The explosive increase in syphilis throughout China and Russia during the past several decades represents a global public health threat for several reasons. 1) Most cases are undertreated and thus collectively offer optimal conditions for the emergence of resistant strains of the syphilis spirochete, *Treponema pallidum*. No penicillin-resistant strains have been recognized to date, but strains resistant to the second line antibiotic agents are now common. 2) The recent discovery of plasmids in *T. pallidum* raises the likelihood of plasmid transfer from other bacteria of various resistance genes, especially those directed toward penicillin-type antibiotics, currently the drugs of choice for syphilis. 3) Compounding the public health threat is the absence of antibiotic successors to penicillin. The development of new antibiotics would take more than a decade, hence the concern for interim measures to treat any emergent multi-resistant strains. Pre-antibiotic treatment of syphilis involved two mechanisms -- 1) agents which are directly toxic to *T. pallidum*, such as heavy metals and 2) fever induction in patients which reduces spirochetal survival, such as malarial therapy and bacterial pyrogens. The appearance of multi-drug resistant strains of syphilis in the absence of effective antibiotic therapy may require reviving and improving upon treatments used previously.

**Keywords:** syphilis; on-antibiotic therapy; resistant strains; plasmids; fever therapy; penicillin
Introduction

There are three reasons for interest in the therapies of syphilis before antibiotics. The first is the recent explosive increase in this disease worldwide. The second is the risk of strains emerging which are resistant to all current anti-syphilis antibiotics -- especially to penicillin and penicillin-related agents, the drugs of choice for syphilis currently. The third reason is the lack of new antibiotics to succeed the penicillin’s. Therefore, past therapies for syphilis (with modern improvements) may offer potential alternatives in the absence of effective successor antibiotics.

In the US after the advent of penicillin in the mid-1940s, the incidence of syphilis fell to 2.1/100,000 by 2000 [1]. But in 2013, the incidence tripled -- to 5.5/100,000 in the population at large and 9.3/100,000 in men, presumably due to increased male homosexual infections [2].

Elsewhere in the world there has been an ‘explosive resurgence’ of syphilis with levels of 32/100,000 in China at large and 77/100,000 in Shanghai in 2008 [3]. The most recent published figures for Russia date only to 1996, when the incidence had risen to 263/1000 throughout the country and 318/100,000 in St.Petersburg [4]. The economic, political, and social conditions accounting for these increases are discussed elsewhere [5]. Data on the overall prevalence of syphilis in India, Indonesia, South America, Africa, and other developing countries are not readily available, but the incidence has likely risen there also.

2. The Potential Development of Multiple Resistant Strains of T. pallidum

The optimal drug for treating syphilis is penicillin or one of its derivatives -- all containing a crucial but vulnerable β-lactam ring. Bacterial strains resistant to penicillin possess the enzyme β-lactamase, which disables the β-lactam ring. No penicillin-resistant strains of T. pallidum have yet been reported, but they seem inevitable from a genetic perspective, as explained later. Persons allergic to penicillin are treated with second-line antibiotics -- e.g., macroides (azithromycin, erythromycin, spiramycin) and tetracyclines (doxycycline, etc.) [6]. Strains of T. pallidum resistant to these second-line antibiotics have appeared. For example, azithromycin resistance was found in 77.3% of the T. pallidum specimens isolated in San Francisco during 2006 [7].

The issue at hand is whether strains may emerge resistant to both penicillin-type drugs and the second-line antibiotics. Each syphilitic is a human incubator harboring in his/her gut and elsewhere a vast array of organisms which interact with one another and transfer genetic information among them via plasmids.

These are small pieces of DNA containing genes, some of which may code for a specific antibiotic resistance. For example, strains of Neisseria gonorrhoeae acquired resistance to penicillin via plasmids encoding β-lactamase activity, which came fromampicillin-resistantstrains of Haemophilus influenzae [8].
The discovery in 1981 that plasmid DNA exists in *T. pallidum* indicated that it has the potential to acquire resistance to penicillin by genetic mechanisms frequently used by other bacteria [9,10]. Another example of plasmid transfer involves a strain of *Klebsiella pneumoniae* -- an enteric organism. It produces an enzyme which breaks down carbapenem -- a β-lactam antibiotic like penicillin G. This enzyme is coded by a plasmid and can move from *K. pneumoniae* to other bacteria -- e.g., to *T. pallidum*. The potential for such a transfer represents “a risk as serious as terrorism” [11]. A major therapeutic threat to the world would be strains of *T. pallidum* expressing multiple resistance -- i.e., to all forms of penicillin and backup agents. There are numerous examples of such multiple resistances in other bacteria -- i.e., in staphylococci, enteric bacilli, *Mycobacterium tuberculosis*, etc. Antibiotic resistance is regarded as the greatest current threat to global public health [12].

