only in terms of etiology but also treatment. He states that turpentine is an excellent remedy for chaude-pisse but does not mention it as treatment of gonorrhea (Paré, 1641).

The English *clap* is also of French origin originating from rabbit huts (*clapiers*) describing the enclosures (and associated sounds) where prostitutes used to practice their trade. The Spanish *gota matinal* is identical to the German *Bonjour Tropfen* and *Tripper* (dripping or drop). *Hussaren Tropfen* is *Goute Militaire* or *Gota Militar*. Less obvious names are quite euphemistic such as the *Whites* or a *Weakness* or the poetical *Fleurs Blanches* (White flowers), preferred by **Mauquest de La Motte** (1655-1737).

3. The Treatment

Historically, attempts at gonorrhea treatment can be broadly divided based on the main therapeutic agent used into three (widely overlapping) periods:

- 1) terebinth (turpentine)
- 2) cubeba, copaiba, matico & hardwickia
- 3) the modern antibiotic era.

Needless to say that any substance known to men, in combination with or as replacement of those mentioned, was at some point also tried, with more or less success.

3.1. Terebinth

Turpentine (*terebinth*) is the oleoresin of the terebinth tree (*Pistacia terebinthus*). Distillation of resin yields *spirit of turpentine*, also called *oil of turpentine* (*Oleum terebinthinae*) or simply turpentine. The distillation product is composed mainly of *terpenes* and some *terpenoids* (Petroianu & Lorke, 2021).

Terpenes are cyclic molecules having the formula $C_{10}H_{16}$ resulting from the condensation of (two or more) isoprene units (C_5). The name is derived from *Terpentin*, the German word for turpentine. Terpenoids are modified terpenes, wherein methyl groups have been moved or removed, or oxygen atoms added. The name

implies similarity to *turpentine*. In contrast to terpenes, the number of carbon atoms in terpenoids is not a multiple of five anymore.

The most prevalent component of turpentine is the bicyclic mono-terpene pinene, with lesser amounts of carene, camphene and limonene (**Figure 4**).

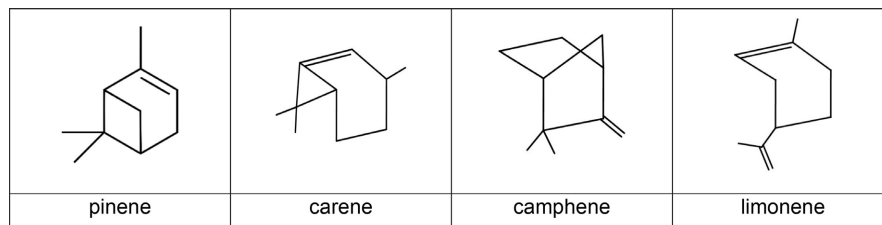


Figure 4. The most prevalent component of turpentine is the bicyclic mono-terpene pinene, with lesser amounts of carene, camphene and limonene.

The use of terebinth for treatment of vaginal discharge is attributed to **Hippocrates** (460BC - 370BC): *Is etiam (fructus terebinthi) in vino et aqua dilutus et potus, fluorem muliebrem sistit* (Diluted in wine and water and drunk, it (the fruit of terebinth) also stops the female flow) (Trousseau & Pidoux, 1839; Hippocrates, 1900; Haller, 1984).

Most scholars understand *fluor muliebris* as referring to any vaginal/uterine discharge, physiologic or pathologic. Chapter XXVI of David **Friedel** (*1689)'s 1726 Book *Expediter Und Bewährter-Medicus* titled *Von dem weißen Fluß, Fluor albus, fluor muliebris, fluor uterinus, Leucorrhæa genannt. Diefier Fluß wird auch Gonorrhæa Mulierum der Weiber. Trippert genannt, weil bey diefer Kranckheit alle Symptomata zu finden, welde in Gonorrhæa virorum obferviret warden* (Friedel, 1726).

Many authors of Antiquity and later see the essence of terebinth as a major ingredient of the mixtures used for the treatment of vaginal discharge. Among the first physicians to recommend turpentine balsam for gonorrhea treatment we count **Marco Gatinaria** (1442-1496) and **Annibal Barlet** (1577).

