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CHAPTER OF BOOK THAT FORMS THE PROCEEDINGS OF A MEETING. Lipkin M. Current knowledge of the cancer latent period. Chemoprevention strategies during colonic cancer development. In Maltoni C, Soffritti M, Davis W. International Forum, The Scientific Bases of Cancer Chemoprevention, Amsterdam: Excerpta Medica; 1996: 61-71.

ABSTRACT. Abeloff MD, Gray R, Tarmey DC, et al. Randomized comparison of CMFPT versus CMFPT/VATHT and maintenance versus no maintenance tamoxifen in premenopausal, node positive breast cancer. An ECOG study. Proc Am Soc Clin Oncol 1991; 10, 43: abstr 47.

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EDITORIALE

La nostra rivista ha sempre perseguito l'obiettivo individuato sin dall'inizio: l'internazionalizzazione. È evidente che ciò sta accadendo perché, grazie all'impegno dei nostri autori, Medicina Historica viene letta e citata da studiosi e appassionati, oltrepassando i confini nazionali. Un'apertura internazionale che risulta essenziale per promuovere lo scambio di conoscenze ed esperienze che rappresenta la finalità principale del ricercatore: crescere e determinare le condizioni di crescita.

Con piacere informiamo i nostri lettori della crescente importanza nelle graduatorie delle categorie in cui Medicina Historica è inserita ("History", "History and Philosophy of Science" e "Medicine miscellaneous") come testimonia l'SJR di Scopus che in un solo anno ha raddoppiato il suo valore. Tutto ciò comporta un indubbio aumento di interesse verso la nostra rivista.

Crescere significa proprio questo: incrementare il numero di lettori e autori, aprirsi a un confronto sempre più ampio, migliorare la qualità della rivista e perseguire un concetto a cui tutti noi dovremmo affezionarci: "imprenditorializzare" la cultura per renderla più accessibile e produttiva e, anche, per accrescere la consapevolezza della necessità di valorizzarla. Quest'ultimo concetto, unito alle caratteristiche che già abbiamo imparato a recepire, siamo sicuri, determinerà un ulteriore sviluppo di *Medicina Historica.*

EDITORIAL

Our journal has always pursued the objective identified from the beginning: the internationalisation. It is evident that this is now happening since, thanks to the commitment of our authors, Medicina Historica is read and cited by scholars and enthusiasts, crossing national borders. An international opening that is essential to promote the exchange of knowledge and experience, which represents the main purpose of the researcher: growing and determining the conditions for progress.

We are pleased to inform our readers of the growing importance in the rankings of the categories in which Medicina Historica is inserted ("History", "History and Philosophy of Science" and "Medicine miscellaneous") as evidenced by the SJR of Scopus that in just one year doubled its value. All this leads to an undoubted increase in interest in our Journal.

Growing up means precisely this: increasing the number of readers and authors, opening up to an ever wider comparison, improving the quality of the Journal and pursuing a concept we should all become attached to: "entrepreneurializing" culture to make it more accessible and productive and, also, to increase awareness of the need to enhance it. This last concept, together with the characteristics that we have already learned to incorporate, we are sure, will determine a further development of *Medicina Historica*.

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Original article: history of medicine

The studies of blood transfusion and the attempts of its implementation into medical practice in 1800–1875: the fate of J.-A. Roussel's device in Russia

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Abstract. Since the beginning of the 19th century, physicians' interest to the study of blood transfusion has increased significantly. The experimental researchers of the first half of the 19th century paid special attention to the issues of intra- and interspecific blood transfusion. In 1860s numerous military conflicts in Europe led to the necessity of studying the issues of blood transfusion's practical application in medicine. A choice of donor's blood source (animal or human), type of blood for transfusion (whole or defibrinated blood), methods of preservation, stock and storage of blood became the main priorities of research during this period. Both blood transfusion experimental studies and human-to-human transfusions conducted in Europe and Russia in 1800-1875 have become historical, scientific and technical ground which preceded and largely determined the promotion and distribution of the first device for blood transfusion which had a commercial success. In 1873 the apparatus invented by a Swiss doctor Joseph-Antoine Roussel took the first prize at the Vienna World's Fair. Roussel managed to sell hundreds of copies of his invention to the armies of Austria-Hungary, Belgium, and Russia, taking advantage of the situation of political tension in Europe. The article presents the key circumstances of the implementation of Roussel's device in Russia in 1874, such as the results of its clinical trials, some financial aspects of the apparatus' acquisition by the Main Military Medical Department, etc.

Key words: blood transfusion, J.-A. Roussel, Russia

Introduction

For many centuries physicians, scientists, philosophers, religion leaders around the world saw amazing opportunities in blood transfusion for treating patients, rescuing dying men as well as for not such trivial purposes as youth regeneration, transferring talents, skills, and knowledge from old people to young ones (1). The unpredictability of the initial blood transfusions performed in the second half of the XVII century led to the prohibition of this procedure. In 1678, the Royal Society in London prohibited transfusions and the French parliament ruled it to be a criminal act. In 1679 the Pope also announced the ban on the procedure (2). The revival of the interest to blood transfusion in the XIX century is associated with the development of obstetrics, experimental physiology, and military surgery.

Statistic data accumulated during military conflicts in Europe in 1850-70s, such as Crimean war (1853–1856), Austro-Prussian war (1866), Franco-Prussian war (1870–1871) by the leading European and Russian physicians inexorably indicated that mortality from hemorrhage reached almost 75 percent of total mortality on the battlefield (3). Therefore, massive loss of blood became the most important issue of military medicine. We presume that the urgent need of blood transfusion practical application resulted in success of the Geneva physician Joseph-Antoine Roussel

(1837–1901) and his apparatus at the Vienna World's Fair in 1873. Roussel's "transfuser", which allowed, as its inventor claimed, to successfully apply blood transfusion in medical practice, became one of the winners of the exhibition in the in the section "Precise scientific devices and instruments of surgery". Taking advantage of the tense international relationships and the agreements between the leading European states (Russia, France, Austria-Hungary, and Germany) in 1873, Roussel managed to gain state orders and become the first official supplier of transfusion devices in the armies of Russia, Austria-Hungary and Belgium (4). For his services he was awarded the national Orders of Franz Joseph (Austria), Leopold (Belgium) and the Holy Prince Vladimir of the fourth degree (Russia) (5).

This study aims to determine the circumstances of Roussel's device acquisition in 1874 by the Main Military Medical Department of Russia for using the apparatus in Russian military institutions as a unique attempt of blood transfusion's mass practical application in medicine during the "pre-Landsteiner's" era.

Blood transfusion in Europe

The short survey of blood transfusion experimental studies and the first human-to-human transfusions in Europe and Russia in 1800–1875 reveals the development of historical, scientific and technical backgrounds which preceded and largely determined the promotion and distribution of the Roussel's device.

Blood transfusion in the XIX century was defined as an infusion of arterial or venous blood of one animal or human to another subject through intermediate tubes under the influence of natural blood positive pressure of donor or using device in which previously this blood had been collected (6, 7).

In the first half of XIX century mainly interspecific blood transfusions between cats, sheep, calves and dogs were practiced. Only by the second part of XIX century French surgeons J.-L. Prevost and J.-B. Dumas had associated the phenomena often observed during unsuccessful transfusions, such as uneven heartbeat, blood in urine and excrements, formation of transudates with the "poisonous" effect of foreign blood. The researchers proposed different explanations of toxic effects of such blood: J. Muller linked it with various shape and size of "blood balls", X.-M. Bishat – with the lack of oxygen in blood (7), Prevost and Dumas considered fibrin as a poison, Ch.-E. Brown-Sequard – carbon dioxide and obsolete parts of body (6), P.L. Panum – decomposition products of donor's "blood balls".

The other area of research was the identification of the factors that determine effectiveness of blood transfusions. The complications of human-to-human blood transfusion caused among researchers the discussions about two methodological issues of this procedure: the sources of donor's blood (human or animal) and what kind of blood – whole or defibrinated – is better to use. Bishat, F. Magendie, E. Martin claimed that animal blood must not be used for transfusions to human (7). Their opponents Muller, Brown-Sequard, Prevost, Dumas, Panum believed that interspecies transfusions are allowed after previous defibrinating of donor's blood.

The works of German Doctor of medicine and surgery Franz Fedorovych Gezellius (1840–1900) who lived in St. Petersburg (8) and British obstetrician Charles Egerton Jennings (1859–1930), member of the Royal College of physicians of London (9) have become two significant sources that allowed us to assess the scope and direction of blood transfusion studies and, especially, their application in medicine during 1800–1875 in Europe and Russia. Both physicians compiled the detailed bibliographic lists of the published papers and reports describing the blood transfusion experimental studies and human-to-human transfusions within this period. Also, in his research Gezellius conducted the statistical analysis of the particularities and outcomes of human-to-human blood transfusion which were carried out from 1819 to 1871 in Europe and Russia. Having analyzed both Gezellius' and Jennings' lists which contain more than 300 published academic papers and newspaper articles, we can assert that about 200 researchers had been studying different issues of blood transfusion and 248 blood transfusions of human blood had been performed in Europe and Russia since the beginning till the last quarter of XIX century (8, 9).

According to Gezellius' statistic data, 146 whole human blood transfusions were performed within

1818–1871, among which 79 were successful and 67 led patients to death (8). In 1818, the British obstetrician James Blundell (1790–1878) was the first one who carried out human-to-human blood transfusion in the 19th century (10). Twelve ounces of whole blood were transfused to the patient, dying of stomach cancer. The patient died approximately in 24 hours. The first successful human blood transfusion Blundell performed in 1825 to the parturient woman to prevent her death from postpartum hemorrhage (11).

The transfusion of defibrinated blood started to be applied in medical practice from 1850s. Gezellius reports that 102 such kind of operations were performed in Europe from 1851 to 1873. However, only 36 of them were successful (8). The high rates of mortality and the complexity of defibrinating procedure limited the spread of this method.

During the XIX century, the technique of blood transfusion was constantly improving, new apparatus and devices appeared, yet all of them were based on the principles developed by Blundell. In direct transfusion, the blood vessels of the donor and recipient were connected by tubes, the donor's blood pressure was the driving force. The formation of blood thrombus, clogging blood vessels, the inability to determine accurately the volume of transfused blood were the main drawbacks of this method. To increase the rate of infusion, various devices (syphons, syringes or cylinders) were used, in which the donor's blood was previously collected, and then it was transferred into the patient's veins under the influence of external (hydraulic or mechanical) pressure. These devices enabled to define the exact volume of transferred blood, but they increased its coagulating. In case with defibrinated blood, it was easier to transfuse and dispense it, but highly qualified assistants and extra time were required (3).

Despite the difficulties which arose and the contradictions among the supporters of different methods of blood transfusion, physicians and researchers were confident in prospects of using this procedure in medical practice. Jennings cited the results of human-to-human blood transfusions performed by Roussel in 1865–1877 as indisputable evidence in favor of using this procedure into medical practice. Roussel's results indicated a nearly 80 percent success rate of his device. The swiss physician claimed in his book that out of 50 direct blood transfusions performed by him, 26 cases were completely successful and 14 – partially (4, 9).

Blood transfusion in Russia

The study of blood transfusion in Russia was based on European research and largely repeated them. However, Russian physicians were wary of applying this method in practice: out of 248 human blood transfusions performed between 1818 and 1871, which were mentioned in published reports, only 5 were carried out in Russia.

Professor of obstetrics of the Imperial Medical and Surgical Academy in St. Petersburg (nowadays – Military Medical Academy named after S.M. Kirov) Stepan Fomich Khotovitsky (1796–1885) was one of the first Russian physicians who proposed using of blood transfusion in medical practice (12). His pupil Andrei Martynovich Volf (1791–1852), Russian obstetrician of German origin, performed the first in Russia human-to-human blood transfusion to a woman suffered from postpartum hemorrhage in St. Petersburg in 1832 using Blundell's method and device (13, 14). He described his successful experience of blood transfusion in the report of the Society of German physicians in St. Petersburg in 1832. However, the paper was published only in 1842 (15). Other researchers, such as academician Ilya Vasilyevich Buyalsky (1789–1866) and F. Gezellius doubted the scientific reliability of results claimed by Volf because he did not specify the important details of this procedure (the amount of transfused blood, the exact duration of the procedure, etc.) in the paper[1].

In 1830s, the inception of experimental studies of blood transfusion in Russia is associated with Buyalsky, a prominent surgeon, medical Academician, Professor Emeritus of Imperial Medical and Surgical Academy in St. Petersburg. Being aware of European prohibitions of blood transfusion, he previously obtained the permission of Medical Council of the Ministry of Internal Affairs[2] that "such kind of operation is allowed

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[1] However, nowadays April 20, the date of the Volf's successful human-to-human transfusion, is celebrated annually in Russia as the national day of blood donor.

[2] The main purposes of this institution were evaluation and implementation of scientific medical research.

and can be conducted (performed)" (16). As most European researchers of that time, he recommended to transfuse the whole venous blood using Blundell's device. Moreover, Buyalsky improved it: he immersed a siphon in warm water to maintain the normal temperature and fluidity of blood which coagulating clogged the tubes, cannulas and holes.

Following Buyalsky Professor of physiology of Imperial Moscow University Alexey Matveyevich Filomafitsky (1807–1849) started to conduct experimental studies in hemotransfusion. The first fundamental work in Russia named "A treatise on blood transfusion as a single mean in many cases to save a dying life, complied in historical, physiological and surgical relations…" was published in 1848 as a result of his 13 years studies (17). Unlike Buyalsky its author was a proponent of transfusion of defibrinated blood.

Filomafitsky explained the cautious attitude of Russian physicians to blood transfusions in medical practice by the lack of knowledge of the blood's physiological functions and unpredictability of the consequences of this procedure. "Before surgery can come up with the easiest and the safest way of blood transfusion from a healthy man to a suffering one… physiology must solve two important questions… should we consider *(blood – auth. note)* simply as a nutrient… or… as the main seat of material life principle, carrying it to all organs", - Filomafitsky wrote (17).

During 1860s, two dissertations with the same title "On blood transfusion" being performed and defended by Vasily Vasilyevich Sutugin (1839–1900) and William Mikhailovich Rautenberg (1840–1879) at Imperial Medical and Surgical Academy in St. Petersburg. On experiments with animals they aimed to explore the possibilities of blood transfusion's application in obstetrics (Sutugin, 1865), in acute anemia and poisoning (Rautenberg, 1867). Sutugin was a supporter of transfusion of defibrinated blood (7), Rautenberg – the whole one (6). Both surgeons performed human-to-human transfusions: Rautenberg carried out transfusions of whole blood in 1867 and 1868, Sutugin – defibrinated one in 1868 (8).

Rautenberg and Sutugin made some important discoveries in blood transfusion experimental studies that were necessary for its application to medical practice. Sutugin determined that fibrin is easily restored in blood within 24 hours (7). Also, Sutugin defined the connection of fatal hemotransfusion with infection caused by donor's blood, which can transmit "common diseases, such as syphilis, scrofula, etc." Experimenting with temperature of donor's blood, Rautenberg found that infusion chilled blood into vein is harmless for animals. This contributed to the solving the problem of donor's blood storage: it became possible to store blood in defibrinated form and keep it at 0°Сfor a week (7). To prevent blood coagulation Rautenberg developed the method of chemical preservation by adding "small amounts of sodium carbonate", which "delaying coagulation… does not deprive it of the qualities necessary for blood transfusion" (6).

Thus, until 1874, the year of Roussel's arrival to St. Petersburg, blood transfusions in Russia had been mainly experimental. The main purpose of the research was finding optimal conditions for using this procedure in medical practice. The fact that most of Russian researchers belonged to the main military medical educational institute of the country – Imperial Medical and Surgical Academy in St. Petersburg – indicates the high relevance of this procedure for Russian military medicine in the second part of 19th century.

Dr. Roussel and his invention

The first model of blood transfusion device was constructed and tested by Joseph-Antoine Roussel in 1864 (18). In 1867, he presented its procedure in front of general medical community at the Paris International Exposition in 1867. Roussel's specific transfusion technique consisted of using a water filled glass tube connecting the donor's afferent radial artery to the recipient's efferent forearm vein. The contraction of the donor's heart and his arterial pressure moved the transfused blood, while water allowed to keep its rheology. Nevertheless, arterial pressure wasn't enough to stop blood coagulation completely (19). Moreover, opening the donor's arteries was associated with additional risks to his life and health. In this regard, Roussel's apparatus for blood transfusion did not receive approval among the medical community of France (19).

After some upgrading, Roussel presented his invention again at the 1873 Vienna World's Fair. From the description it followed that the device allowed "to transfuse from 150 to 300 g. of live blood from a healthy man to a sick patient without any changes in its composition, without contacts with air, without clots in 2–3 minutes". At the same time this blood maintained its normal temperature and the rate of blood injection in the patient's vein was regulated by the surgeon. This time the doctor used whole venous blood and an "artificial heart" – a ball-shaped rubber balloon (4).

Roussel's "transfuser" had three fundamental distinctions from other similar devices (18) (Fig. 1). Firstly, the entire apparatus was made of natural rubber, even silver cannulas and probes were replaced with rubber ones. Roussel presumed that the diversity of materials led to the formation of blood clots: "Any contact with metal, as well as with glass, ivory, etc., is harmful for blood and provokes its coagulation… My transfuser is composed entirely of pure caoutchouc: natural, non-sulphurised, hard neutral substance, which has no effect upon blood, contact with which alters neither the tissues nor the animal liquids" - the author described his invention (4). Secondly, the entire device was filled with warm water (20–25 C°) with sodium bicarbonate. Water, on one hand, heated the apparatus and retained the rheological properties of the blood, on the other, it protected the patient's veins from air penetration. According to Roussel, this improvement had other advantages: it helped to combine transfusion with drug injections and using electricity for stimulating effects. Roussel wrote: "It is quite easy to blend the blood with a certain dosage of medicated water in prescribed solution in the apparatus itself," or "enclose in the transfuser a current of direct electricity, and bring it together with the blood into contact with the heart itself in order to reawaken that organ in the case of apparent death" (4). Thirdly, the procedure of blood sampling from the donor was similar to bloodletting and was performed without a surgeon. Roussel placed a sealed "cupping-cup" filled with water on the donor's arm instead of a cannula in the donor's vein. Two lancets were fixed in the cup, which cut the donor's vein if pressed. As a result, the blood flowed freely into the cup, replacing the water from the system and filling the balloon. After releasing the water, the surgeon pushed a portion of blood into the patient's vein by mechanically pressing the balloon. The balloon had an exact volume, so it allowed maintaining control of the blood transfusion and measuring the amount of flowing blood (20).

The effectiveness of the device was demonstrated with experiments during Vienna World's Fair in 1873 to the Vienna Society of Physicians and International Medical Commission led by Theodor Billroth (1829–1894). This Commission was created specifically for collegial discussion and practical testing of "models for military and sanitary purposes" taking into account the experience of the past Franco-Prussian war (1870–1871) (21). It consisted of prominent researchers, including those who studied blood transfusion in experiments (I.J. Neudorfer, R. Virchow and other), specialists in the organization of sanitary affairs in the army (R. von Volkmann, B.R. K. von Langenbeck, K.von Bardeleben and others). The Russian delegation in this commission was represented by the heads of Main Military Medical Department Nikolai Illarionovich Kozlov (1814–1889), Christian Bogdanovich Ritter (1814–1885), generals Mikhail Nikolaevich Annenkov (1835–1899) and Alexander Karlovich Baumgarten (1815–1883), military doctors Joseph Vasilyevich Bertenson (1833–1895) and Hippolit Osipovich Korzeniowsky (1827–1879) (21). As a result of numerous experiments, this Commission came to a conclusion that "Roussel's transfuser was the ideal practical device for direct blood transfusion, and that it must have been introduced into the arsenal of military surgery" (18). On the base of this decision Austrian military ministry signed a contract with the inventor and included his apparatus into the "surgical tools for army" for war and peace during the Fair (22).

Roussel made significant efforts for promoting his device. With his direct participation the big article describing in a positive light all the advantages of the device and the relevance of blood transfusion in military medicine was published in the Viennese newspaper Militar-Zeitung on the 13th of September 1873 (23). Furthermore, in December 1873, he sent a letter with the application of this article to the Russian Main Military Inspector N. Kozlov. The letter included a "proposal to introduce his invention to military doctors ... in order to demonstrate all the details of the implementation of the tool on patients" (22).

Also, Roussel published French (1876) and English (1877) editions of his book “Blood transfusion” adding the laudatory reviews of the leading surgeons of Britain, Austria and Russia, such as the President of the Clinical Society of London James Paget (1814–1899), the head of Austrian garrison hospital, Staff physician, Professor Ignaz Josef Neudorfer (1825–1898) and Oscar Ferdinandovich Heyfelder (1828–1890) German surgeon, member of the Paris Society of surgery, who practiced in Russia in 1854–1884 (4, 18).

In January 1874, Roussel was invited to Russia, where he signed a contract for the supply of 200 devices and was given the order of St. Vladimir of the fourth degree. He couldn’t achieve similar success in France and Britain. According to Jennings, in 1880s Roussel’s device was not disturbed and actually used in hospitals or in private practice. This apparatus was especially criticized for its difficult construction and a special procedure of bloodletting that lay at the basis of its work. Jennings wrote: “There can be no certainty that the lancet will not perforate the posterior wall of the vein and injure subjacent structures” (9). He was sure that “many stopcocks, its india-rubber bags, and other complex contrivances” complicated the device and required special skills from surgeons to use it (9).

J. Roussel in Russia

In February 1874, Roussel worked in various hospitals and clinics in St. Petersburg, such as the Surgical clinic of the Imperial Medical and Surgical Academy; Maternity clinic; the Naval clinic, and the Prison hospital in St. Petersburg. During this time, he performed public procedures of blood transfusion, which were attended by the leading Russian specialists in blood transfusion, members of the Medical Council of the Ministry of Internal Affairs: Gezellius, Rautenberg, Korzeniowsky and others; military and civilian doctors; students of the Imperial Medical and Surgical Academy, and even the Duke Alexander Constantine Frederick Peter of Oldenburg (18, 20).

The curator of Roussel in Russia was a military surgeon of German O.F. Heyfelder, who was acquainted with Roussel since the Paris International Exposition of 1867 (18, 20). He assisted Roussel in the trials of his device and drew up a detailed report about their results and possibility of application Roussel’s method in the military field. Besides, Russian surgeons, such as I.O. Korzhenevsky, Eduard Yakovlevich Krassovsky (1821–1898) performed transfusions using Roussel’s device independently and under his supervision. Roussel noted that they categorically refused to transfuse animals’ blood to humans (18). However, Heyfelder supported the idea of animal blood transfusion to human. In 1874 he “proposed to the European government to have flocks of sheep on the battlefields for the emergency transfusions of the soldiers” (24).

According to Heyfelder’s report, Roussel performed 23 operations of blood transfusion in Russia. Four operations were carried out for training purposes on people dying in agony to “familiarize doctors with the details of the application and operation of the device” (25). It should be noted that the fact of using dying patients as a live training manual to study medicine as well as the unperturbed attitude of the medical community to it were characteristic for this era. Four successful blood transfusions to patients with scurvy (25), one successful transfusion of venous blood of a lamb and one unsuccessful transfusion of a mixture of blood and water to the patient with suspected cholera were carried out as experimental ones (26). The remaining 15 blood transfusions were performed in patients, whose anemia was the result of one of the diseases: tumors in the pharynx or uterus, red diarrhea; suppuration of an elbow or knee joints or a lumbar muscle; “cancer thinness”, inflammation of the kidneys, “thoracic dropsy”, consumption of the lungs and peritoneum, typhoid, catarrhal inflammation of the lungs, intestinal ulcers, insanity or a “paralytic state” and others. Healthy young peasants of 30-40 years old, the patients’ wives or hospital employees were the donors. As a result of all 15 cases, blood transfusion led to “fast palliative and radical help” (25). However, the serious conditions of three patients with long-term suppuration of a knee joint, pulmonary tubercle and typhoid determined the temporary nature of the improvement, after which all patients died (25).

In general, Heyfelder’s report on the results of clinical trials of Roussel’s device in Russia was positive. He noted that the introduction of this method into medical practice required further experimental study.

Heyfelder wrote: “The physiological effect and indications for the operation should be explained by further observations” (20). Nevertheless, Heyfelder acknowledged that Roussel’s device “might be called the best of the currently known and very suitable for military medical practice” (20). Heyfelder’s report became one of the reasons why the Russian Main Military Medical Department recommended to equip all military medical institutions and district military medical offices with these devices (27).

There was one important aspect of Roussel’s contract with the Russian Military Ministry. Roussel wanted to become a monopolist in supplying the devices for blood transfusion in Russia. He demanded the Main Military Medical Department not to buy and produce devices that are the similar to his apparatus and purchase new improved devices only from Roussel himself (28). It shows that Roussel was keen to make his invention a constant source of his own income (27). The Main Military Medical Department agreed to all Roussel’s demands, and soon after that 200 “transfusers” in the amount of 10,000 rubles were bought from Roussel and sent to the military hospitals in all Russian districts. The necessary rubber parts for his device were produced by the Russian-American rubber manufactory in St. Petersburg, which signed a contract with the inventor (29).

However, using Roussel’s devices as “common methods of surgical care” in mass practice faced a number of difficulties. At first, the conditions and duration of the device’s storage were unknown because it consisted of single rubber, a new material of that time (30). Therefore, additional research of the technical characteristics of the device was required. Secondly, it was necessary to train military surgeons to use the apparatus correctly, and to provide it with detailed specification for using it in hospital practice. The members of the Main Military Medical Department Alexander Alexandrovich Kiter (1813–1879) and Christian Bogdanovich Ritter (1814–1885) were assigned to write the instruction for Roussel’s transfuser (30). However, we haven’t found any confirmation that these guidelines were developed and published.