The most of the 36 million-plus people infected with *T. pallidum* are untreated and collectively represent a global incubator capable of spreading this infectious disease to others throughout the world. A strain of *T. pallidum* resistant to all available anti-syphilis antibiotics may ultimately appear somewhere and spread into the US population via international travel and human sexual promiscuity. The emergence of an epidemic of untreatable syphilis would elicit a search for new anti-syphilitic drugs, but there is little urgency to do so in advance of the need.

3. The Present Therapeutic Void: No New Anti-syphilis Antibiotics

Public health officials are concerned that the ‘developmental pipeline’ for new antibiotic agents ‘is empty’ because many pharmaceutical companies found this area unprofitable, focusing instead on drugs treating common chronic diseases.

Roche “fled the field in 1999.” Eli Lilly “dropped its antibiotic research in 2002,” and other companies joined them in abandoning the area [13]. The fear of drug-resistant bacteria has prompted the US government “to coax companies back to the field,” but the expertise and momentum they once had may take years to regain.

Based on studies by J.A. DiMasi and others, developing a drug from its discovery through clinical trials and final federal approval takes “more than ten years” [14,15]. Another paper estimated 23 years from “start of development” to “profit” [13]. This concern prompted a recent article entitled as a question --“A return to the pre-antimicrobial era? [16].

4. Recent Exploitation of Old ‘Cures’ for Other Infections

An example of an ancient cure being used today is the recent report of “A 1000-Year Old Antimicrobial Remedy with Antistaphylococcal Activity” [17]. It involved a specially prepared mixture of garlic, onion, and ox gall, which proved effective against the biofilm of methicillin-resistant *S. aureus*. This remedy was found in an Anglo-Saxon manuscript (a leech book in the British Museum) describing a cure for an eye infection. Another example of a therapy resurrected from the past is the 2015 Nobel Prize in Medicine awarded to YouYou Tu for determining the active component of an ancient Chinese herbal medicine which is highly effective against the malaria parasite. Arteminin has been isolated from the wormwood plant (*Artemisia annua*) [18]. Like the above recipe found in a medieval medical handbook or the
ancient Chinese herbal cure, the pre-penicillin treatments of syphilis warrant study. A modern assessment of some past ‘cures’ might suggest a potential, non-antibiotic therapy for a multi-drug resistant luetic infection.

The pre-antibiotic treatments of syphilis had an empirical beginning. Early in the 500-year long history of treating syphilis, physicians exploited clinical experiences with patients having skin conditions like that of this disease and were also influenced by prevalent folk notions about infectious diseases. With the newer knowledge of microbiology and immunology, more rational therapies were pursued later. This history becomes apparent when past treatments are surveyed chronologically as they appeared.

5. Syphilis Treated with Mercury

According to early medical accounts, the first cases of syphilis occurred in medieval Spain and Italy and presented with horrendous skin lesions erupting within several weeks of acquiring the infection. Many of its original names reflected the initial clinical presentation: *pustula mala*, *morbo serpentine*, *pestilentiali scorra* (decay), *las buvilla* (pustules), *bubas* (Spanish for bubo), the great pox (in contrast to smallpox). Fig.1.

![Fig.1. Head of a young man with secondary syphillis by Hans Holbein, the Younger.](image)
Foul smelling, purulent lesions were frequently followed by swollen gummatous bone lesions and often by a painful death. The ‘bad legge’ of Henry VIII (1491-1547) was a gumma -- syphilitic periostitis of the tibia [19].

The most widely read, early description of syphilis was that published in 1519 by Ulrich von Hutten (1488-1523), a German poet and satirist, who had contracted syphilis. He described “Boils that stood out like Acorns, from whence issued such filthy stinking Matter … the Colour of these was of a dark Green … the pain itself … was as if the Sick had lain upon a fire” [20]. Hutten complained of multiple bone lesions -- a flux at the top of his head, a draining sore under the last rib, a foul, painful ulcer in the middle of one tibia, and another above his right heel causing unbearable pain upon walking [21].

