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When early modern Europe caught the flu. A scientific account of pandemic influenza in sixteenth century Sicily

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Abstract. The year 1510 marked the first recognition of pandemic influenza. The disease arrived in Sicily along trade routes from Africa and spread along the Mediterranean coasts. When a new epidemic swept over Europe in 1557, afflicting Sicily, the physician Giovan Filippo Ingrassia pursued a new approach to pandemic control. Since an influenza pandemic was a public health emergency, he conceived pandemic planning as a collaborative process between healthcare officials and the Government. He also highlighted the importance of strengthening influenza surveillance as a means for the early detection of an emerging pandemic. While the Sicilian Government had to provide for the community in terms of prevention, treatment was a physicians' responsibility. On September 18th, 1558, Ingrassia held a public lecture introducing an innovative position as regards epidemiology and public medicine: territorial control was the answer to the chaos caused by epidemics.

Key words: history of influenza, epidemics, medical renaissance, sicilian medicine, Giovan Filippo Ingrassia

Introduction

Five centuries of documented influenza

Historians have identified a number of epidemic diseases that afflicted sixteenth century Europe, most notably influenza. Besides literally meaning 'influence', from medieval Latin influentia, the Italian word has also meant *epidemic* since at least 1504. In the mid-eighteenth century it was imported into English as the name for a respiratory infection with a wide range of symptoms. The medical word derives from the Latin locution *ab occulta coeli influential.*

In the late medieval age, the word appeared in Pietro Buoninsegni's description of the epidemics in the years 1357-58: «fu in ditto mese (August 1357) grande influenza di lunghe e mortali infermità in Firenze e nel contado, e morirono molti e buoni cittadini […] Cominciò una influenza di freddo che quasi ogni persona della città e distretto e dintorno s'infreddarono e molti ne morirono» (1, 2).

Although it seems impossible to be certain when the first influenza pandemic occurred, the year 1510 marked the first recognition of pandemic influenza (3). There are a few contemporary chronicles of this event. One written by Tommasino de' Bianchi (4, 5) represents an impressive first-hand account of the disease. It is helpful in the reconstruction of the history of influenza in 16th century Europe as well as graphically describing the dreadful symptoms, suffering, and pain: «Item […] in questo dì 13 lujo in sabato […] non ge reman de polastri in piaza, tuti o la mazor parte son comprati per amalati che son in Modena de una malatia che dura 5 dì con una gran febra, e doglia de testa, e poi se levano e non pare che siano quelli, ma ge reman una tosse teribile che ge dura forse 8 dì et poi se vano liberande a pocho a pocho e de le 10 caxade le 8 ge n'è de amalati et in tal taxe son tuti per tera, e nesuno non perisse» (6).

While contagion had been linked to a few diseases over the preceding 300 years, the notion of infection was almost non-existent in 1510. In effect, although

influenza has been known in Europe since the middle of the 13th century and there are some records documenting six visitations in the 14th century, and four in the 15th, it only began to be studied by the profession from the start of the following century. Only then records of erupted epidemics appeared, together with the circumstances which attended their outbreak and progression, and their characteristic symptoms. In the 16th century, the disease is reported to have prevailed epidemically nine times; in the 17th century, «we have accounts of twelve visitations; in the 18th, of sixteen; and during the present century, there have already been six. Of the epidemics on record, several, as those of 1510, 1557, 1732, 1743, 1782, 1803, and 1837, extended their range from Asia, through Russia and Turkey, to the countries of Western Europe, and, in some instances, to America […]. During the last 150 years, the disease has prevailed epidemically, at intervals varying from three or four, to ten or fifteen years» (7).

Unable to identify microbial agents or understand etiopathological entities, observers like Tommasino de' Bianchi probably did not suspect that these periodic epidemic fevers with coughing might represent a single continually re-emerging disease. The disease of the summer and autumn of 1510 was called, in various European locales, cephalie catarrhale, coquelicot, *poppy* (perhaps because opiates were used to treat it), tussis quinta, or words indicating "hoods", such as capuchon, cocoluccio, coqueluche, cuculionibus, or cucullo, since those affected by the illness seem to have worn coverings over their heads (8).

The 1510 pandemic was followed by recurrent episodes of apparent "seasonal influenza" and by two additional influenza pandemics in 1557 and 1580, resulting in well-documented descriptions (7) 16th century chroniclers recorded how the disease caused moderate mortality describing the basic features by which we know influenza today (9).