In March 1875, Roussel’s 200 devices were received from Geneva. They were examined at the Factory of Military-Medical Preparations in St. Petersburg by doctors Korzeniowsky and Heyfelder and distributed to all Russian military hospitals (31, 32). In addition, the Roussel’s devices were recommended for using in civilian hospitals by the Ministry of Internal Affairs. However, local authorities in Russian regions were not always ready to follow this recommendation. We found the evidence that Trans-Baikal regional administration refused to buy the devices due to its high cost of 50 rubles and unpredictability of blood transfusion procedure itself (33).

Besides the outstanding Russian military surgeon of that time Nikolay Ivanovich Pirogov (1810-1881) wrote that Russian military doctors did not practice blood transfusions en masse during the next Russian-Turkish War (1877–1878) (34).

On the basis of available sources, it can be argued that only military field surgeon Sergei Petrovich Kolomnin (1842–1886) practiced blood transfusion during this period in Russia. During the Serbian-Turkish War (1876–1877) and Russian-Turkish War (1877–1878), he transfused defibrinated human blood to “support the dying life of the sick… or … strengthen weak patients” (35). In total, he performed 12 operations, but the method he used was fundamentally different from Roussel’s one. Kolomnin transfused defibrinated human blood into the patient’s radial artery with the using of another kind of apparatus (35). In 1879, he described this experience in the report “On arterial transfusion of defibrinated blood” at the meeting of the Society of Russian doctors.

Thus, despite the fact that Roussel’s devices were purchased and delivered to Russian military hospitals, they were not widely used in Russian military field surgery in 1870s.

Conclusion

Thereby, at the beginning of the 19th century, the studies of blood transfusion were mainly limited by the frame of intra- and inter-specific physiological experiments. During the second part of the 19th century, both European and Russian scholars were especially interested in the issues of blood transfusion practical application: the effectiveness of the use of whole or defibrinated blood, ways to preserve a donor’s blood, the choice of an optimal donor - human or animal. Russian researchers made a number of important discoveries in the study of practical aspects of blood transfusion. Sutugin discovered the ability of fibrin to recover in the blood within 24 hours and the possibility to store defibrillated blood at 0°C for a week. Rautenberg invented a method of chemical blood conservation by adding small amounts of sodium carbonate.

The success of Roussel's device at the 1873 Vienna World's Fair and its acquisition by the governments of Russia, Belgium and Austria-Hungary for their armies indicated the immediate needs of blood transfusion application in medicine, especially, in military field surgery. Roussel managed to use this situation having offered his device to the military and medical community. He conducted a successful "promotional company" of the device (the letter to the Russian Military Ministry; his book "The blood transfusion" where he described not only the apparatus itself, but also its awards; the book's French and English translations; public clinical trials of his device in the leading European states (Russia, France, Austria-Hungary, and Germany), during and after the Vienna World's Fair). Moreover, he became a monopoly supplier of his devices in Russia. All this reveals Roussel's self-serving desire to make his invention the mean of his income. It is hard not to admit that Roussel's power of persuasion and communication skills which allowed him to enlist support of the prominent European surgeons James Paget and Ignaz Josef Neudorfer, as well as establishing and maintaining good relationships with Russian military surgeons interested in issues of blood transfusion application, were truly extraordinary. Apart from Roussel's unique abilities, this story also reveals how much the needs of practical medicine outstripped the technical capabilities of their implementation. Roussel's efforts were successful in financial terms and fruitless in a medical way. As we know now, in the 19th century blood transfusion still had been an unpredictable and unsafe method, which began its large-scale application only in the next century, after the discoveries of K. Landsteiner.

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Medicine and disability: historical perspective

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Abstract. Disability expresses an object, but principally also a concept with an outline difficult to define. A concept as much undefined as complex. In comparison to its definition, disability as a concept has not yet been untangled definitely even due to the fact that disability represents by itself the difficulty to trace a stable and certain dividing line. With an historical perspective, the present paper offers a discussion of the so-called interpretative models linked to the meaning and the magnitude of disability under a first medical and then sociological point of view. During last decades, in fact, the understanding towards sociological instances in relation with disability have changed remarkably, trying to bridge the gap existing in the past, when disability was observed only as a personal health issue and consequently only under one specific framework of analysis, abstracting it from the boundary conditions and from the society in a de-constructional approach which lead to disregard disability per se. Thus in the times, disability passed from being a personal and medical problem to a phenomenon with its own social impact and a social construction, deviating the observation of disability from the medical and health point of view to a holistic approach, even if with consistent differences in relation to the diverse paradigms of interpretation.

Key words: disability, diversity, models, paradigms

Introduction

Along with UN estimation data, disability affects one out of eight people in the world (1).

Disability expresses an object, but principally also a concept with an outline difficult to define. A concept as much undefined as complex. In comparison to its definition, disability as a concept has not yet been untangled definitely even due to the fact that it represents by itself the difficulty to trace a stable and certain dividing line.

Descending on different ways of understanding and analysis of the disability, different models (2) of interpretation has been elaborated, in particular during last and current centuries.

The following pages offer a scrutiny of the existing models, summarised of necessity.

The analysis will start from the model based on the consideration of disability only under a medical/health point of view, where the individual perspective was exclusive, to approach to more recent and affirmed models related to the social evaluation and social inscription of the disability, where the perspective of and within the society prevailed, to arrive to the most recent models stemming from the social model and affirming a more modern concept of socio-political perspective of disability, where persons with disability are seen as full-right-citizens, with rights not only to be recognised but also fulfilled by the state and the society. Let us then analyse in rapid succession the interpretative models of disability, examining the theoretical paradigms that approach disability in various ways up to nowadays.

We shall utilise the typological approach to theoretical analysis in order to outline the basic characteristics of the various models and approach to disability during last centuries.

Medical-individualistic model

Historically, the medical approach prevailed in the history of every kind of relationship with disability and disability issues in our western societies. This approach represented the interpretation of disability using an exclusive medical point of view and was prevailing since mid-nineteenth century. Up to the upheaval arising from the late sociology attention, the medical model was therefore the most affirmed paradigm of interpretation, which read disability as a condition to be cured, healed or, at least, treated.

The observation point focused on the impairment and concentrated in finding the best way to intervene, to cure. Disability was absolutely a health issue, seen as an impediment, a personal problem of the patient to be solved thanks to medicine. The final objective of the intervention was the rehabilitation or the healing and consequently the emphasis was put onto the pathology or the impediment, in order to reach the goal of the cancelation of the impediment same or to eradicate the disability and give back a healthy body to the society.

The medical model was the right answer to the demand arising from the society linked to rehabilitation and reinsertion of those who were put aside from the productive system due to their impediments. The only way to be part again of the society and to participate in the economic and capitalist or communist system was that one related to healing and rehabilitation. Persons with disabilities were observed as patients and the focus was not on the person, but, on the contrary, on the impairment.

If one would like to understand the current relationship between disability and medicine, therefore a historical point of view is utmost necessary (3).

It is worth to say that up to nowadays there is no precise outline and no systemic formulation of this model of interpretation of the disability under a sole medical point of view (4), but at the same time it is sure that this has been the theoretic basis and the launch pad for the opponents and proponents of different interpretations. And, even if there is no written or fixed definition of the model, it has been and is still adopted by health professionals, philosophers, legal experts and carers chopped in every domain.

At the end of last century, Rhoda Olkin (5) tried to offer a plausible definition of the model:

> Disability is seen as a medical problem that resides in the individual. It is a defect in or failure of a bodily system and as such is inherently abnormal and pathological. The goals of intervention are cure, amelioration of the physical condition to the greatest extent possible, and rehabilitation (i.e., the adjustment of the person with the disability to the condition and to the environment). Persons with disabilities are expected to avail themselves of the variety of services offered to them and to spend time in the role of patient or learner being helped by trained professionals (6).

This way of interpreting disability meant that a person who was unable to heal and "overcome it" thanks to rehabilitation and play their full part in a society created and constructed by those who had no disability was considered as a person deserving of pity, charity and compassion (7). They were viewed as living in a personal situation of tragedy, not able to fully participate in the society, as they did not fit the standard.

This is why the medical model was also defined as the "individualistic model", because of the fact that disability was interpreted and understood as a mere personal imbalance and not a social and shared circumstance.

Despite its name, this model did not relate solely to the medical aspect but its conceptual base nonetheless lies primarily in the dogma starting from the mid twentieth century within modern medicine, according to which illnesses and diseases are factors of imbalance of the underlying physical mechanisms (8).

There was no suggestion that society could change something in itself in the presence of a person with a disability. The boundaries were clear. It was the person "suffering" from the disability who was supposed to adapt to their surroundings and not the opposite. It was therefore a private misfortune, limited to the individual sphere (9) of the person who was unable to adapt to society and correct that imbalance. Disability represented consequently a deviation from the social standard that did not conform with the paradigm of what was considered normal, balanced and complete. It was an individual state of disadvantage (8) that remained personal and did not interfere even minimally with a society that made no effort to change in order to interact with people with disability.

In fact, in the social science, a specific attention has been devoted to the social aspect of the disability only lately (10), after decades of total disregard by side of the fathers of sociology (i.e. Anthony Giddens as per Barton and other sociologists). Therefore, up to some years ago, the reflections were centred on the person with disability as a person to integrate, to heal, to recover, to treat as a patient with a disease to be cured and reinserted in the social context after rehab, it does not matter gender, expectancies, attitudes, desires.

The idea of disability as an illness or something to be eliminated has not disappeared over the years and did not apply only in western society. If a medical and individualistic view is still present pretty much everywhere, I would like to emphasise how the sanctimonious and paternalistic approach - which prevailed up to the eighteenth century at least - has contributed greatly to this interpretation, when disability was viewed as a heartbreak, interpretable from a religious viewpoint as a kind of divine retribution or spiritual test and confining disability in the individual sphere, descending from an own negative dimension. In other circumstances, persons with disabilities deserved marginalisation and reclusion (11) even because differing from the paradigm of normality (12) or because of the visibility of their disability (13).

The impairment was the stigma exemplifying the reason of the marginalisation, which was necessary to avoid contamination and corruption of the integrity of the society. This was done as in the Middle Age when treating lepers and putting them into hospitals outside the borders of the villages. This was the idea linked to sterilisation of persons with disability perpetrated during the Nazi period in Europe, but maintained in the US up to the 1920s and up to 1970s century in other European countries. Eugenics represented a consequence of the obsession linked to perfection of the body as a paradigm for the participation into society.

Social Darwinism added important burdens to this conception of disability as a shame or as an impediment to the personal realisation as a member of the society. Under many points of view disability was seen as an affection of the person, who was totally absorbed by the impediment. The only way to avoid the impediment was the rehabilitation and the cure.

As a matter of fact, it descends the wide importance attributed to the medical approach to disability, seen as the only way to "solve" the problem represented by the impairment.

This approach to the person with disability was utilised as the only one interpretation of disability and still nowadays is seen as the origin of a history of discrimination towards those who could not be healed or rehabilitated thanks to medicine. Hence also the concept of health was put under discussion: when a person with disability is observed as a person in health need, consequently she/he is considered as ill (14-16). This totalising interpretation of disability has given birth to a sequel of critics, which originate other and further interpretative models, still in discussion (17-19).

In addition to what said, moreover, it is interesting to note that the paradigm of the medical-individualistic model enshrines a transversal extent: it was also very popular in the so-called communist countries, where disability was viewed as a personal tragedy to be hidden when it could not be eliminated or cured. This is reflected by the large institutions that, until the early part of this century, held hundreds and hundreds of people throughout eastern Europe, institutionalised because they had an impairment that could not be medically treated or because of the medical treatments they needed. These people, who were necessarily left out of the economic mass production system, were useless to society and were therefore shut away in distant and miserable places (19). This situation continued for decades even after the fall of the communist regimes in eastern Europe and in many cases is still alive.

In the early years of the 1960s, the first activists for the rights of people with disabilities started their political fight to stop disability being viewed simply as a medical condition or an experience exclusively within the personal sphere, and for the introduction of basic concepts such as independence and self-determination. As said, up until then, everywhere disability was considered as a factor of individual health requiring only medical attention or health services. Current times asked to overcome the person with a disability viewed as someone suffering from a negative individuality, a personal tragedy, to be helped in some way, whose experience remained within the private, and therefore personal or individual, sphere.

Social instances and public demonstrations required to set aside the paternalistic or religious approach considering the person with a disability as needing help, compassion and pity, depersonalised in their individual person, which was reduced to the disability or impairment.

Things changed more with the birth of the activist movements and Disability Studies. The first upheavals in the fight for the rights of people with disabilities took place in English-speaking countries (US and UK): years and years of deprivation or discrimination (20) were finally cancelled after lengthy and extenuating battles for rights, protests and marches of all kinds and universally.

From and within these fights a new model of interpretation of disability was born, based on the social consideration of the disability prescinding from the health/medical point of view (21), and - willing or unwilling - its effects are still present in our societies and is influencing also those who remained and remains stick to the medical model.

Social model

Partly on the basis of the interpretation of a society that disables, the studies that began at the end of the 1970s and early 1980s evolved from the medical-individualistic paradigm and started to view disability within its social context, interpreting it as a social construction created by that context. Thanks to the movements for the rights of people with disabilities, as said, the model that would uproot the one previously described took shape in the 1970s. This was the aforementioned paradigm of the social model, interpretation of which has continued to evolve right up to the present day.

Along with this paradigm, disability represents a social construct, a process that denies participation in society and the recognition and respect of people with specific characteristics (based on prejudices of various kinds).

The existence of this preconception forms the basis of the social process of "becoming disabled", which could be frustrated or prevented by altering the social context in which it is placed.

In other words: people are not disabled, they become disabled (9).

A clear theoretical distinction was made between impairment and disability. As above already hinted, impairment was defined as a functional limitation that a person may have as the result of an objective factor. Disability was interpreted as the loss or limitation of the personal or social possibilities of participating in society as a result of social or spatial barriers.

The invention of the expression "social model" is due to Mike Oliver. He did not invent the principles underlying the social model; they came out of the booklet published by the British *Union of the Physically Disabled against Segregation* (UPIAS) in 1976 (22). It was Oliver, however, who named it, after developing the idea as a tool to aid his students to understand the meaning of the model same. He explained:

> [The social model] was basically giving you the opportunity, both personally and politically, to rethink about yourself and your position in society (23).

It enshrined a reversal of perspective: it was not the person with a disability who was supposed to conform with society, by adapting, curing or concealing the disability, but rather society that was supposed to adapt to people with disabilities, removing the barriers it had itself created. Society had created disability, so society was supposed to eliminate it. As interpreted by Pilar Gomiz Pascual.

The context is what defines the "disabled" person, not the impairments or lack of ability of the individual. (4).

Consequently, a radical change in interpretation of the contribution the individual makes to society was being demanded. Up to that moment, the liberal and capitalist doctrine of western society together with the communist doctrine based on the capability to participate to the productive system ensured that people were assessed on the basis of the contribution they could make to society. According to the theory of Parsonian functionalism (24), each individual contributes to the dynamics of society to allow it to progress, in an interdependent and correlated manner. With shared objectives, society thus not only progresses, but also maintains its balance, as it remains within the pre-set standards and complies with the functionalist model. Each member of society is aware of their role and understands the objective they must pursue with their social activity.

With this interpretation, a person with a disability would immediately lose their place in society, as they would be unable to participate fully in the social activities, as the qualities of complete ability and state of health would not be reflected in them. Disability has been observed therefore as an impediment to the total achievement of society's objectives, a threat to order and a deplorable deviation.

The one theorised by Oliver was – and is – a different interpretative model of the entire social system, which no longer had a dominant and perfectly functioning group and minority groups excluded from it for any reason (not only as a result of the disability, but simply because they did not conform with the majority in terms of normality or illness). It was a new social construct that would lead to the end of the state of oppression in which people with disabilities had lived until then, subject to stigma and discrimination, exclusion and marginalisation, and move towards liberation, as clarified by Oliver:

> For me disabled people are defined in terms of three criteria; (i) they have an impairment; (ii) they experience oppression as a consequence; and (iii) they identify themselves as a disabled person. (25)

The social model was at the basis of the new born *Disability Studies*, which questioned the foundations of a functionalist society to obtain an interpretation of disability that would result in a constructionist vision of the social context. For the Disability Studies' scholars, society constitutes thus a social construct, an organism that learns and is created without an objective and established predetermination. Society is no more viewed as a passive being that simply perpetrates standards accepted as "normal", but adapts its own form to its members. This society is therefore constructed with and around persons with disabilities and not despite or without them, so it adapts to them from a functional standpoint.

By distinguishing impairment from the social condition, the first theoreticians and scholars of Disability Studies prepared an all-inclusive model of the theoretical and social framework of disability. The first theorists of this model were, as said, Mike Oliver and other scholars from the so-called School of Leeds and later from the UK, such as Colin Barnes, Vic Finkelstein, Tom Shakespeare, Len Barton, and others.

This new interpretation model viewed disability as a form of oppression caused not so much by the impairment, instead by the society in which the person lived. With its barriers, society works against those with an impairment that disables them - not the impairment itself - and that oppresses and stigmatises the person with a disability. Disability is a social construct that oppresses, segregates, stigmatises and separates and nota a medical issue.

The basic principle at the origin of the social model was the diverse concepts of impairment and disability deepened in the definition also given by UPIAS in "The Fundamental Principles of Disability" in 1976 (26), which:

> Impairment as lacking part of or all of a limb, or having a defective limb, organ or mechanism of the body; and disability as the disadvantage or restriction of activity caused by a contemporary social organisation which takes no or little account of people who have physical impairments and thus excludes them from participation in the mainstream of social activities.
>
> And then it concluded:
>
> Physical disability is therefore a particular form of social oppression (27).

This constitutes the basis of the most holistic and affirmed interpretation of disability and the condition of the person with a disability based on the social model and it was no longer just a personal event limited to the individual sphere or to the medical domain.

Personal is political was one of the slogans used by the activists of the movements of people with disabilities. The experience of the individual was a part of the society and therefore became a political fact and, as such, worthy of attention by the community, who could relegate anymore people to the margins of society, as a result of a personal fact.

And if *personal is political*, then decisions on people could not be taken without the active participation of the people to whom those decisions are referred.

Nothing about us without us was, in fact, another slogan that turned out to be famous, as it summarised the content of the protest so well.

This aphorism is the title of the book of James Charlton (28), who in 2000 published his "Nothing about us without us. Disability Oppression and Empowerment", and shortly became the motto of the whole disability rights movements protesting against oppression, defiance and absence of self-determination freedom and independent living. The concept of the book is that persons with disability know what is best for them and they should be asked.

It was no longer politics or society that could or should make decisions on the person with a disability, but there should be a transparent process in which all those affected by the decision participated, and people with a disability above all.

Cultural model, biopsychosocial model and evolutions

Current theories on persons with disabilities have changed over the years and evolved from the initial medical model to go through the social model towards new ones based on the last, thus not believing that considering society as the sole creator of disability of the individual was truly helpful in moving towards the necessary cultural and political paradigm shift.

Tom Shakespeare in his "Disability Rights and Wrongs" (29) said that "people are disabled by society and by their bodies" (8), thus confirming that disability cannot be approached simply as a social phenomenon prescinding from the possible medical aspect or solely as an impairment relating to the personal sphere. It is the joint presence of these two factors that disables a person with an impairment and prevents them from developing in all aspects: as a person, as a citizen, as a woman or as a man. In fact, one of the criticisms of the social model since its inception, which would lead to its review over the years, was its lack of focus on the medical impact of disability and an underestimation of its scope (30). According to some (4), however, the social model did not ignore at all the medical or biological aspect of a disability.

It was no coincidence that formulation of the social model was followed, over the years, by other interpretative paradigms. Doubts were immediately raised over analysis of the two prevailing paradigms (more on the medical-individualistic one and lesser on the social model), which appeared too focused on several specific and partial aspects, and disregarded the holistic approach to disability. As the years passed and the (also theoretical) concept of disability was examined in greater detail, it became clear that any narrative using theories and concepts based on a mono-dimensional interpretation – such as those adopted within the medical-individualistic and social paradigms – was inevitably partial in nature and, as such, destined for failure. It is no coincidence that, in relation to a disability "it is not possible to tell a single and exclusive story about something that is complex" (8).

The cultural model starts with the points just examined up to now and evolves towards a more open and comprehensive view of disability, moving away from the fixed points that forced the previous models into a corner. This paradigm has evolved from the feminist idea and is based on sociological approaches that also consider other aspects, which were perhaps or partially disregarded in the previous theoretical interpretations of disability.

The foundations of a society that attributes value to certain things and not to others are placed in doubt. Ableism is questioned, as it is the tendency to seek perfection and the obligation to be active and productive according to predefined standards, with an able body always at the centre. This is all considered within the framework of a cultural substratum, as a set that encompasses different but always unequal approaches to people who deviate from the norm, are not able-bodied or perfect. This results in them being stigmatised and discriminated against as "other" with respect to the "whole". Disability becomes a social category of analysis, a line of investigation, a different interpretative model, the outlet of which is Disability Studies. This is why disability becomes more an effect of relations of power than a fact in itself (31). Disability as a system of representation inserted in a social context but dictated by culture.

This means that factors not considered previously become important, such as language, race, gender, psychological and legal aspects. It is an approach to culture that attempts to uproot the cultural paradigms anchored to righteousness and discrimination, without focusing on and stopping at political, social and economic barriers, considered almost exclusively up until then.

People with disabilities are the first being asked to overcome the stigma and to go beyond the barriers that forced them into social isolation (8), by taking action themselves and actively participating in their own liberation from oppression, perhaps deciding whether to define themselves as disabled or not.

Several of these aspects are clearly outlined by Alessandra Fabbri in her autobiography. For example, she says:

> Personally, I hate the image of a handicapped person as a victim. Handicap, I want to emphasise once again, is not a synonym of inactivity, so - and I am being deliberately provocative here - I say, to myself above all "Get up and walk"… which does not mean use your legs, but take action!!!

The cultural paradigm, like the others, has both positive and negative aspects. From an objectively critical standpoint, it could be said that this approach, leaving aside the medical approach entirely is, in some ways, preferable to the social approach. But the paradigm in question currently remains more detached from reality, even though it represents a theoretical framework of criticism of a society and a culture that produces oppression and does not offer practical solutions that could help solve or remove stigma and discrimination. Although it provides drivers for a holistic interpretation of reality, it does not include single steps towards actual liberation, but suggests that it is individuals who must act, together or through the mechanisms of advocacy, to change the status quo. Hence it is not always simple for groups or individuals to achieve actual changes. However, it is certainly appreciable that people with a disability are considered to be the fulcrum of the action, who thus liberate themselves from a series of negative adjectives, ranging from ineptitude to inertia, abjection, passiveness, incapacity and others.

The biopsychosocial model has been developed taking into account the whole environment. It represents a biological, psychological and social approach arising from the reflection of an American psychiatrist, George Libman Engel (33), who elaborated his theory from the '70s and '80s of last century and then was borrowed by other scholars.

The basic idea of this model is that the state of health of a person is influenced by other equally important and essential factors, such those in the biological, psychological and social spheres.

It is another approach to health that is contemplating not the single issue or illness (34), but also and at the same time the boundary conditions of the interested person:

> The biopsychosocial model is both a philosophy of clinical care and a practical clinical guide. Philosophically, it is a way of understanding how suffering, disease, and illness are affected by multiple levels of organization, from the societal to the molecular. At the practical level, it is a way of understanding the patient's subjective experience as an essential contributor to accurate diagnosis, health outcomes, and humane care (35).

The biopsychosocial interpretative model lies within the more general intermediate paradigms, but a special room has been dedicated to it due to its acceptance. As a matter of fact, regarding the positive acceptance it encountered, there are four favourable points to be underlined. The first point is that this model was used by the World Health Organisation for its definition of the functional assessment parameters known as the ICF. Moreover, the second point is that this model recognises that disability is a status deriving from a complex set of factors, ranging from the biological to the mental sphere and the social factor, and this results - at least in theory - in a holistic approach to the individuality of the person and not a partial or reductive one. The third is that this model has been widely applied across the world, although in a strictly medical area. The fourth and last point is that Italian legislation has cited it in various laws over recent years and consequently it merits further examination.

In order to get away from a theoretical framework too closely anchored to constructivism, other interpretative models appeared over time and overlapped each other in part. The term "intermediate paradigm" is used to refer to what, in a certain sense, is a spurious grouping of interpretations that evolved from the rigidity of purely constructivist interpretations, even though they always disdained the exclusively medical approach.

Conclusions

In the ongoing and lively debate between functionalism and constructivism, the social models of interpretation of disability have often reflected and continue to reflect the times when they were implemented. But all the interpretative models that have followed each other over time have been united in their lack of appreciation of the medical-individualist model. The proposal of different theoretical and interpretative frameworks has been followed by discordant or similar discussions and narratives.

As time passed, it becomes increasingly clear that disability is not a single concept definable once and for all, but it is always required an approach that takes its multi-faceted nature into account.

In conclusion, it is worth to underline how the history of the conceptualisation of disability could affect present times and the current approach to disability even under the sole medical point of view, where the impairment has to be cured, healed or a rehabilitation path has to be offered. This can succeed with the full consideration of the impact of the illness or of the impairment in the life of the person with disability, who is no more considered a mere object of cure.

Times and fights produced a deeper awareness of disability as inserted in the social contest and which cannot be separated from the boundary conditions of the persons who have a disability.

A holistic approach to disability produces better results and the impairment and its cure is not to be studied as a separate factor in the life of a person. Therefore we can conclude that a dialogue among different discipline like medicine, biology, psychology, sociology and others could led to a better approach to persons with disability as a whole and not as the *ressemblement* of isolated instances to be examined in different and separate domains.

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REVIEW ARTICLE: HISTORY OF MEDICINE

Historical gender gap in the authorship of the most impacted general nursing journals: a cohort descriptive study

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Abstract. Gender differentiators in the academic world are characterized by a disparity between men and women in their scientific production, as men are more favored in this area than women. The aim of the research is to evaluate any gender differences in nursing scientific production between journals in the sector with an important impact factor. The Web of Science (WoS) citation database was used to select the journals based on the impact factor and the publications of the last 5 years whose data are available, such as from 2014 to 2018. General nursing journals, in the WoS database, with an Impact Factor greater than 2 and published in English language were included in this research. The general nursing journals with an impact factor greater than 2 in 2018 identified in our study are: International journal of Nursing Studies, Journal of Advanced Nursing, Journal of Nursing Scholarship, Nurse Education Today, Nursing Outlook, Nursing Research, Worldviews on Evidence Based Nursing. In total, 2889 names of first authors were recorded in the reference years from 2014 to 2018. Of these 83.7% are female and the remaining 16.3% are male. From our data it emerges how nursing turns out to be against the trend in the field of scientific productivity compared to other disciplines. This counter tendency has its origins in the history of nursing which has always been conceived as an all-female discipline, although history has taught us how several male nurses have made their important contribution in the history of nursing.