Gatinaria, Professor in Padua, in a chapter titled *De ardore urinae* recommends terebinth (Gatinaria, 1604); Gatinaria's role in popularizing turpentine use is highlighted by **Johann Karl Proksch** (1840-1923) in his history of venereal disease (Proksch, 1895). **Barlet** (1577) in seinem Cours de Chymie also recommends spirit of terebinth for gonorrhea (Barlet, 1577).

Elizabeth Blachrie Blackwell (?1707-1758) published 1737 her superb Curious Herbal: Containing Five Hundred Cuts of the Most Useful which are now used in the Practice of Physick To which is added a short Descriptim of ye Plants and their common Uses in Physick. Describing the Turpentine tree (Plate 478) she (or her at the time imprisoned physician husband Alexander Blackwell) writes. The liquid rosin of this tree was preferred by the Ancients to all other Kinds..... It is frequently used for the Fluor Albus and the Gonorrhæa (Blackwell, 1739; Petroianu & Lorke, 2021).

3.2. Terebinth and the Scent of Violets

The popularity of terebinth for treatment of urethral discharge was also likely associated with its ability, when inhaled or ingested, to confer to the urine the fresh scent of violets.

The earliest **specific** reference to the scent of violets (we have been able to identify) is from **Michel de Montaigne** (1533-1592) describing his voyages: in Rome (November 1580), affected by renal colic, he is treated by **Cardinal Rambouillet** (1530-1587), the personal physician of the French ambassador to the Holy See with terebenthine de Venise. Montaigne notes somewhat sarcastically that he observed no other effect than a smell of violets (*urine a la violette de mars*) in his urine (**Montaigne, 1967**).

Dating around the same time (1595) is a case history published originally in Latin by the Swiss physician **Felix Plater** (1536-1614), Professor in Basel: he prescribes terebenthine and *I urine prendra l'odeur de la violette* (the urine will take the smell of the violet) (**Plater, 1660; Petroianu et al., 2018; Al-Tel et al., 2020; Aloum et al., 2021**).

A specific reference to the connection **gonorrhea-terebinth-violet scent** is to be found in the “*Humorous Tales of Lord Gaulard, noble of the Burgundian Franche-Comté*” published (posthumously) by **Étienne Tabourot des Accords**, (1549-1590) in Paris, 1614. The noble-man Gaulard states in a conversation to “.....have the ability, sometimes when (he) pees (his) urine to smell like violets of March. On which, a young lady that heard that those who eat terebenthine to heal the chaude pisse, have urine smelling the same, smiled sweetly” (**Tabourot, 1614**) (**Figure 5**).

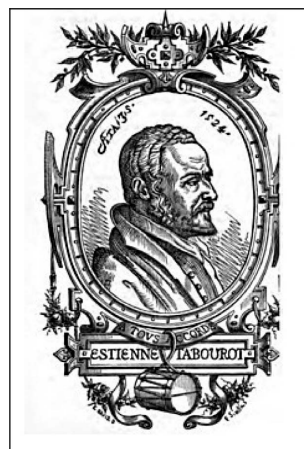


Figure 5. Étienne Tabourot des Accords, (1549-1590) author of the humorous tales of Lord Gaulard.

It is obvious that by the 16th century in Europe this knowledge was common and terebinth ingestion was the drug of choice for gonorrhea treatment. Terebinth use in promiscuous milieu is both mentioned in literature (**Tabourot, 1614; Heinrich Heine, 1844**) and well documented in scholarly publications of the XXth

century pre-antibiotic era (Stekel, 1912; Petroianu & Lorke, 2021).

3.3. Terebinth and Cleopatra

One of the anecdotes circulating in both lay and scholarly publications is that Cleopatra VII (69 - 30 BC), the last Ptolemaic ruler of Egypt, probably best known for her love affairs with Julius Caesar (100 - 44 BC) and Marcus Antonius (83 - 30 BC) used terebinth to augment her attractive power and influence. Terebinth resin was widely used in Antiquity and thereafter, both for medicinal and wine preservation purposes. It is almost certain that the effect of ingestion on the scent of urine could not have gone unnoticed. Considering the importance placed on smelling good by Egyptians, Greeks and then Romans, it appears likely that attempts at manipulation would have been popular or simply mandated by market forces. While the upper class would have been in a position to afford oil of turpentine, the general population was likely to enjoy the similar benefits by indulging in the turpentine containing resinated wines which were standard in those days.