Contagion in the early modern era

In July and August 1510, a *gasping oppression* with cough, fever, and a sensation of constriction of the heart and lungs began to rage, seemingly everywhere at once. The disease spread to almost every part of the known world, from Asia to Africa, Italy and France. It burned out soon after it started and it had a high attack rate but few recognized deaths, these occurring mostly in children or after excessive blood-letting (10), a common treatment for febrile and other diseases. To observers, influenza came to be recognized as a distinct disease with consistent clinical features including acute onset of fever, headache, cough, and myalgia, with uncommon complications that included pneumonia. Its epidemiologic features were understood to include explosive spread with high attack rates and directional movement along travel or trade routes, prevalence in a town or city for no more than four to six weeks, appearance at unpredictable intervals and at any time of year, and low-to-moderate mortality. No plausible infectious disease theory would be proposed until Fracastoro's great book *De contagionibus* published in 1546*;* it took another century for microbes to be discovered and two more to link microbes to human diseases (11).

For centuries, influenza represented an important subject of study and statistics, with its variable symptomatology yet conforming to a pattern, and with mortality rates ranging from low to very high. In many respects, it remains even today an inscrutable menace. In the past, indeed, any of the foregoing epidemics was *influenza*. Many observers had attempted to construct pandemic chronologies, but this was difficult before the late 1700s. Only then a new interest arose in cataloguing and differentiating epidemics, as well as the emergence of international medical literature (12). In effect, influenza pandemics have been reported for at least five centuries, with inter-pandemic intervals averaging approximately 40 years (13).

An important nineteenth-century source provides the survival rates to influenza epidemics. Using the existing data from 1173 until 1875, the German physician and medical historian, August Hirsch (1817-1894) drew up a chronological table divided by year, epidemic season and the European regions in which the disease occurred, and affirmed that influenza held a prominent position among the acute infective diseases by reason of its wide prevalence in space and time. The history of the disease: «may be followed into the remotest periods from which we have any epidemiological record at all, and its geographical distribution, in so

far as we may trust the information before us, extends over the whole habitable globe» (14, 15).

Pandemic influenza in 1557

The pandemic of spring 1557 that hit both sides of the Atlantic was the first documented global involvement (16). Unlike the previous one, this was highly fatal, with deaths recorded as being due to *pleurisy and fatal peripneumony*. It first infested Asia, then Constantinople, and having spread all over Europe, afterwards attacked America. Before autumn 1557, it simultaneously hit all parts of Spain so quickly that: «the greater part of the population in that Kingdom were seized with it almost on the same day» (17).

Thomas Short described the epidemic based on contemporary reports, the disease: «came from the land Melite in Africa, into Sicily; so into Spain, and Italy […]. It attacked at once, and raged all over Europe, not missing a family and scarce a person. A grievous pain of the head, heaviness, difficulty of breathing, hoarseness, loss of strength and appetite, restlessness, watchings, from a terrible taring cough. Presently succeeded a chillness, and so violent a cough, that many were in danger of suffocation». According to this report, there were no mortalities except for some children; the most useful therapies were bole armoniac, with oily linctus's pectoral troches, and decoctions (18). The epidemic was preceded by a *moist* air and swept once again through Europe in 1557, this time apparently originating in the Far East, and it came to be designated *febris catarralis* (11). Parish registries in England record a high mortality rate from 1558 to 1560, representing the first documentation of numerous influenza deaths in a population, and confirm that the disease prevailed for at least two years (19).

A public lecture on influenza in Sicily

From the second half of the 15th century to the 16th, this age of cultural and scientific rebirth opened up new frontiers, not only for medical and pharmaceutical science but also for healthcare. Safeguarding health became a common policy of all those in power in the different States presiding over the Italian peninsula, and throughout Europe.

The 1557 epidemic, just as before, moved westward from Asia, crossing Malta, and invading Sicily (20). During the second half of the sixteenth century, the autonomy of the *Protomedicato* on this island would allow Giovanni Filippo Ingrassia (the Sicilian Protomedicus) considerable freedom to intervene in public health matters and also in his dealings with the highest officers of the Kingdom. In the years he spent in charge of the health of the island, Ingrassia reorganized the practice of medicine and established the institutional framework of the *Protomedicato*: from that moment on an office designed to consolidate public health functions under State control. Its sphere of action encompassed not only the rules about the exercise of medicine, but also the social life of the Kingdom, including not merely health, but also hygiene and poor relief, thereby bridging the gap between old medical theories and innovative practice in early modern Sicily (21). Obviously, infectious diseases were unremitting. Despite this, the Protomedicus had a great new vision; in his role as the authority in charge of public healthcare, he expressed a heartfelt wish for the continued education of physicians. He also insisted that medicine be considered a scientific discipline, one aimed at achieving objective knowledge and avoiding subjective interpretations to guarantee the best treatment. The goal was to develop healthcare policies, as well as to encourage healthy lifestyle behaviours of the population. Since epidemics remained the main public health problem, he radically overhauled the old approach towards prevention. His main concern was to draw up a framework for public intervention, containing three fundamental elements. The first was to strengthen the pillars of public health, first and foremost the surveillance of infectious diseases; the second was to assess the impact of any public health measures implemented to reduce infectious diseases, thereby identifying effective methods for reducing rates of illness and death; in the third he developed a new approach to pandemics, the most serious public health issue, in order to reduce the vulnerability of individuals and communities.

