The Fly in the Ointment: Cantharides in the Holy Infirmary? [1]

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Abstract

Cantharidin, extracted from some very colourful beetles of the Meloidae family, came with a sting in its tail. Although used as a panacea for a multitude of medical problems, it was recognised as a poison, and stringent measures were observed, both in its production as well in its application. It had also multiple side effects, some of which, particularly those that caused genital inflammation were specifically looked for. One of its purveyors included the Marquis de Sade who administered it to prostitutes in non-pharmacological doses. It was also used in simples in the Holy Infirmary of St John on Malta, where it was adequately stocked and used by the physicians there. The medical indications here, presumably, were dissimilar from those sought after by de Sade.

Keywords

Order of St. John, *Sacra Infermeria*, Malta, pharmacopeia, cantharides, Blister beetles.

Introduction

It happens all too frequently, that researching a particular topic in the archives involves going over thousands of dusty parchment folios, in an arduous process of reading, deciphering, translating, and making sense of the gist of what is being written about. Bits of ancillary information are collected which would be outside the scope of the main research question but may be the kernels of future projects and new research tracks. One such bit of information, a sentence in fact, resurfaced recently and

[1] This monograph is based on a talk given by the author on 15 September 2022 at The Royal Society of Medicine Surgery Section Malta Conference, held at Mater Dei Hospital, Malta.

became the scope of the present article. This was one item in a particular account review of the Hospitaller *ricetta* of Augusta of the year 1796-7, sent by the incumbent procurator Chiarandá to the *prudhommes* of the Common Treasury of the Order of St John on Malta. It was an annual account of the income and expenses of the *ricetta* and was an exercise that was sent every year from all the priories, commanderies and other land assets under the administration of the Hospitaller receivers.

> *'5 onze spese per rotoli cinque cantaridi commissionati dalla Venerando Consiglio per uso del Sagro Ospedale'.* [2]

This item indicated that the procurator had spent 5 *onze* to obtain 5 *rotoli* of cantaridi, a sale that was apparently commissioned by the Hospitaller Council at the request of the Holy Infirmary.[3] This item was one of thousands that are read and skimmed over, but this particular one included the word 'cantaridi' which continued to irk, if one forgives the pun. What was (or is) cantaridi? It seemed to be an expensive item as well, as noted in the accounts. After some cursory research, cantaridi was found to be today's cantharides, produced by a group of colourful beetles that secreted this obnoxious substance, which is perfectly lethal if ingested, but was used for medicinal purposes then, and was listed in the medical pharmacopeia of the time. Hence the link between this procured item and the Holy Infirmary. However, medical progress soon made this pharmacologic agent superfluous, except for one small thing. One side-effect of the product was vascular congestion of the peripheries including unrestrained sexual tumescence, and the product continued to be used in the boudoir, under the scintillating name of Spanish fly. Enquiries did come to mind on whether the Holy Infirmary patients developed such side effects and what did the physicians attending them, or even more, the straitlaced Hospitallers make of it at all.

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[2] Archives of the Order of Malta (AOM) 815, fol 8r. (Manuscript, Malta: National Library, 1796-7).

[3] The *onza* was a virtual denomination and was never minted as hard coinage. It was equivalent to two and a half Sicilian scudi. 1 rotolo (old measure) came to about 0.9 kilos of todays' weight.

The Place

The destination for the 5 rotoli of cantaridi (essentially 4.5 kilos containing the active ingredient cantharidin) was to be the pharmacy of the Holy Infirmary, the premier hospital of Malta, and arguably of Europe at the time. Grandmaster La Cassiere started to build the infirmary in 1574, opposite the fort of St Angelo across the harbour. The Hospitallers had started small, but in time, the Old Ward had become too small to accommodate all the patients that needed treatment, and another adjacent ward was built and was finished by the middle of the seventeenth century. Eventually the Old Ward and the Great ward were joined together and the whole place refurbished under Grandmaster Nicholas Cotoner in 1674. This new ward was cavernous, arguably the longest free-standing space at the time. It was 563 feet long and 35 feet wide and had single-occupancy beds (a first at the time) each with its own cupboard for the incumbent personal belongings and his commode.[4] Unusual for the time, it was thought prudent to segregate the patients according to the suspected aetiology of the condition; the Holy Infirmary was compartmentalised, physically and also by curtains, to ring-fence a fever section, a ward for moribund patients and those with suspected serious illnesses, another for dysenteries, a ward for patients who needed lithotomy, a section for surgical patients which included trauma, others who had undergone operations and haemorrhaging patients, a ward for psychiatric patients, and others who needed temporary isolation before being transferring to other places. Later on, a small hospital to cater for female patients was also built in the footprint of the Holy Infirmary (*Ospedaletto*).