Key words: authorship, gender role, nursing, nursing history

Introduction

In the scientific world gender discriminations are defined as an inequality between men and women in their academic production, as male researchers are more advantaged than female researchers (1). The reasons of this benefit are also imputable to their social role in families, as they can ensure less absences in their workplace than women (2).

In 2009, a study was conducted in the USA that highlighted the strong disparity between male and female gender in scientific production, to the benefit of male production(3). A similar study in the UK reported the same trend in the results. In fact, in both studies a strong gender difference was found, despite the increasing portion of women in leadership roles within medicine(4).

In another study conducted in the North America on gender authorship in scientific production over the past 35 years, the first female author's name increased from 5.9% to 29.3% and the last name from 3.7% to 19.3% , respectively(5). In parallel with these results, another study in the UK reported an increasing trend in female authorship as, by analyzing six scientific journals in the last 30 years there has been an increase in the number of female authors in both the first and the last first name(6).

Both in the UK and in the USA, which have the highest number of scientific production, the female gender is still in the minority in the academic world.

These results are even more disconcerting when compared to the number of students enrolled in the degree course in medicine, where in the USA 50% are women and in the UK they are 60%. The same studies show a higher probability of career for men than women, finding the reasons for this trend in the social role of women in her family. While the studies conclude that, although the number of women studying to become a doctor is high, in the academic world this number decreases as many women remain in the basic positions due to the numerous other commitments related to their personal sphere.

In the nursing field there are two studies of gender bias in the North of America which examined the gender of research subjects, but not authors(7,8). In fact, there is no literature of gender bias in the authorship of nursing research. In the USA in 2000, 6.9% of the nursing workforce was male(9), while in the UK 10% of the nursing workforce was male and 11% by 2008(10). In Australia, the portion of men in the nursing workforce grew slightly from 8% in 1995 to 10% in 2007(11).

In Italy, from the analysis of data from ISTAT's Continuous Survey on the Work Force, it emerges that in 2015 in Italy there were 371.000 nurses employed out of over 440.,000 registered in the registers. Of these, 367.000 work in healthcare and 4.000 in different economic activity classes. 77.7% of nurses work in hospital services. Of the 371.000 nurses, 91.000 are men and 280.000 are women. Furthermore, from a survey conducted by Almalaurea in 2015 on a population of 210.000 nursing students, he says that precariousness and unemployment affect women more than men even when women are more hyper qualified(12). In addition, motherhood is professionally damaging to women and, in a male world, mothers continue to make less careers than childless women. This represents a sign of a strong cultural and civil retreat of the country with respect to the objective of achieving equal participation of women in the work context(13).

On the other hand, the male gender turns out to be increasingly interested in those household roles and to prefer safer jobs such as the nurse or the teacher, staying at home more time. In the latest surveys on the increase in the male gender in the professorship showed that the male gender managed to become increasingly predominant in a few years, also reaching more important and more profitable positions than female nurses(14).

Historically, the nursing figure has always been associated with a female figure. Thus, it has become identified as a profession deeply embedded in the gender-based power relations of society. Nursing is an occupation established by women. It supports the stereotypical "feminine" image with traits of caring and gentles in contrast to masculine characteristics of strength, aggression and dominance (15).

The aim of the research is to evaluate any gender differences in nursing scientific production between journals in the sector with an important impact factor. Specifically, we assessed whether there are gender differences in nursing scientific production not only considering the type of journal, but also considering the economic level of development of the author's country of origin to assess how much the economic development of a country affects the scientific production of own citizens.

Materials and Methods

The research strategy

The Web of Science (WoS) citation database was used to select the journals based on the impact factor and the publications of the last 5 years whose data are available, such as from 2014 to 2018, have been taken into consideration as data concerning the year 2019 were not available.

The WoS database was used in this research. Specifically the "Incites" section of the WoS database was adopted to find specific journals for our research.

Inclusion criteria included:

- General nursing journals,
- Journals cited in the WoS database,
- Journals with an Impact Factor greater than 2,
- General nursing journals published in English language.

On the other hand, exclusion criteria included:

- Specific nursing journals,
- Nursing journals with an Impact factor lower than 2,

- Nursing journals published in other languages.

Then, the research was carried out on the websites of the editorial groups that publish the magazines identified in the research.

For each volume belonging to the reference years of our research, editorials, corrigendums and letters to publishers have been excluded. Instead, all the other study types were considered.

For all the research works identified, the name of the first author was highlighted with the aim of identifying his gender and his country of origin.

For the identification of gender and nationality, the sites of the universities and institutions where the authors carry out their research activities were used, or the Researchgate database, which also showed many of the photographs, making research even easier. When we could not trace this information in any way, we sent an email to the address indicated in the work, also explaining the reason for the request.

Finally, after collecting all the data relating to gender, year of publication and nationality, further research was carried out on the World Bank website where the names of each country were associated with its economic level. Specifically, the World Bank classifies the world's economies into four income groups, such as: high, upper-middle, lower-middle and low. This assignment is based on Gross National Income per capita calculated using their Atlas Method. This classification is updated each year on July 1st. In our research work we considered the latest income economy classification.

Data analysis

The research data was collected in an Excel sheet. Subsequently, the descriptive statistics were used to calculate the relative frequency (n) and percentages (%) of the number of authors divided by gender, year of publication, magazine and country of belonging. Finally, the chi square test was used to evaluate any gender differences between the variables considered. The SPSS program of IBM in version 20 was used to evaluate the frequencies and percentages and statistical significance. All inferential statistics values less than or equal to 0.05 were considered statistically significant.

Results

The general nursing journals with an impact factor greater than 2 in 2018 identified in our study are: International journal of Nursing Studies, Journal of Advanced Nursing, Journal of Nursing Scholarship, Nurse Education Today, Nursing Outlook, Nursing Research, Worldviews on Evidence Based Nursing.

In total, 2889 names of first authors were recorded in the reference years from 2014 to 2018. Of these 83.7% are female and the remaining 16.3% are male (Tab. 1).

Furthermore, in Table 1 it can be seen how the number of scientific papers has increased year by year. In fact, considering in total the magazines selected for our study, it can be seen that the number of scientific papers has increased from 492 research papers in 2014 to 682 papers in 2018.

Furthermore, always in Table 1, the number of scientific papers is also different among the journals considered: the International Journal of Nursing Studies has published 756 research papers in 5 years, while the Nursing Research Journal has published 194 works in 5 years.

Considering the gender differences in the international scientific production of nursing, it is noted that there is no statistical significance considering the years of publication (p=0.249). Instead, the gender difference is statistically significant considering the selected journalss (p=0.021). This means that there is no gender difference in the number of scientific publications over the years, that is, that men have published less and less than women in the years considered and that this gender difference is statistically significant in all general nursing reviews with an impact factor greater than 2.

Moreover, by associating with each first author name in addition to its nationality, it was possible to associate the economic level class to each nation considering the World Bank classification.

As a result, only 3 authors come from low-income countries, 17 authors from lower-middle income countries, 251 authors from upper-middle income countries and 2618 authors from high income countries.

Furthermore, the gender difference is statistically significant (p=0.027) considering the two sexes and the economic level of belonging as variables.

Table 1. Frequencies of nursing studies among the journals considered.

Parameter	Frequency (n)	Percentage (%)	X^2 test p value*
Gender:			
Female	2417	83.7	----
Male	472	16.3	
Total	2889	100	
Publication year:			
2014	492	17	X^2=0.246
2015	589	20.4	p=0.249
2016	558	19.3	
2017	568	19.7	
2018	682	23.6	
Total	2889	100	
Journals:			
International Journal of Nursing Studies	756	26.2	X^2=0.027
Journal of Advanced Nursing	462	16	p=0.021*
Journal of Nursing Scholarship	296	10.2	
Nurse Education Today	578	20	
Nursing Outlook	368	12.7	
Nursing Research	194	6.7	
Worldviews on Evidence Based Nursing	235	8.1	
Total	2889	100	
Income economies:			
Low-income economies	3	0.1	X^2=0.115
Lower-middle income economies	17	0.6	p=0.027*
Upper middle income economies	251	9.4	
High income economies	2618	89.9	
Total	2889	100	

*$p<0.05$ is statistically significant.

Furthermore, in Table 2 all the countries to which the authors belong are highlighted, always divided according to their genre (Tab. 2). It is interesting to note how in the three Countries with a low-economy income, such as: Ethiopia, Malawi and Nepal, the trend in scientific nursing production remains unchanged. In all three countries the only work published in one of the journals included in the research reports a woman as the first author.

Discussion

Although our study, considering scientific productivity, finds itself at odds with the world of current literature since the female gender manages to obtain better results in the field of nursing scientific productivity(16). In fact, numerous studies in the literature report a gender disparity in the number of male authors decidedly higher than the female ones in the academic field for many disciplines, medical and non-medical(17-19).

In the nursing field, this trend is in against trend as the female gender is predominant and in Countries with a poor economy. Therefore, gender disparity exists in the nursing field, but in contrast to other disciplines, medical and otherwise. This against trend found not only in our results but also in numerous studies in the literature could be explained by the predominance of the nursing profession for women. As such, nursing

Table 2. Geographic distribution of nursing studies

Country	Female(n)	Male(n)	Total (%)
Albania	1	0	1 (0)
Aruba	4	7	11(0.4)
Australia	244	53	297(10.3)
Austria	3	1	4(0.1)
Azerbaijan	0	1	1(0)
Bahrain	1	0	1(0)
Belgium	30	15	45(1.6)
Botswana	1	0	1(0)
Brazil	5	1	6(0.2)
Canada	134	24	158(5.5)
Chile	1	0	1(0)
China	136	16	152(5.3)
Cyprus	2	3	5(0.2)
Colombia	0	1	1(0)
Korea, Dem. People's Rep.	0	1	1(0)
Croatia	1	1	2(0.1)
Denmark	21	2	23(0.8)
Egypt	1	1	2(0.1)
Ethiopia	1	0	1(0)
Philippines	2	2	4(0.1)
Finalnd	46	1	47(1.6)
France	10	3	13(0.4)
Germany	16	15	31(1.1)
Ghana	1	0	1(0)
Japan	16	3	19(0.7)
Jordan	5	4	9(0.3)
Greece	1	3	4(0.1)
India	3	0	3(0.1)
Indonesia	2	0	2(0.1)
Iran	7	3	10(0.3)
Ireland	27	11	38(1.3)
Iceland	7	0	7(0.2)
Israel	21	1	22(0.8)
Italy	29	27	56(1.9)
Kazakhstan	0	1	1(0)
Lebanon	10	3	13(0.4)
Malawi	1	0	1(0)

(continued)

Table 2 ***(continued)*****.** Geographic distribution of nursing studies

Country	Female(n)	Male(n)	Total (%)
Malaysia	3	2	5(0.2)
Malta	1	0	1(0)
Papua New Guinea	1	0	1(0)
New Zeland	13	7	20(0.7)
Nepal	1	0	1(0)
Norway	25	5	30(1.0)
Holland	68	12	80(2.8)
Oman	2	5	7(0.2)
Pakistan	3	0	3(0.1)
Palestine	1	0	1(0)
Poland	3	1	4(0.1)
Portugal	5	3	8(0.3)
Czech Republic	4	0	4(0.1)
Serbia	3	0	3(0.1)
Singapore	15	2	17(0.6)
Slovakm Republic	1	0	1(0)
Slovenia	4	2	6(0.2)
Spain	87	30	117(4)
South Africa	8	0	8(0.2)
Korea, Rep.	45	4	49(1.7)
Sudan	1	0	1(0)
Sweden	74	7	81(2.8)
Switzerland	12	8	20(0.7)
Thailand	5	0	5(0.2)
Taiwan, China	31	3	64(2.2)
Tasmania	1	0	1(0)
Turkey	34	3	37(1.3)
United Kindgom	240	87	327(11.3)
United States of America	904	87	991(34.3)
Venezuela, RB	0	1	1(0)
Total	2417	472	2889

profession remains stereotyped as a female occupation(20-22).

In fact, the concept of female profession is embodied in society and men who choose nursing as a career risk challenging traditional gender-defined roles and stereotypes (23).

This is also due to the low remuneration that prevented the man from providing financially for the expenses of his family.

However historically men have played an important role in organized nursing from 330 A.D. during the Byzantine Empire. Moreover, military, religious and lay orders of men known as nurses have a long history of caring for the sick and injured during the Crusades in the 11th century (24). During the Civil war in the USA men served as nurses. In Germany, during the Prussian war 1870-1871 John Simon founded the experimental field hospital in Germany.

The first male nursing school was founded by- Darius Odyen Mills in 1888 in the Bellevue Hospital in New York city, America. This school educated and trained only psychiatric male nurses (25).

Despite the fact that society has forgotten the male contribution to nursing, stereotyping it only with the feminine image and the perception of the male nurse as an anomaly. While nursing is almost all female, there is some evidence of a male predominance in senior positions. This trend is not reflected in the gender bias in authorship. Moreover, an important methodological obstacle to understand gender disparities in the academic world has been the difficulty to reconstruct full publishing careers for scientists of both gender across the several academic population. Consequentially, many of the available gender difference studies are based on case studies limited to specific countries, disciplines and institutions. It is therefore difficult to compare and generalize the results on the academic career possibilities between States of different continents as socio-cultural and legislative contexts are different. This is why in our study we have chosen to consider as a comparison element the genre of the first author of the authorship of magazines with a high impact factor. In literature other studies have adopted the same comparison factor considering also longer periods of time with a lower number of journals.

It would be desirable in future studies to also compare the authorship with the academic title of the nurse authors, highlighting any gender bias.

Our study wanted to photograph the gender situation in the scientific nursing world. The female gender in the reference years 2014-2018 appears to be predominant in authorship as the first name in the magazines considered.

Further studies are desirable to understand if this predominance persists in the working world.

Conclusion

From our data it emerges how nursing turns out to be against the trend in the field of scientific productivity compared to other disciplines. This counter tendency has its origins in the history of nursing which has always been conceived as an all-female discipline, although history has taught us how several male nurses have made their important contribution in the history of nursing.

Further studies may be necessary to confirm this countertendency, such as for example expanding the range of Impact Factor values to be considered, or using other library references with other databases to expand the number of authorships and verify whether this countertendency can still be confirmed and if so the historical stereotype of Nursing connected to the female figure may persist over time.

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Original article: paleopathology

Dental palaeopathology seen through historical, archaeological and biological sources in ancient Herculaneum (79 AD, Italy)

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Abstract. In the mid-eighteenth century, King Charles III of Spain started to explore the ruins of the ancient city of *Herculaneum*. Since then, several medical and surgical instruments made of bronze and iron have been found. The archaeological digs carried out in 1982 in the area corresponding to the ancient shoreline of *Herculaneum* brought to light not only human remains of about 250 victims killed during the eruption of Vesuvius in the year 79 AD, but also remains of carbonised food and other organic-based materials. Collaboration between different disciplines, including Archaeology, Physical Anthropology, History of Medicine, History of Odontostomatology and Palaeopathology, can provide us with more comprehensive pictures of diseases of the past, not only based on historical, literary and archaeological sources, but also directly on human remains. Through such an interdisciplinary approach, valuable information can be obtained on pathologies of the oral cavity and their distributions, on medical therapies and treatments, and on accessibility to healthcare, including odontostomatological care. An integrated study has allowed us to obtain useful data to reconstruct the habits and lifestyles of the ancient people of *Herculaneum*. In this report, three cases are presented to illustrate the importance of integration of data inferable from such different sources.

Key words: dental palaeopathology, *Herculaneum*, archaeological sources, historical sources, anthropological sources

Introduction

The ancient city of Herculaneum was located in the centre of the Gulf of Naples (Campania, Italy), and spread along the low hillsides of Mount Somma–Vesuvius. The fame of Herculaneum is due to the catastrophic volcanic eruption of Vesuvius that has been dated to the year 79 AD (1). The details of the sequence of relevant disastrous events consequent to the eruption of Vesuvius have been handed down to us by Pliny the Younger, the grandson of the General of the Roman fleet Pliny the Elder. In the famous letter that Pliny the Younger wrote to Tacitus to inform him of his uncle's death, the gravity of the circumstances can be perceived immediately. This indicated that over a very short time, the pyroclastic flows that rapidly descended the hillsides of Vesuvius buried entire cities and their inhabitants under tens of metres of volcanic material (2).

The first sporadic explorations of Herculaneum started under the patronage of King Charles III of Spain, in the XVIII century (3), and these contributed to the accidental rediscovery of this city. However, it was only between the 1920s and 1950s that there were substantial changes in the history of the research conducted in *Herculaneum*, due to the appointment of

Amedeo Maiuri as Superintendent of the Excavations and Antiquities of Campania. The start of these profitable open-pit excavation campaigns had significant impact on the definition of the urban and suburban layout of the ancient city, as well as on the rediscovery of its inhabitants (4). The research conducted in the 1980s under the direction of Giuseppe Maggi was then fundamental. Indeed, in these years the new data that emerged during the excavations of the vast suburban area of *Herculaneum* shed new light on many aspects of the inhabitants that had until then remained unsolved. Unlike *Pompeii*, where hundreds of human remains were found of those who encountered their death during the eruption, in *Herculaneum*, the almost total lack of victims within the city led to the hypothesis that most of the inhabitants had managed to escape before the city was completely buried (5).

From 1982, hundreds of human remains belonging to the protagonists of the huge tragedy that followed the eruption were found on what was identified as the ancient shoreline of *Herculaneum* (6–10). This was even more sensational following the discovery of further human remains inside and in the immediate vicinity of the western *fornici* (port warehouses) (11).

It was in these two areas that the first of the six pyroclastic flows (known as *surge I*) that reached *Herculaneum* during the final stages of the eruption killed those who had survived until then. Studies conducted on the remains of the victims have provided useful data that have allowed clarification of the possible dynamics that led to the deaths of hundreds of *Herculaneum* inhabitants. For those who had still been unable to find shelter or refuge inside the port warehouses, their deaths were probably instantaneous due to the rapid exposure of the bodies to the intense heat of the pyroclastic flow. This is different from those who had managed to access the port warehouses by this time. From studies of the chromatic and thermal alterations suffered by the bones of those who were found in and near the port warehouses, it appears that they did not suffer the direct effects of the violent thermal exposure of *surge I*. In this case, it is likely that their deaths occurred as a result of burn shock, without excluding possible serious obstruction of the respiratory tract as a consequence of inhalation of the ashes contained within the pyroclastic flow (7,12,13). The arrival of successive flows of mud and pyroclastic materials definitively buried the remains of the inhabitants of this ancient city, thus sealing them for centuries in their final positions at the time of their deaths. The singularity of these circumstances of the burial of *Herculaneum*, together with the exceptional nature of the main cause of death of its inhabitants and the extraordinary state of conservation of the archaeological and osteological material, has provided researchers with a unique opportunity to reconstruct the lives and ways of life of its inhabitants.

The considerable osteological sample on which it was possible to conduct multiple interdisciplinary studies has allowed a more in-depth picture to be constructed of the last moments of life of those who had tried in vain to find shelter in environments that they deemed most safe, and who had hoped to flee by sea. This population has thus provided considerable information on an ancient community whose people did not die from natural causes or following illness, but from a catastrophic natural event.

The relevance of integrated and interdisciplinary studies

In recent years, the growing interest in the status of health and disease of ancient populations has generated ever-closer collaborations between different disciplines. These here have included Archaeology, Physical Anthropology, History of Medicine, History of Odontostomatology, Palaeopathology, and other related disciplines.

In the case of *Herculaneum*, the palaeobiological studies carried out on the osteological remains of the victims of the eruption have already provided large amounts of useful information. This has included an understanding of not only the habits and lifestyles of the victims, but also their status of health and the pathologies with which the general population was afflicted. These osteological remains constitute the primary source through which it is possible to derive direct information about medical or dental interventions, although it is not always possible to observe the results of these operations at a macroscopic level. Therefore, there is the need for interactions between data inferable from the interpretation of the material evidence that survives in the archaeological artifacts (including medical and surgical instruments), and the study of the biological remains of an osteological or organic-based nature, without neglecting the data obtainable from literary sources. For example, the instruments and remains of organic-based substances that can be associated with odontostomatological treatments and practices make it possible to trace their field of use. However, the medical texts may well be the valid tool for an understanding of the real dental skills and knowledge in the ancient world.

Therefore, using such interdisciplinary approaches, efforts are being made to understand the pathologies of the oral cavity and how these pathologies were distributed in this population of *Herculaneum*. Once all possible useful historical, social and cultural information has been obtained, this can help us to understand on the one hand what therapies were applied or applicable to promote the maintenance of good health of the oral cavity, and on the other hand what surgical procedures were known and exercised by the Roman physicians at the time of the eruption. In this perspective, the main sources of information have allowed an in-depth picture on these topics to be defined: (i) direct biological sources represented by the osteological and dental remains of the victims of the ancient city; (ii) literary sources coeval to the I century AD; and (iii) archaeological evidence related to elements associated with treatment of dental pathologies; e.g., surgical instruments, food and other organic-based remains.

Biological sources

Palaeopathology is the scientific discipline that deals with investigation and reconstruction of the state of health and disease of ancient human skeletal remains. It is considered to be one of the primary sources through which bioanthropological information can be obtained. The teeth are not only the most highly mineralized tissue of the human body, but also the hardest and most chemically stable ones. Indeed, teeth are preserved even after the deterioration of their supporting structures. Furthermore, in contrast to bone tissue, teeth interact directly with the environment during chewing, and for this precise reason, they can provide information on both the type of diet and the health of an individual.

Literary sources

Aulus Cornelius Celsus and Scribonius Largus were two of the main medical authors for the writing of technical–scientific treatises on *Ars Medica* in the I century AD. They both provided exhaustive and sufficiently detailed summaries on the dietetics, pharmacology and surgery of the time. However, the works of Pliny the Elder and Pedanius Dioscorides are no less important.

Aulus Cornelius Celsus

The encyclopaedist Aulus Cornelius Celsus is particularly significant here, as he handed down to us what is considered to be the first systematic treatise on theory and medical practice of the I century AD: *De Medicina*. These eight books make up the corpus of a treatise that not only carefully and thoroughly illustrates the complex medical and surgical panorama of his time, but also allow better delineate of the specific aspects of the general medicus and the chirurgus. As indicated in the preface of the seventh book of *De Medicina*, the medicus chirurgus was considered to be a professional figure who specialized in body care through application of a skilful, young and firm hand (14).

Of further interest, Celsus traced an exhaustive and meticulous picture of the individual and specific symptoms associated with innumerable pathologies, along with their relevant treatments. Therefore, this treatise is a true encyclopaedic collection of all of the therapeutic and surgical treatments known at the time, to combine the high anatomical and physiological knowledge of the time with the instrumental knowledge of Celsus.

Several surgical instruments were mentioned for which the uses are reported in terms of both general and more specific interventions. Although most of the Roman medical instruments were indeed multifunctional, for dental practices Celsus referred in particular to two specific tools. In Chapter XII of Book VII, the encyclopaedist mentioned the *forfex* and the *rizagra*, referring to diseases of the mouth that required the work of the hand.

Convinced of the importance of pharmacology, Celsus referred to an analgesic therapy in relation to dental pathologies. From what is detailed in the *De Dentibus* section, immediate extraction was not always suggested for toothache. This intervention was expressly recommended only if various plant-based medicines did not improve the pain, or when the tooth was loose enough to be extracted without consequences for the periodontal bone of the maxilla or mandible. Also, in relation to the danger of this intervention, for the maxillary dentition, Celsus mentioned possible bruising related to the temples and the eyes. In this case, he considered it essential to first incise the gingiva to prepare for the release of the tooth, which was then extracted with forceps. It was also important that the tooth was extracted straight, to prevent the roots from breaking the bone in which it was held, particularly for the molars. Similarly, extraction of teeth fractured due to caries could also pose a risk in terms of laceration of the bone under the gingiva. For the treatment of caries, among the suggested analgesic remedies there was the use of an ointment prepared with hot flour and figs, that was applied both inside and outside the oral cavity. On the other hand, for severe carious cavities with consequent gingival suppuration and with extraction being necessary, Celsus indicated that the cavity should be filled with a lead amalgam. This was designed to avoid breaking the dental crown during the intervention, which was carried out using the *rizagra*. An alternative to the use of lead amalgam and instrumental extraction of the crown was seen by the use of a zested peppercorn or an ivy berry, which would facilitate the fragmentation of the crown itself. More generally, to relieve toothache, which was considered among the worst pains that one could suffer, Celsus believed that it was useful to keep in the mouth an astringent solution based on cinquefoils root mixed with wine, or henbane root combined with salt and zest of poppy boiled in wine and mixed with honey (14). The juice of figs cooked in vinegar were equally useful as an analgesic, which were mixed with *mulsum* and apples. As an alternative to these remedies, he suggested the application to either the cheeks or directly to the sore part woollen bandages soaked in a compress based on zest of unripe and dry pomegranate mixed with zest of pine, opium, galbanum, myrrh or cardamom.

For stomatology and pathologies of the soft parts of the oral cavity, such as mouth ulcers and suppurations of the gingivae and aphthae, the danger of these pathologies was stressed beyond the difficulty of therapeutic treatment (15). Even in this case, before carrying out surgery, Celsus believed that efforts should first be made to treat both the inflammation and the most serious ulcers using topical treatments based on compresses made with the same natural substances used for dental pathologies. Similarly, the knowledge of useful practices for complete healing of fractures and dislocations inherent to the mandible and maxilla was vast (14).