We have to remember that, at the time, public health authorities were concerned only with plague, the disease that dominated the Renaissance, here con-

sidered the period from approximately the beginning of the thirteenth century to the middle of the seventeenth century. Italy was far ahead of other European countries in the field of public health, and gradually the local authorities began to control general standards of hygiene, registration of deaths, prostitution, movement of foreign merchandise and the selling of food. Public health measures were related to the social and economic factors of the time. The concept and practice of public health, however, was basically a creation arising from the perils of the plague and when this disease subsided in Italy, at the end of the eighteenth century, so did the controls. The physicians were a homogeneous group. However, the different social contexts in which they moved and the different types of patients they attended to were important elements of discrimination in a society with precise class distinctions. G. F. Ingrassia's attitude reflected a social reality: medicine had its rules and principles and they were true and well established (22).

When the severe influenza epidemic afflicted Sicily in 1557 and 1558, due to his great fame of physician, Ingrassia was asked by the Senate to intervene in an advisory capacity. While addressing the Government of Palermo, he made a statement: it was the doctors' responsibility to deliver therapies to individual patients. The administration had to ask advice on how to provide for the collectivity (23). Therapy was therefore supposed to be the domain of physicians, who were directly responsible to their patients, but the Healthcare Authority had the duty to care for the collectivity, dealing not only therapy, but also prevention. Ingrassia had to provide the Senate of the Kingdom of Sicily with practical advice on both aspects. As therapies were of no value in the majority of cases, Ingrassia generally put more emphasis on prevention than on therapy.

The 1500s was an age of prodigious decisions, a *turning point*, which marked the beginning of an effort to control and instill organization in healthcare. Health laws and regulations had yet to satisfy the need for prevention, the importance of which grew as it became increasingly difficult to control the terrible epidemics which slaughtered the population at regular intervals. At the first sign of an epidemic, a strict division of urban space was implemented, even the surrounding areas were closed off and no one was allowed to leave them, on penalty of death.

G. F. Ingrassia firmly sustained that territorial control was the answer to the chaos of epidemics. The short paper *Ragionamento sopra le infermità epidemiali*, contained *in nuce* all those principles he was to implement during the pestilence and can be considered a precursor. This earlier work, written some years before the great plague by this «politically active Palermitan plague fighter», and inspired by influenza epidemics, was published together with a tract about two monsters born in Palermo. The report about the epidemic was delivered before the city magistrates, and with admirable succinctness dealt first: «with the history of plague and epidemics in Sicily during the sixteenth century, the definitions of pandemic and epidemic, the signs of plague, notions of contagion, and 'atoms' in the air, all supported with copious references to Hippocrates, Galen, Aristotle, and other classical authorities. The final two folios, however, concern remedies directed to the ruler of Sicily: prayers for forgiveness of sins; purification of the air by burning fires; removal of stagnant water what was green and smelly at the drapery (Panneria) under the church of Santo Spirito; covering the stream of the tanners; cleaning water troughs of waste usually filled with dead dogs, cleaning public roads, purging stench with perfumes and big fires, covering wells, canals and aqueducts to stop fetid vapours polluting the air, and provisioning the population with good bread and meat (carne di gienco), which will be of the greatest protection for the afflicted poors as well as the healthy during an epidemic» (24).

In order to answer the Senate's questions on the origins of the illness and remedies against it, the Sicilian physician gave a public lecture in the presence of the city's powers that be on September 18, 1558. While not departing from the Hippocratic medicine, he introduced the doctrine of *seminaria principia*, learned from Fracastoro, which would be further developed in his treatise on plague in 1575. Ingrassia's ideas about epidemiology and public medicine were innovative. From the very beginning, Ingrassia offered us a taste of his modus operandi *per causas*, which validates the originality of his medical humanism, based on the rejection of any argument not confirmed by experience and the inductive-deductive research method applied to public health. He propounded that, along with the causes and consequences of the disease, it was

necessary to know the urban conditions in order to seek a remedy. As a public official, he knew the extent to which plans were ignored and regulations violated. City council protocols could only help to establish the scale of resources (human, financial, administrative) allocated to incentivise participation and to ensure a modicum of cooperation.

