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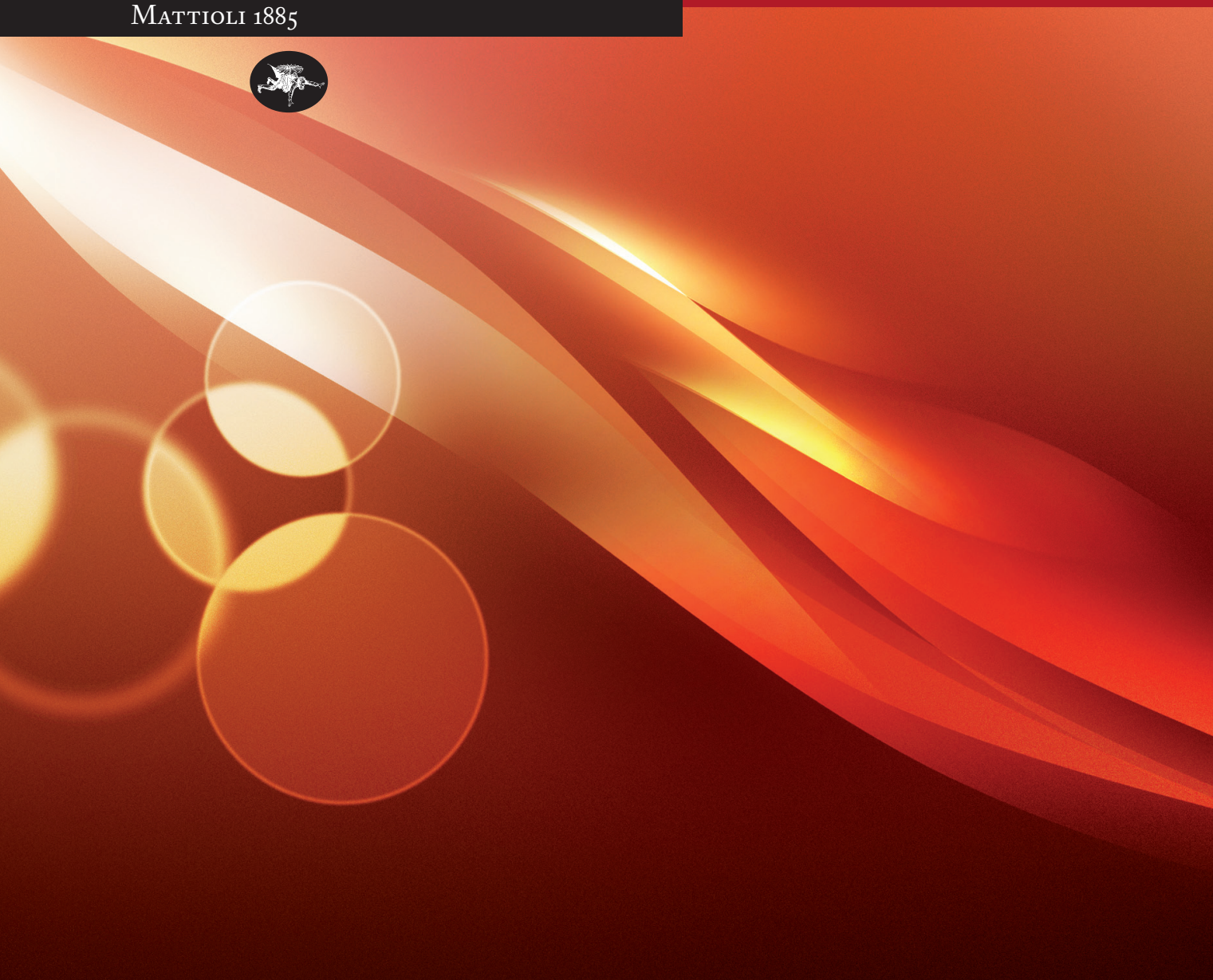

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Loc. Vaio - 43036 Fidenza (Parma)
tel 0524/530383
fax 0524/82537
www.mattiolihealth.com
E-mail: redazione@mattioli1885.com

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Editoriale

Di nuovo una storia vecchia. L'emergenza Coronavirus

Viviamo quello che non avremmo mai creduto di dovere vivere. I meno giovani tra noi medici ricordano che, superata la metà del secolo scorso, con il trionfo dei farmaci antibiotici, si era andati baldanzosi a sperare che il mondo occidentale non avrebbe più dovuto temere le malattie infettive. E oggi invece? Siamo tornati ad averne paura, dopo lo spavento dell'AIDS e di altre gravi evenienze diverse degli ultimi decenni. Davanti a noi ricompare una storia vecchia. In tanti anni di insegnamento nelle facoltà di medicina, spiegavo agli studenti che l'improvviso arrivo della peste nera, alla metà del Trecento, aveva sorpreso i medici e li aveva trovati impotenti a curare il nuovo terribile flagello. Raccontavo che allora, a supplire i difetti di una medicina che ignorava la natura del male, la difesa dal contagio era stata assicurata solo dalle magistrature di governo, con i "cordoni di sanità" sui confini e con severe regole di isolamento dei luoghi dove era presente il morbo. E raccontavo come, alla ricerca dei colpevoli del contagio, la società del tempo si era macchiata della tragedia dei processi agli untori. Mi sembrava utile ricordare anche il colera del XIX secolo, quando si protestava rimproverando alle autorità certi provvedimenti restrittivi che recavano danni all'economia del paese. Negli anni del mio insegnamento universitario, quelle erano storie lontane nei secoli, storie che la nostra potente medicina moderna guardava solo con curiosità antiquaria, confidando nelle proprie indubitabili capacità di diagnosi, di cura e di prevenzione. Ma ogni volta, chiudendo le lezioni sulla peste e sul colera, volevo suggerire un dubbio agli studenti. Se tornasse la peste bubbonica (che inspiegabilmente si era eclissata dall'Europa nel Seicento) e quando episodicamente ricompare il colera, dicevo, oggi non ne avremmo paura perché sappiamo come curarci. Ma dicevo anche: se arrivasse invece una pandemia influenzale grave, come la Spagnola del 1918, cosa potremmo fare? Era un messaggio teoricamente valido e certamente serio, ma confidavo che valesse solo in via teorica. Non immaginavo che sarebbe poi veramente successo quel che è successo. Mentre la scienza medica ricerca e discute e mentre i medici e gli ospedali curano come possono gli ammalati, la difesa dal morbo è garantita solo dall'intervento puntuale della politica che organizza i moderni "cordoni di sanità", come al tempo della peste.

Giuseppe Armocida

Editorial

An old story again. The Coronavirus emergency

We all are experiencing what we could not believe we would ever live.

The youngest among us doctors remember that, after the middle of the last century, with the triumph of antibiotic drugs, we hoped the western world would no longer have to fear infectious diseases. And nowadays, instead? Once again, we are being afraid of it, after the fear of AIDS and other serious events in recent decades. An old history appears another time in front of us.

In many years of teaching in medical schools, I explained to students that the sudden arrival of the black plague in the mid-fourteenth century had surprised doctors and found them powerless to cure the new terrible scourge. Then, I told that, to compensate for the defects of a medicine that ignored the nature of evil, the defence against contagion was ensured only by government magistrates, with the "cordon sanitaire" on the borders and strict rules of isolation of the areas where the disease was prevalent. And then I told how, in search of the perpetrators of the contagion, the society of the time committed the crime of the processes against the "plague-spreaders".

It also seemed useful to me to recall the cholera of the nineteenth century, when people protested by reproaching the authorities for certain restrictive measures that caused damage to the country's economy. Over the years of my university teaching, those were centuries-old stories that our strong modern medicine only looked at with antiquarian curiosity, trusting in its unquestionable skills of diagnosis, treatment and prevention.

Nevertheless, every time, concluding the lessons on plague and cholera, I used to suggest a doubt to the students. If the bubonic plague returned (disease that inexplicably eclipsed from Europe in the seventeenth century) and whether cholera episodically reappeared, I told, today we would not be terrified because we know how to cure ourselves.

But I also used to ask them: if instead a serious pandemic flu, like the Spanish one of 1918, arrived, what could we do against it?

It was certainly a serious message, but I was confident that it was only theoretically valid. I did not imagine that would have occurred what then really happened.

While medical science researches and discusses and while doctors and hospitals treat the sick as best they can, defence from the disease is guaranteed only by the punctual intervention of politics that organizes everywhere the modern "cordon sanitaire", in the same way as at the time of the plague.

Giuseppe Armocida

Medicina Historica 2020; Vol. 4, N. 1: 7-11

A memory of Solferino ("Un souvenir de Solferino") in Italy. The role of a book on the origin of Italian Red Cross Society

Duccio Vanni[1], *Fabio Fabbricatore*[2], *Paolo Vanni*[3], *Simone Vanni*[4]

[1]Assistant Professor Florence University, Florence Italy; [2]Doctor Cap. Comm. CRI Torino Committee CISCRI, Turin Italy; [3]Professor Emeritus Florence University, Florence Italy; [4]Director of Emergency Department at Empoli's Hospital (Empoli – Firenze) Italy

Abstract. In this article the authors describe the role that the book "Un Souvenir de Solferino" had in Italy for the foundation of the first Italian Red Cross Committees starting from the one in Milan.

Key words: Italian Red Cross, Solferino, Henry Dunant, Red Cross history.

An important history between Red Cross and Medicine

The Red Cross history is part of the history of medicine, as we sustained in same of our previous works(1, 2). Certainly the Italian Red Cross was born from the ideal inspiration coming from the pages of "Un Souvenir de Solferino"(3) by Henry Dunant (the 1862nd edition) after he assisted to the tragedy of the wounded soldiers in Castiglione delle Stiviere.

At that time the conditions were very favorable to humanitarian, fraternal and particularly innovative ideas; and these were universally connected to the birth of the Red Cross.

Even in Italy, as elsewhere, these ideas, as seen in the light of nascent patriotism, are believed to be the origin of the renewal for military health service.

The horror of the war described by Dunant in the "Un Souvenir" and later in his "Memories" (4), generated patriotic yearning and humanitarian impulse towards the suffering: this will also contribute strongly to the unification process of Italy.

This parallelism is acceptable in relation to the historical and political situation of Italy.

The cry for freedom is well connected to civilization and progress, a progress that begins as soon as the conditions of barbarity are won by an ideal and human world, in which the wolf and the lamb will live together in a fraternal and friendly atmosphere realized by a superior justice.

Here we find the real antagonism: the barbarity and the servitude versus the liberation, the goodness and the exaltation of the gifts that man received from God.

This explains the triumph of the idea of Red Cross in Italy, and the reason why the souls of patriots and good-will men were inflamed by it.

This is true for Red Cross origins, but a change occurred between 1882 and 1884, in which the Italian Red Cross became a state institution. This involves the principle of its independence. Thus, it became an auxiliary service of the armed forces, in aid of Military Health Service.

What happened in Italy in that dramatic June 24th, 1859 -date that inspired the publication of "Un Souvenir di Solferino"- began with a question mark about the real date of arrival of Henry Dunant in Castiglione delle Stiviere.

Did he arrive in Castiglione on the evening of 24th or the morning 25th of June, as stated in his correspondence with George Baumberger? And did he stay in Palazzo Bondoni Pastorio or in another hotel of the city, as we can read in one of his letters to Rudolph Müller (5)?

We agree with Roger Durand that Dunant's famous *short* book should have been entitled "A Souvenir of Castiglione delle Stiviere", because it is in that place that Henry Dunant was inspired by the creation of the Red Cross, facing of human suffering; so it is the name of Castiglione that should enter the indelible memory of the history.

From June 25th to 30th Don Lorenzo Barziza, a priest from Castiglione, distinguished himself for his work of humanitarian aid by organizing 12 temporary hospitals.

For this undertaking he receives the *Légion d'Honneur* from Napoleon III: it is strange and mysterious that Henry Dunant will never speak of Lorenzo Barziza, even if they were both in Castiglione in those days!

At the beginning of the writing of Italian Red Cross history (5), the discussion focused on one of Henry Dunant's Italian precursor: Ferdinando Palasciano. It is true that the medical-scientific neutrality of Palasciano is not that of the heart and piety of Dunant.

Despite everything, we are aware that we cannot write the history of the International and Italian Red Cross without mentioning the work of the great surgeon from Capua, Ferdinando Palasciano, who is closely linked to that of the surgeon from Geneva (but originally from Piedmont), Louis Appia .

Between January 1861 and January 1862, several meetings were held at the Pontaniana Academy in Naples in which Ferdinando Palasciano spread his ideas on neutrality.

He also financed a race on the publication of 100 aphorisms for military surgery, and the award was assigned in part to Dr. De Vita and in part to the Dr. Appia. These aphorisms were published in the Manual of Military Surgery by Ferdinando Palasciano (6) (Fig. 1).