These offensive skin lesions and other manifestations of venereal syphilis were treated with mercury administered by one of three routes. Ointments containing mercury (unguentum Saracenicum) were described in a 1498 treatise by a doctor in the Spanish court [22]. Long before him, Arabist physicians (those writing in Arabic, including Persians and Jews) treated leprosy, eczema, and other skin afflictions with mercury inunctions [23]. These salves were introduced to Western Europe by the returning crusaders and medieval scholars who translated Arabic medical texts into Latin. A second form of mercurial treatment emerged from the efforts of Middle Eastern and European alchemists to make gold by firing various ores in furnaces.

They knew that heating cinnabar (HgS) releases elemental mercury into the air and probably suspected that this heavy metal was absorbed into their exposed skin. Doctors exploited this suspicion. Several sixteenth-century woodcuts depict an infected person sitting inside a round oven-like chamber over pans of cinnabar being heated at his feet.

Fig. 2

Fig. 2: Cinnabar oven for treating syphilitics by exposing them to mercury vapors.
A third route for mercury, *per os*, was promoted by Paracelsus (1493?-1541), a Swiss-German alchemist and physician, who prescribed pills of calomel (mercurous chloride, HgCl). The presumed curative dose of mercury in any form or route is dangerously close to a toxic level [24]. Over a long period, the absorption of too much mercury leads to ulcerations of the lips, tongue, palate and jaw with a resulting fetid breath, excessive salivation, and loss of teeth. The end-point in mercury therapy for syphilis was originally judged to be a copious secretion of saliva -- "some few liters per diem" [25]. It was reasoned that *pituita*, the body humor presumably causing the symptoms and signs of syphilis, was in excess and could be expelled via saliva. But this therapeutic complication was later avoided by using instead botanical agents newly discovered in the West Indies and imported from there and the Far East.

6. Guaiacum and Other Botanical Agents

A common medieval notion held that the cure for a disease could be found in the land where it originated. Syphilis has been thought to have been brought into Europe by Columbus’ sailors infected while in the West Indies. When it was first learned that natives there used an extract of bark from the local guaiacum tree to treat skin lesions, this seemed a possible source of medicine for healing syphilis in Europeans. *Guaiacum officinale* is an evergreen which reaches thirty or so feet high and has leaves like those of the arbutus tree. According to several sixteenth-century authors, this botanical treatment came to Spain around 1508 or 1517 [26]. An early woodcut shows a man chopping wood fragments from the log of a guaiacum tree, a woman boiling them to extract the active agent, and a doctor administering the potion to a patient in bed. Fig.3. Footnote 1.

Fig.3. Preparing a decoction from Guaiacum wood
A short-lived rival to guaiacum was China root (Smilax sinensis). This was imported into Europe around 1535 from the Far East among various new herbs and spices – cinnamon, cloves, ginger, and nutmeg. All were examined for potential medicinal properties. Locally grown rhubarb (Rhaponticumrheponticum) was also tried in treating syphilis. Andreas Vesalius (1514-1564), the Belgium anatomist, during his later career became prominent as physician to Emperor Charles V of the Holy Roman Empire and received frequent requests for medical advice from European doctors. His response to an inquiry about treatment for syphilis with China root was contained in a long letter later published as the China Root Epistle, 1546. He seemed skeptical of its medical value and later declared that “a China root decoction is far inferior to a guaiacum extract” [27]. Another new agent imported from China was sarsaparilla (Sassafrasizumu), which Vesalius penned as Spartam parillam. However, he recommended using familiar, local herbals “rather than those foreign roots and stumps [sold to us] so dearly” [27]. Here he had in mind locally grown rhubarb (Rhoponticum rheponticum). Footnote 2.

7. Malarial Fever Therapy

When a syphilitic was given guaiacum (or one of the above agents) in place of mercury, toxic symptoms of the heavy metal generally subsided and the person soon felt better. Some aspect of the body’s natural reparative functions may have contributed (see below), but the credit for the lessened symptoms was often given to the botanical. However, by the seventeenth century guaiacum was no longer considered a reliable cure for syphilis, although it was recommended by several notable eighteenth century physicians– Hermann Boerhaave (1668-1738) and Jean Astruc (1684-1766).