Scribonius Largus

Scribonius Largus was another important figure in the panorama of the history of medicine inherent to the pharmacology and treatment of pathologies of the oral cavity. Contemporary to Aulus Cornelius Celsus, Scribonius handed down one of the most valuable and detailed pharmacopoeia treatises of the ancient Roman world: the *Compositiones* (16).

In his work, Scribonius reported the nomenclature of more than 200 species of plants and about 100 mineral and animal-derived substances that were used for the preparation of countless drugs. The 271 medical recipes are meticulously ordered based on the diseases that affected the human body from top to bottom, from head to foot, and from general to specific (17). Scribonius was scrupulous in his details of the compositions of the drugs, the doses of the ingredients, the methods and timing of the administration, and in some cases, the description of the equipment and the containers necessary for their preparation. These details also showed particular knowledge in relation to both the toxicities of some substances and his direct experience in the practice of medicine (18).

Like Celsus, Scribonius also referred to painful affections of the teeth and gingivae and the most serious pathologies relating to the mouth, throat and uvula, which included the *cancer os corripit*: mouth cancer (17). On buccal affections, Scribonius clarified the importance of carrying out differential diagnosis to distinguish the abscess (parulis) from the benign neoplasia (epulis), which originates from the gingival mucosa. In the treatment of painful phenomena associated with teeth, Scribonius stressed the importance of using analgesic preparations, with most used as mouthwashes based on cinquefoils herb root cooked in wine, or alternatively based on cypress berries decocted in water. As an alternative to mouthwashes and decoctions, Scribonius recommended application directly to the teeth of a poultice based on henbane root that had previously been boiled in water and was subsequently wrapped in linen bandages. As an alternative analgesic therapy, the *Compositiones* also suggested direct chewing of wild mint leaves, purslane, pyrethrum root and oleander leaves, all of which are vegetable substances recognized for their sedative, analgesic, astringent, anti-inflammatory and antibacterial properties. When the pain disappears, to prolong the soothing effects of the medicaments, it was necessary to spread a poultice composed of giant hogweed juice, incense and seedless raisins directly to the tooth. If the teeth loosen, it was considered appropriate to consolidate them by gargling using donkey milk or hot wine, to which dock or sorrel roots had been added. In this regard, it was also useful to apply a remedy based on alum and honey, or alum amalgamated with sour vinegar and cedar resin. When the gingivae were painful, Scribonius recommended the application of soft wool balls soaked in very hot oil.

Based on its emollient and water-repellent properties, the use of wool in the medical field was highly appreciated, both as a means of containing or absorbing compresses, and for covering surfaces affected by contusions, fractures or wounds. The choice to use treated wool as an adjuvant in the application of medicaments was well expressed in the treatise of Scribonius and in *De Medicina* and *Naturalis Historia*. Specifically, Celsus and Scribonius referred to the use of wool treated and soaked in sulphur, which was known for its anti-inflammatory properties, to both soothe a toothache and as a bandage to protect the head in case of parotid affections. Pliny the Elder also gave indications for the use of treated wool, which he said should be soaked in olive oil, wild fig juice, vinegar, old wine or honeyed wine, to both relieve toothache and heal general affections of the mouth (19).

Pedanius Dioscorides

Some decades after Scribonius, there was Pedanius Dioscorides, who was a Greek physician, botanist and pharmacologist who practiced in Rome at the time of the Emperors Claudius and Nero. In his vast *Materia Medica*, Dioscorides defined in detail the medical uses of plants, minerals and diverse products of animal origin. It is interesting that innumerable therapeutic properties were recognized for all of the substances described. For the problem of faltering teeth, toothache or carious cavities, Dioscorides suggested a medicament based on a specific mineral substance: the *sori*. Furthermore, for the treatment of gingivitis and aphthae, or only to strengthen teeth that were no longer fully firm in the alveolus, Dioscorides recommended the use of schistose mixed with vinegar or honey (20).

Pliny the Elder

The *Naturalis Historia* of Pliny the Elder has also been dated to the I century AD, in which an immense amount of information was collected about the medical knowledge of his time (21). Indeed, it includes extensive descriptions of substances of animal, mineralogical and botanical origin that were used for the preparation of innumerable medicaments. For dental precepts, Pliny the Elder focused on various problems relating to the oral cavity, as the treatment of toothache and the healing of caries. Unlike Celsus and Scribonius, who showed a more scientific approach to these problems, Pliny the Elder also made numerous references to magical or ritual practices that involved the use of decoctions or mixtures based on things like frog hearts and earthworms boiled in oil, or the ashes of wolf or fox heads, and bull bile. Nevertheless, in *Naturalis Historia* he also considered it appropriate to use analgesic mouthwashes based on medicinal herbs that were known for their soothing and anti-inflammatory properties, such as mallow, giant hogweed and henbane root.

Archaeological evidence

Medical and surgical instruments

The discovery of a considerable number of surgical instruments in both *Pompeii* and *Herculaneum* testifies that the knowledge in the medical field was already relatively advanced when these two cities were destroyed (22). In the dental field, the Roman physician would probably have made use of a vast *instrumentarium*, which would have included several elements, such as the *forceps herculanensis* and the *rizagra*, as cited by Celsus (14,23). The first of these, the *forceps herculanensis*, was a bronze instrument made up of two curved, notched and joined branches interpreted as *odontagra*, and was useful for the removal of unstable teeth within its alveolus (24). However, although the rizagra was probably a multifunctional tool, in the dental field it was interpreted as pliers, for extraction of dental roots.

Remains of carbonised food

The archaeological site of *Herculaneum* is unique in its kind, as the pyroclastic material produced by the eruption of Vesuvius not only buried and sealed the city, thus killing its inhabitants, but also resulted in carbonization of diverse organic-based materials, such as wood and food. The remains of innumerable foods not only made it possible to understand how the diet of inhabitants was very rich and varied, but also offered new perspectives on the relationships between health and nutrition in the Roman period (25). Food had a key role in Roman medicine, as many foods were recognized as having healing properties for various diseases.

Dental palaeopathology seen through the diverse sources of information

Below we provide three examples that illustrate the importance of integrating data from these different sources of information.

Plants, food and therapeutic remedies in the I century AD

In the ancient world, the boundary between substances of vegetable and animal origin that are normally consumed as a meal or for medicinal purposes was very blurred. It is not infrequent that written sources indicate the names of plants and foods to be used in the preparation of drugs. These drugs were mostly composed of medicinal plants or foods known for their calming, astringent, antibacterial, anaesthetic and antiseptic properties, and they were processed differently depending on the part used and on the result that was desired. Most of the substances were first macerated or mixed with water, oil, wine and honey. Subsequently, they were generally administered through the skin and mucous membranes in the form of ointments, infusions, decoctions, poultices, powders and mixtures.

Celsus, Scribonius, Pliny the Elder and Dioscorides provided examples of the *continuum* perceived in these ancient times between dietetics and medicine. Furthermore, for pathologies that affected the masticatory system, they referred in their works to the intake of specific fruits, vegetables and substances of animal origin, including honey (26). In light of these considerations, it is essential to try to define any possible correlations between the organic remains found in *Herculaneum* and the possible curative remedies applied both generally in the medical field, and more specifically in the odontostomatological field. For example, among the organic remains preserved, the figs and pomegranates are of particular interest, as the use of these two specific fruits (both fresh and dried) was recommended to relieve toothache, and to treat pathologies inherent to the soft parts of the oral cavity. Generally, once the pomegranates and figs had been collected, they were stored under several layers of straw before being crushed using a press, to improve their drying (27). Analyses carried out on samples of these specific fruits revealed how this particular conservation method resulted in the proliferation of actinomycetes, such as *Streptomyces* spp. These were then unknowingly ingested by the inhabitants, together with the antibiotics that they produced (28). On the other hand, the study of bone remains has shown how the ancient inhabitants of *Herculaneum* took doses of antibiotics during their lifetime (e.g., tetracyclines, streptomycins). It has been hypothesized that the Romans unknowingly produced these natural antibiotics and ingested them for therapeutic purposes, by ingesting fruits contaminated with *Streptomyces* spp.

Indeed, although the consumption of pomegranates and figs was probably intermittent, and although the levels of natural antibiotics that they contained would have been relatively low, there was low frequency of non-specific bone infections in *Herculaneum*. Furthermore, there was low incidence of inflammatory processes localised to the tissues adjacent to the apex of the dental roots (i.e., periodontium and alveolar bone).

For medical treatments, medicines based on *Punica granatum* (pomegranate) or *Ficus carica* (fig) were also suggested for the treatment of mouth and tongue ulcers, canker sores, gingivitis, and diverse pathologies related to the palate and uvula, and also for when the gingivae withdrew from the teeth. Recent studies have confirmed that the ingestion of pomegranate leaves, fruit, seeds and bark is useful to counteract the actions of various pathogens, due to their antifungal and antimicrobial properties (29). In contrast to the scarcity of non-specific diseases, there was high incidence of infectious pathologies, such as brucellosis. This suggested the hypothesis that not all of the inhabitants obtained regular doses of natural antibiotics through their food. Although it cannot be said with absolute certainty that there was any correlation between ingestion of foods containing natural antibiotics and the treatment of some infectious diseases, it is believed that these protected part of the population from infections (30).

Thus, the biological and archaeological evidences support the literary sources, where Pliny the Elder, the pharmacologist Dioscorides and medical authors as Celsus and Scribonius list the medicinal uses to which specific fruits, such as pomegranate, were intended for their remarkable properties.

Environmental factors and their influence on dental pathologies

Analysis of the dentition of the ancient inhabitants of *Herculaneum* revealed low incidence of infectious pathologies. In contrast, there was higher frequency of individuals who suffered from dental enamel hypoplasia, which is a pathology associated with a physiological disorder of enamel formation during childhood. As the enamel cannot be remodelled through life, defects in the development of enamel can be clearly seen, to provide a snapshot of the moment when the period of physiological stress occurred.

To determine how much of the information reported in historical sources can be confirmed by biological sources, a study was carried out on the dentition affected by enamel hypoplasia. The aim was thus to identify any correlations with the disastrous earthquake of 62 AD, as mentioned by Lucius Annaeus Seneca, Publius Cornelius Tacitus and Gaius Suetonius Tranquillus. The data obtained showed that among the victims, there were two age groups that showed relevant models of enamel hypoplasia; a first peak occurred among the individuals who were approximately 6 years old at the time of the earthquake, and a second group involved those who had undergone a moment of severe physiological stress approximately 10 years before the earthquake. From a bio-anthropological point of view, the bimodal distribution of enamel hypoplasia can be interpreted as the consequence of two different historical moments that were characterized by instability in the supply of food resources or by a lack of hygiene conditions, with the consequent epidemic episodes. Considering the ages of the individuals who showed the first peak of enamel hypoplasia and the date of the earthquake of 62 AD, there indeed appears to be a correlation between these two events (31). The high proportion of individuals with enamel hypoplasia has also been interpreted by some as a consequence of endemic fluorosis (32). In such cases of marked hypomineralisation and severe alterations of the enamel, a correlation has been proposed between a form of chronic fluorosis and an excessive content of fluorine in the drinking water (33). On the other hand, in the Vesuvian area, the presence of toxic levels of fluorine in the soil and the aquifers can be associated with its geovulcanological nature. Indeed, during volcanic activity, Vesuvius released fluorine in a highly soluble form, which will have easily penetrated the underground layers and subsoil. In many cases, this would have then entered plants and waters subsequently ingested in the daily diet of the local population. The high concentration of fluorine in most of the teeth of the *Herculaneum* inhabitants is important evidence that they mainly drank heavily contaminated groundwater.

Therefore, the historical evidences provided by Seneca, Tacitus and Suetonius, together with geovulcanological and archaeological information, report on how the consequence of diverse environmental factors could influence the health of the inhabitants of *Herculaneum* prior to their death by the eruption of

Vesuvius, being this information supported by the biological sources.

Dentists and applied dentistry

Generally, in the first Imperial period, the figure of the *medicus*, and even more that of the dentist, remains to be defined. It is not possible to establish with certainty who specifically dealt with surgical or topical treatments of pathologies inherent to the oral cavity. For the dental profession, it is not certain whether these professionals were specialized physicians, as we understand today, or if they were figures who generally dealt with the treatment of various pathologies that included those associated with the oral cavity. Nevertheless, as deduced from the medical treatises, even if the figure of the dentist was not well defined, there were different therapeutic treatments and surgical procedures known and applied in the dental field.

The medical treatises of the I century AD testify that extraction was the most widespread dental practice, which was considered to be particularly dangerous when not performed correctly and with a skilful hand. Indeed, an unsuccessful intervention might prevent correct healing of the periodontal bone. It is plausible that the first professional dentists were aware of having to completely remove both the tooth and the root using specific tools that were suitable for this surgery. In general, although direct evidence of dental extractions is relatively rare for the ancient world, the discovery of a *taberna* that was apparently used by a barber–dentist at the Temple of Castor and Pollux in the Roman Forum shed new light on the subject (34). The research conducted on the numerous teeth, instruments and containers for medicaments found in this environment, led to the hypothesis that there was in Imperial Rome the figure of an expert professional who practiced systematic and accurate dental extractions (35).

Further archaeological evidence on the dental techniques applied in relation to the instability of the teeth was provided by the discovery of a dental prosthesis in the Roman necropolis of Viale della Serenissima in Rome. This dental bridge was created with the support of gold thread, and testifies directly to the implementation of these dental precepts that were well documented in literary sources (36). For the *Herculaneum* context, although the loss of *antemortem* teeth was frequently recorded for the victims of the Vesuvian eruption, no orthodontic appliances, or remains thereof, were found, along with no more general evidence of surgical treatments associated with dental extractions.

However, although hypotheses about these possible practices cannot be advanced, studies carried out on the oral cavity of a victim allowed the description of a case of healed maxillofacial fracture. This applied to an adult female individual whose examination of the maxillofacial region revealed evidence of dislocation and fracture of the mandibular right condyle, as well as traumatic dental injuries. The traumatic injuries observed were interpreted as the result of a probable violent impact that directly involved the chin region. In this case, the force of the impact was then transmitted in the direction of the mandible, maxilla and the related teeth. In particular, the indirect impact between the two dental arches resulted in fractures of three dental crowns. The morphology of the lesions, together with the location and their extension, suggested that these occurred following an accidental fall, which would have occurred when the individual was aged between 7 and 15 years old (37). Unfortunately, there was no certain evidence of any medical surgical intervention practiced for treatment of the fracture of the mandible and its relative dislocation, although it is certain that no dental extraction was performed.

Therefore, it is deduced from the medical treatises coeval to the I century AD, such as those of Celsus and Scribonius, that there were different therapeutic treatments and surgical procedures known and applied in the dental field, with archaeological evidences supporting this information. Unfortunately, at this moment, among the biological remains from *Herculaneum* no evidence has been found of the practice of medical-surgical interventions or therapeutic treatments.

Conclusions

The analysis of skeletal remains not only allows the study of the history and evolution of diseases of past populations, but also allows reconstruction of their health conditions. Furthermore, the collaboration between different disciplines has provided a more comprehensive and in-depth picture of diseases of the oral cavity in the *Herculaneum* population. In particular, this relies not only directly on the human remains, but also on historical–literary and archaeological sources.

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Case report: paleopathology

Exhumation and anthropological study of the skeletal remains attributed to Liutprand, King of the Longobards (690 ca AD-744 AD)

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Abstract. Liutprand, one of the greatest Longobard sovereign, was born at the end of the 7th century and died in 744 at the age of about 55 years. According to the Historia Langobardorum of Paolo Diacono, he was King of Longobards from 712 to 744. The bones of Liutprand suffered from many translations in the centuries and this is the main problem for the validation of the authenticity of the remains. The bones appeared extremely fragmented and in a poor state of preservation. We performed imaging studies (CT and RX), ^{14}C dating and isotopic analyses. According to anthropological examination, most of the remains belonged to a robust male with strong muscular insertions and an age of death between 40 and 50 years. Moreover, three left tibiae were detected, one of which presented an altered and enlarged proximal diaphysis by bone thickening due to a severe form of osteomyelitis. The presence of a circular depression with a diameter of about 10 mm at the point of maximum thickening could represent the trace left by a pointed object that caused the perforation of the bone and the subsequent infection with osteomyelitis. ^{14}C dating indicated that only one individual lived in the era compatible with that of Liutprand, while the other two were more ancient, albeit a few decades, to the Longobard king. Isotopic data showed a rather high nutritional status, with a varied diet rich of meat and fish. Currently it is not possible to define the identity of the three individuals for lack of archaeological data and for the fragmentary nature of the bones. The age of the subjects, the robust constitution and the nutritional data suggest a belonging to a high social class, perhaps devoted to war activity.

Key words: Liutprand, Longobards, osteology, osteomyelitis, paleodiet

Introduction

Liutprand, son of Ansprand and Theodorada, was one of the greatest Longobard sovereign and King of Italy from 712 to 744. The fundamental source about the information on his life is the *Historia Langobardorum* of Paolo Diacono, where his military exploits and political qualities are narrated (1). However, little is known about his early life. He was born in the late 80s or early 90s of the 7th century and died at an approximatively age of 55 years. Once received the crown, he reorganized the kingdom, improving the administration of justice and taxation, and promulgating hundreds of laws, becoming, after Rotari, the most active Longobard legislator. He defined himself as a 'Catholic king' and the Longobard as 'Catholic people' and strived for the strengthening of the Church. He increased the possessions of the kingdom, but died while negotiating with Constantinople in January 744.

The remains of king Liutprand suffered from many translations in the centuries, and this is the most problematic issue to recognize the authenticity of the osteological remains. The first grave was in the chapel of Sant'Adriano, where Ansprand, father of Liutprand, was buried some years before the son (1). The chapel was part of the Longobard cemetery of Santa Maria *ad Perticas* (Pavia, north of Italy), no longer existing. According to the willing of the Abbott Ulrico, in the second half of 12th century the remains of Liutprand were translated in the Cathedral of San Pietro in Ciel d'Oro and located in a monumental mausoleum (2). A new translation took place after the Council of Trento: the bones were placed in a niche in the floor of the church, in front of the first right column of the choir (2).

At the end of July 1895, after finishing the restoration of the aisles, the vaults, the roof and the perimeter walls of San Pietro in Ciel d'Oro, the renovation of the paving of the church started from the first two pillars to the main entrance. At a depth of about 25 cm a 85x37x28 cm lateritious case containing several bones was found. Once extracted together with fragments of corroded wood and some nails (which would suggest that the remains were first locked in a wooden cassette), the priest and historian Majocchi transported the remains to the Civic Museum of History, of which he was curator from 1894. Prof. Dr. Rodolfi and Prof. Zoja of the University of Pavia, with assistants Dott. Bergonzoli and Fiammenghi performed the anthropological analyses of the bones in order to seek correspondence with the physical description of the Longobard King made by the chronicles. After this first modern survey (2), the bones were posed in a new niche in the base of the pillar where they were found in January 2018 during the exhumation performed by our Division.

Materials and methods

The bones, contained in a wooden box dated to the end of the 19th century, appeared extremely fragmented and in a poor state of preservation. The anthropological studies took place on site in a temporary laboratory set up in the premises annexed to the Cathedral. Standard methods for anthropological examination of the skeletal remains were used to reconstruct the biological profile of the subject (3). The minimum number of individuals was determined on the basis of the most represented bone, while the individual reconstructions were obtained by associating the bones for strength, size and symmetry (4). Sex was assessed on the basis of the morphological features of the pelvis (5) and of the single bones based on discriminatory metric methods (6, 7, 8). Age was determined on the morphological variations of the pubic symphysis (9), of the auricular surface of the pelvis (10, 11), on the dental wear (10), on the reduction of the dental pulp with ageing (12) and on the variations of the sternal extremities of the ribs (13). The study of dentoalveolar pathologies was performed according to the methods described by Minozzi and Canci (14), while the age of onset of enamel hypoplasia was calculated using Reid and Dean's method (15). Stature was calculated by Trotter and Gleser's regression formulae (16, 17). As for the development of muscle attachments, the method of Mariotti and coworkers (18, 19) was used. Analysis of stress markers (i.e. enamel hypoplasia and Harris lines) and paleopathological evidences were performed to obtain information on lifestyle and health conditions (20, 21).

Imaging studies (CT and RX) on the skeletal remains selected among the most intact or of paleopathological interest were performed at the "San Matteo" General Hospital in Pavia. For the digital radiographs, an Italray X-FRAME DR workstation was used with the following parameters: 0,4-0,6 mAs, 50-120kVp and FFD (Film-Focus distance) 110 cm. CT images have been acquired with a GE VCT Lightspeed 64s machine with 32-36 cm FOV (Field Of View), 0,625 mm section thickness, 99 mAs and 120 kVp.

Some samples of bone fragments were selected in order to make ^{14}C dating. Samples from the three tibiae have been chemically pre-treated in the 'Laboratory for isotopic measurements' of the Department of Environmental, Biological, and Pharmaceutical Sciences and Technologies (DiSTABiF), University of Campania 'Luigi Vanvitelli'. The radiocarbon content have been quantify via Accelerator Mass Spectrometry (AMS) in the INFN – LABEC laboratory (Laboratory of nuclear techniques for Cultural Heritage) of Florence. Calibration of dating results was obtained using OXCAL software v.4.2 – IntCal13 (22).

Finally, stable isotope analysis was conducted on the bones of the three individuals to gain nutritional information (carbon and nitrogen isotopes in compact bone). The samples were prepared and measured at the "IRMS Laboratory" of the University of Campania 'Luigi Vanvitelli' (Italy), and were processed to isolate the organic phase (collagen) by adopting a modified procedure from the Longin method (23). The instrumentation used for the measurement consists of a Delta V Advantage Mass Spectrometer (Thermo Scientific) coupled with an EA 1112 Series Flash Analyser (Thermo Scientific). Finally, the quality of the extracted collagen is always checked by verifying the parameters suggested by De Niro (24).

Results

Anthropological analyses

The bones were very fragmented and in a poor state of preservation. During the previous exhumation labels with the name that identified the bone had been affixed on the fragments; the relative identifications were almost all correct. Some segments showed traces of glue due to attempts of restoration. Despite the high fragmentation, it was possible to identify most of the bones and divide them into their anatomical districts. When possible, the restoration and reconstitution of the skeleton using vinyl glue was performed.

Anthropological examinations allowed attributing most of the fragments to a robust adult male (called Liut X), whose skeleton is however incomplete. The attribution was made based on the bone dimensions, cortical thickness, and presence of ageing signs (degenerative joint disease). We have identified only few fragments of the skull, including two small pieces of the temporal bone and fragments of the maxillary arch with the relative teeth, mainly represented by the posterior teeth, and two isolated mandibular molars. The maxillary dentition presented dentoalveolar diseases, such as a slight reabsorption of the edges of the alveoli and an alveolar pocket, due to periodontal disease. The two premolars and the second right maxillary molar showed erosion of the collar due to caries. Calculus was present on almost all maxillary teeth. The wear on the occlusal surfaces suggested an age of death between 35 and 50 years, which was also confirmed by radiographic examination of the maxillary canine, which, based on the reduction of dental pulp, indicated an age between 43 and 50 years. Some hypoplastic lines on the surface of the front teeth indicate at least three episodes of stress, due to illness or malnutrition, occurred in childhood (between 2.3 and 3.4 years of age). Two fragments of a robust right clavicle with marked muscular insertions and few fragments of ribs represented the skeleton of the trunk. The sternal extremity of a rib suggested an age of 35-45 years. There were only two vertebrae, medium-sized and without arthrosis, and some fragments of the sacrum. The bones of the pelvis were represented by a large left acetabulum, some fragments of the iliac ala and the pubic symphysis, all compatible with a robust male individual between 35 and 45 years. The appendicular skeleton was represented by both large and robust humeri, with very strong development of some muscle insertions. Of the forearm only the proximal and distal epiphyses of the right radius, without arthrosis on the articular surfaces, remained. Of the hand, we detected only the third and fourth right metacarpals, without alterations.

The lower limbs were represented by an almost complete right femur and by several fragments attributable to the left controlateral, medium-large sized and with strong muscular insertions. The head of the femur was compatible in size with the acetabulum of the pelvis. There were also numerous fragments of femur that were difficult to attribute, but the reconstruction and restoration of the fragments of the *linea aspera* already present in the femurs attributed to Liut X, allowed to identify a second adult male with the same robustness and dimension of the first subject. As for the tibia, the situation is more complex, since we detected three left tibiae not certainly attributed to any subject for lack of clear matches (Fig. 1). Two tibias, represented by segments of diaphysis and distal epiphysis, belonged to two adult males, called Liut B and Liut C, similar for morphology and muscle development. The radiological examination of the tibia of Liut B showed a single Harris line, or of growth arrest, referred to an episode of stress occurred between 13 and 17 years of age, while the individual Liut C, besides evident signs of fusion of the epiphyseal cartilage of growth characteristic of a young adult, revealed several striae of Harris formed between 18 and 20 years of life (Fig. 2)

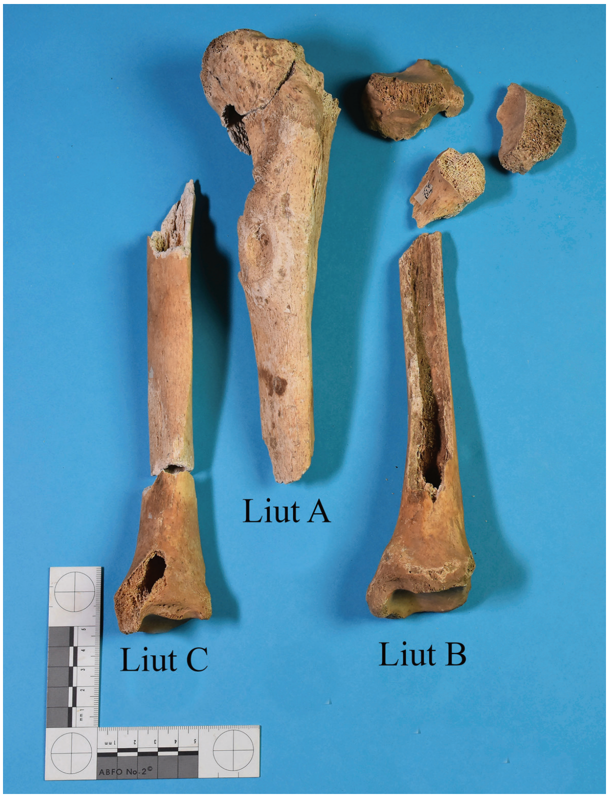


Figure 1. The three left tibiae (called Liut A, B and C).