While from a practical point of view such use would have been perfectly possible for the Queen, there is, to our knowledge, no contemporaneous hint at such practice. Turpentine ingestion for this specific purpose is attributed to Queen Cleopatra much latter by English physician Edward Brodie **French** (1912-2000) in a chapter on Alimentary and Genito-Urinary System in Macleod's *Clinical Examination* and repeated (without citing sources) in a later edition by **John Apley** (1908-1980) and Australian-American Wilfried Niels **Arnold** (1906-2014) in his book on van Gogh (French, 1964; Apley, 1973; Arnold, 1992).

Edward Brodie was the grand-son of Henry Hutchins French (1849-1917), a chemist-pharmacist from Florenceville in Surrey, owner of a successful brokerage business of colonial goods. As such, early exposure to exotic volatile oils and fascinating stories about Pharaonic Egypt might have been the source that ignited his phantasy. His uncle, Herbert Stanley French (1875-1951) i.a. physician to his Majesty's household, authored a book titled *Laboratory Methods and Tests* where he states that after administration of turpentine the urine takes the smell of violets (French, 1913). Interaction with him and his stories, as well with those of his father, Ronald Edgar French (1880-1949), also a distinguished physician, might also have contributed.

3.4. The Copaiba Era

Pedro Álvares Cabral (1468-c.1520) landed 1500 in what is now Brazil and laid claim to it in the name of King Manuel I of Portugal. Eventually exotic products from the New World reached Europe and became part of the pharmacologic armamentarium. Among the first and many physicians to recommend copaiba balsam for gonorrhea treatment we count **Willem Piso** (1648) (1611-1678), **Michael Ettmüller** (1680) (1644-1683), **Emanueli König** (1708) (1658-1731), **John Quincy** (†1722) and **Benjamin Bell** (1792) (1749-1806), to name only a few.

Copaiba balsam became the favorite treatment for gonorrhea, at least for those who could afford and tolerate it (Piso, 1648; König, 1708; Quincy, 1722; Bell, 1792).

Copaiba balsam is the sap (oleoresin) collected from the trunk of South American *Copaifera* trees. The balsam is steam distilled to give copaiba oil, a yellowish liquid with a characteristic odor and an aromatic, bitter taste. Copaiba essential oil is a complex mixtures of monoterpenes and sesquiterpenes, β -bisabolene, β -caryophyllene, α -bergamotene, α -humulene and α -copaene being the major components (Leandro et al., 2012) (Figure 6). Being a natural product, the individual content varies dramantly). Copaiba oil is classified as non-toxic (Tisserand & Balacs, 1995).

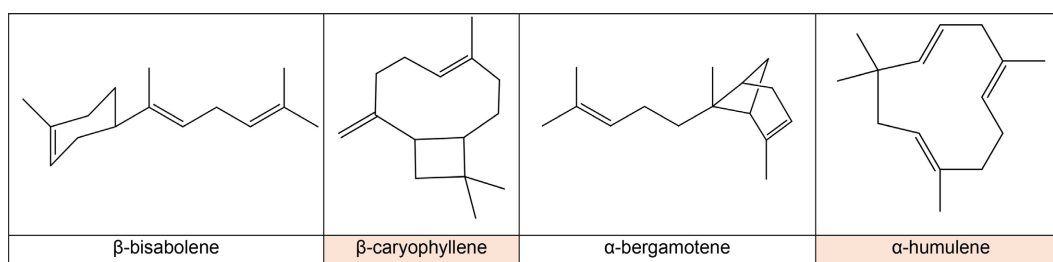


Figure 6. Copaiba essential oil is a complex mixture of monoterpenes and sesquiterpenes, β -bisabolene, β -caryophyllene, α -bergamotene, α -humulene and α -copaene being the major components.