In November 1862 the first edition of "Un Souvenir de Solferino" was published. In spite of all, in our opinion this little book is a sort of Gospel for the Red Cross volunteers. In those pages there are all the prophetic values of international lay humanitarianism,


AFORISMI

SULLA CURA DELLE FERITE

PER ARME DA FUOCO

DEL DOTTOR

ACHILLE DE VITA

AFORISMI

SUL TRASPORTO DE' FERITI

DEL CAVALIER

LUIGI APPIA

STAMPATI
per cura dell'Accademia Pontaniana

NAPOLI
STAMPERIA DELLA REGIA UNIVERSITÀ
1862

Fig. 1 Manual of Military Surgery funded by Ferdinando Palasciano

and there is the past, the present and the future of the Red Cross.

In November 1863, in Milan, Luigi Zanetti translated "Un Souvenir de Solferino". This edition has been forgotten in the chronology of the various translations quoted in the historical "Centennial Edition" on the anniversary of the birth of Dunant, in 1928. Giorgio Ceci, a Red Cross volunteer, has rediscovered the Zanetti edition that we reprinted in 2009 (7).

In January 1864, Dr. Cesare Castiglioni, distinguished patriot of Milan, student and scientist, as well as president of the Italian Medical Association of Milan, set up a commission for the creation of an "Aid Society to the wounded and sick soldiers in wartime" (that later became the Red Cross), according to the principles of the Geneva Constitutive Conference (October 1863).

The Milanese commission invited the 50 sections of the Italian Medical Association to follow its exam-

ple. No doubt that the Red Cross in Italy began essentially thanks to doctors.

In January 1864, Guido Corsini (8) also tried to create an "Association for the rescue of wounded soldiers" in Florence, but he did not have the same success as Castiglioni. He succeeded in setting up only a first provisional committee in 1865. Henry Dunant cites him in one of his many publications, "International charity on the battlefield"(9), released in the same year.

June 15th, 1864 is the official day of birth of the Milan Committee of the "Italian Medical Association for the relief of the wounded and sick in wartime": the Italian Red Cross was born! King Vittorio Emanuele II, who was its patron, recognized the association, and Prince Umberto was elected its honorary president. Article 1 of the statute proclaimed: "The objective is to save the wounded and sick soldiers in wartime, and to assist with all means the army health service in wartime". We also mention article 14: "In times of peace, we must prepare for war".

A short chronology:

November 1863, Milan

First Italian translation of "Un Souvenir by Solferino" by Luigi Zanetti, published a few months after the third edition of Henry Dunant (February 1863), who gave his authorization to Zanetti.

December 27th, 1863

Ferdinando Palasciano read at the Pontaniana Academy his third memory on the neutrality of wounded soldiers, in which he claimed his pioneering position with the "Manual of Military Surgery" (authors Achille De Vita and Louis Appia) that perhaps aided Appia to be invited to Geneva to be part of the "Committee of the Five" (4)

January 1864

Dr. Cesare Castiglioni, President of the Milan Italian Medical Association, established a commission for the creation of a "Society for the rescue of wounded and sick soldiers at war", according to the suggestions made by the Geneva Constitutive Conference of October 26th to 29th, 1863. The Milan Committee invited fifty of the Italian medical association's headquarters to follow his example.

January 1864

Guido Corsini's patriotic invitation to Florence for the constitution of the same association for the relief of wounded soldiers. See "International charity on the battlefields".

The neutrality of the wounded soldiers in wartime had already been supported by Ferdinando Palasciano in the siege of Messina in 1848 (communication of his widow Countess Olga of Wavilow) (10) and then in Pontanian Academy of Naples. However, in two authoritative medical history texts, Arturo Castiglioni and Adalberto Pazzini indicated Sir John Pringle (1707-1782), author of "Diseases of Armies", published in 1810, as the "inventor" of the Red Cross.

Similarly, the French pharmacist Henri Arrault wrote to Napoleon III and claimed the birthright of the idea of the Red Cross. George Sand took his defense and spoke of the war between the two "Henri / Henry", Arrault and Dunant.

Really, the cruelty of war and the advent of modern weapons, combined with the uselessness of an inexorable death due to the lack of care, had already been known for a long time.

We also recall that at the Statistical Congress in Berlin in September 1863, Dunant's friend, Dr. Basting (4) aroused the applause of the military doctors talking about neutrality for the injured soldiers, as well as the structures and the people who assist them.

Henry Dunant distinguished himself on this from the ideas of Palasciano, but not from those of Arrault.

August 8th to 22nd, 1864

The Geneva Diplomatic Conference adopted the Convention to improve the conditions of soldiers "injured on the battlefield".

The king of Italy, Vittorio Emanuele II, was officially represented in that conference by the Italian consul in Geneva Giovanni Cappello and the division physician Felice Baroffio, both knights of the order of Saints Maurice and Lazarus.

Cesare Castiglioni reported in his moral and economic account of November 25th, 1866, that he had participated and had the honor to speak on a personal basis, and to explain what was being done then in Italy in this regard.

He was accompanied by Dr. Pietro Castiglioni. Ruggero Belogi reported that also Dr. Comisetti was present, but the official documents of the Conference don't mention him!

It is certainly however (11) that Comisetti wrote a letter that Dunant read to the members during the same conference.

Accession and ratification of states to the Geneva Convention of 1864:
1. France, September 22th, 1864;
2. Switzerland, October 1st 1864;
3. Belgium, October 14th, 1864;
4. Holland, November 29th 1864;
5. Italy, December 4th, 1864.

United Italy, newly established in March 1861, was the fifth nation ratifying the treaty!

August 28th, 1864

4th memory of Palasciano on the neutrality of the wounded soldiers. He argued that "his" idea of neutrality received full approval and valuable historical support from the now concluded Geneva Conference.

He regretted that the impulse of improving lives of wounded veterans came not from eminent medical experts but from the travel impressions of Mr. Dunant, an amateur nurse.

Thus all the rights that medical science had already acquired on such significant progress of civilization through its publications were ignored (10).

December 11th, 1864

Florence became the capital of Italy.

December 11th, 1864

Meeting of the Milan Committee of the "Italian Association for the rescue of injured or sick people in wartime".

Adoption of the first regulation.

Some other commissions of the Italian Medical Association had responded to the call of June 15th, 1864 issued by the Milan Committee.

15 committees were formed, including Bergamo (the first), then Brescia, Como, Cremona, Ferrara, Florence and Monza. The Milan Committee was divided into 4 sections, each with a different function:

1st - fundraising,
2nd - object collection,
3rd - food preservation,
4th - preparation of medical and nursing staff and rescue teams, perhaps the beginning of what will be the military corps of the Red Cross (June 1th 1866).

The doctors asked for the honor of carrying the sword, which at the time was not granted. The ladies could not participate in the fourth section.

Conclusions

Our ambition was to take a bird's eye view on what "Un Souvenir de Solferino" produced in Italy.

The first part of our study evokes the age of enthusiasm aroused by the book. This was associated with voluntary dynamics, with the horror of the suffering of the victims sent to the slaughter of war and to the patriotic fervor.

The second part is based on the overall consolidation of the Italian Red Cross. In that time, there were no wars that concerned us directly, but civil emergencies for which the Italian Red Cross had to change. This second part can be read as the *bureaucratization* of the humanitarian institution from 1882 - 84 onwards.

It is in the first period, from 1863 to the proclamation of Florence as the Capital of Italy, that "Un Souvenir de Solferino" was translated and published in Italy. In the second period, we forgot it so that in the 5th International Conference of the Red Cross in Rome, in 1892, also Dunant was almostforgotten: 500 lire of financial aid was assigned to him when known that he lived in misery.

Certainly with the *bureaucratization* of the Italian Red Cross the fundamental ideas of "Un souvenir de Solferino" have been subjected to the needs of "government diplomacy", and perhaps not only in Italy.

Finally, we argue that "Un souvenir de Solferino" is the real Gospel of the Red Cross volunteer and that the readings, studies and ideas about that "Gospel" can be infinite, like his memory.

In our several publications we define "Un Souvenir" as the *Alpha and Omega* of the Red Cross (12). Indeed, this book contains all the past, the present and the future of the Red Cross for centuries to come.

What today is called "advocacy" -the protection of the vulnerable- was suggested and predicted by Henry Dunant 150 years ago!

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Correspondence:
Duccio Vanni Assistant Professor
University of Florence, Florence Italy
E-mail: duccio.vanni@unifi.it

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Original article: history of medicine

Empiricism and common sense: the management of public health in the Kingdom of Sicily (1575-1860)

Lucia Craxì

Department of Biomedicine, Neuroscience and Advanced Diagnostics (Bi.N.D.), Institute of Pathology, University of Palermo, Palermo, Italy

Abstract. The research outlines the evolution of the public health management system in the Kingdom of Sicily between the second half of the 16th century and the first half of the 19th century, emphasizing the specific features of the Sicilian case and highlighting the possible causes. It frames the evolution of public health institutions in Sicily both in the process of centralization and organization of the administrative apparatus of modern State, and in the development of medical theories concerning contagion. Through the analysis of the legislation and of the documentation produced by the competent bodies, it has been proved that there is no break in continuity in the activity of the various institutions that manage public health along the time span investigated. Special attention is devoted to the role of doctors within these institutions and to the relationship with medical science. The analysis shows that the competent bodies based their choices on an empirical approach, making prudential choices that took into account both the miasmatic theory and the contagionist theory.

Key words: public health, Sicily, contagion, institution

Introduction

Between the end of the Middle Ages and the beginning of the Renaissance, Italy played a groundbreaking role in the development of a public health management system and in the organization of health policies, by virtue of the advanced administrative tradition of many of its pre-unitary States (1). Between the 14th and 16th century, the major States of northern Italy, coping with the spread of the epidemic of plague of the mid-fourteenth century, elaborated a cutting-edge health organization, considerably ahead of the rest Europe (2). In this case the plague did not only work as a disruptive force, but also as a durable spur to adopt suitable structures to face it, and to deal with health and sanitation issues after it.

For this reason, a comprehensive study of plague epidemics should not only consider the history of the disease and of its diffusion, but also encompass an in-depth investigation on health institutions and on their bureaucratic apparatus: such an approach can make medical history an integral part of social history, rescuing it from being too specific a sector (2). Public health history, as a part of social history, considers the disease as a "structure" of society, a negative structure which heavily influences the development of society itself. Based on this historiographical framework, the study of health institutions, but also of political bodies responsible for controlling public health, becomes fundamental in the historical reenactment of our society.

During the 14th century, in cities such as Florence, Venice and Pistoia, new institutions to control public health raised as an evolution of institutions which dealt with food supply problems. By the end of the same century, these institutions had already stopped being provisional, as evidenced by the inception of the

Magistrato di Sanità [Health Office] in Venice in 1486 (3). By and large we can state that public health offices in Italy, during the 15th century, carried out an enormous amount of work, gathering legislative, judicial and executive powers. Their jurisdiction extended from the control of the *lazzaretti* [Lazarets], to sanitation, control of foodstuffs, repression of begging, surveillance of prostitution, up to the examination of the *fedi di sanità* [Health certificates] and the regulation of the quarantine for ships.

The rise of these structures and of the related legislation was not a result of the work of the medical class, but it was the consequence of the administrative evolution of many pre-unitary States - which were approximately nine in the time span between the Restoration and the Unification of 1861 - and it can therefore be framed in the broader process of centralization and organization of the administrative apparatus, which characterizes the birth of the modern State (4). Overall, the medical profession did not play a major role in public health management; however, the connections between medical associations – already established between the second half of the 13th and the 14th century – and health offices were rather intense: the latter employed doctors for advice and reports, including at least one representative of the medical profession on the staff. As for the medical science, as it was taught and learned in universities, its contribution was rather poor. During the 16th and the first half of the 17th century, in the face of the outbreak of epidemics, the most appropriate and concrete response was not provided by medical science, which was still heavily influenced by the Galenic theory, but by the health offices which, by working more empirically and concretely, restructured and expanded their skills. Moreover, the practice of prevention was a forced choice, due to the inability to cure, as treatments suggested by medical science were mostly ineffective, or even harmful.

As time went by, the existence of permanent health offices in the main cities became routine, while smaller cities, still lacking permanent health offices, began to elect temporary magistrates in emergency cases (5). Overall, we can identify a common development outline and a high level of information exchange in the organization of health policy structures among pre-unitary Italian States.

In a basically uniform framework, the case of Sicily is somewhat different: prone to contagion due to its role as a commercial crossroad of the Mediterranean, the Kingdom of Sicily organized contingent or permanent health control systems with different timing and methods, showing mismatches with the national reference framework (6).

Subjects and methods

Given the lack of systematic studies on the subject (7,8), the research outlines the structure and evolution of the public health management system in the Kingdom of Sicily, from the beginning of the Modern Age to the era of the Lieutenancy (1816-1860), to underline the specific features of the Sicilian case, highlighting the causes of these features, and also to understand if there is a break in continuity in the activity of the various institutions that managed public health along the time span investigated. To this end, the articulated legislation on the subject and the rich documentation produced by the competent bodies were analyzed.