Two analyses of G. F. Ingrassia's essay

The Sicilian physician, Liborio Giuffrè, Head of the Medical Clinics of the University of Palermo, and fellow of the Royal Academy of Science in Palermo from 1886 (25), examined Ingrassia's report on the 1557 influenza epidemic, and conducted an exegetical study of the text. Since this had originally been printed together with another essay, it was not easy to find (26). Prof. Giuffrè affirmed that the city of Palermo had been the first in which influenza occurred in Italy. The Senate of the capital of the Kingdom of Sicily was so concerned about the occurrence of so many epidemic diseases that it petitioned Giovan Filippo Ingrassia to ascertain precisely what the contagion was, and what measures needed to be taken against this public health threat. The well-known anatomist had returned from Naples to Palermo a few years earlier, in 1553, to hold medical lecture. In 1558, G. F. Ingrassia's talk took the form of a "Proclama", being printed only in 1560 (27).

This prototype of a public lecture was addressed to Sicilian magistrates. By way of introduction, Ingrassia declared that he had been asked to discover the true state of the city, and the *causa primiera* of the contagion: «Illustre signor Pretore, et voi spettabili signori Giurati, le Signorie vostre ne fecero questa proposta, cioè che le dicessimo in che stato si trova oggi la Città, circa le infermità che corrono. Secondariamente qual sia la causa primiera, cioè donde proceda et habbia origine cotal mortalità di gente et concorso di infermitadi, quali regnano in questa città. Terzo che esito pensiamo che deggiano avere, cioè quando s'averanno a finire. Et ultimo che le volessimo dichiarare se ci è qualche rimedio, col quale potesseno sue Signorie al male presente occorrere, come quelli che hoggi hanno la cura di questa Città» (28).

Finally, he was asked to state whether the epidemic would soon come to an end and whether there were any remedies to it. As mentioned earlier, his reply contained an admonishment: therapy should be solely the concern of the doctor who was directly responsible to the patient; the Health Deputation should care for the community. However, duties and expertise could not be so neatly separated, because physicians concerned themselves not only with therapy but with prevention as well, and they were expected to provide the Health Board with scientific advice on both aspects (28).

Although the disease had quickly spread *universalmente per tutto il Regno* and it was clearly an epidemic, it was not particularly virulent. Ingrassia left a brief but comprehensive description of the influenza of 1557, enabling epidemiologists to use and compare it with the data available for other places for the same period . While not deviating far from the doctrines of his day, Ingrassia's approach embraced modern theories. He emphasised that those unacquainted with medical science, even if they were the governors of the city, should have absolutely no power to identify the therapies needed; their duty was to lay down the rules and ensure their compliance. It was doctors who had to devise and implement therapies (24).

Giuffrè concluded his essay by saying that he wanted to report all Ingrassia's proposals to demonstrate how they actually constituted the fundamental principles of public hygiene and health measures. The Sicilian Government was called on not only to care for the sick and poor, and to supervise comestibles and medicines, but also to take steps to remove all plausible causes of illness, such as dirty roads, the presence in the town of *fornaci* (furnaces), the presence of swamps and marshlands, the lack of drains for dirty water, and so on. This shrewd observer highlighted a key issue: environmental pollution. G. F. Ingrassia described the pollution of the water in wells situated near public and private latrines. Even in the 16th century, he tried to prevent and abate such insanitary conditions by tackling the problem of public sanitation; consolidating the water and sewer system, along with other measures aimed at improving the hygiene and cleanliness of cities. In terms of epidemiology and public medicine, the ideas of this illustrious Protomedicus represented the pinnacle of achievement in the second half of the six-

teenth century. He stood out in this field no less than in that of anatomy, in which his important discoveries led him to be regarded as much more than a scientist, but as an innovator contributing to the progress of science.

The second exegete of Ingrassia's discourse is a scholar of our time, Luigi Ingaliso. He confirms the ideas expressed in the essay containing a description of symptoms suggesting that the Sicilian epidemic was one of the first cases of influenza in Italy (29). Ingaliso's thesis, widely shared, states that almost twenty years prior to the plague of 1575, Ingrassia had already analysed the causes of the spread of an epidemic, as well as drafting a prevention programme. Examining the text of the *Ragionamento*, it is possible to understand how the issues present in the *Informatione* on the origin of evil and possible remedies (30), had already existed from the mid-sixteenth century: the *regimento preservativo*, introduced by Ingrassia in 1575, had been proposed years before to the Senate of the city in the *Ragionamento*, and, almost twenty years after, was more effective in defeating pestilence than any treatment.