The Drug

Cantharidin is derived from an insect, and the extract has been known as Spanish fly, although the insect is neither a fly, nor inhabits exclusively the Iberian Peninsula. Its colloquial name was also not a recent invention, as the insect from which the potent powder was made

[4] Paul Cassar, An English Visitor to the Holy Infirmary of the Order of St John in Malta in the 17th Century, *The St Lukes Hospital Gazette*, 3:2 (1968), 139-142.

in the eighteenth century was also known as *musca spagnuola*. The source includes several colourful species of the coleoptera order, from the Meloidae family, and is found in North African and European habitats. Species like *Hycleus Lugens*, an aposematically coloured beetle, secretes cantharidin, whereas another with the unequivocal name of *Lytta vesicatoria*, also produces cantharidin and its name also suggests the clinical reaction of this chemical. Cantharidin is the anhydride of cantharic acid. The cantharidin content of an average beetle is about 0.2 to 0.7 mgs of active substance. 0.1 mg of cantharidin will blister the skin if touched and ingesting an average of 10 beetles will prove fatal.

The use of Cantharidin goes back to Greek and Roman times. Since the days of Hippocrates, it had been used in a wide spectrum of medical conditions and illnesses including dropsy, rheumatism, carbuncles, leprosy, and gout. Even then, it was known that it would trigger an inflammatory process in skin and genitalia if given in increasing doses.

Spanish fly beetle - *Lytta vesicatoria* (Linnaeus, 1758)

Cantharides in the Early Modern Period.

The pharmacopoeias of the seventeenth and eighteenth centuries included cantharidin in their stock of essential pharmacological agents in reputable pharmacies. Beyond this, they also listed the main indications for its use, as well as tentative suggestions where the extract might prove useful. Other comprehensive texts also describe the preparation of the extract, suggesting a desire for some sort of uniformity to obtain a semblance of standardization. However, this was brought to nought

when different texts gave differing *modus operandi*, while, at the same time, attempting to encompass the whole spectrum of the then known pathologies.

Nicolas Lemery, well versed in the pharmacopoeias of his time, describes meticulously how the beetles were to be collected, exposed to the vapour of hot (vinegar) acid and killed, and then sun-dried for several days.[5] Once this process was done, the dead insects were crushed to a very fine powder.[6] It was suggested that while this process was being carried out, the person was to protect himself by using a mask to limit inhaling the penetrating corrosive, as well as to wear adequate clothing as skin contact with the powder would cause vesiculation.[7] Lemery suggested that the fine powder in the form of a paste could be applied behind the ears, on the nape of the neck, and over the interscapular region on the upper back depending on the medical indication. These were various, from regional eye, gum and nose diseases to apoplexy, general paralysis, catarrhal effusions, and sciatica. It was stressed that the extract was not to be used for internal use and that it was a poison.[8]

Another pharmacopeia lists cantharidin as being produced from a specific beetle, *Meloe vesicatorus*, and also gave its vernacular name of

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[5] Giuseppe Donzelli, *Teatro Farmaceutico, Dogmatico, e Sparigico del Dottor Giuseppe Donzelli etc..* (Venice: A. Bortoli, 1726). This text gives one method of producing the extract cantharidin: *Recipe pulpae cantharidum unciam femis, spiritus nitri optimi unciam unam. Digere spatio vigintiquatuor horarum, deinde adde spiritus vini camphorate uncias tres; fiat digestion per aliquot dies, & postea filtratioperagatur. Quae usurpatur ad urinam ciendam, ad renum & vesicae ulcera; gonorrhaeam; & arthritidem vagam scorbuticum.*

[6] Isabella C Grima, *'Medicine Maker and Dispenser' - The Apothecary and his Art in Early Modern Malta'*, unpublished PhD dissertation, Department of History, University of Malta (2017), 271.

[7] Bernardino Ramazzini, *Le Malattie degli Artefici*, (Venice: Domenico Occhi, 1745), 271.

[8] Nicolas Lemery, *Dizionario overo Trattato Universale delle Droghe Semplici* (Venice, Gio Gabriel Hertz, 1721).