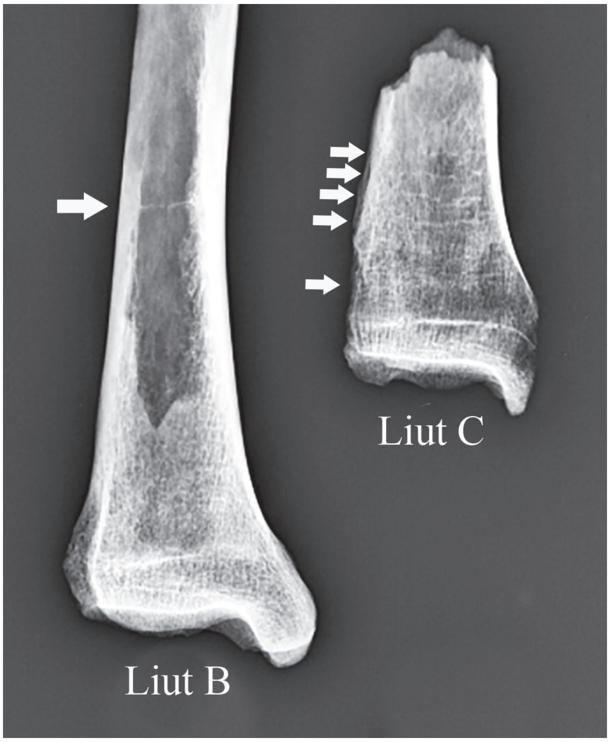


Figure 2. TC examination on the distal tibiae of Liut B and C. The tibia of Liut B (left) showed a single line of Harris, while the bone of Liut C (right) revealed several striae of Harris formed between 18 and 20 years of life.

(25). The third tibia, attributed to a male called Liut A, showed evident pathological alterations. Indeed, the upper third of the diaphysis was completely altered and enlarged by bone thickening due to a severe form of osteomyelitis. The presence of a circular depression with a diameter of about 21 mm at the point of maximum thickening represents a cloaca with signs of bone repair (Fig. 3a). The reparative process has however led to the healing of the lesion before death, which should have occurred between several months and a pair of years after the traumatic event (Fig. 3a'). Computed Tomography and 3D Computed Tomography reconstruction highlighted the 0.7 mm raised crateriform lesion, centrally depressed, with blunted edges (fig. 3b-c). The bottom of the lesion showed no fistula or cloaca, thus suggesting a complete healing of the disease. The right distal epiphysis and some diaphysarian segments of both sides of the fibula, the left astragalus and calcaneus, and some mid-sized metatarsals were non-attributable.

In summary, most of the remains are attributable to a medium-large, robust male with strong muscular insertions, and with an age of death between 35 and 45 years (Liut X). Few bones belonged to a second adult male with strong muscle insertions, and of similar strength and size, and to a third male subject of medium size and young age (Liut C).

Carbon-14 dating

The analyses provided a range between 430 and 770 AD (Fig. 4) In particular, the pathological bone (Liut A) belonged to a male who lived between 430 and 640 AD, therefore about a century before Liutprand. The second subject (Liut B) lived from 600 to 770 AD, while the last individual (Liut C) had a range

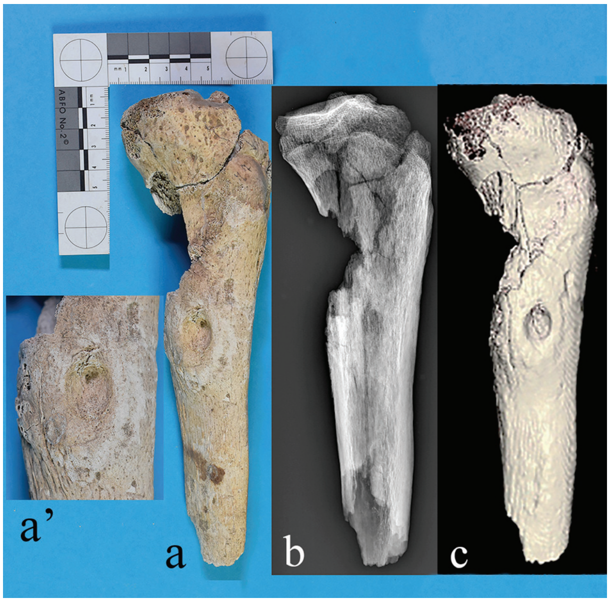
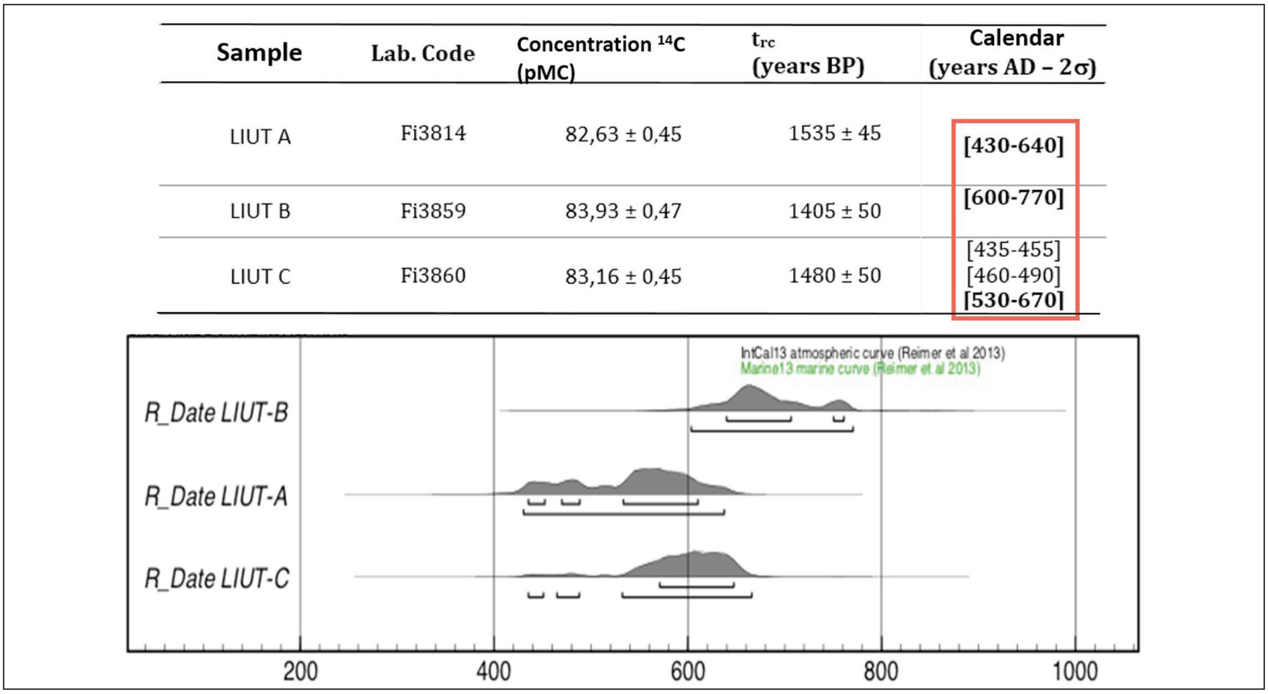


Figure 3. The tibia of subject Liut A. The proximal diaphysis is altered and enlarged by bone thickening due to a severe form of osteomyelitis. The presence of a circular depression with a diameter of about 21 mm at the point of maximum thickening represents a cloaca with signs of bone repair (a-a'). Computed Tomography (b) and 3D Computed Tomography reconstruction (c) highlight the 0.7 mm raised crateriform lesion, centrally depressed, with blunted edges.

of 530 to 670 AD. These data therefore show that only one subject (Liut B) lived in the era compatible with that of Liutprand, while the other two were earlier, albeit a few decades, to the Longobard king. Therefore, in the individual reconstruction, the tibia Liut B was associated with the individual Liut X.

Isotopic Mass Spectrometry – the paleodiet

Isotopic data show a rather high nutritional status for the time, with a varied diet based on meat and occasionally integrated with fish. In particular, the results show that the Liut B sample presents different values of isotopic ratios compared to the other two, indicating a higher percentage of marine food in the diet (Fig. 5). In order to make a quantitative assessment of the fish/meat ratio, we used the FRUITS software, in particular the scheme presented by Fernandes (26). We have therefore obtained a marine contribution to the diet of the three samples respectively: Liut A: 9%, Liut B: 16%, Liut C: 9%.



Sample	Lab. Code	Concentration ^{14}C (pMC)	t_{rc} (years BP)	Calendar (years AD – 2σ)
LIUT A	Fi3814	82,63 ± 0,45	1535 ± 45	**[430-640]**
LIUT B	Fi3859	83,93 ± 0,47	1405 ± 50	**[600-770]**
LIUT C	Fi3860	83,16 ± 0,45	1480 ± 50	[435-455] [460-490] **[530-670]**

Figure 4. Carbon-14 dating analyses from samples of the three tibiae.

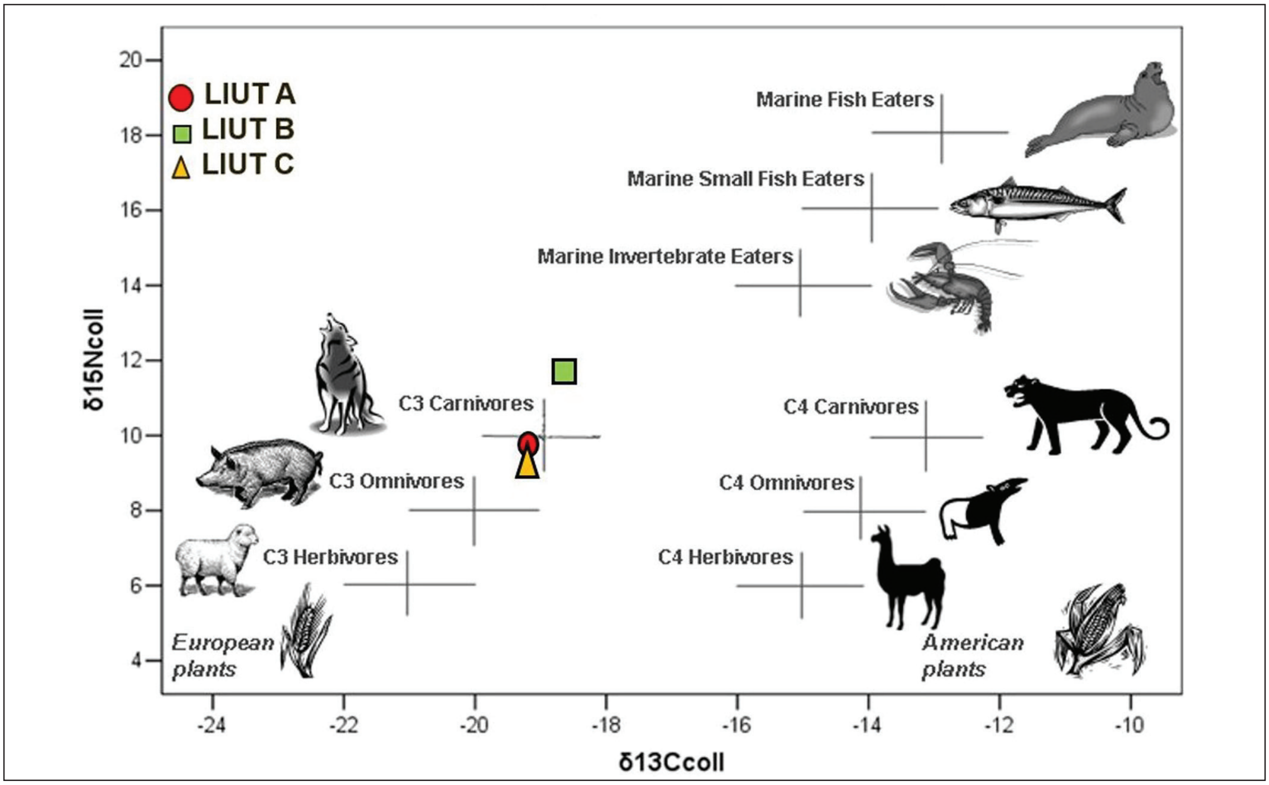


Figure 5. Paleodiet by stable isotope analysis (carbon and nitrogen isotopes in compact bone).

Discussion and conclusions

Currently, it is not possible to define the identity of the three individuals for lack of archaeological data and for the fragmentary nature of the bones. Moreover, it is worth keeping into account that the subdivision of the bones into individuals was carried out by matching the remains according to size and symmetries, with the aim of outlining the minimum number of individuals and, moreover, while there is certainty between the correspondence of two contralateral bones, it is not possible to ascertain whether the bones of one anatomical district really correspond to those of another, in the same individual (for example if an upper limb corresponds to the lower limb of the same subject). Considering this, most of the remains can be attributed to a robust man with strong muscular insertions, with a death age between 40 and 50 years, called Liut X and to whom, after dating, the tibia Liut B has been attributed. There is also a second male individual, also robust and with strong muscular insertions, to whom the pathological tibia (Liut A) has been attributed. A third individual, also male and of medium size, but dead in juvenile age has been identified according to the tibia Liut C. On the basis of radiocarbon dating, only the tibia Liut B is compatible with the period in which Liutprand lived, since the other two are anterior. Surely the pathological tibia Liut A, with outcomes of osteomyelitis probably due to an injury, belongs to an individual who lived about a century before the sovereign. In accordance with historical sources, since the second half of the 12th century the skeletal remains of Liutprand have undergone at least three translations.

At the time of the first translation, it is possible that the bones of other individuals was collected from the chapel of Sant'Adriano located inside the Longobard cemetery of *Santa Maria ad Perticas*, where also Ansprand, father of Liutprand, was buried. But no individual among the dated ones, if not Liut B himself, is close in chronology to Liutprando's father. However, it is likely that Liut A and Liut C also are individuals of Longobard ancestry from the same cemetery of Pavia, but from older tombs. Paleodiet studies showed that all subjects had an excellent level of nutrition, rich in both meat and fish. Despite the limits due to the smallness of the sample and the absence of comparative fauna, the isotopic values fall within the ranges observed in some upper-class families of the Italian Renaissance, such as the Medici of Florence, the Aragonese of Naples (27) and the Guinigi of Lucca (28). The age of the subjects, the robust constitution and the nutritional data suggest a belonging to a middle-high social class, perhaps devoted to war activity. Future molecular studies may reveal a possible degree of kinship between the individuals and clarify the identity of the subjects.

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Adult stem cells in cardiovascular medicine: historical overview and ethical issues

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Abstract. The regenerative capacity of adult tissues depends on tissue-specific stem-cell populations that maintain stable numbers by self-renewal and possess the ability to differentiate into distinct cell lineages. Adult stem cells are found in children, as well as in adults. Regeneration and renewal in adult mammalian tissues has been studied in several compartments such as the hematopoietic, endothelial, mammary, intestinal, neural, skin, muscle, and hair-follicle tissues. Regenerative medicine places emphasis on cell-based therapy, particularly stem cells, to repair or replace damaged tissues/organs, and is a topic of major current interest. While the use of adult stem cells in research and therapy does not require the destruction of an embryo, the use of embryonic stem cells is much more controversial. Even the performance of clinical trials with adult stem cells, however, have important ethical implications. This review, after a brief historical overview, concisely examines the findings of clinical trials in cardiovascular medicine and focuses principally on the ethical issues.

Key words: adult stem cells, randomised controlled trials, heart diseases, ethical issues in cardiovascular medicine

Abbreviations: randomised controlled trials (RCTs), congestive heart failure (CHF), acute myocardial infarction (AMI), ischaemic heart disease (IHD), ischemic heart failure (IHF), primary angioplasty (PCI), coronary artery bypass graft (CABG), New York Heart Association (NYHA) class, Canadian Cardiovascular Society (CCS) angina grade, left ventricular ejection fraction (LVEF), left ventricular end-systolic volumes (LVESV), therapeutic misconception (TM).

Historical overview

In 1868, Ernst Haeckel (1834-1919), an illustrious German biologist and one of the greatest morphologists of the 19th century, used for the first time the term “Stammzelle”- that is “stem cell” - to describe the unicellular organism from which multicellular organisms would be developed (1). The term “stem cell” was taken up by Haeckel in his book Anthropogenie (2) but the concept was clarified in the 3rd edition of the same book (3) in which the German scientist attributed to ‘Stammzelle’ or ‘Cytula’ a double meaning, both as a unicellular progenitor of all multicellular organisms and as a fertilized egg from which all the cells of an animal or human organism develop. The new term was also introduced to point out that the fertilized egg cell was different from the original egg cell, chemically, morphologically and physiologically. Haeckel noted that the stem cell ‘is partly of fatherly and partly of motherly origin; and we will now no longer find it astonishing if the child, who develops from this stem cell, inherits individual characteristics from both parents’ (4)

In the late 19th century, August Weismann (1834-1914) elaborated the theory of the continuity of the ‘germ plasm’ (‘Keimplasma’). ‘Germinal plasma’, segregated in the nucleus of germ cells (egg cells and spermatozoa) since the early stages of embryonic development, transmitted hereditary characters from one generation to the next (5). Following the debate on this theory, the term stem cell was used to indicate an embryonic cell capable of giving rise to specialized cells.

To verify Weismann's theory, two great embryologists of the time, Theodor Boveri (1862-1915) and Valentin Haecker (1864-1927) conducted studies in animal embryos to identify the earliest germ cells that presumably carry germ-plasm.

Both Haecker and Boveri called 'stem cell' ('Stammzelle'), the common precursor cell of the primordial germ cells and of the primordial somatic cells (6,7). According to Boveri, in the very early stages of the embryo development, a stem cell is divided into two daughter cells, one of which retains the stem cell features and the other gives rise to somatic cell precursors. So, in 1892, Boveri adopted Haeckel's term of 'Stammzelle' highlighting also a stem cell's capacity for self-renewal as well as for differentiation into specific types of somatic cells or germ cells (7).

In the same years, the concept of "stem cells" also spread in other areas of bio-medical research. In 1896 Artur Pappenheim (1870-1916), one of the leaders in modern haematology, researcher at Virchow's Pathological Institute in Berlin, in his studies of hematopoiesis attributed the name of "stem cell" to the common progenitor cell of the red and white blood cell lineages (8). Moreover, he believed that the stem cell was an embryonic cell capable of giving rise to diverse cell types, from germ cells to tissues of the entire body (9). The unitarian model of hematopoiesis, which proposed a stem cell as the common precursor of the entire blood system, was supported, in the early 1900s, by other eminent researchers, including Wera Dantschakoff (1879-), Alexander Maximow (1874-1928) and Ernst Neumann (1834-1918), professor of pathology of Königsberg (10-12).

Thus, the concept of stem cells was born in Germany in the late nineteenth century within the context of important embryological questions such as the theory of the continuity of the germ plasm and the hematopoiesis.

Characteristics of adult stem cells

Adult stem cells are undifferentiated cells that are found in many different tissues in juvenile as well as adult animals and humans. They can give rise to both cells like themselves and to differentiated cells (13-15). The regenerative capacity of adult tissues depends on tissue-specific stem-cell populations that maintain stable numbers by self-renewal and possess the ability to differentiate into distinct cell lineages.

Scientists have discovered adult stem cells in bone marrow more than 50 years ago and cell transplantation has been developed clinically for over 40 years in patients with haematological malignancies, e.g. haematopoietic stem cell transplantation in patients with leukemia. Later, the blood stem cells have been used in transplants for patients with several other diseases.

In later years, researchers have found adult stem cells in many more tissues than they once thought possible. By the 1990s, several studies had confirmed that nerve cells in the brain can also be regenerated from endogenous stem cells. So it has been hypothesized that adult stem cells of different tissues could lead to treatments for numerous conditions that range from type 1 diabetes, to cardiovascular diseases, to neurological diseases.

However, the adult cell-based therapies for the treatment of these conditions, such as heart disease, have only been possible since 2002.

Findings from clinical trials: a brief précis

Most pre-clinical and clinical studies in cardiovascular regenerative medicine have analyzed the treatment with different types of stem cells of acute myocardial infarction (AMI), chronic ischaemic heart disease and congestive heart failure (CHF).

Stem cells and acute myocardial infarction

Over the past 2 decades, randomised controlled trials (RCTs) have tested the use of autologous bone marrow-derived cells as a treatment to the repair and regeneration of damaged vascular and cardiac tissue after AMI. Systematic reviews and meta-analysis on cell therapies for patients with AMI suggested that cell therapy does not appear to have beneficial effects (16-17). In agreement with these data, an updated systematic review analysed data from a total of 41 RCTs with over 2700 patients treated with autologous adult bone marrow stem cells as a therapy for AMI. Cochrane's review concluded that there is insufficient evidence for a beneficial effect of cell therapy for individuals with AMI, as most of the results were obtained from small trials that showed no relevant clinical differences (18). The authors believe that there is currently insufficient evidence to suggest that cell therapy reduces mortality and morbidity beyond standard therapy. Larger clinical trials are required to more concretely evaluate the efficacy of cell-based therapies post-AMI.

Stem cells, chronic ischaemic heart disease and congestive heart failure

Ischaemic heart disease (IHD) is very widespread throughout the world and individuals with CHF are increasing (19). The use of stem cells is a promising method for the treatment of chronic IHD and CHF but it is an experimental therapy used in clinical trials that is not part of standard clinical practice. Currently, patients with these diseases are treated with pharmacological therapy and, whenever possible, with primary angioplasty (PCI) or with heart surgery (or coronary artery bypass graft - CABG) (20) to make the heart's revascularisation. Revascularisation has reduced the death rate associated with heart disease and heart failure, but in some patients, symptoms persist even after revascularisation. Recently, on these patients, whether or not they also undergo revascularisation, a new bone marrow stem/progenitor cells treatment was studied.

The mechanism of action of such therapies remains unclear. Therefore, in the last years, a large number of RCTs has been performed producing results that require further evaluation. Early trials and systematic reviews have demonstrated that cell therapy may result in some improvements over conventional therapy (21-24). In following systematic reviews it was observed that cell therapy may reduce the risk of mortality in the long-term in people with chronic IHD and CHF and that there are no major adverse events associated with the treatment (25-26). Some evidence suggests that cell therapies have a beneficial effect on people with IHD and heart failure (27-28). A systematic review, that included 38 randomised controlled trials with 1907 participants (1114 cell therapy, 793 controls), described that treatment with bone marrow-derived cells administered to people with chronic IHD or CHF, can lead to a reduction in deaths in participants followed for at least 12 months (29). However, the same authors considered the quality of evidence as low and the results have to be confirmed in larger, subsequent randomized clinical trials.

A recent meta-analysis shows that stem cell transplantation is a effective and safe treatment which improves some indices of cardiac function (NYHA class, CCS grade, LVESV and LVEF) but does not reduce mortality in patients with IHF(30). However, it is necessary to verify the data with further well-designed clinical trials.

Ethical issues

In addition to the requirements commonly required to make a clinical trial ethical (choice of study design and endpoints to optimize the response to the clinical question; selection of participants using appropriate scientific criteria, protection of privacy and guarantee of dissemination of results, review and approval of research by independent individuals, etc.), the complex procedure used in stem cell trials requires particular attention to the evaluation of the risk-benefit ratio and informed consent.

Evaluation of the risk-benefit ratio

Role of uncertainty

All international documents on ethics in clinical research are based on the principle that risks for recruited persons must be fewer than the intended benefits (31).

The most predictable risks are those related to the psychological distress of undergoing multiple invasive procedures, to the uncertainty of the arm where the participants are randomized and to the possibility of receiving ineffective treatment (32).

The potential physical and psychological risks must be minimized and justified from the potential benefit for the participants.

But, in the application of innovative techniques such as regenerative medicine, risks and benefits are always characterized by uncertainty that arises also from some peculiarities of stem cells, such as:

- Self-renewal and differentiation of stem cells are difficult to control and often lead to heterogeneous results.
- Stem cells represent a completely novel product, requiring the assays that ensure the purity, stability, safety, and validity of the final product. Concerning safety issues, transplantation studies with human cells inserted in animals cannot with precision predict the immune or other metabolic responses in patients. Hence, preclinical evidence of safety is of utmost importance as stem cells can also cause tumors or ectopic tissue formation.
- Stem cells require careful monitoring of the patient since, once transplanted, they persist for many years in the body (33).

Therefore, the extent of uncertainty is related to the tests already carried out and the type of stem cells used (34-35). The complex mechanism of the action of stem cells, the inherent risks to the invasive procedures and often the lack of correspondence between animal models and humans, tend to increase uncertainty in regenerative medicine trials when compared to those traditional pharmaceuticals (34-36).

Potential benefits for participants, science and society

In a clinical trial it is important to minimize the risks and increase the individual benefits and those benefits that pertain to science and society, in order to obtain a favorable risk- benefit ratio. The aim of a clinical trial is to be useful to both the individual and to society by improving scientific knowledge. New knowledge is obtained with large randomized trials and not with small and often uncontrolled studies. In addition, to improve knowledge it is important to stimulate preclinical studies related to clinical outcome. This is called "reciprocal value" and guarantees that trial promotes further research, even though no beneficial results are observed (37). It is also very important that the negative results of the trials are published[33] and that outcome measures are used in future trials to facilitate the comparison of the results.

Informed consent

Informed consent is at present a needed condition both for therapy and research. Modern informed consent results from fundamental principles expressed in the Nuremberg Code: the value of a person's autonomy and the respect due to persons. It is necessary to protect the decision-making autonomy of trial participants by formulating an adequate informed consent, which pays particular attention to four essential aspects: disclosure of information, understanding information, decision aids, voluntariness (38-39).