3.5. The Cubeb

The trade activities of the Dutch in the Far East (*Vereenigde Oost Indische Compagnie*, VOC) culminating with the establishment of a permanent trading post in Java (1603) increased the availability of products from that part of the world (cubeb, *Hardwickia balsam*). In Hunter's *Treatise on the Venereal Disease*, Philip Ricord (1800-1889) summarizes the situation at the end of the XIXth Century: "After copaiba, we must rank cubebs.Since it is cheaper, and more easily obtained...., it generally deserves the preference..... The turpentine....are much less powerful" (Hunter, 1853).

Piper cubeba (tailed pepper; French *poivre à queue*; German *Kubebenpfeffer*, *Stielpfeffer*): Cubeb was widely used to treat gonorrhea, especially in the English speaking world of the XIXth Century. The first mention of the pepper as possible treatment is from none other than John Crawford, Esq. Surgeon, Honourable East India Company's Service, Bengal (1783-1868). He writes "I beg leave to communicate to the public, through your Journal, that the cubeb pepper has been for the last three years used by European practitioners on the island of Java with wonderful success, in the cure of gonorrhea virulenta and gleet." Crawford does not claim credit for the discovery as he states "there is little merit to be ascribed to any individual for the discovery..... for the history of It..... is as follows. An officer of the Indian army, sailing up the Ganges, contracted an inveterate gonorrhea, and had recourse to the usual applications without effect. One of his Indian servants proposed the cubeb, and it was used with success" (Crawford, 1818). Crawford is

of course better remembered for signing the contract that made Singapore a British Colony.

The **Companion to the Latest Edition of the British Pharmacopoeia** from 1866 states that “*The unripe fruit of *Cubeba officinalis*, dried, imported from Java. Gently stimulant, with special direction to the urinary organs. Given in gonorrhea, most safely when the inflammation is confined to the mucous membrane of the urethra. For gonorrhea 1 to 2 drachms, of the powder, wrapped in moistened wafer paper*, three or four times a day*” (Squire et al., 1866) (Figure 7). In the *avoir-dupois* system the dram (drachm) weighs $\frac{875}{32}$ grains, or approximately 1.77 grams metric. The dose recommended is between 5 and 14 g daily.

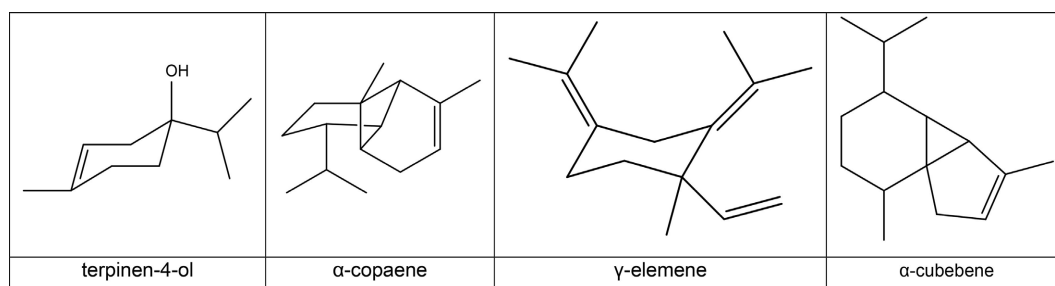


Figure 7. Cubeba essential oil is a complex mixture of monoterpenes and sesquiterpenes, terpinen-4-ol (42%), α -copaene (20%), and γ -elemene (17%) α -cubebene (6%) being the major components (Andriana et al., 2019). Being a natural product the individual content varies dramatically).

3.6. *Piper Angustifolium*

(spiked pepper: French: matico; Spanish: matico, hierba del soldado; German: Bambuspfeffer). This plant, widely used in the Americas by indigenous people, was popularized in Europe starting with the late 1830s by **Thomas Jeffreys** (1774–1852), physician at the *Liverpool Dispensary and Fever Hospital*, later President of the *Provincial and Medical Association*, forerunner of the *British Medical Association* (Jeffreys, 1839, 1845) (Figure 8). Matico and its essential oil was reviewed by Taylor, 2006 (Figure 9).



Figure 8. Illustration from Henri Ernest Baillon (1827-1895), *Histoire des plantes* (1866-1869), vol. 3, p. 472, fig. 510 by Auguste Faguet (1826-1900).