There is another explanation for syphilitics feeling better when mercury therapy was replaced by a botanical-- namely, the febrile response produced by the new therapy of guaiacum, China root, or sarsaparilla. All three are sudorific – i.e., produce sweating “with warmth in the stomach” [26]. Indeed, four centuries later, fever therapy became the prescribed therapy for neurosyphilis, as discussed shortly.

But first, of anecdotal interest here are the circumstances surrounding the cure of syphilis claimed by Benvenu to Cellini (1500-1571), a Florentine goldsmith and favorite of several popes. He had acquired syphilis “from the fine young servant-girl [he] was keeping” and claimed that “taking the wood” (guaiacum) cured him. However, near in time to this remission, he had gone shooting in the marshy campagna near Rome, where he contracted malaria [28]. Paul Luttinger speculated that malarial fever may have relieved the symptoms and signs of his syphilitic infection [29].

In the late 1800s, Julius Wagner von Jauregg (1857-1940), a Viennese neurologist and psychiatrist, had become interested in the impact of fever on psychoses when he saw an institutionalized female patient who had contracted erysipelas and who soon recovered from a severe mental illness which may have been tertiary syphilis. In the medical literature Wagner-Jauregg discovered other case reports of psychotic patients who improved after becoming infected with typhoid, typhus, intermittent fever, recurrent fever, erysipelas, or others diseases [30]. At the time it was expected that many persons with syphilis would develop symptoms and signs of general paresis (paralysis).Wagner-Jauregg found that Austrian army officers with syphilis did not become paretic if they had also contracted malaria or relapsing fever [31]. So convinced did he become of the benefit of fever in neurosyphilis that he initiated clinical trials of his own.
He induced fever in syphilitics with tuberculin (1-10 mg) and observed in many the remissions their neuropsychiatric symptoms and signs. Injections of Old Tuberculin induce a low grade fever lasting 18-36 hours in those who have had active or latent tuberculosis, which included over 1/7th of Europeans of that period [32,33,34]. But Jauregg’s most publicized therapeutic experiment involved injecting neurosyphilitics with a mild form of malaria (*Plasmodium vivax*), a fever-inducing parasitic infection which could be suppressed with quinine.

Other physicians soon began using malariotherapy in uncontrolled studies of neurosyphilitics and reported clinical success rates of 33% to 51% and only a 5% mortality [35]. Persons with tabes dorsalis (the ‘wasting’ paralysis of neurosyphilis) were hospitalized for three-weeks of Alternate-day fever therapy involving five-hour long hot baths and extended periods wrapped in heavy blankets.

In other such syphilitics, fever was induced with intravenous injections of malarial blood or a bacterial vaccine. Malaria therapy entailed injections of 2-10 cc of whole blood taken from a person with tertian malaria.

The subjects experienced 12-16 chills over that many days before the infection was terminated with quinine [36]. A 1931 medical text summarizes in a table 35 studies involving 2356 cases of general paresis treated with malaria and reported a 27.5% “full remission” [37]. The bacterial vaccine treatment involved a course of 18 to 23 injections of a killed typhoid organisms administered every second or third day and sufficient to produce a fever of 103° to 104°F [38].

This protocol was often repeated two months later. Clinical fever therapy gained experimental support from laboratory studies on the thermal lability of *T. pallidum*. This spirochete does not grow readily in regular bacterial cultures but can be propagated in the testes of infected rabbits, maintained in suspensions for exposure to various experimental conditions, and then tested for viability/infectivity by injection into other rabbits. Schamberg reported that rabbits given syphilitic inoculations did not become infected if then subjected to a hot bath of 45°C [113°F] for fifteen minutes on eleven consecutive days [39]. Weichbrodt and Jahnel also infected rabbits with syphilis and reported that spirochetes in their chancrees disappeared and scrotal syphilis was cured when the animals were promptly kept at a temperature of 42°-44°C for thirty minutes. Exposure to the higher temperature for a longer period was often fatal [40]. The human body can safely withstand a fever of 41.5°C to 41.7°C for five hours, but a temperature of 42.5°C (107.6°F) is dangerous for more than a short period [41].