- *Disclosure of information*: As with all innovative procedures, even in stem cell applications, the disclosure of information to participants on the risks and benefits of the study is critical because of the high uncertainty. Disclosure is only clear when standardized procedures that present known risks are used.
- *Understanding information:* Another critical aspect is to understand the information provided. In fact, participants in these trials may misunderstand the purpose, the risks, and the potential benefits and often do not appreciate important differences between research and treatment, a phenomenon called "therapeutic misconception" (TM).[40] TM exists when individuals do not understand that the defining purpose of clinical research is to produce generalizable knowledge, regardless of whether the subjects enrolled in the trial may potentially benefit from the intervention under study or from other aspects of the clinical trial (40-41). The risk of TM could be further increased by the application of invasive interventions (42) and by the promise of regeneration, which creates high expectations especially in patients with advanced or termi-

nal disease. Some scholars believe that the TM is favored by the often recurring consideration that researchers, as they are also medical doctors, carry out their research for therapeutic purposes. This belief could facilitate the exploitation of the participants (43). Additionally, older participants as well as those with a lower grade of education are more inclined to TM. For this, attention needs to be paid to the linguistic aspects, giving written and oral information which is clear and easy to understand, in order to avoid confusion. For example, terms such as cell therapy could generate TM (44). In addition, to enhance the participant's understanding, it is important to repeat the information in different ways, also using face-to-face communication and audiovisual information.

- *Decision aids:* It is difficult to make patients understand risks, benefits and uncertainties especially as the estimate of the individual risk / benefit ratio is often unknown. It is important to implement a shared decision-making process using aids such as pamphlets, videos or web-based tools. There is growing evidence that decision aids may improve congruent choices (45). Comorbidities and older age of participants could reduce decision making.
- *Voluntariness:* To provide informed consent, trial participants must have in-depth knowledge of the purpose, methods, risks, benefits and alternatives to research. Full awareness of all the information acquired allows individuals to make rational and free decisions about their enrollment in a clinical trial consistent with their interests.

Discussion

Adult stem cell therapy opens new perspectives for the treatment of many pathologies, including cardiovascular diseases.

In the past twenty years, researchers have studied the efficacy and safety of various adult stem cell populations in many clinical trials. Although initial results were encouraging, subsequent large-scale randomized trials have highlighted modest benefits in patients receiving this therapy. The reasons for these differences are largely due to variations in trial methodology, such as the differences in the choice of cell source, cellular concentration, timing of delivery and clinical conditions of the examined patients. And last but not least to the lack of standardized protocols (46). The results from recent studies show that it is necessary to adhere to rigorous standards in conducting future stem cell clinical trials.

Furthermore, there are great uncertainties about the mechanisms of action at the base of cellular therapy in cardiac diseases. In the first studies it was hypothesized that stem cells had the ability to produce new heart tissue or develop blood vessels. Instead, preclinical studies suggest that these cells release cardioprotective paracrine factors that activate endogenous pathways resulting in myocardial repair (47,48). It has been hypothesized that cardio-protective paracrine factors produced by stem cells are enclosed in extracellular membrane vesicles, such as exosomes and microsomes, which transfer RNA, microRNA, proteins, lipids to perform cardioprotection. The hypothesis that vesicles can replace stem cells in therapy is very interesting from a clinical and commercial point of view, but must be confirmed by further studies (49,50).

The research done on adult stem cells has been relatively free of serious ethical issues but the realization of clinical trials, indispensable to raise relevant evidence on long-term safety and efficacy of stem cells therapies, is scientifically and ethically challenging (51).

Indeed, due to the complexity of the procedures and the possible use of stem cells in the field of regenerative medicine, it is considerably more difficult to construct protocols for randomized controlled trials on cell therapy compared to the trials that evaluate the effectiveness of traditional pharmaceuticals, surgical procedures or medical devices. Moreover, as this is a rapidly expanding field, preclinical knowledge is rather scarce and animal models may not be good predictors of what happens in humans (52,36). It is also important to emphasize the economic interests that gravitate around the use of stem cells. The great public interest and the pressure exerted by companies on researchers and desperate patients induce hyper accelerated translation of interventions in the clinic (53,54). Often, to concretize in a short time the expected results, no major clinical trials are funded, that are long lasting and costly and necessary to have sure responses (55).

Therefore, the progress of clinical trials is conditioned and patients may take unnecessary risks.

Conclusion

Future research should focus on developing new strategies to follow stem cells post-delivery, in order to improve the knowledge of their molecular mechanisms. Further studies are still needed to clarify if stem cell regenerative therapy is clinically efficacious and can be routinely utilized in clinical practice. To that end larger studies that use clinically meaningful endpoints should be conducted. In addition, in clinical trials efforts must be concentrated to minimize risks, obtain appropriate informed consent, reduce the likelihood of the therapeutic misconception and facilitate a good translation from research to clinical practice. As clinical research is increasingly sophisticated and interactions between different actors increase, the ethics of clinical trials becomes increasingly complex.

These observations are also valid for randomized controlled trials using different types of stem cells and are applicable to other medical fields, in addition to cardiovascular medicine.

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Medicine education through a gender lens

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Abstract. A gender approach is a fundamental ethical and scientific commitment to ensure the best care for each person, respecting the differences and thus achieving an effective personalized medicine. Italy is the first country in Europe to formalize the inclusion of the concept of "gender" in medical curricula, but the implementation is not the same across universities. Students (330) enrolled in the first-year of the Medicine and Surgery course at the University of Genoa (a.y. 2019-20) were asked to answer a questionnaire on the relevance and usefulness of a gender dimension in medical education, consisting of five closed-ended questions as well as two one open-ended questions. The development of a gender approach is viewed very positively by 71.14% of the students. The majority of first year students agree with a personalized view of medicine. The knowledge of gender medicine is also considered very useful within the educational programs by 82.84% of the students. However, the answers about which medical areas should benefit more from a gender approach reveal that students have still a superficial view of the subject. Only half of the students (52.73%) consider it useful to include a brief course on the history of gender medicine. The findings show that future physicians are responsive to the value of a gender approach in medicine. Further studies are needed to investigate how such gender-oriented efforts should be outlined in medical training to be most effective, not forgetting taking into account the different gender approaches in different cultures and healing systems.

Key words: gender attitudes, gender differences, medical education, medical curricula, physicians, gender medicine

Introduction

The vast literature and substantial scientific evidence show how men and women can not only present different clinical and symptomatic manifestations for the same pathology, but also develop substantially different therapeutic responses (1-4). One of the best-known cases is that of heart disease, which has long been defined primarily as a male pathology, causing inadequate therapeutic responses and higher mortality rates in the female population (5-7). In 1991, Bernardine Healy, caught the attention of the scientific community on the "women question" publishing on the New England Journal of Medicine an article expressively titled "The Yentl Syndrome". In this article, the American cardiologist described the persistent discriminatory attitude of doctors towards women, expressly recalling the 19th-century heroine of Isaac Bashevis Singer's short story, who had to disguise herself as a man to attend school and study the Talmud (8). This article was a starting point for good work in the cardiology field. On the contrary to what has happened for heart disease, osteoporosis has been mainly considered as a typical pathology in women and men have often been neglected or untreated (9). The exclusion of women from clinical trials for the development of new drugs until very few years ago led to the marketing of products that proved to be harmful to the female population (3, 10-12).

The first researches and related health policies were developed in the USA and Canada in the late 1980s (13, 14), where the need for structures for sex and gender-specific approaches had been recognised much earlier than in Europe. Early research was predominantly focused on protecting women's health and only later the application of the gender perspective to medicine has become synonymous with a better medicine for all - men and women - and a more effective, efficient and sustainable health care system (15).

In recent years, then, specific courses in universities and new training and awareness-raising policies have been instituted, also at the instigation of the WHO, which has promoted their enhancement by including gender in the social determinants of health and urging the Member States to include this type of perspective in health policies and the organization of health systems. In 2009, the WHO stated that "ness and policies, and health programmes must consider gender from the outset (…). The process of creating this knowledge and awareness of - and responsibility for - gender among all health workers is called gender mainstreaming" (16). The policy framework for health and well-being in the WHO European Region, Health 2020, adopted in 2012, as well as the sustainable development goals of the Agenda 2030 (17) include gender mainstreaming as a mechanism to achieve gender equality and ensure universal health.

At the educational level, starting from 2002, the Columbia University in New York has instituted the first course of gender medicine titled "A new approach to health care based on insights into biological differences between women and men", which shows an exclusively biological cut to gender differences, which was not yet framed in the holistic view that has been spreading in the last few years.

Afterwards, Gender Medicine courses have been included in Medical degree programs in several universities (18).

Only now, the diffusion of Gender Medicine begins to play an important role and this is mainly due to its widespread introduction in university and vocational training (19-22).

In Italy, the first institutional initiatives for the promotion of gender medicine date back to the end of the 1990s. In our context, the attention was initially focused on the specific theme of women's health (23). Over the last decade, however, there has been a progressive widening of the gender perspective with a growing focus on the personalisation of care and the effectiveness of a new approach to medicine for women and men. The creation of the National Observatory on Women's Health at the Ministry of Health in 2005 and the establishment of the Women's Health Commission of the Ministry of Health represented two turning points at the Italian level.

A recent milestone in the application of Gender Medicine in Italy is represented by the Law n. 3 of 11th January 2018 entitled "Application and dissemination of Gender Medicine in the National Health Service". In fact, Article 3 expressly provides for a plan aimed at the diffusion of gender medicine via its teaching and at the promotion of adequate levels of training for medical personnel, which has to keep updated on the subject (24). In particular, in paragraph 4, the article provides for the promotion of specific studies in the degree courses of the health professions.

Although the attention for gender medicine has been spreading all over the world, with the approval of this law, Italy has become one of the first countries in Europe to formalize the inclusion of the concept of "gender" in the medical training course. This political measure is an essential prerequisite for ensuring the best care for each person and, thus, for achieving an effective personalized medicine.

In order to be compliant to the new educational demands, some Universities (in particular Padua, Siena, Ferrara) has already started, on a spontaneous basis, pilot training courses on the gender approach (23).

The School of Medicine and Surgery of the University of Genoa, after having offered in the last few years educational activities for a gender sensitive medicine, ranging from disciplines of biomedical to clinical medicine, has planned a short course of Gender Medicine for the first-year Medical students in a.y. 2019-2020.

Monitoring student's knowledge and attitude to the newly introduced subject, is vital for the planning-of an adequate training and for the high critical issues of this emergent topic. This study aims at investigating the perception of Italian Medical students to the gender approach in the prevention of disease and in the definitions of treatment methods. To date, there are few investigations on this issue in Italian universities.

Methodology

We used an online questionnaire containing 4 closed questions, pertaining the evaluation of important gender medicine approaches, and 2 semi-closed questions on the students' knowledge and interest towards the introduction of a gender approach in different medical areas.

The survey involved all the students (330; 170 males, 160 females; 18-29 years old) enrolled in the first year of the Medicine and Surgery course at the University of Genoa (a.y. 2019-20), who attended the teaching of "Human Sciences" (first year, first semester) , which featured a short in-depth course on gender-related health issues.

Students were asked to fill in the questionnaire online via the UNIGE learning platform AulaWeb in December 2019. Participation was voluntary and fully anonymous.

Participants were asked to indicate their level of agreement or disagreement with each statement in a set of closed-ended questions and to respond to 2 open-ended questions on what they think Gender Medicine is about. A 10 point Likert scale was used. Respondents scoring 7–10 were considered to "agree strongly" with the statements, whereas those scoring 0–4 to "disagree strongly".

Results

We collected 239 valid answers in the online survey (66,9% female, 33,1% male).232 had complete answers to the open-ended questions. The response rate to the closed-ended questions was 72.4% and 70,3% to the open-ended questions.

The results of the survey indicate that there is a wide variety among students in the perception of Gender Medicine.

To the question "Do you think it is useful to include a short course on the history of gender medicine?" in the History of Medicine course (Fig. 1), just

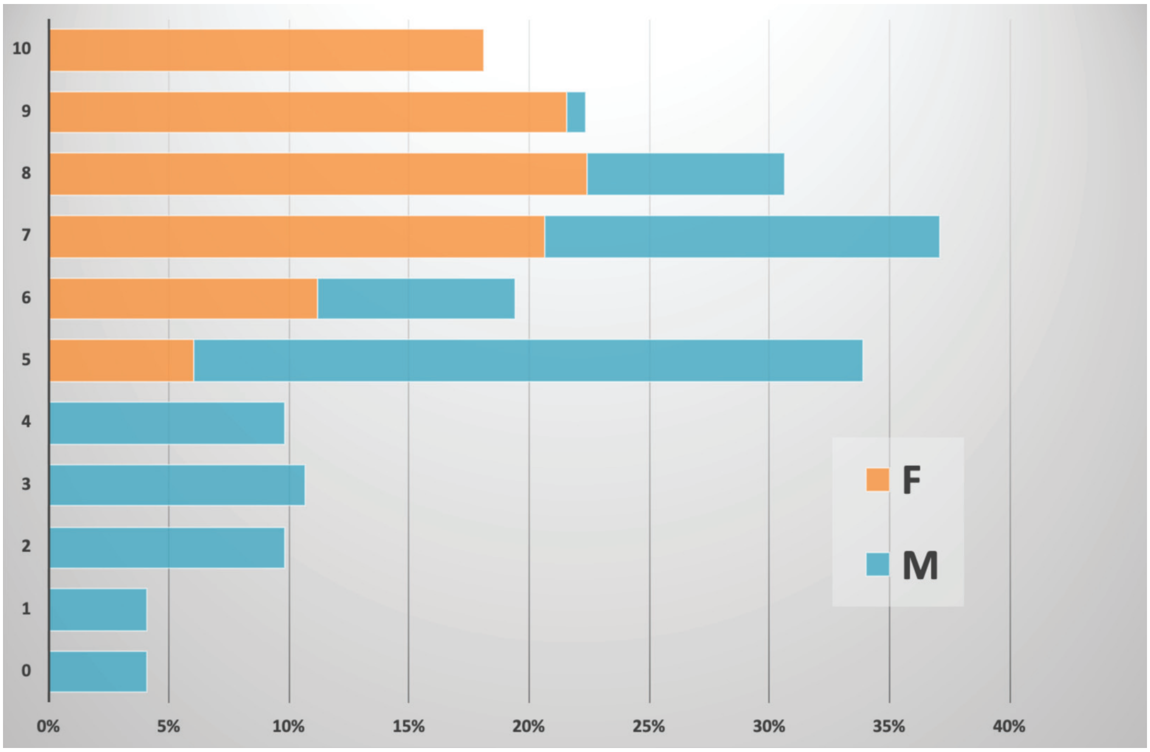

Figure 1.

over half (52.73%; over 88% female) fully agree, 20.5% of the students (all males) strongly disagree (0-4), and the remaining 26.78% are indifferent (5-6).

When asked whether a gender approach in different medical teaching is important (Fig. 2), the majority of students (71.14%) responded positively, only 21.76% were indifferent, and the rest (7.11%) did not agree at all.

A good knowledge of Gender Medicine is considered very useful by 82.84% of the students (over 90% female), not at all useful by 4.6% the remaining 21.76% do not think it is an aspect to be considered and valued within the educational programs of the degree course in Medicine. 198 students considered it very important to know the gender differences when the health care worker takes care of and treats patients, as showed in Fig. 3.

The majority of first-year students believe that little attention is paid by health professionals to gender issues, as highlighted in the Fig. 4.

Additionally, it is worth noting that some students are not fully aware of the meaning of the term "gender", which is often confused with "sex" As a matter of fact, When asked "what is gender medicine for you?", most students (63%) referred just to biological differences between men and women. Only 34% of the students were able to identify the specific aspects of a truly gender-sensitive approach.

The remaining 3% could not answer the question or indicated an answer not related to the issue.

There were several Very interesting answers to the open question.

A first point that emerged can be outlined in the following answer, given by a female students, about the meaning of Gender Medicine:

> gender medicine does not give space to generalisation and is based on the centrality of the person.

As for the concept of a personalised medicine, the following male student's answer can be considered representative of 65% of the students:

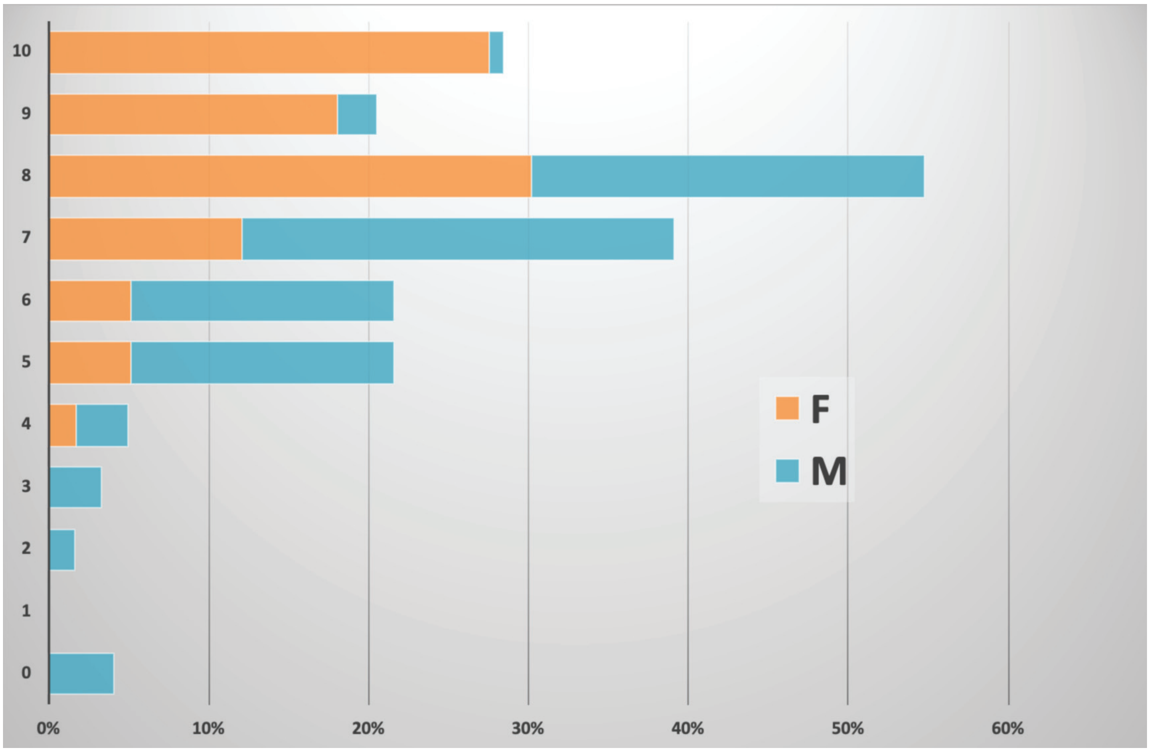

Figure 2.

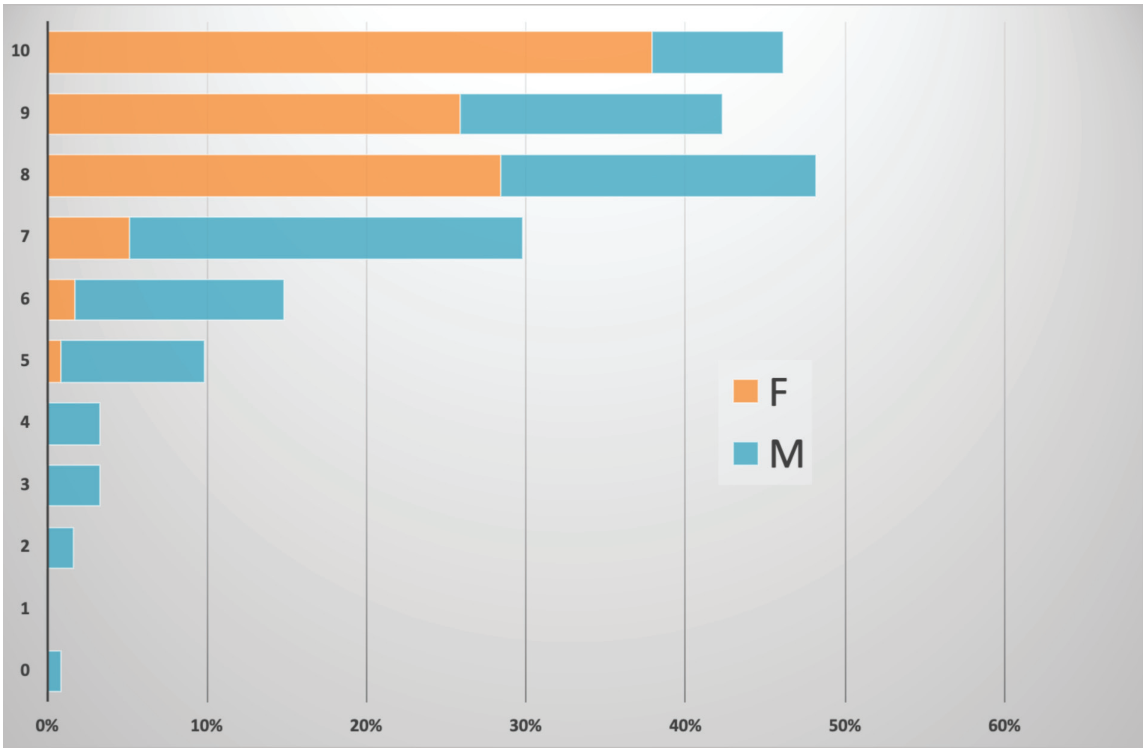

Figure 3.

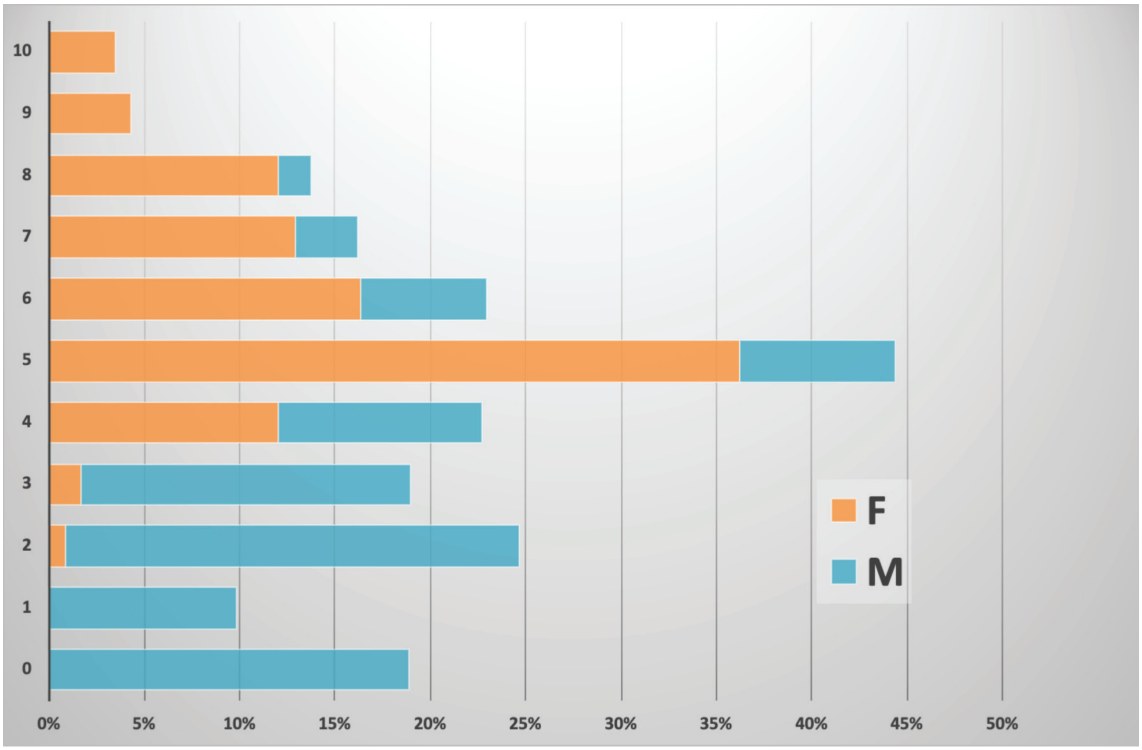

Figure 4.

> personalizing the therapeutic strategy, bringing to the treatment of patients the best available science, data and cutting-edge technologies to obtain a better diagnosis and follow-up than the generic model.

Most first-year students share a similar view on the importance of a holistic view of the patient. In fact, 83.5% of the answers are in line with this definition:

> A treatment path has to consider the biological profile of the patient but with equal attention his/her personal, social and cultural dimension. Many students (85,4%) agreed with the following female student's observation: personalized medicine, centered on the patient and the personalization of therapies, already includes the consideration of gender differences, being aimed at ensuring the best care to each person.

The second open question was about the medical areas in which the student most believed a gender approach was applicable. The answers reveal a lack of knowledge on the subject. However, according to the survey, The most suitable specialties are paediatrics, psychiatry and oncology, which together account for 65% of the answers. There are many students who have identified surgery and orthopaedics as fields of application (16%). Of the remaining responses, 14% indicated all specialties and 5% were undecided.

To sum up, two key aspects have emerged from the survey: firstly, it is vital to identify in which cases gender-based differences are significant; secondly, the current academic system needs to introduce the "teaching gender competence" in medical training and curricula to ensure the most personalized care as possible.

Discussion

The high response rate of first-year medical students allowed a sufficiently deep pilot analysis of the situation with respect to the knowledge of gender medicine and to the perception of the usefulness and relevance of the gender approach.

The inclusion of a specific and deepened gender approach in the course of "Human Sciences" at the UNIGE School of Medicine responds appropriately to the national guidelines and consolidates the interdisciplinary approach between the medical areas and the humanity sciences. Indeed, a better understanding of women's demand for health than men and orienting research/therapeutic interventions inevitably require raising awareness among future physicians through gender focus as early as their curricula. Therefore, an appropriate medical education in line with a gender-based approach is now recognized to be crucial in order to ensure everyone the best available treatment, thus reducing the level of error in medical practice and decreasing the costs of the National Health Services.