Most of the acts and laws pertaining to the establishment and the organization of public health institutions in the Kingdom of Sicily are included in two printed volumes of the 18th century. The first, titled *Statuti del Magistrato di Sanità* (9), was edited in 1728 by Agostino Gervasi, *consultore protomedico* [Chief Physician Consultant]. A second edition of this volume with new documents added was edited in 1773 by Vincenzo La Grua Talamanca, head of the newly established *Suprema Generale Deputazione di Salute Pubblica* [Supreme General Public Health Deputation], *protomedico del Regno* [Chief Physician of the Kingdom] and *pretore* [Mayor] of the city of Palermo.

The second important source is a volume entitled *Governo Generale di Sanità del Regno di Sicilia e instruzioni del lazzeretto della città di Messina* (10), edited by Pietro La Placa in 1749. The volume includes a collection of documents related to the foundation of the *Magistrato di Salute*, but also provisions and laws on how to face the plague of 1743 which hit the Kingdom of Sicily.

Most of the documentary production of the health institutions of the period under examination is collected in a single documentary fund stored in the

State Archives of Palermo and has been analyzed in depth. The repository is named *Suprema Deputazione Generale di Salute Pubblica poi Soprintendenza Generale di Salute Pubblica (1731-1864)* (11) and consists of 1205 volumes. This repository constitutes the essential reference for a detailed reconstruction of health policy and organization in Sicily.

Results

Magistrato di Sanità di Palermo (1575-1740)

Between 16th and 19th century, several institutions managed public health in the Kingdom of Sicily, showing a blend of competences that is a typical feature of the modern State at its inception. The event that spurred the first arrangement of a public health institution on the island was the plague of 1575; on this occasion the establishment of the *Magistrato di Sanità di Palermo* (1575) was a boost towards specialization of public health control functions by the State. Although this institution had wide jurisdiction and was independent from the viceroy, its competence was limited only to the area of the city of Palermo, while the task of general superintendence on public health affairs still belonged to an institution with very broad and varied competences, the *Tribunale del Real Patrimonio* - supreme body of financial administration -, to which every local health deputation was required to refer.

The sources agree on indicating 1575 as the year of the creation of the *Magistrato di Sanità di Palermo*, a body which had the duty, according to its statute, to protect public health (12). The instances and causes of the establishment of this body are clarified in a document, dated Palermo 24th July 1575, by the viceroy Don Carlo Aragona Tagliavia prince of Castelvetrano, in the name of the sovereign Filippo II (9):

Affine di allegerire il concorso delle genti, e facilitare la cura degl'infermi di detto morbo, per rimediare ai disordini che da' disubbidienti si venissero a commettere intorno le guardie, o altre cose necessarie, che voi ordinerete, abbiamo provisto farvi le presenti, per le quali vi diamo licenza, autorità, e potestà di poter voi durante questo sospetto (se bisogno vi parrà) oltre ai diputati eletti, eleggere altre persone atte e disposte, e quelle crescere, e diminuire, o mutare a vostra volontà, e così ancora di chiamare, e far venire quei diputati, che si trovassero assenti, ed ancora di poter promulgare bandi con pene a voi benviste, e farsi tutte quelle ordinazioni, che vi parranno necessarie, e contro ai trasgressori delle vostre ordinazioni, e bandi, e de' nostri bandi promulgati per occasione di detta sospezione di peste, e contro ai disubbidienti ai mandati vostri procederete, si opus fuerit, a tortura, frusta, condannazione ad ultimo supplicio, a galere, bruciamento di loro robe, ed alla esazione di pene per voi imposte, o imponende.

[In order to reduce the influx of people and to facilitate the treatment of the people suffering from this disease, to reduce the acts of disobedience against the guards and for other needs that may arise, we have established to give you license, authority and power to to appoint, in addition to the elected deputies, other suitable people; to increase, change or replace them as you wish; we also authorize you to recall the absent Members and to issue notices with the penalties that you think are appropriate and to give all the orders that will seem necessary to you. We also authorize you to proceed, if necessary, against violators of your notices and orders and notices promulgated by ourselves in the occasion of the plague, with torture, flogging, forced labor, fire of their stuff, and any other penalty you will choose.]

The *Magistrato di Sanità* was born as an extension of the *Senato* [Senate] of Palermo, by virtue of an expansion of the competences of the *Senato* itself. The king entrusted the *Senato*, in an emergency situation, with the arduous task of managing and controlling the infection, in order to maintain public order. Once the emergency was over, the action of the *Magistrato di Sanità* became more tied to prevention, only to take on a role of coordination and control in the case of new infections. The staff of the *Magistrato* underwent some variations and tended to rise numerically on the occasion of new infections, as a demonstration of the inclination of this institution - like many others in modern States - to elasticity and adaptability. At the time of its establishment, the *Magistrato di Sanità* was chaired – as it has been up to the end – by the *Pretore* of Palermo and it included the city's *Capitano di giustizia* [Head of the Police] and nineteen knights "of the most respectable and provident" (10), plus a consulting deputy who, at the time of its foundation, was Giovan Filippo Ingrassia, *Protomedico del Regno*. Later, the number of deputies

grew to twenty-nine elements, and it was then reduced to twelve by the viceroy Marcantonio Colonna in 1582, to simplify and fasten its work. In 1624 the plague returned, brought on a ship coming from Tunis, admitted inside the harbor by the viceroy Prince Filiberto of Savoy, against the advice of the *Magistrato di Sanità*. The staff was then again expanded and the Magistrato di Sanità consisted at that time of: the *Pretore*, the *Capitano di Giustizia*, the entire *Senato* of the city of Palermo – which had only one vote –, three princes, three knights, six doctors – headed by the *Protomedico del Regno* –, and the well-known physician Marco Antonio Alaimo. Basing on these data, we can deduce that during the plague doctors tended to play a more prominent role within the Deputation. However, their reliability was grounded not on their professional role, but on their former experience in institutional roles in the Kingdom. After the end of the plague the composition of the *Magistrato di Sanità* remained the same until 1658, when Don Pietro Martinez de Rubio, archbishop of Palermo and president of the Kingdom, resized it again, establishing that it would be composed only by the *Pretore*, the *Senato* and four knights (noble deputies), all over the age of forty, plus three medical consultants, including the city's *Protomedico*.

The *Magistrato di Sanità* had a wide range of powers and the right to impose very severe penalties, ranging from a fine to a death penalty, whilst the viceroy had been explicitly forbidden to meddle in affairs related to public health, a very strong temptation, given the economic interests that were called into question in the case, for example, the block of trade with a foreign nation or, more simply, the quarantine of a ship.

Supremo Magistrato di Commercio (1740-1743)

Despite the wide powers granted, the *Magistrato di Sanità di Palermo* remained an institution with limited territorial competences, while the function of coordination and general supervision continued to be under the power of the *Tribunale del Real Patrimonio*.

In 1740, following a reform plan implemented by the Borbone dynasty - recently ascended to the throne of Sicily – which aimed, among other things, at regenerating commerce, the function of organization and management of public health was diverted to a newly established body, the *Supremo Magistrato di Commercio* (1739) (10, 13, 14, 15), showing the intrinsic connection perceived between the matter of public health and that of commerce and above all of exchanges with foreign countries across the sea. The *Supremo Magistrato di Commercio* was an institution with wide competences, established at the same time in the Kingdom of Naples and in that of Sicily, with the aim of freeing economic activities from the slack judicial system (16, 17). It was endowed with wide regulatory functions of economic activities, and in particular of commerce, with broad powers of intervention and control in the field of internal traffic, merchant navy, tax collection, manufacturing and mining activities, fishing, urban supplies, roads and bridges. The office exercised vigilance over the consulates of the arts, over exports and the salt trade, it had inspection duties in the field of work, as well as the power to set the prices of the products and, last but not least, the jurisdiction over all the lawsuits of trade; it was also a monitoring center with statistical skills and a laboratory for assistance and promotion of commercial and manufacturing activities. The scope of the functions of the *Supremo Magistrato di Commercio* and its authoritativeness soon aroused resentments in the *Senato* of Palermo and in the other tribunals, which felt dispossessed of jurisdictional rights, as well as in ecclesiastical circles, unfulfilled in the demand for certain commercial privileges, and in the corporations, which did not tolerate undergoing checks. We find this situation echoed in the Parliaments of 1741 and 1746, where the suppression of the institution was unanimously called for. Although such a pardon was not granted, the Sovereign, in fact, satisfied Parliament's requests by resizing to such an extent the powers of the *Magistrato di Commercio* [Trade Office] (Reale Rescritto, 24 April 1747) to make it an institution of little relevance, with jurisdiction only over trade cases between Sicilians and foreigners. With such reduced tasks, this court survived for about fifty years, then disappeared silently by the end of the century. Already in 1743 however, the competences related to the superintendence of public health had been switched to another institution.

The transitional period (1743-1746)

It was the last and late surge of plague, which struck Sicily in 1743, which once again stimulated a

reorganization of the public health system (18,19). Under the impact of the epidemic, the authority of general superintendence was transferred to the *Magistrato di Sanità di Palermo*, which became the central body and later, after the plague ended, without any substantial change to its composition, became *Suprema Deputazione di Salute Pubblica* (1746). According to the sources, already before 1743, the powers of the *Magistrato di Sanità di Palermo,* on special occasions, had already been extended, by explicit order of the King, beyond the territorial boundaries of competence. In the *Governo Generale di Sanità del Regno* it is even specified that (10):

regola era non di meno del suddetto tribunale [il Tribunale del Real Patrimonio, n.d.r.] di udire in ogni occorrenza i sentimenti del Senato, e Diputazion della capitale, e di non allontanarsi punto dagli stessi: e se talora accadea, ch'ei pensasse altramente di quanto venivagli da loro suggerito, ne trattenea la disposizione, infino a tanto che ritornata l'esamina della controversia innanti il medesimo Senato, e Diputazione, facendovi assistere il suo procurator fiscale, per riferire in voce i motivi della diversa opinione di esso tribunale, deliberavasi il conveniente; sempre però attenendosi al parere del Consiglio di Sanità.

[It was the norm for the aforesaid court [Tribunale del Real Patrimonio, n.d.r.] to listen to the advice of the Senate of Palermo and its deputation, and not to depart from it. If it happened sometimes that the Real Patrimonio Court had a discordant opinion, it postponed the decision until it was re-discussed in the senate and in the deputation, at the presence of its own prosecutor to report verbally why the court had a discordant opinion. Only after this passage did the court deliberate, always trying to stick to the opinion of the health council.]

The sources argue essentially that the *Magistrato di Sanità di Palermo* played a role of general superintendence to some extent even before 1743, albeit through the *Tribunale del Real Patrimonio* and – for a few years – the *Supremo Magistrato di Commercio*. Facing the spread of the plague in 1743, the need for speed and efficiency would lead to the ultimate formalization of this role of coordination for the deputation of the capital. With the real dispatches of the 9th and of the 29th of June 1743, the king officially ruled that the provisions of the *Magistrato di Sanità di Palermo* on public health would be attended throughout the Kingdom; the viceroy, on the 27th of the same month, officially transferred the role of general superintendence from the *Supremo Magistrato di Commercio* to the *Magistrato di Sanità di Palermo*, followed by the royal approval with dispatch of the 19th of July of the same year. From then on the *Magistrato di Sanità di Palermo*, established as *Supremo Magistrato*, had its own staff made up of a notary, ministers and junior officers. Also the internal composition of the institution underwent modifications and a numerical growth, with eight new members added: two belonging to the ecclesiastical order - the metropolitan archbishop and one of the canons of the cathedral -, four among the first barons of the Kingdom, who had already been praetors of the city, and two lawyers of the *Senato*. Further on, two other noble deputies will be added and one of them will be entrusted with supervising the drafting of dispatches and orders. The first to hold this office was Pietro La Placa, who had already demonstrated his abilities as chancellor of the city.

Suprema Deputazione di Salute Pubblica (1746-1819)

When the plague ended, a royal diploma of April 4th 1746, executed on May 7th of the same year, officially established the transformation of the *Magistrato di Sanità di Palermo* into «*Magistrato di Salute, supremo, generale, e indipendente per tutto il Regno di Sicilia*» [Supreme, General and Indepent Health Office of the whole Kingdom of Sicily] entrusted with «*direzione di tutto ciò, che conviene alla conservazione della comune salute* » [the direction of all that is useful to the preservation of common health] (9).

In addition, all rights, faculties, jurisdictions and privileges, which the body had enjoyed since 1743, were confirmed by the King, keeping its status and composition substantially unchanged. Even physically the Deputation did not change the place of its meetings, which remained the senatorial hall; even the placement of seats, bearer of deep symbolic and hierarchical meanings, remained unchanged.