Recall that 16th century syphilitics who were subject to mercury fumigation in oven-like chambers endured severe sweating conditions. Some died during the treatment. But for others who survived, the prolonged elevated body temperature may have ‘produced a cure’. In summary, fever was the common therapeutic denominator in the cinnabar-oven treatment, botanical sudorifics (guaiacum, China root), malarial infections (natural and iatrogenic), and bacterial (tuberculin) vaccine therapy.
8. More on Mercury and Other Metals

In the mid-nineteenth century, physicians resumed using salts of mercury as a treatment for syphilis, which was given then by parenteral routes. In the 1860s Guiseppe Profeta (1840-1910) injected luetics with calomel (mercurous chloride, HgCl) [31]. The bichloride form (HgCl2) was later given intramuscularly by Berkeley Hill (1834-1892), University College in London and by G. R. Lewin (1820-1896), Charité Hospital in Berlin [42]. During and after the First World War, mercury oxycyancide and colloidal mercury sulphide were administered intravenously [43]. But none of these produced convincing cures.

Besides mercury, Paracelsus had also promoted the clinical use of various other metals, such as arsenic, antimony, bismuth, copper, and iron. In 1863 arsenic acid was chemically linked to the dye aniline (aminobenzene) by a French professor of medicine and pharmacy, P-J-A. Béchamp (1816-1908), who tested the complex on luetics. More familiar is the work of the German bacteriologist/immunologist Paul Ehrlich (1854-1915) with atoxyl (sodium arsenilate), which had first been used in treating trypanosomiasis and only later syphilis. But atoxyl injures the optic nerve, causing blindness. This prompted Ehrlich to synthesize and test many other related organic arsenicals, of which two proved safe to use -- arsphenamine (Compound 606) and later neoaarsphenamine (Compound 914).

In the early twentieth century, the injection of bismuth salts was also introduced in the treatment of syphilis. In 1919, Wilhelm Kolle (1868-1935) reported that a rabbit retaining a deposit (“a plug”) of bismuth in one ear was resistant to infection by an inoculum of the spirochete. The animal became susceptible to chancre formation once the plug was excised, suggesting the prophylactic value of a chronic, slow release of this metal into the circulation [43]. In the 1930s, one treatment schedule for luetics included three intramuscular injections sequentially over a six-week period of arsphenamine, a bismuth salt, and a mercury compound. Evidence of this treatment persisted in the patient’s buttock indefinitely, since the heavy metals (Hg, Bi) remained visible as radiopaque spots on fluoroscopy or X-rays of the lower abdomen.

During the decades before the advent of penicillin in the mid-1940s, the clinical management of syphilis was the specialty of dermatologists, who spent “from one fifth to one third” of their efforts on this one disease. Each touted his own treatment protocols. One author covered Modern Clinical Syphilology in 1326 pages exclusive of the indices [43].

Apart from the trio of IM injections noted above, many other regimens were employed. For treating early syphilis, Harry Beckman gave intramuscular injections of arsphenamine (Salvarsan, Compound 606), mercury by inunctions, and oral potassium iodide [37]. In the treatment of early syphilis J.H Stokes and V.C. Garner administered 20-40 injections of arsphenamine in combination with bismuth. A British venerologist recommended 14 weekly injection of neoarphenamine with bismuth [43]. Another suggested Compound 914 and bismuth followed by iodides for two weeks. Five US syphilis clinics pooled their patient data in the 1930s and found a 6.5% cure rate based on physical examination and negative serologies after a six month observation period [43].
9. Iodine

In the early 1800s, potassium iodide was introduced for treating luetics. This therapy stemmed indirectly from the age-old remedy for goiter. The ashes of sea weeds and burnt sponge had been prescribed by Roger of Palermo (fl. 1210 AD) for relieving bronchocele (goiter). It was from the ashes of kelp that iodine was isolated in 1811 by a French chemist, Bernard Courtois (1777-1838) [44]. In 1819, J-F. Coindet (1774-1834) of Geneva began administering potassium iodide to goitrous patients. Because their bronchoceles shrunk in size, he speculated that iodine may cause general absorption of fibrous tissues of other diseases [45,46]. Such tissues in syphilitics include gummas, which are masses of epithelioid and giant cells surrounded by fibroblasts and infiltrated with capillaries, lymphoid cells, and infectious spirochetes. Favorable clinical results were reported from Dublin and Paris. Syphilitics also reported general relief after bathing in the warm iodine springs at Halle, Austria [47,48].