In determining prevention measures, it was crucial to establish the causes of the epidemic. On 18 September 1558, Ingrassia answered the questions posed by the Senate of Palermo about the nature of evil, the outcome and the remedies. In the *Ragionamento*, Ingrassia, while not departing from Hippocratic-galenic medicine, introduced the doctrine of *seminaria principia*, learned over the years by reading Fracastoro, which was to be developed further in the *Informatione*. Ingrassia's ideas represent the most innovative medical science in the second half of the 16th century in the field of epidemiology and public medicine, which is why the arguments of the Protomedicus can be summarised by the following questions: a) what state is the city in; b) what are the causes of the disease; c) how long will it be active and what may be the consequences; d) is there any remedy to it. He rejected all reasoning not supported by experience. In seeking the cause of the disease, he cites many examples of epidemics, distinguishing between *vera peste* and *febbre pestilenziale*, where the former is described as contagious and mortal; with possibly occult causes, maybe of divine or demoniac origin, or deriving from Astral influences. The 1558 influenza epidemic in Palermo was, instead, a *pestilential fever*, called a *pandemio*, i.e. a disease which can be contagious for the whole population. It was caused by «corrottione di cibi» (rotten food), but, some years after, Ingrassia was to classify diseases based on how the disease was spread (31, 32).

Conclusion

Ingrassia's medical theory was the basis of the Protomedicus' action during the plague years; his method was supported by keen vigilance, a strict quarantine policy, confining plague victims and suspects to the *lazzaretti*, as well as aiding the poor.

It is to be underlined that the culture of plague opened a new chapter in the history of medicine, as the study of this peculiar disease involved not only an attempt to understand its pathology, but also its modes of transmission and the social characteristics of the victims. Consequently, medical thinking evolved considerably due to the plague. Many academic medical treatises on the plague were published during the sixteenth century. From erudite definitions, remote causes and cures, physicians now discovered their most "valiant remedies" in public health: strict segregation of the healthy from the diseased, cleaning streets and latrines, addressing the long-term causes of plague-poverty. In the heartland of Counter-Reformation Italy, physicians along with those outside the profession questioned the foundations of Galenic and Renaissance medicine, even the role of God. Assaults on medieval and experimental medicine did not need to await the seventeenth century Protestant-Paracelsian alliance in northern Europe. Instead, creative forces planted by the 1575-8 pandemic sowed seeds of doubt and unveiled new concerns and ideas, even within that supposedly most conservative form of medical writing, the plague tract. Relying on Health Board statistics and dramatized by eyewitness descriptions of events and suffering, these writers created the framework for the plague classics of the eighteenth century. The crisis of 1575 «fundamentally altered doctors' approach to and thinking about plagues from individual patients to the community». Giovan Filippo Ingrassia, by including in his recommendations ordinances and decrees,

designs for building hospitals, quarantine orders, isolation of those infected, cleaning the streets, disinfecting houses, regulations for butchers, punishments for thieves stealing infected goods, was the first physician to pay attention to tracking a disease, tracing the possible paths of its arrival to a region and detailing its spread within neighbourhoods once it had entered a city, and improving public controls against the spread of the disease by every means possible. In his efforts to understand and to contain the disease, he anticipated the field of epidemiology, born in the nineteenth century (25).

In this context, the problems due to an environment in which men lived in poor housing in close proximity to rats and fleas were aggravated by malnutrition, Ingrassia's call to improve public hygiene was probably the most original contribution to sixteenth century thinking devoted to identifying the problems of Palermo and the proposed attempts to solve them by the urban modernization of the Capital. Despite this, the serious health problem of the discharge of stagnant waters, especially those outside the Royal Palace of Palermo, remained unresolved. Despite worsening hygiene conditions, the Protomedicus' petitions yielded no other result than the cleanup of the Papireto site. Only during the plague years, did the magistrates of Palermo order the marshes be dried to purify the air of the city, an action the Protomedicus had been demanding repeatedly for decades. Finally, we must point out that when this speech was published, this publication was a true bibliographic rarity and remained so up until the end of the 19th century (29). Moreover, this short essay deserves recognition as confirmation, if any was needed, of the role of Giovan Filippo Ingrassia as a forerunner in the history of science. In the period we have examined here, he assigned himself two tasks: first, to do his work, and second, to make political leaders aware of the risks. Just as in the past, preparatory efforts require resources. Only the political process can allocate them.

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