Mosca Spagnuola.[9] It describes its mode of action in the treatment of medical ailments as an irritant, inflammatory agent, vesicular vehicle, ulcerating, and the cause of the excruciatingly painful condition of strangury. The extract could be used in various forms; as a tincture to resolve 'white tumours', joint rheumatism and, also as a wart remover from hands and feet.[10] It could be used as an ointment to promote vesicular ulcers,[11] and as an empastrium for the removal of warts and rheumatic and white swellings associated with joints.[12] As the latter application, it was also used to treat venereal and cancerous swellings. As a paste it could be applied over the sacrum in the lower back for the treatment of bladder paralysis and application in front over the pubes, for the management of retention of urine. It was also used topically over paralyzed legs, on the neck for the treatment of angina and behind the ears for ophthalmic problems.

Von Plenck's *Materia Chirurgica ovvero Dottrina del Medicamenti Soliti Usarsi alla Cura de'Mali Esterni*, went a step further, however. A small section in his book discussed non-topical applications for preparations containing *cantaridi, coccionella and aquavita*. 10 to 30 drops of this formulation were given with an infusion of barley, or a syrup of the root sap of the marshmallow (*Althaea officinalis*), together with the mucilaginous product of gum arabic. The dose was increased slowly, drop by drop, and the endpoint was apparently the appearance in the progressively agitated patient of urinary strangury.[13]

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[9] Joseph Jacob von Plenck, *Materia Chirurgica ovvero Dottrina del Medicamenti Soliti Usarsi alla Cura de'Mali Esterni* (Venezia: Giuseppe Orlandelli, 1783).

[10] A tincture consists of an extract of plant or animal material dissolved in ethanol. Solvent concentrations of 25-60% are common but may run as high as 90% in chemistry. A tincture is any solution that has ethanol as its solvent.

[11] An ointment or unguent is a semi-solid substance that has a topical application. It is usually a soothing preparation and is spread on wounds.

[12] An emplastrium is a type of dressing containing various types of medications, made of white leather/linen spread covered with adhesive plaster which will stick to any part of the body.

[13] von Plenck, 1783, *op. cit*., 250.

It is then strange that, although popular over the continent, Maltese pharmacies did not apparently stock this panacea. At least two pharmacy inventories, spanning the sixteenth and seventeenth centuries, did not list this extract in their inventories of over 200 formulations.[14] When compared to others, it seemed a costly preparation and possibly its indications were limited. It might be that the general Maltese physicians were somewhat circumspect in the use of cantharidin as a medication and that Maltese patients were possibly reluctant to be exposed to its myriad side-effects. Its existence and use must have been known to one and all as one particular pharmacopeia published locally gave a list of all the simples used in eighteenth century Malta, including cantharidin.[15]

However, physicians at the Holy Infirmary, responsible for the good health of members of the ruling faction of Malta, the Knight Hospitallers, not only knew about cantharidin and its indications but actively asked for it to be brought to Malta and used. A notarial contract between the *speziale* Giovanni Antonio Azzuppard and the Order of St John dated 7 July 1664 gave a price list of the medicines procured by the pharmacist to the Order and it included cantharidin. At that point, 1 lb (*libbra*)of the extract cost 2 scudi and 6 tari (one *Onza*).[16]

The Abuse

As with all medications, then and now, abuse and misuse of medicines could cause side-effects which result in morbidities and

[14] Paul Cassar, (1976), Inventory of a Sixteenth Century Pharmacy in Malta, *The St. Luke's Hosp. Gazette*, XI, (1976), 26-34. (99 items of materia medica stocked in the pharmacy). See also by the same author, Paul Cassar, Pharmacists, Patients and Payments in 17th Century Malta, *The Pharmacist*, 21 (Jan-June 1991), as well as Paul Cassar, Two Centuries of Medical Prescribing in Malta 1683 -1882. *The St. Luke`s Hospital Gazette*, 4:2 (1969), 105-112.

[15] Lorenzo Farigiani, *Taxa recens pretii omnium pharmacorum* (Malta, 1769).