The *Magistrato di Sanità di Palermo* therefore lost the status of local body to become a central government body, although it continued to be chaired by the *Pretore* of Palermo and it maintained its staff substantially

unchanged. This occurrence can be read as part of the project of specialization of the offices – already begun in the previous period – and of progressive centralization of jurisdictions, implemented by the reformism of the Borbone dynasty (20). In this respect the Kingdom of Sicily seems to be against the national trend, aiming, between the plague (1743) and cholera (1837), at the abolition of previous health institutions (21). Maybe we could read this attribution of competences to an already existing body of established tradition as the *Magistrato di Sanità di Palermo*, as an expression of the second stage of the reformism of the Borbone in Sicily, no longer too innovative or damaging towards the consolidated privileges of the cities and of the barons, but more reassuring and respectful of tradition (15).

Soprintendenza Generale di Salute Pubblica (1819-1860)

After the Restoration, in 1819, the royal decrees issued in the field of public health modified the previous institutional arrangement (22). The protection of health on the island was entrusted to two separate bodies, both dependent on the *Ministero Luogotenenziale dell'Interno* [Lieutenancy Ministry of the Interior] – therefore belonging to the central administration – and existing in the same form as *citra Pharum* [in the Kingdom of Naples]: the *Soprintendenza Generale di Salute Pubblica* [General Superintendence of Public Health], with executive power, and, subject to the latter, the *Magistrato di Sanità* – already established in 1743 – (23), with advisory and deliberative power. Already in 1818, a royal decree of November 18th had appointed a temporary commission in Palermo for public health affairs. On March 23th of the following year the *Soprintendenza Generale di Salute Pubblica* in Sicily was established with a royal decree. On October 20th of the same year a law on public health was also issued in the *ultra* and *citra Pharum* domains. The subsequent legislation defined the system in detail: the royal decree of January 1st 1820 regulated health matters in detail, designating the Superintendent as director of the health service for each province, while local deputations had the role of last execution agents of the internal health service. The same decree also subordinated the *Magistrato di Sanità* to the *Soprintendenza Generale di Salute Pubblica*, fixed the salaries of the employees, established the tariffs and rights to be assigned and, last but not least, drew up a classification of local health deputations. It is interesting to mention that the *Soprintendenza Generale di Salute Pubblica* operated in absolute continuity with the previous *Suprema Deputazione di Salute Pubblica*, to such an extent that that the archive that preserves the documentation produced by these two bodies is unique and the series are ongoing.

Conclusions

After a diachronic analysis of the management of public health in the Kingdom of Sicily, some general observations are needed, which can be sound for the entire period under analysis.

Firstly, there is a considerable continuity in the methods of action of the institutions that managed the issue of public health in the Kingdom of Sicily, as proven by the coherence and continuity of legislative and documentary production.

Another consistent fact is represented by the wide decision-making power recognized by the ruler to an institution which, given the importance of the matter, has the power to impose very harsh penalties – even the death penalty – to crack down on public health offenses. The experiences of epidemic diseases arriving in Sicily mainly from the East resulted in a progressive strengthening and a stiffening in external health defense, with very heavy disciplinary measures, which even included the gallows in the case, for example, of the infringement of a default by a ship.

Another key element is the close link between trade and public health; this link, shown by the jurisdiction recognized to the *Supremo Magistrato di Commercio*, is justified by the fact that health prevention was seen almost exclusively as protection from an external threat; this is probably due to the fact that there was awareness that, if the contagion had arrived within the boundaries of the Kingdom, few if not null measures would have been effective to face it. This idea clearly emerges in the *Statuti del Magistrato di Sanità* (9):

il più valevole sforzo, per abbattere un sì possente nemico [the plague, n.d.r.] par che debba solo riporsi nel fargli argine colle più esatte vigilantissime cure, per isfuggire

l'assalto, non potendo egli in altra guisa vincersi, che col tenerlo sempre lontano, il che sarebbe vano a sperarsi, senza invigilare colle più esatte diligenze sulle persone, merci, o altre robe da introdursi nel proprio paese, e soprattutto quelle, che da paesi turchi, o barbari procedessero, colle quali insieme si sono spesso i pestiferi semi introdotti.

[The most useful effort to bring down such a powerful enemy [the plague, ed.] is to stem it as carefully as possible, to avoid spreading, since you cannot defeat it in any other way, than always keeping it away. It would be useless to hope, if you do not pay close attention to people, goods, or other things that are introduced into your country, and especially those who come from Turkish or barbarian countries, with which pestiferous seeds are often brought.]

In an age when medicine was not yet able to provide a unique and scientifically sound explanation about the etiology of infectious diseases and the processes of its spread, nor to guarantee effective treatment solutions, health magistrates, mainly devoted to urban administration, often operated in uncertainty. The preventive measures adopted show an empirical approach to the problem, which leads both to the miasmatic theory and the contagionist theory, basing the decisions more on common sense than on a single medical theory. The case of Sicily is akin to those of the other Italian States and we can observe that the discriminating element to become part of health institutions is not a specific competence in the medical field, but rather being "wise men" with proven political and administrative experience. Even the minimum age limit of forty for the noble deputies of the Health Deputation is an indication that common sense - which is presumed to go with age – and experience were believed to matter more than medical expertise.

The doctors, with some exceptions, play an advisory role within the health institution both peripherally and centrally. They are entrusted with the task of identifying health risks at the peripheral level, where the risk can be first identified, through drafting reports. The analysis of the reports of the doctors of the local Deputations clearly show that until the end of the 18th century most of the physicians involved adopted the miasmatic theory. Moreover, despite the insights of doctors such as Girolamo Fracastoro and Gianfilippo Ingrassia and despite the first experiments of Redi and Spallanzani, the theory of spontaneous generation and, with it, the miasmatic theory will be definitively refuted only later by Pasteur. In the meantime, the miasmatic theory, with its simplicity, its logic and its internal coherence, persisted as the most accredited hypothesis by virtue of its authority.

Even at the central level the work of the physicians is mostly limited to an advisory role, as evidenced by the fact that the votes of the three deputy doctors are merely consultative, but not deliberative, consistently with what happened in other Italian States (24-25). On the other hand, executive choices are taken by the heads of the Deputation. In some cases, as for Ingrassia or Alaimo, the head of the Deputation could also be a doctor, but the chance for a doctor to play an apical role and to make executive decisions is not linked to specific medical and scientific skills, but to the fact that he is considered a wise man belonging to the administrative structure. Moreover, even advice and instructions inspired or drawn up personally by eminent doctors such as Ingrassia and Alaimo are often considered confusing and impractical, or even useless and harmful (9-10).

Only in the second half of the nineteenth century, when Social medicine was born, we will finally see physicians in Italy as active players in the field of public health management (26).

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Correspondence:
Lucia Craxì
Department of Biomedicine, Neuroscience and Advanced Diagnostics (Bi.N.D.)
Institute of Pathology, University of Palermo, Palermo, Italy
E-mail: lucia.craxi@unipa.it

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The tumor-endothelium interaction in pioneering studies and the revisited concept on the angiogenesis process during tumor progression and metastasis

Manuela Rizzi[1], *Matteo Gallazzi*[1], *Francesca Tosetti*[2], *Lorenzo Mortara*[1]

[1]Immunology and General Pathology Laboratory, Department of Biotechnology and Life Sciences, University of Insubria, Varese, Italy; [2]UOSD Molecular Oncology and Angiogenesis Unit, IRCCS Ospedale Policlinico San Martino, Genoa, Italy.

Abstract. The growth of solid tumors and their dissemination require the continuous formation of new capillary blood vessels. However, the association of uncontrolled growth of tumors and angiogenesis, i.e. the mechanism that allows the formation of new blood vessels starting from pre-existing vessels, dates back to 1971, in relation of Judah Folkman's works. Since then, his group and other researchers added new key results confirming the important role played by angiogenesis in tumor growth and metastasis, and multiple efforts have been made to exploit this knowledge in developing innovative anti-cancer therapies. In this article, we discuss seminal works regarding molecular mechanisms involved in aberrant tumor angiogenesis, biology of endothelial cells within extracellular matrix, function of diverse pro- and anti-angiogenic factors, roles of metalloproteinases and pro-tumor effects played by stromal and immune cells in the tumor microenvironment. Interestingly, growing evidences indicate a key role played by inflammatory and stromal cells in both tumor development and progression. The present article also aim to provide up-to-date information concerning new therapeutic concepts involving tumor vessels normalization and anti-angiogenic agents, among which inhibitors of metalloproteinases and of the main angiogenic factor, vascular endothelial growth factor (VEGF) or its receptors, and the combination of them with immune checkpoint blockade, that seem to be the most promising ones at present.

Key words: tumor angiogenesis, biology of endothelial cells, anti-angiogenic agents, tumor vessels normalization.

Introduction

Angiogenesis is defined as the formation of new blood vessels from pre-existing ones, in a tightly orchestrated balance between pro- and anti-angiogenic stimuli. All the contemporary knowledge about tumor angiogenesis is based on the pioneering works of Judah Folkman in the 70s, when he first hypothesized that tumor cells communicate with normal host cells allowing angiogenesis-dependent growth of solid tumors (1, 2).

Folkman proposed that tumors are strictly dependent in their induction and dissemination on the incessant triggering and growth of new blood vessels. He postulated that angiogenesis phenomenon functions as an active physiological feature regulated by biological factors and that tumor angiogenesis is driven by specific molecules released by tumor cells that can be potentially inhibited by new developed pharmacological agents. Such complex multistep process involves not only plasma proteins extravasation and extracellular matrix (ECM) degradation, but also endothelial cell proliferation and migration, as well as capillary tube formation.

Such process is very important in many stages of human life, such as vascular remodeling in the embryo female reproductive cycle or wound healing. In physiological conditions this phenomenon is tightly regulated since in healthy tissues angiogenesis is quiescent, due to the dominant influence of endogenous inhibitors over angiogenic stimuli (3). On the other hand, in pathological conditions (e.g. cancer development)

aberrant angiogenesis occurs disrupting the equilibrium by an increased secretion of pro-angiogenic factors and/or a down-regulation of endogenous anti-angiogenic components (3-6).

Both normal and tumor angiogenesis share some basic characteristics, as both types of new vessels formation involves the migration and invasion of both precursors and mature endothelial cells into the surrounding stroma, requiring the degradation of the existing basement membranes, as well as an active proteolytic remodeling of the resident ECM, mainly performed by a large family of enzymes, collectively named matrix metalloproteinases (MMPs). Basically, new vessels could be generated through two different mechanisms, involving or not sprouting events. In non-sprouting angiogenesis the new vessels derive from the splitting of an existing capillary in two or more tubes following resident endothelial cells proliferation. On the other hand, sprouting angiogenesis involves endothelial cells invasion of the surrounding ECM, where they re-organize to form tubular structures and recruit pericytes (7). Stimuli regulating new vessels formation are quite the same in both physiological and pathological angiogenesis and in both cases, ECM displays a pivotal role as a reservoir of regulatory factors. Among pro-angiogenic factors there are many cytokines (i.e. IL-1, IL-8) and growth factors such as VEGFs, vascular endothelial growth factor a protein family first described at the end of the last century, which earliest identified member was named VEGFA, or VEGF (8), fibroblast growth factors (FGFs), angiopoietin, transforming growth factor β (TGF-β), platelet derived growth factors (PDGFs), epidermal growth factor (EGF) secreted by inflammatory cells (e.g. mast cells and macrophages), pericytes, keratinocytes (during epidermal wound healing) or tumor cells. Both normal and tumor tissues could also produce anti-angiogenic factors (e.g. angiostatin, endostatin, thrombospondins, interferons (IFNs), vasostatin) to modulate new vessels formation locally as well as in distant sites (3, 5, 7, 9).

Therefore here, together with the aim to discuss and to highlight subtle interactions between various and complex signals involved in the initiation and triggering of tumor angiogenesis during tumor progression and metastasis, we also have the purpose to point out the relevance of innovative therapeutic strategies associated to inhibition of this process, such as those involving tumor vessels normalization and combination therapies using anti-angiogenic agents and immune checkpoint blockade, that seem to be the most promising ones at present.

Tumor angiogenesis

Folkman's hypotheses were based on the evidence that in physiological conditions vascular endothelium is a relatively quiescent tissue that can be activated to a rapid proliferation phase by appropriated stimulatory signals (5, 10, 11). According to Folkman's theory about tumor angiogenesis, solid tumor development could be separated into two stages, whose main difference is represented by vascularization.

In 1984 Folkman's group discovered a tumor growth factor named fibroblast growth factor 2, also known as basic fibroblast growth factor, which is endowed with angiogenesis inducing capacity (12). Two years later, in 1986, Harold F. Dvorak published an interesting review, based on his previous experimental studies on vascular permeability and angiogenesis in tumors, discussing the similarities between solid tumor stroma generation and wound healing, defining the solid tumor a wound that does not heal (13). Both stromal tumor and cutaneous wounds are characterized by a fibrin clot, which provides a scaffold for the migration of different biological elements, including new formed blood vessels, macrophages, neutrophils, lymphocytes, fibroblasts and myofibroblasts. Dvorak pointed out that wounds, similar to tumors, secrete a vascular factor and this event induces the release of fibrinogen from the blood vessels, causing blood vessels sprouting and providing a matrix through which they can spread.