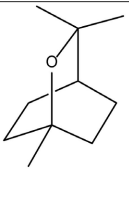
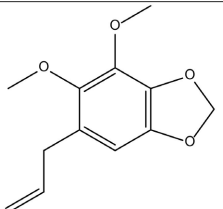
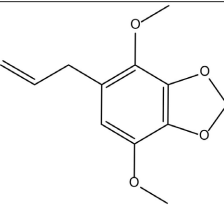
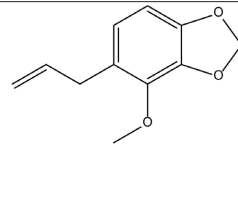
			
Eucalyptol	Dill-Apiole	Apiole	Croweacin
60%	42-74%	28-38%	29%

Figure 9. *Piper angustifolium* (matico) essential oil is a complex mixtures of monoterpenes and sesquiterpenes, Being a natural product the individual content varies dramatically. Dill-Apiole, Apiole, Eucalyptol and Croweacin seem to dominate. (Drissi et al., 2022).

3.7. Hardwickia Balsam

(Indian Copaiba): *Hardwickia binate*, also known by the Hindi name **Anjan**, is an Indian tree that grows some 25 m high. The *Anjan* (*Hardwickia*) was named after English soldier and naturalist **Major-General Thomas Hardwicke** (1756-1835), who lived in India for many years. The balsam is similar to Copaiba balsam (**Figure 10**) (Shingade & Kakde, 2021; Misra et al., 1979).

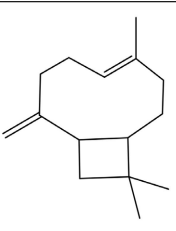
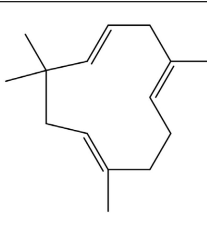
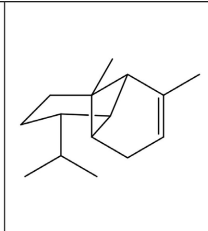
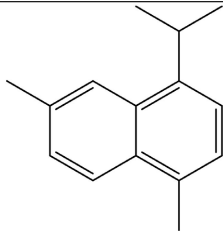
			
β -caryophyllene	α -humulene	α -copaene	cadalene

Figure 10. *Hardwickia* Balsam (Indian Copaiba; Anjan): *Hardwickia binate* is an Indian tree, *Hardwickia* balsam main constituents being β -caryophyllene, α -humulene, α -copaene, and cadalene. Being a natural product the individual balsam content varies dramatically.

3.8. Turpentine, Copaiba, Cubebs and the influence on Galenical pharmacy

While the availability of turpentine, copaiba-, cubeb- and *Hardwickia*-oil and resin increased over time, the tolerability was a major limiting factor. The 1871 *Dictionary of Medical Sciences* of **Amédée Dechambre** (1812-1886) describes the effect of copaiba as such that “*if taken by mouth, already repulsive by fragrance, it (copaiba) affects the palate by one of the most atrocious tastes one can imagine, soon to be followed by burning and acidity in the throat*”. Often the affected were so disgusted by copaiba (copahu) that “*there are those who prefer to keep the evil than to use the remedy*” (*qu’il s’en trouve qui aiment mieux garder le mal que faire usage du remède*) (Mothes, 1836). Along the same lines **John Laws Milton** (1820-1898) writes that “*perhaps without exception the most potent and generally used ...is copaiba, as nauseous and disgusting a drug as ever administered. Even*

if it were an infallible remedy, the odour it gives to the breath would be a serious obstacle. But it is far from infallible, it fails in at least half the cases it is given for” (Milton, 1876).

French pharmacists can be credited with the development of a number of innovations making administration of such remedies less punishing; the demand for turpentine, copaiba and related remedies was a driving force for such developments as gelatin capsules, gluten capsules and cachets (*velamenta amylacea*).

French pharmacist **Stanislas Limousin** (1831-1887) is credited with the introduction of cachets enclosing medicine and thus greatly facilitating their administration. In fact, such cachets were developed and used much earlier by the parish priest of the village of Pérols (curé of Pérols), **Joseph Lambert Arnal** (1798-1867), albeit not for venereal diseases but for malarial intermittent fever (Petroianu, 2022; Limousin, 1878).