[16] See also Grima (2017), *op. cit*., appendix XII, 373. Price list of medicines as recorded in the contract between the *speziale* Giovanni Antonio Azzuppard and the Order of St John (7 July 1664).

sometimes death. With cantharidin, one particular side-effect was actually sought for and promoted, and poisoning was usually seen after its ingestion for an aphrodisiac misadventure. Under the misconception that a larger dose would empirically result in a greater status of manhood, certain poisoning was a given. It was also difficult to gauge what constitutes use and abuse, as death usually overtook the recipient if it was the latter. The fatal dose of cantharidin varied between 10 and 65 mgs, and ingestion of 1mg/kg body weight invariably procured death. How the client died obviously varied. Concomitant with the whole spectrum of medical indications, there was an even bigger variety of complications, most of which proved fatal. Most commonly, the recipient died of renal failure, caused by a desloughing of the internal membranes; this caused lumbar pain, dysuria, proteinuria, haematuria, and renal failure. The local contact on ingestion also caused gastro-intestinal irritation and blistering, which resulted in dysphagia, abdominal cramps, haematemesis, vomiting, bloody diarrhoea, and vicious colic. Cantharidin could cause total loss of the mucosal lining of the digestive system which is fatal.[17] It is currently not approved by the Food and Drug Administration in the United States.

The complications of cantharidin, particularly the pubic congestion in men and women, were known from ancient times. According to the Roman historian Tacitus, Augustus Caesar's wife Empress Livia (58BC-29AD) supposedly slipped pulverised ground beetles into food to entice men into sexual indiscretions for which they could be blackmailed later on.

The French surgeon Ambroise Parè (1510–1590) described a case in 1572 of a man suffering from ‘the most frightful satyriasis’ after taking a potion composed of nettles and a cantharid extract. This is perhaps the same man of whom Paré relates that a courtesan sprinkled a cantharid powder on food she served to him, after which the man experienced ‘violent priapism’ and anal bleeding, from which he later died. The same

[17] DJ Karras, SE Farrell, RA Harrigan, FM Henretig, and L Gealt, Poisoning from "Spanish fly" (Cantharidin), *American Journal of Emergency Medicine*, 14:5 (September 1996), 478-483.

Paré also cites the case of a pre-Tridentine cleric who died of haematuria after swallowing a dose of cantharidin with which he intended to augment his sexual libido.

Catherine Monvoison, known also as La Voison, (1640-1680) was a French fortune teller and part-time poisoner who worked on commissions.[18] She was purportedly hired by Madame de Montespan, official mistress of King Louis XIV, to provide her with a concoction of dried mole, bat's blood and Spanish fly, which was to be laced on the royal food.

Giulia Tofana was to become the quintessential seventeenth century Italian widow maker. She specialised in concocted bespoke poisons, exactly tailored to the client's needs and aspirations; this included the premier item *aqua tofana*, compounded with care and sold to lady clients who, earlier on in their marital state, began to regret their union to their husband, and with hindsight, were marked men. One is unsure whether *aqua tofana* contained cantharidin, but it certainly included arsenic, lead and belladonna. It was a family run business, and in the end Tofana was allegedly responsible for 600 deaths, mainly of married men. Eventually fate caught up with Signora Tofana, when in 1659, she was executed by the Papal authorities.

The French writer Donatien Alphonse François, notoriously and better known as the Marquis de Sade (1740–1814), was also a proponent and frequent user of cantharidin. In one of his exploits, it was said that he gave aniseed-flavoured pastilles laced with Spanish fly to two prostitutes at a couple of orgies in 1772, poisoning and nearly killing them in the process. Eventually the law caught up with him, and he was sentenced to death for that (and a raft of other misdeeds, including the crime of sodomy), but was later reprieved on appeal.

[18] Jean Christian Petitfils, *l'Affaire des Poisons*, (Paris: Place des éditeurs, 2013).

Conclusion

The pharmacopoeia texts of early modern Europe are replete with information on the procurement, manufacture, medical indications, and complications as well as non-medical abuses of cantharidin. Although this information was certainly known to the local physicians and pharmacists, this dubious pharmaceutical product was not stocked and used locally, as indicated by two inventories of two pharmacies of the time. It was however procured by one particular *speziale* for the needs of some members of the Hospitaller Order of St John, and it was indeed stocked in abundant supply in the Holy Infirmary.

This monograph does present some minor itches that eventually will have to be scratched. What was the reason/s for the absence of cantharidin in what otherwise were two well-stocked pharmacies in Malta? The extract was listed in both the continental pharmacopeias as well as those printed locally in Malta. Was it only used by the higher echelons of society in Malta and why was it only stocked, it seems, at the Holy Infirmary? These are all queries that merit an answer, and this particular topic is certainly not exhausted at this point.