In 1831, Robert Williams, a professor of chemistry at the Royal College of Surgeons, advocated treating luetics with potassium iodide, expecting an effect on their gummatous lesions [47]. Favorable results from administering KI were reported in 1836 by William Wallace (1791-1837) of Dublin and confirmed by Philippe Record of Paris [48].

However, iodides have “no [direct] spirillicidal action” [43]. It was suggested that they might render gummatous lesions more penetrable by potent antisyphilitic agents [37,43]. In any cases, the supposed beneficial effects prompted the admonition, “When one doesn’t know the how and why, then one gives iodine” (Wenn man nicht weiss Wieso und Warum, Dann gibt man Jodkalium) [49]. The above notion of enhancing penetration explains why many later syphilologists included iodide along with arsphenamine and heavy metals (Stokes 1934).

10. Penicillin and Other Antibiotics

In 1928, Alexander Fleming (1881-1955) observed lysis of bacterial colonies growing on a nutrient agar plate which had become contaminated with Penicillium notatum. The mold released a factor into culture medium which inhibited the growth of many common pathogenic bacteria. A decade later Howard Walter Florey (1898-1968) and Ernst Boris Chain (1906-1979) isolated penicillin and showed in animal experiments that it cured various bacterial infections while being non-toxic to the host. During the early 1940s, production of penicillin was begun at Oxford and soon developed on an industrial scale in the United States. Later studies showed that penicillin was the most effective chemotherapeutic then known against pus-forming cocci, many bacilli, and the treponemes [50]. Penicillin approximated the magic bullet (the therapia sterilisansmagna) sought previously by Ehrlich for syphilis. Three classic papers demonstrating its clinical effectiveness against this disease were published together in 1994 [51,52, 53].

11. An Additional Concern

Apart from the threat of penicillin-resistant strains of T. pallidum emerging, a remote worry is whether virulent strains could appear producing the horrendous clinical states and early deaths reported when venereal syphilis occurred in Europe during the several the decades after Columbus’ first voyage.
An epidemiological explanation for this initial picture is that the population then had little or no natural/herd immunity to this newly imported disease. It is difficult to judge herd immunity to syphilis in present day populations.

R.J. Knell suggested that in the early 1500s those syphilitics with grossly repulsive skin lesions had fewer sexual encounters for transmitting the Columbian strain, which then faded from the population leaving the milder endemic European strain [54]. If this was the explanation, then such a highly virulent treponemal strain might one day spontaneously reappear as it did in Columbus’ time but perhaps would be replaced ultimately with a less offensive strain by the social selection of sexual partners.

12. Conclusions

As noted earlier, while *T. pallidum* strains resistant to second-tier antibiotics now exist, no penicillin-resistant strains of *T. pallidum* have yet been reported [6,55]. But their eventual clinical appearance seems inevitable. Their presence would be suggested if an acutely infected person did not respond clinically to penicillin therapy. Such resistant strains may already exist somewhere in the millions of untreated syphilitics but could only be verified by expensive laboratory/rabbit studies.

The early treatments of syphilis might be considered if ever strains of *T. pallidum* resistant to both penicillin and the back-up agents are recovered from a patient. Fever treatment (malariotherapy) was effective in relieving the signs and symptoms in many persons with neurosyphilis in the past, presumably because of the sensitivity of *T. pallidum* to high body temperatures. While syphilis therapeutics has been wedded to the concept of a ‘magic bullet’ killing the infecting spirochetes (*einemagische Kugel*), the other important consideration in this disease process is the host. Also to be exploited is the protection offered by the host’s immune response in the form of vaccines, a subject treated elsewhere [5].

**FOOTNOTE 1.** An early recommendation for guaiacum was presented in the 1519 book by Ulrich von Hutten. He received eleven courses of mercury with only painful results but later claimed a total cure after taking guaiacum for two years. However, his condition relapsed four years later, and he died at age thirty-five [26].

His medical story was read by Girolamo Fracastoro (1478/83-1553), an Italian physician, who was prompted to amend a poem he had composed by adding a third part about guaiacum. It related the story of a shepherd named Syphilus, who had contracted the loathsome skin disease but was cured with the botanical -- hence the disease’s later common name ‘syphilis’.

**FOOTNOTE 2.** In De contagion (1546), a treatise describing epidemics of his period,

Fracastorihad written that it “is characteristic of doctors to be always introducing novelties [new agents], since they thus acquire greater authority and make more money” [56].

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