Unfortunately, in the field of medical training, there are still few Italian universities that have provided, in a structured way, a gender approach as an integral part of the training process (23). The Italian academic system seems still to struggle to recognize this subject as an essential disciplinary component of the educational curriculum of students who undertake medical or health care courses. Indeed, only a profound synergy between technical-scientific skills and the humanities can fully qualify a health care staff capable of taking care of the patient in a global way , thus guaranteeing its centrality in the care relationship (25).

The initiative of Genoese medical School demonstrated awareness of the relevance in adopting a gender approach already from the first approach with the medical sciences, in order to ensure the adequacy of research, prevention, diagnosis and treatment. Recognising biological, social and cultural differences related to the gender dimension is crucial to outline programmes and actions, to organise health services, to stimulate research, to inform and communicate correctly and comprehensively. The planning and the organisation of an academic education focused on a gender-sensitive approach to health shows a growing awareness of the relevance of personalisation in care.

The issue of gender differences in common diseases has gradually assumed central relevance also from an ethical point of view. The use of the sex and gender perspective in research and clinical practice, as well as in health planning, is considered as an element of innovation enhancing the fundamental ethical principles of equity and distributive justice (26). In 1998, World Health Organization (WHO) included gender medicine in the Equity Act, indicating equity as a principle to be applied to access care for women and for men as well as to pertinence in care and personalize therapies. In addition, WHO underlined the relevance of this approach creating a women's health unit, which in 2000 evolved into the Department of Gender, Women and Health (GWH).

Even the Italian National Committee for Bioethics (CNB) emphasized the principle of equal consideration of women in experimentation and underlined the need for an adequate medical training in this respect (27). Likewise, the CNR's Commission on Research Ethics and Bioethics has also pointed out the need to enhance academic training on the specificity of women in the general field of health, highlighting the serious repercussions that an androcentric approach can have on research itself and on the exercise of the constitutionally protected right to health protection (28).

The implementation of training activities, now explicitly foreseen as a commitment in pre and post-graduate university courses (degree courses in medicine and surgery, pharmacy, biology and health professions, and related specialization schools), as indicated in the Italian "Plan for the application and dissemination of Gender Medicine", approved by the Italian Ministry of Health in 2019 (29), is the prerequisite for a correct introduction and application of Gender Medicine.

Achieving an effective personalization of care means adopting an intersectoral approach between medical and human sciences areas that takes into account gender differences, that supports research (biomedical, pharmacological and psycho-social) based on gender differences, that is able to raise awareness among health professionals through targeted education. This has been well highlighted by our students, who declared that knowledge of Gender Medicine can be useful for the care and treatment of patients.

Unfortunately, the research results show that the path of awareness raising of future physicians is still long. In fact, although a high percentage of students (71,14%) recognizes the relevance of a gender approach in the various medical courses, a high percentage of students still declares themselves indifferent (21,76%). This result should be carefully considered in order to plan training initiatives inserting this "new" dimension of medicine in all medical areas.

Only by proceeding in this direction will it be possible to guarantee the best care to each person, further reinforcing the ethical concepts of "patient centrality", "personalisation of therapies" as well as "appropriateness of the interventions".

From another perspective, the students' perception of a limited consideration of gender issues by health professionals themselves and therefore also by their teachers who are themselves professionals emerges. In fact, most respondents think that health professionals pay little attention to gender issues. This suggests that there is a lack of in-depth knowledge of the value of applying such an approach and that the indifference shown by many respondents can be attributed to a lack of familiarity with the potential of a gender-based approach to medical problems. In fact, in the open answers the indifferent students showed that they are not able to define gender medicine and to frame its potentialities.

These considerations suggest therefore the need for a continuous training along both the whole educational program and the working path, which would enable health professionals to understand the importance of personalized medicine, as a medicine capable of looking at each person in its very own specificity. Moreover, it is not only recognized that only a deep synergy between technical-scientific and humanistic competences can fully qualify a health worker able to take care of the patient in a holistic perspective and guarantee his centrality in the care relationship (25).

In this sense it should not be forgotten that a gender approach requires a very high effort, being characterized by an interdisciplinary approach involving humanistic, social and individual approaches.

It is astonishing the limited interest of students to face a path also historical on gender medicine and suggests a lack of awareness of the importance that the knowledge of the historical evolution of a discipline or approach can have in the development of a critical epistemological reflection on the development of medicine and its continuous changes (30). This deserves a special attention and it requires a reflection on how and when it would be more functional to introduce in the medical curriculum also a historical view of medicine and also of gender, so that it can be appreciated not only for its cultural value, but also for the input it offers in the approach to the person, to his needs and to his expectations of care.

In summary, the information acquired in this pilot study allows us to state that there is a good degree of awareness of the importance and usefulness of a gender approach applied to medicine. It is indeed a valuable tool to better understand the complexity of life in order to prevent, cure and heal the person in his uniqueness. At the same time, however, there is a need to identify the most effective organization in order to give the gender approach the right space in the medical curriculum. From the students' answers, in fact, an interest emerges in treating the gender approach not only from a historical-evolutionary point of view, but also in the preclinical and clinical fields.

Conclusion

Although the survey was conducted in a single university context, it represents a valid starting point to understand how gender culture could be conveyed.

the results presented offer an interesting cognitive framework: it is in fact an "open and flexible container" that can be integrated and improved in the subsequent stages of the research, when additional actors involved in the university education system, such as trainers and professionals, who were excluded from the preliminary survey , will have the opportunity to share their perception of the usefulness and relevance of gender medicine, which will probably differ from that of the students.

A proper introduction of the gender perspective in medical education requires that teachers, academies, and policymakers are involved together In addition to deepening the Genoese situation through the point of view and expectations of future doctors, the study wanted to offer an input to stimulate people's interest to the gender perspective and to point out the still widespread ignorance on the subject. Moreover, we wanted to outline the benefits of the introduction of a historical perspective on gender in the first course of the medical curriculum.

Further research is needed to find out how such gender-oriented endeavours should be outlined in medical specialisation areas, not forgetting the different approaches to gender among different cultures and different healing systems.

In this study we have dealt mostly with training, but it is only thanks to research that training finds lifeblood. Unfortunately, there is still a long way to go in order to reach a gender balance in both preclinical and clinical research. Even today, most of the experimental work in medicine does not take into account the relevance of gender and the possible consequences of not considering this biological variable adequately. This happens despite it is well known that dealing with a properly selected sample is vital in order to make reliable claims.

Also in clinical trials it is crucial to implement the stable use of cohorts of patients with a fair distribution between the two sexes. It is indeed undeniable that a thorough knowledge of the biological and cultural differences allows physicians to intervene with the most appropriate treatments.

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ORIGINAL ARTICLE: BIOETHICS

The contribution of ethical reflection during the Coronavirus pandemic. A comparative analysis

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Abstract. The Coronavirus pandemic has deeply marked all ordinary health care activities and has dictated matters usually faced by the medicine of disasters. The most critical and dramatic dilemma has been the triage and the urge to select patients for Intensive Care Unit (ICU) because there was no place for all at the same time. The need to decide in a very short time has made this decision even more complex. The data of the Italian situation and namely of Lombardia reveal it clearly. Worldwide, there have been many different views on triage, sometimes with very peculiar emphasis. In this paper we will illustrate the contributions of the Unites States compared to the European ones. We have critically analyzed different views and we have highlighted that nevertheless there are several shared elements such as clinical criteria, if we consider only them we might underestimate the uniqueness of the patient, including vulnerable ones. There is a huge gap between the US view and the European view when it comes to the appointment of the final decision maker in triage. We propose the criteria of proportionality as a guide line to take decisions in triage because it allows to integrate collective public health objectives and the principle of ensuring protection for the individual patient. Finally, we envisage the potential role of ethics consultation in this pandemic scenario.

Key words: Covid-19 disease, triage, proportionality, clinical ethics consultation

Introduction

The Coronavirus pandemic has deeply marked all ordinary health care activities and has dictated matters usually faced by the medicine of disasters. The most critical and dramatic dilemma has been the triage and the urge to select patients for Intensive Care Unit (ICU) because there was no place for all at the same time.

The need to decide in a very short time has made this decision even more complex.

The data of the Italian situation and namely of Lombardia reveal it clearly. Worldwide, there have been many different views on triage, sometimes with very peculiar emphasis.

In this paper we will illustrate the contributions of the Unites States compared to the European ones. We have operated a choice among many articles and guide lines about this matter, and we have prioritized those most quoted in literature. We have critically analyzed different views and we have highlighted that nevertheless there are several shared elements such as clinical criteria, if we consider only them we might underestimate the uniqueness of the patient, including vulnerable ones.

There is a huge gap between the US view and the European view when it comes to the appointment of the final decision maker in triage. We propose the criteria of proportionality as a guide line to take decisions in triage because it allows to integrate collective public health objectives and the principle of ensuring protection for the individual patient. Finally, we envisage the potential role of ethics consultation in this pandemic scenario.

The situation in Italy

In Italy we have detected the first patients with a COVID-19 disease at the end of February 2020. In the following months there have been more and more people infected with a sensitive increase of hospitalizations to face the serious breathing syndrome caused by the virus (Fig. 1) (1).

Lombardy has been particularly hit by the virus, with a remarkable increase of patients in need of a ICU recovery (Fig. 2) (2) (Fig. 3) (3).

The clinical evolution of the disease and its manifestation has been very different. Same patients Covid-19 affected were coming to the Emergency Department just presenting the most severe grade of respiratory distress, with PaO2/FiO2 ratio <100 mmHg, requiring immediately breathing assistance through the use of Noninvasive ventilation Continuous Positive Airway Pressure (CPAP) and intubation with invasive approach in case of deterioration of gases exchange.

The greatest number of patients showed up with respiratory dyspnea, fever, cough; they didn't develop early respiratory distress in few hours, but same time in few days, same time in few weeks.

The number of patients hospitalized was growing day by day and daily same patient started to need respiratory assistance. Fortunately, in the most of cases the patients were treated successfully with noninvasive devices like helmet, to ensure bio-restraint with a filter at entrance and at exit way, in CPAP and with increased oxygen amount. These patients were located in different wards, infectious disease ward, internal medicine ward, pneumology ward, with the restriction of surgical activities. Same cases didn't have benefit from CPAP and they needed invasive assistance with tracheal intubation and mechanical ventilation, sedated in Intensive Care Unit. The mortality rate for these patients intubated will raise the 45% in most of ICU and for patients aged or with co-morbidity will arrive over.

Our experience attests that in early days the clinical course of COVID-19 patients in ICUs follows a very differentiated path which makes it difficult to predict an evolution. There are elderly patients who stabilize in the first days and then take a sudden turn

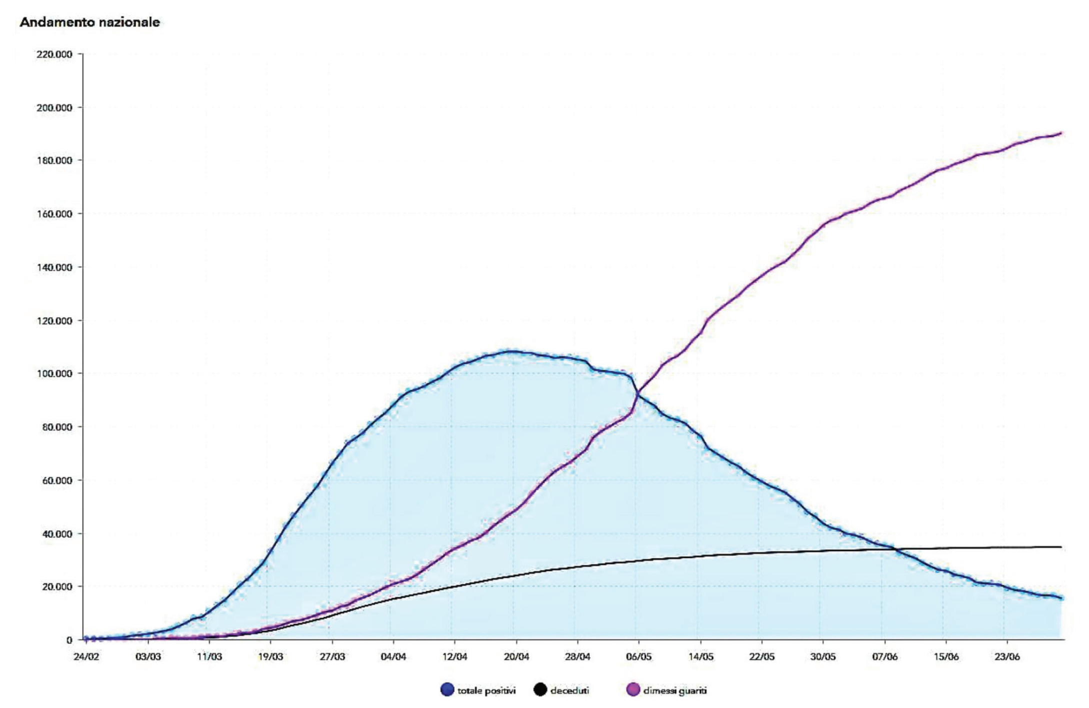


Figure 1. Trend in Italy - people positive, healed, deceased from 2020, Feb 24th thru 2020, June 30th.

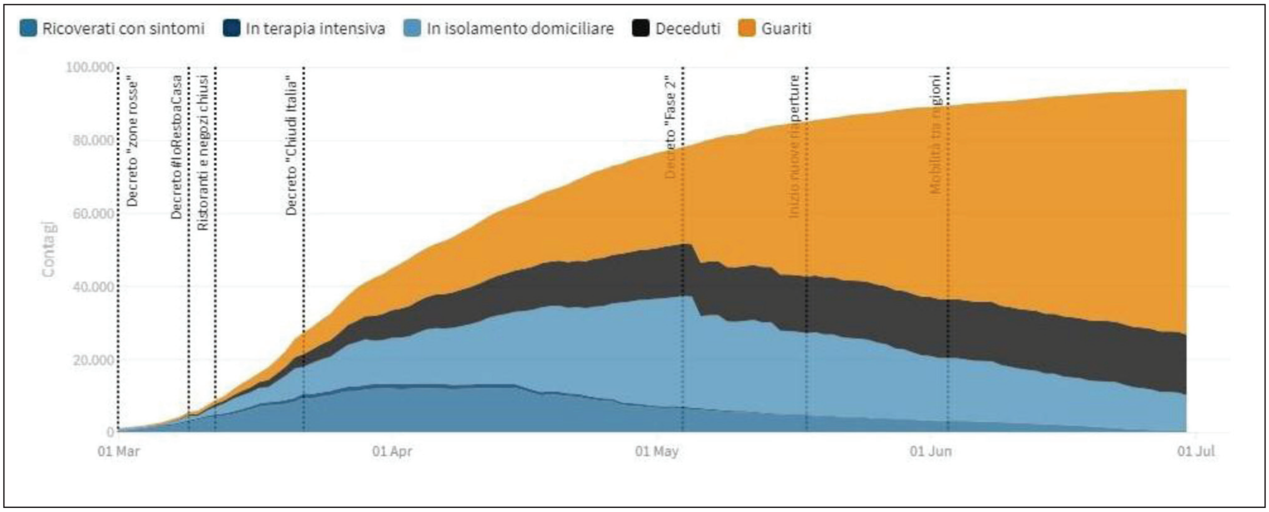
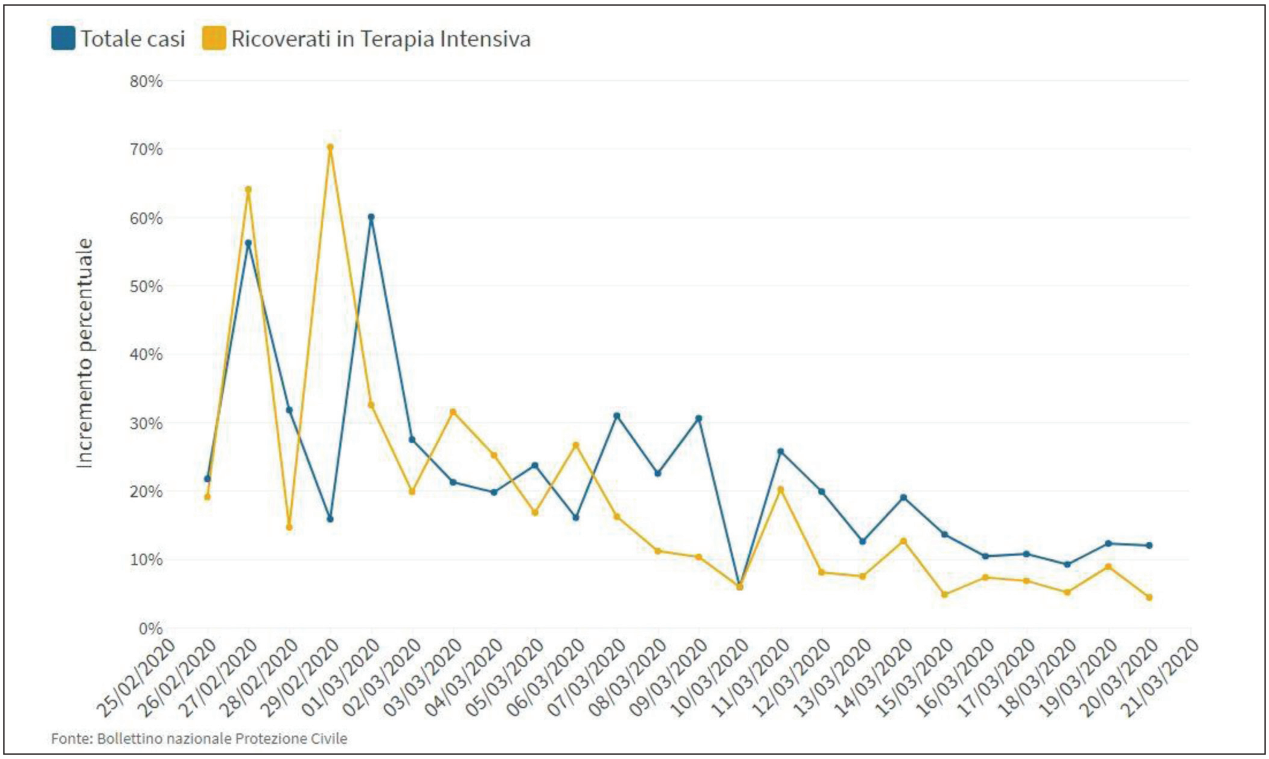


Figure 2. Trend in Lombardia – positive patients hospitalized, in ICU, confined at home, deceased and healed till 2020, June 30th. Temporal indication of restrictions and special measures.



Fonte: Bollettino nazionale Protezione Civile

Figure 3. Percentage increase of patients admitted in ICU with severe acute respiratory syndrome coronavirus 2 in Lombardy related to the total number of patients admitted in hospitals between February 25th, 2020 and March 21st, 2020.National Civil Protection Department.

for the worse. There are young patients who get over the acute phase after 20 days in ICUs, entering a rehabilitation phase in other units and after a few days there must go back to ICUs for unexpected deterioration. Because of this complexity, in order to ensure the best allocation of available resources, patients require continuous monitoring along with the review of all decisions already taken.

Triage: comparative analysis

During the acute period of the pandemic, we have seen many hospitals facing a new dramatic dilemma: which are the decisional criteria to be used to select patients for ICU when those who could benefit of an ICU treatment are more than ICU places available?

This is a very dramatic, difficult and complex decision with a tough impact not only on patients and their relatives but also on care givers and the Health Institution besides society as a whole.

The Italian National Committee for Bioethics (ICB) affirms: "We must evaluate how to manage the inevitable conflict between collective public health objectives (to ensure maximum benefit for the largest number of patients) and the ethical principle of ensuring maximum protection for the individual patient in exceptional situations: a dilemma difficult to solve in the concreteness of choices, as shown in the extensive literature on the subject" (4). The decision of triage is the last resort, when all possible alternatives are no longer feasible: the use of therapeutically approaches less intrusive when appropriate, increase of beds, transfers to other hospitals. (5,6).

If we analyze several publications about the triage, we can notice different proposals associated to some geographic areas.

In the US, the most important ethical principle is the maximizing benefits. This entails giving "priority saving the most lives and at maximizing improvements in individuals' post-treatment length of life" (7). To realize this purpose, they use clinical criteria, specifically the short-term prognosis. To define priorities, the clinical indications are described as follows: "The color (blue, red, yellow, or green) determines the level of access to a ventilator. Blue code patients (lowest access/palliate/discharge) are those who have a medical condition on the exclusion criteria list or those who have a high risk of mortality and these patients do not receive ventilator therapy when resources are scarce. Instead, alternative forms of medical intervention and/or palliative care are provided. However, if more resources become available, patients in the blue color category, or those with exclusion criteria, are reassessed and may be eligible for ventilator therapy. Red code patients (highest access) are those who have the highest priority for ventilator therapy because they are most likely to recover with treatment (and likely to not recover without it) and have a moderate risk of mortality. Patients in the yellow category (intermediate access) are those who are very sick, and their likelihood of survival is intermediate and/or uncertain. These patients may or may not benefit (i.e., survive) with ventilator therapy. They receive such treatment if ventilators are available after all patients in the red category receive them. Patients in the green color code (defer/discharge) are those who do not need ventilator therapy" (8). Non-clinical factors cannot be used because they are discriminatory: "Prioritizing individuals according to their chances for short-term survival also avoids ethically irrelevant considerations, such as race or socioeconomic status" (9). This choice ensures a balance between "the need to protect vulnerable populations with the principle of treating all patients in need of a ventilator equally" (8), granting an objective approach that may be viewed by the public "as fairer than decisions based on more subjective criteria" (9). Only when "all available clinical factors have been examined and the probability of mortality among the pool of patients has been found equivalent, only then may young age be utilized as a tie-breaker to select a patient for ventilator therapy" (8). The matter of the age as a criterion for selection has been thoroughly debated. In the US there is a certain convergence towards a view which affirms that: . "Saving more lives and more years of life is a consensus value across expert reports" (7). As a consequence of this statement they "make it justifiable to give priority to maximizing the number of patients that survive treatment with a reasonable life expectancy and to regard maximizing improvements in length of life as a subordinate aim" (7). In this perspective, they give reasons for "removing a patient from a ventilator or an ICU bed to provide it to others in need is also justifiable and that patients should be made aware of this possibility at admission" (7, 10). In the event that there were several patients with same prognosis and same age, "equality should be invoked and operationalized through random allocation, such as a lottery, rather than a first-come, first-served allocation process" (7).

In Europe, the Italian view is certainly important as Italy has been the first European country to face the pandemic. In the contribute titled: *Recommendations* *for the allocation of intensive care treatments in exceptional, resource-limited circumstances* of the Italian Society of Anesthesia. Analgesia, Resuscitation and Intensive (SIAARTI), they declare that: "we must aim at guaranteeing intensive treatments to patients with greater chances of therapeutic success favoring the *greatest life expectancy*. In this sense, the need for intensive care should be integrated with other aspects, including: the severity of the disease on one hand, the severity and number of preexisting comorbidities on the other" (6).

In Italy we have discussed a lot about age as a non-clinical criterion in Triage. The ICB evaluates: "the clinical criterion to be the most appropriate reference point for the allocation of the same resources: any other selection criterion, such as for example age, sex, condition and social role, ethnicity, disability, responsibility for behaviors contributing to the pathology, costs, is deemed ethically unacceptable by the Committee" (4). With regard to the matter of the age, SIAARTI clarifies: "An age limit for the admission to the ICU may ultimately need to be set. The underlying principle would be to save limited resources which may become extremely scarce for those who have a much greater probability of survival and life expectancy, in order to maximize the benefits for the largest number of people" (6).

We notice a considerable affinity between the US and the SIAARTI views: they both focus on clinical criterion, even if the age as a non-clinical criterion has a secondary role in the US stance.

This is also confirmed because the US views tends to reduce the evaluation of the effectiveness of a short-term intervention, while SIAARTI associates the effectiveness to the life expectancy.

The criterion of proportionality in triage

We think it is correct to use the criterion of proportionality to carry out the triage (11, 12).

Also, ICB seems to assume this criterion as a landmark, even distinguishing between appropriateness and proportionate: "Clinical appropriateness means the medical evaluation of the effectiveness of the treatment in relation to the clinical need of each individual patient, with reference to the severity of the onset of the pathology and the prognostic possibility of recovery. This treatment must always be proportionate, that is, consider the balance of benefits and risks with respect to the patient, considered from the point of view of both the objective and subjective clinical dimension (perception of pain and suffering, perception of the invasiveness of treatments, etc.)" (4).

During this severe pandemic, the care for the single patient must necessarily be part of a wider evaluation of the care for other sick people, considering the criterion of justice. The criterion of proportionality considers both the clinical indications than the preferences of the patients, together with the duties, that is the implications on the patient any third party, single, group or community (12). For this reason, the criterion of proportionality enables to integrate collective public health objectives and the principle of ensuring protection for the individual patient. We do not agree with the statement of the SIAARTI document when it is said that "the criteria for access to and discharge from the ICUs should include also principles of distributive justice and appropriate allocation of limited healthcare resources, in addition to clinical appropriateness and proportionality of care" (6, 13).

The criterion of proportionality allows a choice on a case-by-case basis, without falling into arbitrariness. In literature, there are many recalls to the need of analysis that is attentive to the uniqueness of every person even in the dramatic scenario of a triage. The Comité de Bioética de España states that "any criteria or protocol adopted to allocate scarce resources can never be applied mechanically or automatically: every human being has the right to consideration" (14). Similarly, also the SIAARTI document highlights that "ICU admission criteria should be discussed and defined for each patient as early as possible" (6). The position of the Conselho Nacional de Etica para as Ciências da vida (de Portugal) is more precise as the ethical analyisis case by case is parallel to a clinical analysis: "In situations where there may be limited resources, namely medical equipment necessary for the maintenance of life, careful ethical consideration is required, case by case, in parallel with the assessment of respective clinical criteria" (15).