This important result was the basis for other successes such as the cloning of the most powerful angiogenic protein, acting as a highly specific mitogen for endothelial cells: the VEGF discovered by Napoleone Ferrara's team (8). This was the same vascular permeability factor (VPF) that Donald R. Senger and colleagues from Harold Dvorak's group, identified in 1983 in culture supernatants of guinea pig tumor cells, then widely known as VEGF (14, 15). VEGF is a potent vascular permeabilizing agent, being effective

within one-two minutes from injection into normal skin or other tissues of experimental animals.

The intensive studies by H.F. Dvorak's group, which led to the evidence that cancer cells secrete VPF/VEGF, showed that its activity was not inhibited by anti-histaminases and other classic inhibitors of vascular permeability (16). Furthermore, unlike wounds, where VEGF production is stopped after healing, in tumors, there is no extinction of its production, and this phenomenon is at the base of the continuous process of tumor vascular neoformation and spread.

In 1990, Noel P. Bouck's team reported the identification of another inhibitor of angiogenesis: the protein thrombospondin-1 (17) and later Folkman's group discovered two important endogen anti-angiogenic factors: angiostatin, a fragment derived from plasminogen, in 1994 (18) and endostatin, derived from type XVIII collagen, in 1997 (19). The idea that endothelial cells may switch from a resting state to a rapid angiogenic growth phase was postulated by Douglas Hanahan and Folkman in 1991 (20) and further detailed by subsequent investigations (21).

Overall, most solid tumors before reaching few millimeters in diameter, seem to be able to survive thanks to oxygen and nutrients derived by simple diffusion, but after exceeding a critical diameter, they need blood supply by new vessels in order to expand (5, 6, 9, 22). To achieve a progressive increase in size, an essential requirement for solid tumor expansion lies is triggering the angiogenic switch through pro-angiogenic stimuli predominance over inhibitory factors. Given that tumors cannot make capillaries on their own, they must recruit them from the host, and it is currently well accepted that tumor blood vessel formation is a complex process involving many stages where the activated endothelial cells sprouting from pre-existing vessels is essential for angiogenesis.

Compared to normal vessels, new endothelial structures demonstrate a great functional as well as anatomical heterogeneity, appearing to be immature, irregular in shape and branching, with little and fragmented basement membrane and fewer intracellular junctions, making them highly permeable, allowing tumor cells to easily enter in the blood flow and metastasize in even distant regions.

Moreover, it is well accepted that there is a continuous crosstalk between the tumor and its microenvironment, including innate immune and stromal cells, such as tumor-associated macrophages natural killer (NK) cells and other cellular components (Figure 1) (23-26). Growing evidences suggest a crucial role played by inflammatory cells within the tumor microenvironment (TME) for both tumor development and progression (27). Among the host features representing tumor hallmarks (28), there are evading immune destruction and tumor-promoting inflammation, which, together with the immune cell-based induction of angiogenesis, underline the fundamental impact of innate immune cells in cancer (23, 25).

Among immune cells, NK cells are effector lymphocytes involved in tumor immunosurveillance upon interaction with tumor cells, and though they can control tumor growth by their cytotoxic activity (29) they can also acquire altered functions, ranging from attenuation of their killing activity, to tolerogenic behavior and acquisition of pro-angiogenic activities (30-33). Two main cell subtyes of peripheral blood NK cells have been identified in humans: the $CD56^{dim}CD16^{+}$ and the $CD56^{bright}CD16^{-}$ NK cell subset, representing about 90–95% of NK cells and 5–10% of peripheral blood NK cells, respectively. The TME-dependent unfavorable feature of NK cells depends on the expansion and function modifications of the $CD56^{bright}CD16^{-}$ NK cell subset. However, the $CD56^{bright}CD16^{-}$ NK cells, being

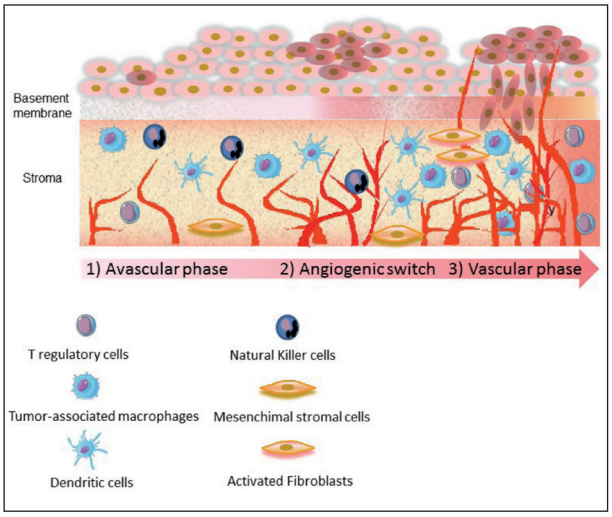

Figure 1. Tumorigenesis and invasion strongly depend on angiogenesis.

poorly cytotoxic, can release several cytokines, including IFNγ, GM-CSF, and TNFα and this latter could exert a potent stimulatory effect on endothelial cells, resulting also in normalization of tumor blood vessels, as well as on activation of innate and adaptive immune responses, reverting the microenvironment anergy (34). Targeting TNFα to tumor vessels in combination with chemotherapy is an interesting novel anti-tumor strategy (35). For these reasons, NK cells could become a suitable therapeutic target to modulate the immunosuppressive and pro-angiogenic TME and possibly become powerful cytotoxic anti-tumor effectors (33, 36). Furthermore, from a therapeutic point of view, the emerging concept of normalization of tumor blood vessels, introduced by Rakesh K. Jain in 2001, in particular for combined anti-angiogenic therapies (37) is of great importance. Indeed, tumor-associated vasculature consist of an abnormal leaky and immature irregular vessel network in close contact with cancer cells, fibroblasts and inflammatory immune cells and abundant ECM molecules such as collagen and hyaluronan. Tumor vessels normalization consists of vessel with a mature phenotype, fortified with perivascular cell coverage, and a more organized and uniform distribution of the vasculature throughout the tumor tissue. One useful approach to reach vascular normalization is the inhibition of VEGF or its receptors through anti-angiogenic agents, such as bevacizumab, and of note, the resulting normalized vessel structure induced intra-tumor high endothelial venules and reinforced tumor perfusion, thus favoring more homogeneous delivery of drugs, oxygen, and enhanced immune cells infiltration and in particular antitumor cytotoxic T lymphocytes (38-40). However, it has also been reported that a high and too prolonged infusion of anti-angiogenic drugs can definitely reach an opposite effect, thereby inducing hypoxia, immunosuppression, tumor progression, and treatment resistance (41). Moreover, the tight interconnection between tumor angiogenesis and metastatic potential is recognized as a prognostic indicator, as increased angiogenesis correlates with worse prognosis in different types of human cancers, among which gastric cancers (5), non-small cell lung cancers (NSCLC) (6), melanoma (42), and renal cell carcinoma (RCC) (43).

Folkman defined the concept of tumor dormancy, the condition related to a steady state in which competent transformed tumor cells do not develop into a clinically detectable cancer (44) until endothelial cells of host vessels are activated from their physiologic latent status to a rapid growing status by soluble molecules released by tumors or by signals delivered by tumor-conditioned innate immune cells (Figure 1). This is probably due to the absence of stimulatory signals, or to inhibitory mechanisms or a combination of these. This phenomenon appears to be present in the early stages of primary cancers, or to the remains of primary tumors as is the case for undetectable disease recurrences and micrometastases that could subsequently reactivate after a latency period and evolve in a clinically detectable disease (45-47).

Although tumor dissemination and metastases strictly depend on neoangiogenesis in response to tumor-mediated release of stimulating factors from the surrounding ECM (e.g. FGF2, VEGF, IL-8), it has to be highlighted that tumor cells are able to escape from the primary neoplasm, to invade blood and lymphatic vessels, but the growth of a new cancer lesion represents only a very small subpopulation of those cells forming the primary bulk tumor (7, 22).

Pro- and anti-angiogenic factors

Tumor angiogenesis depends on pro-angiogenic stimuli produced by both tumor cells and immune cells present in the surrounding microenvironment, such as macrophages, mast cells and lymphocytes attracted to the tumor site. Among the most important pro-angiogenic factors involved in tumor metastases there are many growth factors, such as VEGF, placental growth factor, FGF, PDGF, and interleukins, such as IL-1, and IL-8, without forgetting ECM degrading enzymes. Many of these pro-angiogenic factors act directly, typically VEGF and angiopoietins, while others show an indirect action as FGF, PDGF and ILs. As stated before, tumor angiogenesis also involves a disregulation of the normally occurring anti-angiogenetic equilibrium that normally occurs in physiological state. Among the natural inhibitors of angiogenesis, the most important are trombospondin-1 and -2, IFNs, angiostatin, endostatin, vasostatin (3, 5, 9, 18, 19).

Among tumor promoting agents, the plays a pivotal role. VEGF is a homodimeric 40-45 kDa heparin-binding glycoprotein, acting as endothelial specific mitogen which exerts pro-survival and anti-apoptotic activities. VEGF represents the major promoting factor of tumor angiogenesis since it facilitates tumor growth, dissemination and metastasis, as demonstrated by its overexpression, along with VEGF receptor, in the majority of tumor cells and in tumor-associated blood vessels (4). Interestingly, VEGF could also induce fenestrations in small vessels even in tissues where micro-vascularization is not normally fenestrated, thus accounting, at least in part, for the high permeability of tumor vessels (3, 5, 22).

Furthermore, a key anti-angiogenic role is played by IFNs. IFNs activity is critical in angiogenesis as they inhibit capillary endothelial cells migration by blocking both the production and the efficacy of tumor pro-angiogenic factors (9).

The recombinant humanized anti-VEGF monoclonal antibody bevacizumab (Avastin), developed by N. Ferrara and colleagues (Genentech, San Francisco Inc.), recognizes all VEGF isoforms and blocks binding to the VEGF receptor (48). This prototypical anti-angiogenic agent has been used in eleven important trials and more than two million patients affected by advanced solid tumors, comprising metastatic colorectal, non-small cell lung, ovarian, renal and cervical cancers. Phase III clinical trials demonstrated a significant advantage in objective response rate (ORR), overall survival (OS) or progression-free survival (PFS) in patients treated with bevacizumab in combination with chemotherapy (41-43). In contrast, its use in metastatic breast cancer was discontinued due to the lack of efficacy and a low safety profile. Disappointedly, resistance to bevacizumab is apparently acquired by angiogenesis inhibition itself, which exacerbates the tumor hypoxic microenvironment, with consequent stabilization of the hypoxia inducible factor 1 and 2 (HIF-1, HIF-2) and HIF-dependent genes (41). This condition, in turn, leads to the activation of a compensatory pro-angiogenic program, which represents a critical issue, still requiring further investigations. In this context, stromal and immune cells, which play a crucial role in supporting tumor dysmorphic neo vascularization by unbalanced release of growth factors and cytokines with pro-angiogenic activity (FGF, PDGF), deserve great attention as potential targets of therapy (43).

Tumor angiogenesis and extracellular matrix remodeling: a potential therapeutic target

Tumor invasiveness relies both on active cell migration and the ability to degrade to a limited extent the surrounding ECM in order to achieve tumor invasion. ECM degradation is mainly accomplished by MMPs, a wide family of Zn^{++} and Ca^{++} dependent proteases, working at neutral pH. MMPs are present in approximately all human cancers, as they can be produced by both surrounding stromal cells and tumor cells: in the last case, enzymes are generally sequestered on the cell surface and concentrated at the leading edge of tumor migrating cells. Due to their ubiquitous presence in the tumor environment, they could affect tumor spread in many different ways (e.g. by promoting tumor angiogenesis of metastases dissemination). However, the ECM degrading activity of MMPs is counterbalanced by a naturally occurring family of inhibitors called TIMPs (tissue inhibitors of metalloproteinases), which are able to inhibit angiogenesis as well as tumor growth and metastasis (7, 9, 49-54).

MMPs, as an enzyme family, are known to directly influence the angiogenetic process by either degrading the basement membrane by the direct cleavage of matrix components, or by cross-activating each other, thus allowing endothelial cells invasion, or by cleaving pro-angiogenic factors (e.g. cytokines as well as growth factors) in order to maintain the angiogenic phenotype. Among all the MMPs' family members, MMP-2 and MMP-9 (known as gelatinases) play a pivotal role in driving angiogenic processes both in physiological and pathological conditions by cleaving basement membrane components as well as through the modulation of angiogenic regulators such as IL-8, platelet factor 4 (MMP-9) and FGF receptor 1 (MMP-2). The first evidence of the role of ECM degradation in tumor dissemination dates back to early 1980s, when L. Liotta and coworkers recognized the involvement of basement membrane degradation in tumor metastasis. Liotta and colleagues' studies resulted in the identifica-

tion of MMP-2, a degrading enzyme of type IV collagen, the major component of the basement membrane (51, 52). Following such studies, the MMPs family rapidly expanded to include more than 20 different enzymes, many of which were first identified by their overexpression in tumor cells. Scientists' understanding of tumor environment remodeling rapidly grown up and actually it is known that gelatinases are not the only MMPs involved in tumor angiogenesis, but also MMP-1 and MMP-14 (also known as MT-MMP-1) play a role (7, 53, 54). As ECM degradation is strictly associated with tumor progression as well as neovasculature spreading, many studies focused on MMPs inhibition with the aim of blocking tumor dissemination. Considering that MMPs and TIMPs expression in physiological conditions and in the TME is different and undergoes specific regulatory patterns, starting from 1990s nearly every pharmaceutical company developed its MMPs inhibition research program. For these reasons both *in vitro* and *in vivo* studies focusing on MMPs inhibition using natural (TIMPs) and synthetic compounds to block tumor dissemination, began and even reached the clinical trial stage (53-55).