3.9. Modern Antibiotic Era

First therapeutic successes were reported with **merbromin** (Mercurochrome-220; a derivative of the organic dye **fluorescein** complexed with **mercury** and **bromine**) (Figure 11). **Adolf von Baeyer** (1835-1917) synthesized fluorescein in 1871 from phthalic anhydride and resorcinol while **Edwin C White** complexed 1920 fluorescein with **mercury** and **bromine** yielding dibromo-hydroxy-mercury-fluorescein (White, 1920; Eyre et al., 1928). **Edmund B Piper** (1881-1935) of Philadelphia reported 1922 the first intravenous use of the substance in humans, to be followed 1923 by the demonstration of a bacteriostatic effect in animals by **Justina H Hill** (1893-1980) and **John A. Campbell Colston** (1886-1971) and clinical use by **Hugh H. Young** (1870-1945) and co-workers at the Johns Hopkins Hospital (Piper, 1922; Hill & Colston, 1923; Young et al., 1925).

Also of some therapeutic use was hyperthermia in the form of **Kasten-dampfbad**, or **Schwitzkasten** with turpentin, soon to be followed in the early 1930s by the introduction of sulpha drugs (sulfanilamide, sulfapyridine, sulfathiazol) and then cell wall antibiotics penicillin and ceftriaxone (White, 1926; Kampmeier 1983).

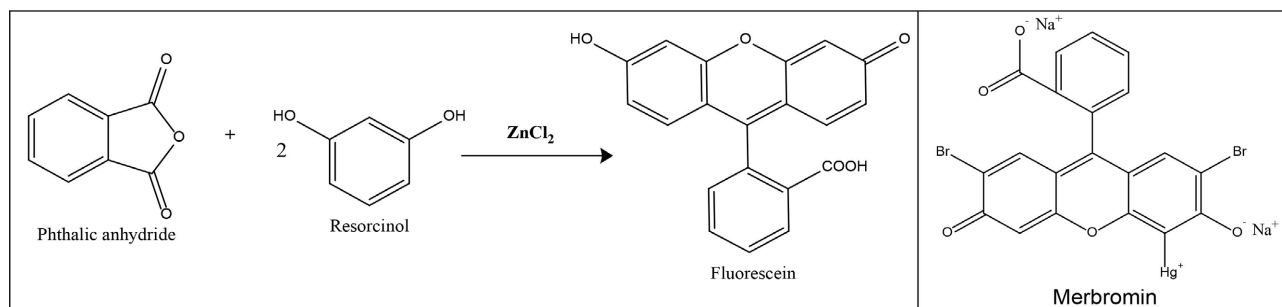


Figure 11. Adolf von Baeyer (1835-1917) synthesized fluorescein in 1871 from phthalic anhydride and resorcinol while Edwin C White complexed 1920 fluorescein with mercury and bromine yielding dibromo-hydroxy-mercury-fluorescein.

4. Conclusion

Terebinth resin was widely used in Antiquity and thereafter, both for medicinal and wine preservation purposes. It is almost certain that the effect of ingestion on the scent of urine could not have gone unnoticed. Considering the importance placed on smelling good by Egyptians, Greeks and then Romans, it appears likely that attempts at manipulation would have been popular or simply mandated by market forces. Terebinth remained the main therapeutic agent for gonorrhea until the advent of modern antibiotics. The discovery and establishment of trade relations with the New (West) Indies and East Indies increased the availability of alternative but not necessarily superior remedies (Copaiba, Cubebs, Matico and Hardwickia Balsam). The common denominator of all these cures was a horrible taste that inspired French pharmacists to improve tolerability. French pharmacist **Stanislas Limousin** (1831-1887) is credited with the introduction of *cachets* enclosing medicine and thus greatly facilitating their administration. In fact, such *cachets* were developed and used much earlier by the parish priest of the village of Pérois (*curé of Pérois*), **Joseph Lambert Arnal** (1798-1867), albeit not for venereal diseases but for malarial intermittent fever.

Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

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