The idea of an analysis case by case is very significant especially in a pandemic: from one side it is necessary to refer to general criteria to ensure same treatment and possibilities to every citizen; on the other hand it is clearly necessary to operate a choice keeping into account the uniqueness of every single patient. Proportionality combines several criteria, it enables an accurate case-by-case evaluation, considering the patient's changing conditions and the clinical progression attempts, without discriminating the most vulnerable subjects. The clinical criteria refer to the urgency and efficacy of the intervention: they enable the staff to evaluate what the patient's prognosis will be if they undergo invasive mechanical ventilation operations to be implemented in the ICU. The efficacy of the intervention depends on the patient's previous comorbidities, such as severe diabetes, heart disease, nephropathy or liver disease. In this perspective "Age, in turn, is a parameter that is taken into consideration in view of the correlation with the current and prognostic clinical evaluation but it is not the only parameter or even the main one" (4). As illustrated before, age is considered in relation to a clinical profile and not as an independent criterion, to grant everybody a treatment with the same opportunities. However, we need to recognize that an older patient usually has more pathologies than a younger patient; as a consequence, the prognosis of the former is likely to be less favorable than the latter. Thus, if we ground our decision on clinical criteria only, when we compare two patients, the most vulnerable will always be at a disadvantage.

If we contemplate the whole existential and clinical situation, a young handicapped patient would not be penalized as everybody might think; on the contrary he would benefit from this approach. In most cases, if we ground a decision on clinical criteria only, because of his comorbidities the final evaluation would penalize him when compared his situation to other patients. If we used equity as a yardstick based on just a few clinical indicators, as a matter of fact we would always discard the most vulnerable patients. Piccinni et al correctly affirm that: "we are aware that this approach fatally introduces parameters such that some health care resources are allocated to certain people in preference of others (specifically of more fragile and vulnerable subjects, because the age and the comorbidity are related to the survival rate)." (13).

Therefore, the risk of positions illustrated by M.Z. Solomon et coll. is real; they affirm: "Near-term survivability, moreover, can be assessed independently from disability. Consider two patients with Down's syndrome, one with adequate cardiac function, the other with cardiovascular disease. Down's syndrome is an inappropriate triage consideration, but worse baseline cardiac function confers lower survivability with Covid-19. Cardiac dysfunction could therefore be integrated into the scoring system, but only if the criterion applied to all patients, not just those with Down's syndrome. Patients with adequate heart function, irrespective of physical or mental disability, would then have the same triage score. Patients with preexisting cardiovascular disease would receive lower scores because they're less likely to derive benefit from the intervention, not because of disability" (16). We agree with the statement that affirms: "rationing decisions should not be based solely up on age or disability" (17): however, this implies that differences among people must be recognized and not repressed (18); only in this way we can practically realize an actual and not just declared equality. The patient' history and will would seem impractical to use in times of pandemic, given the urgency of the situation. Reality has shown, at least in our experience, that it was not impossible to retrieve the patient's history. Some patients arrive in the Emergency Room in very critical clinical conditions which impose an immediate transfer to the ICU; however, most of them are first admitted to other departments for a diagnostic classification. That is the crucial time to make a good decision through an interdisciplinary and shared judgment by those in charge of the patient, a decision that needs to consider the patient's history.

The patient or the patient's relatives can tell one's history. In this evaluation we need to examine the treatment burdens, in particular the patient's ability to withstand the invasive therapies if one were to be hospitalized in ICU. In its document SIAARTI takes the same stance: "ICU admission criteria should be discussed and defined for each patient as early as possible. Ideally, this would include the creation of a list of patients that should be considered for ICU admission in case of clinical deterioration, given the availability of ICU resources when admission is needed" (6).

The resolution based exclusively on few and stringent clinical criteria - such as a short-term prognosis - entails a decision which will not be open to ambiguity with reference to equality and equal treatment and is easily applicable even with an algorithm (19). However, this method cannot keep into account the differences among people to make them actually equal. This position sounds abstract and not appropriate to put in relation and to integrate the collective public health objectives and the principle of ensuring protection for the individual patient, the respect of principles of autonomy and the need for solidarity (20).

Who decides the triage

The team in charge to assess the proportionality of the intervention and therefore the adequacy of the transfer to ICU must be composed by the doctors responsible for the patient's care, both those who are currently managing it (for example the infectious disease specialist or the pulmonologist) and those who will have to manage it (the intensivist). Since they are aware of the actual situation in their respective departments, the inclusion of all these professionals ensures a shared valuation compatible with the overall scenario of the entire hospital.

In this perspective, for several reasons it is not acceptable that the demanding and dramatic moral decision to allocate ventilators is taken by an outsider committee composed by people who are not directly involved in the care of the patient. US authors defend this view. Their considerations are the following: "The angst that clinicians may experience when asked to withdraw ventilators for reasons not related to the welfare of their patients should not be underestimated — it may lead to debilitating and disabling distress for some clinicians. One strategy for avoiding this tragic outcome is to use a triage committee to buffer clinicians from this potential harm. We believe that such a committee should be composed by volunteers who are respected clinicians and leaders among their peers and the medical community. Advantages of this approach are that it allows the physicians and nurses in charge to maintain their traditional roles as fiduciary advocates, including the opportunity to appeal the initial decision of the committee when appropriate. While working together to ensure consistent and unbiased decisions across patient groups, the committee also has the flexibility to consider factors that may be unique to a given situation. As circumstances change and the availability of ventilators increases or decreases, the committee can adjust its rationing criteria to produce the best outcomes. Finally, when a hospital is placed in the unavoidable but tragic role of making decisions that may harm some patients, the use of a committee removes the weight of these choices from any one individual, spreading the burden among all members of the committee, whose broader responsibility is to save the most lives" (10, 7, 17). The World Health Organization also shares this view: "To the extent possible, the interpretation of allocation principles should not be entrusted to clinicians who have pre-existing professional relationships that create an ethical obligation to advocate for the interests of specific patients or groups. Instead, decisions should be made by appropriately qualified clinicians who have no personal or professional reasons to advocate for one patient or group over another" (21, 8). A recent research about the components and their background has highlighted that in the policies considered: "Eighteen (78.3%) of these 23 policies specify that this physician should be trained in critical care and 7 (30.4%) emergency medicine, and 11 (47.8%) specify that this physician should be the chief medical officer or the officer's designee. The other most commonly required or recommended disciplines to compose the body are nurses (20 policies [87.0%]), ethicists or ethics committee members (16 [69.6%]), chaplains (8 [34.8%]), and respiratory therapists (8 [34.8%]). Two (7.7%) policies require or recommend a community member. Nine (34.6% of all policies) exclude individuals who are providing direct patient care from making triage decisions, and an additional 4 (15.4%) recommend that these individuals be excluded" (22).

The thesis of a triage committee composed by physicians with a role outside direct patient care is not to be found in European articles. SIAARTI affirms that: "The decision to withhold or withdraw life-sustaining treatments must always be discussed and shared among the healthcare staff, the patients and their proxies, but should also be timely" (6). The US paradigm does not seem appropriate for the following reasons. The first reason concerns the meaning of giving care, which necessarily means attention to the patient. How can the physician be deprived of his responsibility to provide care by an external committee? Secondly this perspective would sanction the reduction of the medical act to a technical performance. In complex cases, this would legitimate that a doctor does not take on the inevitable moral responsibilities of his profession. Finally, it is said that being involved also emotionally, does not help in making good decisions. But a good decision is made not because we neutralize the subjects, but rather because we also identify and interpret one's emotions to reach an ethically pertinent judgment. When in front of crucial and demanding choices, doctors usually do not ask to be relieved of their responsibility but they want to be accompanied and not left alone.

We agree with the following perspective: "If doctors are left to make decisions about prioritization on their own, they face great difficulty in justifying these decisions. This is because it would be up to the doctor to demonstrate that it was necessary to make a choice between patients. A national policy is urgently required to ensure that the maximum benefit may be derived from the limited number of ventilators that are available" (23). Also, SIAARTI acknowledges that "Other purposes of the recommendations are to share with clinicians the responsibility in the decisions making process, which can be emotionally burdensome, carried out in individual cases" (6). However, the policy does not exempt the physician by his responsibility, mainly moral, to interpret the general indication of a specific framework towards a certain patient.

In this frame, the role of the ethics consultant comes in as a member of the clinical team; his task it to help and facilitate the attending physicians to take responsibility for the decision (24, 25).

The need of a shared choice among caregivers is often recalled in literature, especially in case of a pandemic when decisions are urgent and dramatic: "It is also important that the therapeutic decision concerning the different patients to be treated, according to the severity of their pathology, is as far as possible the result of consultation between several doctors, to ensure comparison between different points of view and the most correct choice possible, and, just as importantly, to allow the sharing of the responsibility and burden of a decision that will always be agonizing" (4). The risk is to reduce the sharing only to clinical aspects, so that the doubt about a choice is only technical and not moral. The position of SIAARTI is not very clear on this: "A second opinion (e.g. from Regional Healthcare Coordination Centers, or from other recognized or designated experts) may be useful when dealing with particularly difficult or distressing cases"(6). The Comitè Consultatif National D'Ethiquè "considers that health care teams need ethical support, which could be provided by an *ethical support unit*, assisted by regional health agencies and guided by the experience of ethics committees, while drawing on the expertise of the clinical ethics groups of teaching hospitals" (20). Even if attentive about ethical matters and the need of an expert support, the French position is still quite generic. The position of the Comité de Bioética de España is similar (14).

With regard to the communication to relatives, those who defends the idea of an external committee give the following reasons: "In addition to removing the responsibility for triage decisions from the bedside clinicians, committee members should also take on the task of communicating the decision to the family. The treating clinicians may be motivated to try to comfort the family by telling them that mechanical ventilation is not being provided because it would be futile and by reassuring them that everything possible has been done. Though well intentioned, such inaccurate representations could ultimately undermine public trust and confidence. Having the committee members communicate these decisions would ensure that the message is clear and accurate, helping to prevent confusion or misunderstandings" (10).

Instead, we think that thanks to the health shared path we have proposed, the attending physicians is the most appropriate person to disclose their decision to the patient and his relatives through a participatory and empathetic communication.

The proposed decision-making process would also help to soothe the severe moral distress felt by many care givers in this pandemic phase (26). The moral dilemmas at the root of this experience must be thoroughly handled within the department through debated and shared decisions (27) and not simply delegated to a psychotherapy outside the working context.

In this perspective, we achieve to give reasons for the role of the ethics consultant (28). Differently, he would have a role only when defining the guidelines prior an epidemic (29) and he would be totally absent in the direct management of triage during the epidemic itself. This is McCullough's position who affirms: "The task of bioethicists and bioethics organizations in response to the COVID-19 pandemic and those that will follow it is simple: Call for organizational leaders and government officials to support physicians who already know what should be done about severe scarcity and how to do it by deploying the professional ethics of triage The role of clinical ethicists is restricted to contributing to the rapid and reliable organizational adaptation of existing triage guidelines into organizational policy. The resulting policies will require only deliberative clinical judgment about the interpretation and clinical application of objective triage criteria. The skillset of the clinical ethicist does not include deliberative clinical judgment, making clinical ethics consultations in individual cases unnecessary" (30).

Conclusion

The Coronavirus pandemic has raised complex and dramatic dilemmas. There is a fundamental issue which permeates the general debate and specifically the bioethics discussion: to face this situation, do we need exceptional measures and therefore new criteria or do we apply ordinary criteria adjusted for the new situation? Hence, are physicians adequately trained and educated to face such a scenario?

If we leaned towards the first option, we would answer that physicians are not adequately trained and educated to face a pandemic.

The perspective we have proposed, i.e. the criterion of proportionality, allows us to give an in-between answer which holds a tension between these two polarities. This criterion imposes to learn from every single case and context in a circular approach between an individual profile and a general overview. Therefore, since it is not possible its deductive application, we need to develop a thought with a profile of novelty, because of the exceptionality of the situation.

The more complex the situation is, the more a multidisciplinary and shared approach is required. This way we will be able to integrate the general view in the definition of national and domestic policies with the specificities of each and every case (12).

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Girolamo Fabrici d'Acquapendente's "nasogastric tube" Strategies for artificial nutrition between the XVI and XVII centuries

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Abstract. The contribution focuses on the idea proposed by Girolamo Fabrici d'Acquapendente to use a nasogastric tube to feed patients who are unable to open their mouths and independently take food and drinks.

Key words: Girolamo Fabrici d'Acquapendente, nasogastric tube, artificial nutrition

It is well known that artificial nutrition is currently used in those patients who are unable to feed themselves independently. The history of this technique is quite antique (1-6). Besides some purely empirical practices, we focus now on procedures designed during the Modern Ages, when scientific revolution started to settle on medicine. The first methods of artificial nutrition, supported by a renewed context of anatomical knowledge, were proposed by two members of Padua's medical school. As far as we are able to reconstruct, Girolamo Capodivacca (d.o.d. 1589) was presumably the first one to use a tube to introduce liquid food into the aesophagus (7). Another, less known or analysed, method was proposed by the surgeon and anatomist Girolamo Fabrici d'Acquapendente (circa 1533-1619) in his *Opera chirurgica*, developed between the late XVI and the early XVII centuries.

Girolamo Fabrici d'Acquapendente, whose 400th death anniversary has just been celebrated, held the Surgery and Anatomy Chair of the University of Padua from 1565 and taught these disciplines for about fifty years, until almost the year of his retirement. During his magisterium, the stable anatomical theatre was built. It was inaugurated in 1595 and can still be visited nowadays at Palazzo del Bo, the historic site of the University of Padua (8). Among his works we remember the *De visione De voce De auditu* (1600) (9), the *De formato foetu* (1600) (10) and the *De venarum ostiolis* (1603) (11). In addition to the anatomical field, Fabrici also distinguished himself in the surgical field: he was *par excellence* the surgeon of the golden age of Padua's medicine (16th-17th centuries). All his surgical knowledge was collected in the aforementioned work *Opera chirurgica*, of which several editions have been conserved starting with that of 1619. This work is divided into two parts: the first focuses on the various pathologies that can be treated with surgery, while the second reviews the different types of operations and surgical operations, dividing them according to the various anatomical districts of relevance (12).

By exposing the various operations related to the teeth (13), Fabrici briefly dwells on the inability of some patients to chew - and, consequently, feed themselves naturally - or simply who present difficulties or inability to open their mouths (presumably due to tetanus induced trismus, neurological trismus, trauma, etc.) (*De dentium Chirurgiis, caput XXXII*) (14-16). In relation to this situation, Fabrici puts forward the hypothesis, presumably not turned into practice, of being able to use a curved silver cannula, which, passing through a nostril, flows directly into the pharynx, close to the palate and introduces liquid food, or possibly medication, that the patient may swallow (14-16). The surgeon describes the device and its use as follows: "*you come to the patient's help, with a method I have recently imagined; this method consists in the use of a small, curved silver cannula, through which we introduce the food in liquid form directly into the palate, passing through the nostrils*" (14). Fabrici believed that this medical device and this method could represent a possible innovation even if he admitted that it was possible to meet the danger of suffocation (extended original Latin text: "*Vel tandem succurritur modo a me nupertimè excogitato et est, ut per fistulam argenteam paulò recuruatam per nares in palatum liquidum cibum immirtamus et probus (uti opinor) est modus, praecipuè si cannula agnino intestinulo obuoluatur nisi fortè eam secum afferat difficultatem, ne cibo è naribus cadente epiglottis in laryngem recuruetur, quamobrem suffocationis periculum imminenter: quem modum (ut libere, et ex animo dicam) non fui expertus, nam si suffocationis periculum aliquod imminere ex ploratum fuerit, hic modus abigendus erit; sin secus,recipiendus, quod in sano homine experiri licebit*") (14).

It is however interesting to underline how, although this practice cannot be defined as a surgical procedure in the strict sense, at the time of Acquapendente every "manual" intervention on the patient was up to the *chirurgus* (surgeon) and not to the *medicus physicus* (physician) who, in order to make the diagnosis and prescribe drugs, simply felt the pulse and "examined" the urine. In fact, the gap between a purely intellectual medicine and a practical and manual medicine even if cultured, at the time, was still particularly strong.

What is striking about Fabrici's proposal is the precise intent to take care of the patient through all the possible and technically permitted medical strategies of his time, effectively outlining a fully comprehensive treatment of the patient.

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The Babiński sign: from "toes phenomenon" to "great toe phenomenon"

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Abstract. The Babiński sign is one of the most important signs in clinical neurology. It refers to the extension (dorsiflexion) of the great toe following stimulation of the sole. However, in the first description of this sign, Joseph Francois Félix Babiński (1857-1932) did not mention the movement of the great toe, but of all toes. The terms used by Babiński in his first description of the sign is "orteils" (toes, in the plural), and not "grand orteil" (great toe). This article traces back the initial descriptions of the Babiński sign made by the great French neurologist of Polish descent and other influential neurologists of the 19th Century. Contrary to what is commonly believed, the Babiński sign was not described in its complete form from the very beginning: it took some time for its discoverer to fully realize that what characterized the sign was the extension of the great toe alone, and not of all toes.

Key words: Babiński sign, Extensor cutaneous plantar reflex, History of Neurology, Joseph Francois Félix Babiński

The extensor cutaneous plantar reflex is one of the most important signs in clinical neurology. It is also known as Babiński sign (BS), from the name of Joseph Francois Félix Babiński (1857-1932), a French neurologist of Polish descent who was a pupil of Jean-Martin Charcot (1825-1893) at La Salpêtrière, Paris (1). Babiński described this sign in a very short article published on February 22, 1896 (2). This article had no references, was written with brevity and clarity, without mentioning the number of patients in whom the BS had been studied, and not reporting the part of the sole that was stimulated.

This BS can be elicited in patients with damage to the central nervous system motor pathways (3,4). The BS refers to the extension (dorsiflexion) of the great toe following stimulation of the sole. However, the first description of this sign does not mention the movement of the great toe, but of all toes. The terms used by Babiński in his first description of the sign is "orteils" (toes, in the plural), and not "grand orteil" (great toe) (1). It was only in 1898 that Babiński recognized that the extension is predominating in the great toe or the first two toes (2). The movement is more evident in the great toe due to the structure of the metacarpophalangeal joint and the limited extension of the little toes. The movement arises from the contraction of the extensor halluces longus muscle, which has its insertion at the terminal phalanx of the great toe.

In an article published in 1903 in the Revue Neurologique, the neurologist André Léri (1875-1930) – who had studied under Babinski – still wrote about toes extension (in the plural), although in a note he mentioned the existence of a reflex of the great toe in abduction (3). Interestingly, in the same issue, the Romanian Neurologist Gheorghe Marinesco (1863-1938) wrote that "the toes phenomenon [phénomène des orteils] consists, according to Babinski, in a movement of extension which is more evident at the level of the great toe, whereas the other toes extend a little, remain immobile, or even flex" (4).

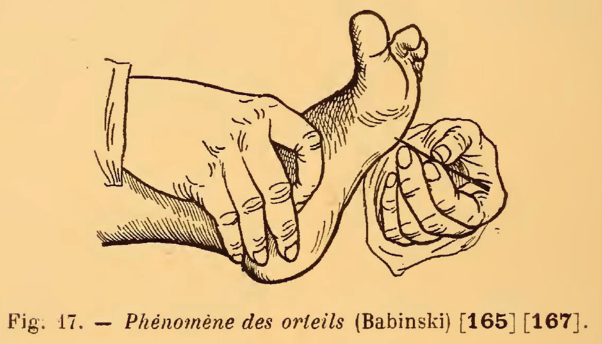

Fig. 17. — *Phénomène des orteils* (Babinski) [**165**] [**167**].

Figure 1. Drawing illustrating the Babinski sign with extension of the great toe alone. From: Babinski J, Froment J. Hystérie-pithiatisme et troubles nerveux d'ordre réflexe en neurologie de guerre. Paris: Masson et Cie; 1917.

In 1903 Babiński completed his initial description, by drawing attention to the abduction of the toes ("the fan sign", "signe de l´éventail") (5). Thus, in 1917, when discussing the signs useful to differentiate organic from hysterical hemiplegia, Babiński provided a comprehensive description of the sign: "the reflex movement of toes following stimulation of the foot sole is usually inverted: the toes and particularly the great toe instead of flexing extend on the metatarsus (phenomenon of the toes). The extension of the great toe is often associated with the abduction of the other toes (the fan sign)" (6). Of note, the corresponding figure clearly illustrates the extension of the great toe alone (Fig. 1).

Hence, although initially Babiński described the sign emphasizing the extension of all toes ("phénomène des orteils", "toes phenomenon"), later on - probably recognizing that extensions of all toes not always occur - he narrowed the definition by drawing attention to the extension of the big toe, and the abduction of the other toes. The BS was not described in its complete form from the very beginning, but it took some time for Babiński to fully realize that what characterized the sign was the extension of the great toe alone, and not of all toes.

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Book reviews

Renzo Dionigi-Filippo Maria Ferro, *"Non è la prima volta...Epidemie e pandemie. Storie, leggende e immagini"*, Varese, R & F (edizione on-line), 2020, pag. X + 88.

The book, just released in an online-only edition, is the work of two doctors who, while practicing their profession at high levels, one in the surgical field and the other in the psychiatric field, have cultivated historical disciplines in an equally professional way (history of medicine and history of art). The theme of the book is the pictorial representation of epidemic diseases, with particular regard to the plague epidemics that afflicted Europe in the fourteenth, sixteenth and seventeenth centuries. In the book, preceded by a passionate preface by Alberto Lolli, some medieval miniatures on the subject of pestilence are remembered and described. The figures of some saints who over time have been invoked by the population as protectors and healers in times of plagues are then sketched: San Rocco, San Sebastiano, Santa Rosalia and especially San Carlo Borromeo. Some pictorial and sculptural representations of these saints are splendidly represented and analytically commented in the book. There is no shortage of curious news such as those concerning the Caladrio, a fabulous animal that in the Middle Ages was considered the bearer of reliable prognostic signs on the auspicious or inauspicious outcome of the epidemic disease that had afflicted the individual sick. A chapter is also dedicated to recent scientific representations, processed through the electron microscope, of the coronavirus responsible for the last modern pestilence: the COVID-19 pandemic.

The text of the two illustrious doctors, as well as esteemed university professors, can be defined as a "divertissement", as Gianmarco Gaspari already suggests in the afterword. According to the Treccani dictionary, this French word indicates in the Italian language an "activity (even demanding) done for fun or leisure", according to the Garzanti dictionary a "literary or artistic composition characterized by the playful elaboration of a theme". In fact, the two authors deal with undoubted competence, but also with undisguised pleasure, the theme they have assigned themselves. They talk about topics that they know very well (the history of art and the reflections that the history of medicine produces on artistic manifestations), but they do not fail to emphasize the socio-political aspects of art and medicine. As scientists as they are, they also make some encroachment into the medical-biological disciplines, expressing their opinion on the pandemic in progress, on the prophylactic measures adopted to combat it, on its consequences at an individual and community level.

The reader, fascinated by the text and by the elegant graphics, is left with the regret that the two authors, with considerable historical skills in both the medical and artistic fields, wanted to limit their treatment only to some of the many plagues that humanity encountered in his long journey and among the many representations that artists of various eras and geographical areas have provided of such plagues.

Massimo Aliverti

Ottaviani R. (a cura di), Percorso tra i meandri della storia dell'Arte Medica, Sesto Fiorentino (FI), <<apice libri>>, 2019, pag. 302.

The volume contains a large collection of lessons on historical-medical topics that the curator, together with prof. Paolo Vanni and other university professors from the Florentine area, held for several years at the "University of the Free Age" in Sesto Fiorentino.

The curator, to better orient the reader and provide a greater organicity to the text, has divided the lessons into some distinct sections: "History of medicine", "Disease and prevention", "History of surgery", "History of nursing", "History of hygiene", "History of the Red Cross".

In each section, the topics covered are many. As regards the general history of medicine, there are lessons on the most ancient Florentine hospitals, on the role of women in medieval medicine, on Giacomo Leopardi's pathography, on the cosmetics used by women over the centuries. In the same section there are also lectures on illustrious doctors of the past such as Giovanni Battista Morgagni (1682-1771) and Karl Landsteiner (1868-1943). With regard to diseases and their prevention, lessons appear on individual diseases (tetanus, scabies, leprosy, Spanish flu), but also on love sickness and the Mediterranean diet. As regards the history of surgery, lessons on heart transplantation, bowel surgery and orthopedic surgery are reported; there is also a brief lesson on Giuseppe Garibaldi's famous wound in his right foot. The section on the history of the nursing profession is entirely dedicated to some women who, from the Risorgimento to the Great War, honored this health activity. The history of hygiene is summarized in a few lessons dealing with Public Health. A larger group of lectures is instead dedicated to the history of the Red Cross, in particular to the birth of this international organization and to the figure of its creator Henry Dunant (1828-1910). In this last group of lectures, there is also the history of the Order of Malta's health activity.

As a whole, the volume is perhaps a little too affected by the occasion that gave rise to it: the curator's desire to produce a paper documentation of the commitment made by her, as by other experts in the history of medicine and health, in many years of lessons at the University of the Free Age of Sesto Fiorentino (but also at the Red Cross History courses organized by Prof. Vanni). Not all lectures appear to be of the same tenor, alternating developments supported by in-depth historical-medical research, with others of a prevalently popular nature.

The volume, however, has the merit of mentioning, even in a collection of texts essentially intended for a non-specialist public, little-known figures in the history of health, deserving of a rediscovery by the experts. I mention the Tuscan doctor Giovanni Torgioni Tozzetti (1712-1783), interested in the problems of public health and environmental hygiene of the Grand Duchy which recently passed under the Lorraine dynasty. I mention the Tuscan doctor Pietro Betti (1784-1863), an important administrator of Florentine healthcare and reformer of medical-surgical teaching in Florence. I mention the Milanese princess Christina of Belgioioso (1808-1871), organizer of the hospital system of the Roman Republic and a pioneer of social and health care for the disadvantaged classes. I mention the Swiss doctor of Italian origins Louis Appia (1818-1898), one of the first supporters of the idea of the Red Cross alongside Henri Dunant.

A further merit of the volume now printed is to pay homage to prof. Paolo Vanni, passionate student of the history of medicine and tireless scholar of the history of the Red Cross, as recalled by the same editor in the first pages of the book.

Massimo Aliverti