The first MMPs inhibitor to be developed and clinically tested was batimastat, a broad spectrum injectable competitive peptidomimentic drug. Such compound was an efficient inhibitor of the main MMPs involved in sustaining tumor angiogenesis but, due to its poor solubility and very low oral bioavailability, along with a high toxicity profile with severe systemic side effects, its development was stopped in phase III clinical trial. Researchers thus developed a new and more bioavailable analogue, marimastat (53-55). Marimastat is known to act as a potent MMPs inhibitor acting as a competitive inhibitor that mimics enzymes' substrate. Even if such compound is a strong tumor angiogenesis inhibitor, its low cytotoxicity is not sufficient to efficiently suppress tumor cells growth and proliferation. Also in this case, clinical trials did not revealed a significant improvement in patients' OS and considering the severe systemic side effects (mainly represented by musculoskeletal pain and inflammation) its development was discontinued (53-55). In the attempt to overcome the adverse side effects linked to peptidomimetic drugs, pharmaceutical research pointed to the development of MMPs inhibitors based on small chemical molecules. The first product of this new research branch was CGS27023A (Novartis®) a chemical inhibitor specifically targeting gelatinases and acting as a Zn^{++} chelating compound. Such new drug showed a great potential in reducing tumor angiogenesis, but due to its low anti-proliferative effects along with the poor tolerability, its development was abandoned (53). Prinomastat was then developed as an optimized version of CGS27023A and entered clinical trials as anti-angiogenic drug. Unfortunately, also in this case, the ongoing phase III clinical trials were withdrawn before completion due to the lack of efficacy in patients with advanced disease (53). To date there is only one approved drug inhibiting MMPs: Periostat, a chemically modified doxycycline approved for periodontal diseases. Such drug inhibits MMPs by chelating their structural cations, thus showing an additional way of action unrelated to its well-known antimicrobial power (7, 53, 54).

Even if Big Pharma interests in developing MMPs inhibitors to be used as powerful cancer therapeutics rapidly fall down, the knowledge about ECM remodeling and MMPs role in sustaining tumor angiogenesis continues to accumulate. Nowadays, it is well accepted that MMPs still represent an interesting target for anti-cancer drugs development. In the light of the currently available scientific knowledge, it is clear that the above-mentioned clinical trials display a great drawback: they enrolled patients with cancers at different stages and were designed to evaluate OS. Currently, it is generally recognized that gelatinases play a pivotal role in the angiogenic switch at early stages after tumor neovascularization: in light of these considerations, these studies might have been more successful if they were conducted with patients with early stage cancers, or to test their efficacy as preventive agents for patients undergoing surgical resection of primary tumors. According to the latest information available, MMP inhibitors development focuses on the design of highly potent and selective compounds and/or on innovative delivery systems assuring preferential drug accumulation in the TME in order to overcome severe systemic side effects (7, 51). Moreover, the anti-angiogenesis drugs can be combined with immunotherapies, in particular the combination with immune checkpoint blockades (ICB), consisting of monoclonal

antibodies directed to PD-1, PD-L1 and CTLA-4, aimed at the blockade of inhibitory pathways on tumor-infiltrating lymphocytes (56). Indeed, targeting the tumor vessel compartment for example, could lead to local endothelial cell triggering that can increase the T-cell homing necessary in the involvement of anti-tumor T effector cells (57).

Combining tumor anti-angiogenic agents and immune checkpoint blockade

The use of the combination of anti-angiogenic drugs and ICBs as initial hypothesis concept has become a solid rationale for many new clinical tests currently underway, in particular for advanced melanoma, NSCLC and RCC (58). In a phase III trial the combination of an anti-PD-1 antibody (pembrolizumab) with a tyrosine kinase inhibitor of VEGF receptors (axitinib) resulted in improved OS, PFS and OS rates in comparison to the standard of care of patients with advanced or metastatic RCC (59). Other studies showed synergistic effects between bevacizumab and ICB treatment by enhancing antitumor immune activation in the TME as well as systemically in both RCC metastatic patients in combination with anti-PD-L1 antibody (atezolizumab) in a phase Ib trial, and in melanoma patients in combination with anti-CTLA-4 antibody (ipilimumab) in a phase I trial (60,61).

Tumor progression is a multi-step process in which developing tumors incorporate a series of genetic and molecular alterations, up to reach about 1-2 mm in diameter, until they switch to the angiogenic phenotype. The angiogenesis phenomenon is responsible for a faster tumor progression and invasion and is carried out by tumor cells, activated fibroblasts, tumor-associated macrophages and NK cells. This complex process consists of numerous interactions between tumor, endothelial, stromal and inflammatory cells, with also important effects played by various soluble pro-angiogenic factors, among which in particular different types of MMPs that are involved in the initial phase of degradation of basement membrane of the ECM and in the regulation of the angiogenic process.

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Correspondence:
Prof. Lorenzo Mortara
Immunology and General Pathology Laboratory, Department of Biotechnology and Life Sciences (DBSV), University of Insubria
Via Monte Generoso 71
21100 Varese, Italy
E.mail: lorenzo.mortara@uninsubria.it

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Paleopathology of a 19th century mummy of a nobleman from Popoli, central Italy

Luca Ventura[1], *Gino Fornaciari*[2], *Antonio Calabrese*[3], *Lorenzo Arrizza*[4], *Antonio Fornaciari*[2]

[1]Division of Pathology, San Salvatore City Hospital, L'Aquila, Italy; [2]Division of Paleopathology, Department of Translational Research and New Technologies in Medicine and Surgery, University of Pisa, Italy; [3]Division of Radiology, Santissima Trinità Hospital, Popoli, Italy; [4]Centre of Microscopies, University of L'Aquila, Italy

Abstract. A natural, well-preserved mummy belonging to a 35-40 years old male was found in the Church of the Holy Trinity in Popoli, Abruzzo region, central Italy. His fine clothes and burial location suggested that he was of high social status and had an important role in the church community. Most likely, he was a nobleman and a member of the Holy Trinity congregation. Two artifacts, a medallion and a relic of Saint Philomena, helped to date back the individual's time of death to the early 1800's. To conduct scientific analyses the body was secured to a cardboard layer by a plastic film and submitted to external examination, digital radiology, and computed tomography scanning, as well as histologic examination of samples obtained by video endoscopy. Anthropological investigations allowed us to observe pathological conditions as poor dental health, pulmonary pathology and a left renal stone. The renal stone was endoscopically removed and submitted to binocular stereomicroscopy, scanning electron microscopy also with microanalysis and X-ray diffraction analysis. The ovoid mass measured 22x16x15 mm, showing surface spherical buds and a nucleus of sharp-edged crystals with concentric laminations. Chemical elements were C, O, N, Ca, P, K, S, Cl, Na, arranged in calcium oxalate monohydrate (whewellite) (90%) and calcium phosphate (hydroxylapatite) (10%). The stone composition indicates a high animal protein intake by the subject, confirming that he belonged to high social class. The co-existence of caries, without major arthritic changes indicates that this man lived a life free from extensive labour. In fact, his death appears to be related to infectious complications of renal urolithiasis.

Key words: Paleopathology, Natural mummies, Central Italy, Nephrolitiasis

Introduction

The Church of the Holy Trinity in Popoli (Province of Pescara, Abruzzo region, central Italy) was erected in 1500 by the lay congregation of the Holy Trinity and reconstructed in 1734 (1). In a side room near the altar, under the floorboards, there is a crypt conserving human remains in various states of preservation. Although a thorough examination of this room could not be carried out, the crypt appeared to contain the remains of at least eight individuals (2).

During a first preliminary exploration, one individual still in a wooden coffin, directly below the crypt opening, was discovered. The coffin lid was pulled slightly back from the head end and, once removed, revealed a well-preserved mummy covered in dust. Visual examination suggested that the body belonged to a well-dressed male, possibly a priest. The recovery of the body and the preliminary investigations were presented on an episode in a television series called "The Mummy Road Show" by the National Geographic Channel (3).

Here we present the final results from the complete paleopathological investigation of the mummy.

Materials and Methods

An initial nondestructive investigation with portable X-ray examination (4) was conducted inside the crypt. Subsequently, it was determined that further examination would require removing the mummy from the crypt. Thus, the body was wrapped in clear plastic film in order to secure it to a cardboard layer and minimizing the risks during its recovery. The mummy was moved to the nearby hospital to be submitted to digital X-ray examination and computed tomography (CT) scanning.

Direct radiograms in different projections were obtained with the digital system GMM Opera T. CT scanning was performed by using a Siemens Somatom Balance scanner with 1 mm thick sections, obtained at reconstruction intervals of 3 mm, at 70 mA and 130 kV, with maximum FOV 44.2 x 44.2 cm, generating a total of 754 scans. Tomodensitometric evaluations were carried out according to the Hounsfield scale. Sex determination was made on the basis of the morphological features of the pelvis and skull (5). Age at death was assessed on the basis of the dental wear pattern (6).

Video endoscopy was performed in order to remove a stone from the abdomen and to recover artifacts from the individual's clothes, as well as to obtain biopsies from thoracic organs. Right thoracic tissue samples were rehydrated using Sandison's solution (7-8) for three days. The rehydrated specimens were routinely processed to obtain histologic sections stained with hematoxylin-eosin, Masson's trichrome, Grocott's, and Ziehl-Neelsen stains. The abdominal stone was investigated with binocular stereomicroscopy (BSM) with a LEICA S8APO stereomicroscope, and scanning electron microscopy (SEM) with energy dispersive X-ray analysis (EDX) using a Philips XL30/CP scanning electron microscope equipped with OXFORD-IncaEnergy microanalysis. Multiple tiny fragments from surface and inner portions of the calculus were submitted to X-ray diffraction (XRD) analysis with a Philips X'Pert PW 1830 X-ray diffractometer.

Results

After a preliminary cleaning, the burial clothes appear to be made of fine linen with floral print covering the entire jacket, changing our initial hypothesis that the body belonged to a priest (fig. 1). These fine clothes and the burial location could suggest an important role of the subject in the church community. Most probably, he was a nobleman and a leading member of the congregation of the Holy Trinity. No sign of evisceration and/or surface manipulation of the body was noted. Mummification was likely due to the dry cool environment in the crypt.

Determination of sex revealed male features. Age at death was estimated to be 35-40 years.

X-ray examination showed a metallic artifact within the clothes at about left lateral waist level and a ring between the crossed hands of the subject. From a paleopathological point of view, x-ray revealed the presence of a renal stone in the left lumbar region (fig. 2). A lateral radiogram of the head, at the dental arches, caries as well as evidence of periodontal disease.

Total body CT scanning confirmed the presence of the kidney stone and the artifacts (fig. 3), also displaying postero-basal pleural adherences in both lungs, more pronounced in the right side. Additional CT findings

Figure 1. The mummy removed from the crypt, after surface cleaning.

Figure 2. Digital radiogram showing the metallic artifact at left lateral waist, the stone in the left lumbar region, and a ring between the hands.

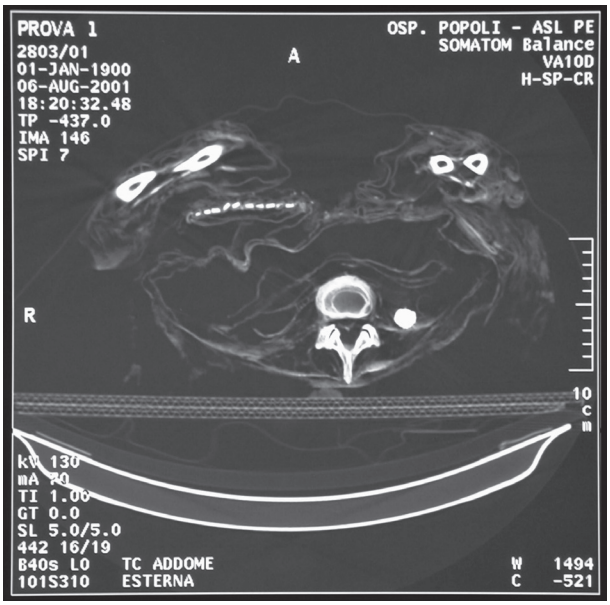

Figure 3. CT scan showing the stone and the metal artifact.

were represented by amorphous material (remnants of encephalic organs) in the posterior cranial fossa, along with portions of the meningeal tissue, also visible within the spinal canal. Tissue remnants were also present inside the orbits. Thoracic and abdomino-pelvic organs appeared extremely well preserved and readily recognizable. All these findings confirmed the natural mummification process, which appears to have been due to rapid dehydration, possibly related to the dry climate. Caries were recorded in first inferior molars, second right superior molar and third left superior molar. All inferior premolars have been lost *intra vitam*.

Video endoscopy found a small pouch among the folds of the clothes, which was removed and carefully opened. The metallic artifact inside the pouch is a medallion with the inscription and the figure of Saint Philomena. Additional items found in the pouch included an intricately folded piece of paper with an inscription referred to a piece of the shirt of the above mentioned Saint. Endoscopic biopsy from the right thoracic region, along with subsequent histologic examination of the specimen revealed fibrous tissue with calcification, fibromuscular tissue, fungal spores attached to the fibrous tissue, and presence of ectoparasites (fig. 4 A, B).

The stone extracted under endoscopic guidance was a brownish ovoid mass with small superficial spherical buds and measured 22 x 16 x 15 mm (fig. 5). The external surface, examined by BSM and SEM, showed a central core with small spherical nodules. The cut surface, observed with BSM, showed a central nucleus composed of sharp-edged crystals and various concentric laminations, pale and dark brown in color. Chemical elements detected with SEM-EDX were C, O, N, Ca, P, K, S, Cl, and Na. XRD analysis revealed

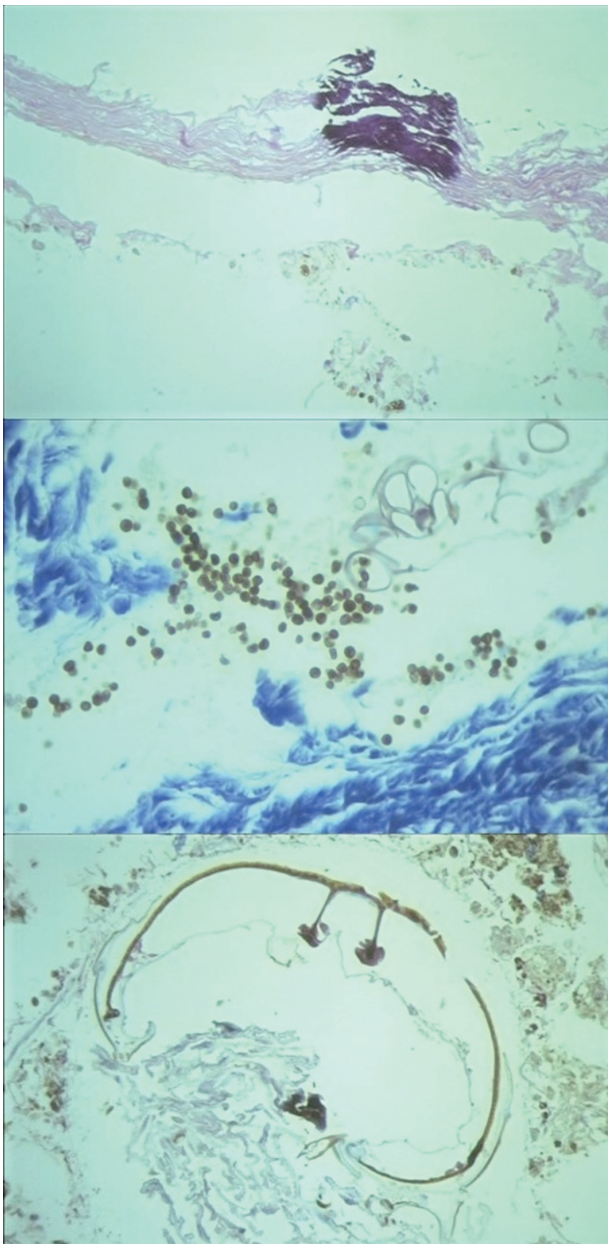

Figure 4. From above to below: calcified fibrous tissue (Hematoxylin-eosin, low-power magnification); fungal spores (Masson's Trichrome, medium-power magnification); ectoparasite structures (Masson's Trichrome, low-power magnification).

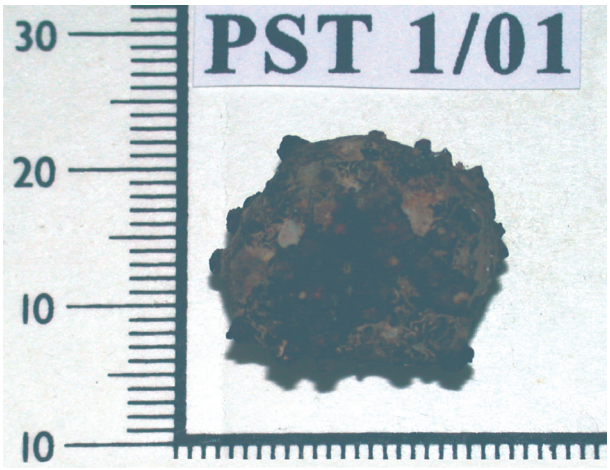

Figure 5. The brownish, ovoid stone with small spherical buds on the surface.

that the calculus was composed of calcium oxalate monohydrate (whewellite) 90% and calcium phosphate (hydroxylapatite) 10%. No trace of uric acid was found in this material.

Discussion

Several examples of mummified bodies were discovered in the inner Abruzzo region. Most of these spontaneous preservations are due to the cold and dry climate of this land. Historically belonging to the territory of L'Aquila and subsequently included in the Pescara province, Popoli is located in an area already known for preserving other examples of naturally preserved mummies (9-10). In this particular area, the important series of Navelli and Goriano Valli were also studied (11-12). As a matter of fact, the inner Abruzzo region should be considered one of the most relevant areas for natural mummification in Italy (13-14).

The discovery of the mummy of the Church of the Holy Trinity allowed us to apply several modern investigation techniques in order to carry out a complete paleopathological study of the subject. The analysis revealed considerable data regarding the social status, age in antiquity, sex, age at death, dentition, biomechanical stress, skeletal, pulmonary and renal pathology of this individual.

The preservation conditions of the body were evaluated through visual inspection and CT scanning. The presence of internal organs and the absence of filling materials or skin cuts allowed us to define a well-preserved, natural mummy, obtained by a rapid dehydration mechanism in cold environment.

The analysis of the medallion and the relic found inside the pouch of the clothes would highlight the significant role of the subject within the Church of the Holy Trinity. As important individual in the ecclesial community it had to be guaranteed to him, as to other members, the safe journey to the afterlife by including religious icons relevant to the times. People adopted Saint Philomena as their patron saint after the year 1802 and the cult spread rapidly to the southern Italy and Abruzzo region (15). This suggests that this burial may have occurred at the very beginning of the 19th century.

The subject was a middle-aged man, with dental, pulmonary and renal pathologies. The presence of significant dental caries and renal pathologies, without major arthritic changes (16) suggested he was not subject to extensive labor. Bilateral, basal adherences in lungs suggested recurrent episodes of pneumonia. The muscular bundles in the sample from the right lung indicates diaphragm muscle, and the presence of calcifications in such tissue is suggestive, but inconclusive for tuberculosis. Additional staining to demonstrate the eventual presence of acid-fast bacilli inside the calcifications gave negative results. The presence of fungal spores and hyphae is very common in mummified remains, and they may be easily confused with red blood cells even by expert pathologists unexperienced in ancient tissues (17-18). The ectoparasite more likely represents the result of a *post mortem* contamination.

The analyses of the removed calculus demonstrated that the subject suffered from renal stone disease. Urolithiasis is an ancient disease, the first paleopathological documentation of which dates back to the Paleolithic Age (19). At present, bladder stone disease is endemic in rural or impoverished areas, whereas renal stone disease is mainly an affliction of the industrialized countries of Western world (20). This explains the scarce mentions of renal colic from upper tract stones found in historical sources, and conversely the frequent references to bladder stones in the past (21). The diagnostic approach employed in this particular case is cutting edge, and enabled us to correctly diagnose

nephrolithiasis and to establish the type of renal calculus (19, 22). The chemical composition of the stone supports the hypothesis of high animal protein in the subject's diet, confirming once again that he belonged to high social class. In fact, a diet rich in proteins with small uptake of vegetables well explains the nephrolithiasis (23).

Unfortunately, also due to the lack of written sources, it was not possible to trace the identity of the subject but we could identify the cause of death. In fact, after our diagnostic reasoning, urinary sepsis may be considered the probable cause of death.

As prostatic hyperplasia is uncommon before the fifth decade of life and no other cause of urinary obstruction was found, a chronic illness such as chronic renal failure appears unlikely in this case (24). The death of the subject could be related to acute infectious complications of renal urolithiasis with or without hydronephrosis.

In conclusion, the mummy of this anonymous nobleman provided valuable information about the life and times in early 1800's Italy. The minimally invasive analysis coupled with a multidisciplinary approach revealed considerable data demonstrating the state of health of this individual at the time of death. The results obtained in this particular case are significant to the local community as well as to Abruzzo region, and should encourage the entire recovery of the Crypt to study the entire anthropological sample.

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Correspondence:
Luca Ventura
Division of Pathology, San Salvatore City Hospital,
L'Aquila, Italy
E-mail: luca.ventura@tin.it

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A case of juvenile nasopharyngeal angiofibroma belonging to the Pathology Museum of Turin

Luisa Ferrari
Department of Oncology, Pathology Unit, University of Turin, Turin

Abstract. The Pathology Museum of the University of Turin houses historical dry and wet specimens dating back to the end of XIX and begin of XX century. Among these specimens, a case of juvenile nasopharyngeal angiofibroma was discovered during the study of the diagnostic re-evaluation of the Collection. Juvenile nasopharyngeal angiofibroma is a rare non-capsulated vascular neoplasm predominantly arising in adolescent males. It suggests that this neoplasia could be androgen dependent, but this hypothesis remains controversial and its origin is still not clear. It is considered a benign neoplasm but locally aggressive and it could spread to the base of the skull and into the cranium. The museum wet-specimen dates back to March 31th 1911, as shown on the autopsy report which number is reported on the original label on the jar. The specimen was collected performing the autopsy on a 14years old boy who died of unknown reasons, most likely for epistaxis or suffocation. The only pathological finding is the nasopharyngeal lesion. Macroscopic examination of the specimen shows that on the base of the skull there is a huge polypoid lesion. Histopathology shows an edematous fibrous stroma and staghorn blood vessels irregular in size and shape. The tissue appears to be well preserved despite the long extended period in fluid. The original diagnosis was "Nasopharyngeal polyp" and it was actually the name of juvenile nasopharyngeal angiofibroma before the first official report of this lesion in the year 1948.

Key words: pathology museum, nasopharyngeal angiofibroma

Introduction

The Pathology Museum of Turin has an ancient history since their foundation dates back to 1818. Doctor Giovanni Pietro Gallo started to collect the most particular pathological specimens founded performing autopsies. In following years, the collection grew and in 1872 there were more than 1000 specimens (1). When Professor Pio Foà became Director of the Institute of Pathology, a new kind of collection started: not the strangest specimens like a Wunderkammer, but specimens with a scientific interest, although not so spectacular. The director especially collected neoplasms and infective diseases. His follower Professor Ferruccio Vanzetti was instead interested in cardiovascular pathology (2) and collected many specimens of tertiary syphilis. Nowadays, the Pathology Museum houses 304 wet specimens representative of many neoplastic and infective diseases. In recent years, a project of diagnostic re-evaluation of the specimens with modern techniques of pathology has started. This project includes the sampling of the specimens with a conservative approach respecting the macroscopic integrity of the specimens (3). Core biopsy is the technique of choice in the huge masses without sections already present, whereas the old sections, can be useful for new sampling without damaging the specimens. Then the study of the sampled tissue is carried out using histochemistry, immunohistochemistry and if possible molecular biology as well. This study allows the diagnostic re-evaluation of the specimens starting from the original diagnosis on the label. The

old diagnosis are not often so easy to understand for a modern pathologist. Therefore old books of Pathology are used for a better comprehension. The most useful book is the text of Pio Foà. Professor Foà wanted Italy to have a Pathology book in its own language, until then there were no any books from Italian authors. The book "Trattato di Anatomia Patologica" dates back to 1921 (4). Pio Foà personally wrote the chapters of haematology and respiratory system. This book helps to understand the old diagnosis especially when they use terms that now are not so clear according to the modern classification of pathology. The integration between autopsy report, histology of the specimen and bibliography allows a correct diagnostic re-evaluation of these old wet specimens.

Material and methods

Among the specimens of the collection of the Pathology Museum of Turin a case of "nasopharyngeal polyp" has been re-evaluated. This diagnosis is reported on the original label (Fig. 1) together with the number of autopsy. The autopsy was performed on March 1911. Its number is 12238. It was the case of a 14years old boy. There is not a certain cause for the death, but there is the description of a huge mass "as big as an egg" on the base of the skull. No other pathological findings are reported. The jar appears in poor condition: the fluid is reduced and the specimens is not fully covered. The fluid shows a dark brown colour and it is impossibile to see the specimen inside the jar (Fig. 2). Surely, this specimen needs to be restored in a future. Despite these bad conditions, the wet specimen shows an excellent preservation, probably due to the first fixation. Inside the jar there are two halves of a lower skull. The left half exhibits a lesion on the base of the skull which occupies the nasal cavities, therefore a possible cause of death of this boy was suffocation (Fig. 3). The lesion is grey and soft and there is no evidence of a capsule, even if it is well demarcated. A small sample was taken from a hidden surface of the lesion without damaging the specimen. Haematoxylin-Eosin stain was performed for a first evaluation of the morphology.

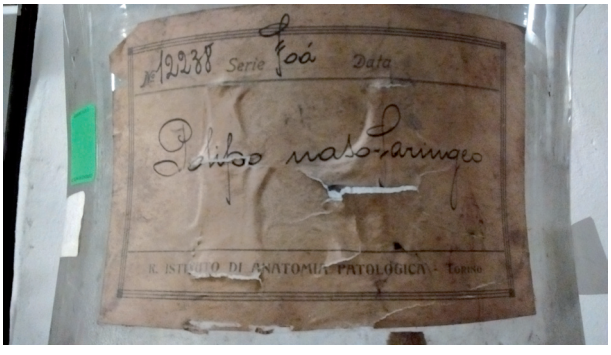

Figure 1. Original label on the jar

Results

Histopathology shows a loose edematous stroma with few cells interspersed with many staghorn

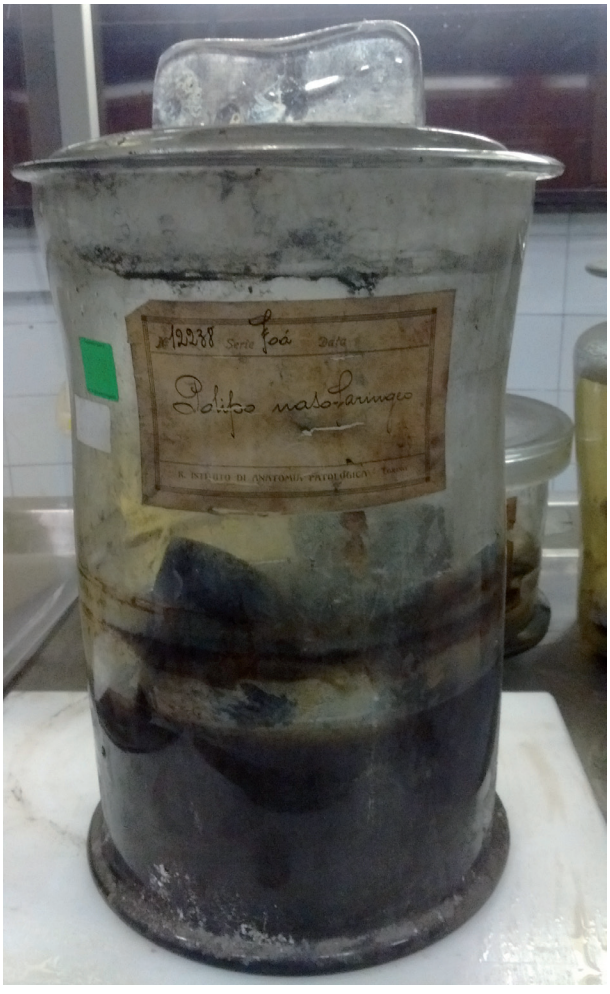

Figure 2. The jar in original conditions

Figure 3. The wet specimen

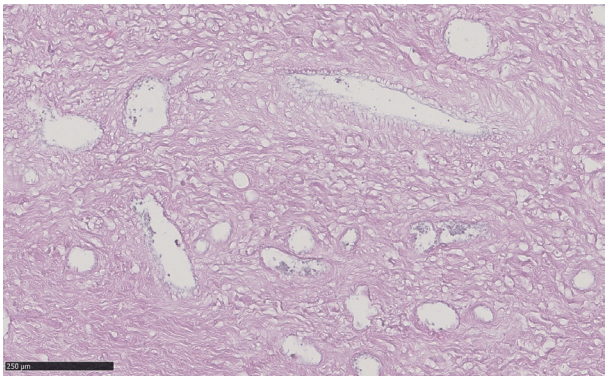

Figure 4. Pathological section H&E stain 10x magnification

blood vessels irregular in size and shape (Fig. 4). The morphological preservation is good despite the poor conditions of the jar. The morphology of the lesion is pathognomonic for nasopharyngeal angiofibroma. Therefore the diagnosis does not require further specific investigations such as histochemistry or immunohistochemistry.

Discussion

Juvenile nasopharyngeal angiofibroma is a very uncommon neoplasm, usually unilateral. It is benign but locally aggressive and it could spread to the base of the skull and into the cranium (5).Usually this lesion is located on the superior edge of the sphenopalatine foramen, but any other localisation in nasal cavity and nasopharynx is possible as well. The clinical presentation is very typical: a nasal obstruction with epistaxis, rhinorrhea and pain. Nowadays these lesions are diagnosed by MRI and angiography and early diagnosis is required for an early treatment. An early diagnosis allows a combination of preoperative embolization and surgical resection and the prognosis is good (6). The innocuous presentation of symptoms often delays the diagnosis and advanced lesions are more difficult to treat. This lesion affects typically male between 14 and 25 years of age, probably due to the high expression of androgen receptor of this neoplasm. Some authors suggest hamartoma and malformation theory, but the origin of juvenile nasopharyngeal angiofibroma is still not understood. Historically Greek, Roman and Arabian doctors used the term nasal polyps for all the masses within the nasal cavities or nasopharynx. In year 1847, Chelius wrote "fibrous nasal polyps commonly occur in person about the time of puberty" (7). Surgical texts of the early XIX century describe often how to remove these bulky lesions which could produce a typical face known as "frog face". Legouest in 1865 noted the predilection of these lesions for young male (8) and Gosselin in 1876 (9) noted the possibility of spontaneous regression after puberty. Chaveau in 1906 suggested the name of juvenile nasopharyngeal fibroma (10), Friedberg in 1940 first used the term angiofibroma (11). The first article in literature about juvenile nasopharyngeal angiofibroma dates back to 1948 (12). Therefore the diagnosis of "Nasopharyngeal polyp" on the label was correct according to the knowledge of the time. This is the second museum specimen showing this disease reported in medical literature. The other case was that of a specimen of a maxillectomy performed in 1841, which was diagnostically re-evaluated in 1987 (13).

Conclusion

This case shows a rare neoplasm that killed a young boy in absence of surgical treatment. This specimen shows the spread of this lesion demonstrating how it can evolve in its natural history and how this lesion can be lethal even if it is biologically benign. Probably the boy died for suffocation but an epistaxis is possible too. Unfortunately, the autopsy report can not help to understand the final cause of death. This specimen increases the importance of wet pathological specimens as historical heritage and biological archive as well.

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Correspondence:
Luisa Ferrari
Department of Oncology, Pathology Unit, University of Turin, Turin
E-mail: luisa_ferrari@libero.it

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A "pithecoid feature" in skulls confirming possible neuro-psychiatric disorders. The diagnoses of an anthropologist of the nineteenth century

Rosagemma Ciliberti[1], Anna Siri[2], Silvia Iorio[3], Liliana Lorettu[4]

[1]Section of Forensic Medicine and Bioethics, Department of Health Sciences, University of Genoa, Via De Toni 12, 16132, Genoa, Italy; [2]Unesco Chair, Antropology of Health. Biosphere and healing systems, Dept. Educational Sciences, University of Genoa, Italy; [3]Department of Molecular Medicine, Unit of History of Medicine, Sapienza University of Rome, Italy; [4]Department of Medical, Surgical and Experimental Sciences - University of Sassari -AOU Sassari, Italy

Abstract. B*ackground and aim:* The interest for the morphological research of degenerative signs aimed at identifying personality pathologies characterized positive anthropology of the late nineteenth century. The increasing exploitation of statistical-epidemiological methodologies together with the recent neuroscientific acquisitions, risk dangerous effects on mono-factorial models on the understanding of antisocial behavior. *Methods:* Through historical analysis of the research carried out by the positivist anthropologist Giuffrida Ruggeri on the lack of the glenoid dimple of the temporal of the alienated, the authors examine the criticality of rigid and one-way psychopathological interpretative approaches also in relation to recent applications of neuroscience. *Results:* Increasingly, the scientific approach seems to abandon an interpretative vision anchored to rigid biological and statistical parameters to embrace a dimension adequate to the singularity and complexity of man. In this approach, neurosciences contribute to supporting the circularity of the interpretative model of antisocial behavior. *Conclusion:* Far from a deterministic return that assigns a decisive role to constitutional factors, new knowledge leads us to reflect on mutual, continuous and harbingers of biology and the environment in the characterization of the human being, in a constructive dialogue with ethics.

Key words: Giuffrida Ruggeri, aggressiveness, structural cognitive modifiability, neuroscience, epigenetics, violence, determinism, free will

Introduction

The "positivist anthropology" of the late nineteenth century sought in abnormal craniometrics characters the connection with certain pathological conditions.

The psychiatric and anthropological literature of 19th century showed several contributions which demonstrate how criminal anthropology influenced the psychiatric thinking of the time leading it to identify the deviated features both degenerated and both ancestral. In particular, the atavism theory carried out some anthropologists to find specific correlation between the anatomical features and the "abnormal" behaviors.

In this contribution, we want to re-examine an interesting research published in the Phreniatry Review which illustrates that some morphological characteristics of the skulls, conserved in collections of psychiatric institutes, were closely linked to degeneration and madness.

This is the article by Professor Vincenzo Giuffrida Ruggeri entitled "A new pithecoid character in 13 alienated patients (absence or incompleteness of the glenoid dimple of the temporal), called Giuffrida-Ruggeri's stigma"(1).

The well-known professor of anthropology taught at the most prestigious Italian universities (Rome, Pa-

via, and Naples) and undertook a series of researches on the anatomy of the human skull, on facial morphology and on the various somatic characters of the populations of northern Italy, on topics of normal and pathological anthropology (1–5).

Giuffrida believed that the glenoid dimple, where the condyle of the jaw is inserted, is found neither in the felines nor in the rodents and was missing especially in anthropomorphic apes.

The professor, in fact, conducted this research in the Natural History Museum of Florence and analyzed several anthropomorphic skulls where he found a flat surface instead of the glenoid dimple of the temporal, characteristic of modern man. However, the anthropologist observed the lack of glenoid dimple of the temporal in thirteen skulls of alienated people at the Craniological Museum of the Psychiatric Institute of Reggio-Emilia.

The cases

The first skull that Giuffrida examined, numbered 399, had belonged to an epileptic man from Modena who died at the age of twenty. The professor examined the skull anthropometrically, as was the practice of positivist anthropology. It denoted an ovoid, brachycephalic a leptorrhine nose with a normal nasal aperture between the interorbital distance. The condyles of the mandible and the right glenoid dimple were described as normal. However, he emphasized that the left one was extended anteriorly, thus exceeding the spheno-temporal suture, thus lacking any trace of articular tubercle, there was a flattening where the glenoid dimple must have been. Among the other anomalies that he pointed out he also noticed the opening of the metopic suture and the spheno-basilar suture. The encephalon weighs 1322 grams.

The second skull that he examined, numbered 185 of the craniological collection, belonged to a male, also of Modena and also an epileptic and who died at the age of 34 years. The craniometry showed a hyper brachycephalic form. The absence of the glenoid dimple was recorded on the right while the left one appeared normal. The encephalon weighs 1380 grams.

In his report he also inserted skull number 1154 which had belonged to a Modenese who had been diagnosed in the medical record as "maniac for alcoholism", they were also outlined under the anthropometric profile as brachycephalic. In this case both glenoid dimples were flat. The weight of the encephalon is 1145 grams.

The skull numbered 789 belonged to an epileptic man from Modena who died at the age of 41. In this case the craniometrics index showed a plagiocephalic and a mesaticephalic form. The right glenoid dimple was completely absent, being described as a flat and uniform surface extending from the spheno-temporal suture to the zygomatic bone. Among the other "pithecoid" characters, Giuffrida also reported the protruding raised eyebrows and the asymmetrical occipital hole in its shape and located largely in the right half of the skull. The brain's weight was 1125 grams.

In the investigation he examined the skull belonging to a woman from Modena, who was suffering from pilgrim lipomania and died at the age of fifty-five. Also in this case the cephalic calculus delineates a skull of brachycephalic form and the right glenoid dimple extends forward occupying the space where it was normally occupied by the articular tubercle while the left glenoid dimple extends less forward. Other atavistic features of the skull are recorded at the level of the jaw, which was strongly asymmetric as well as asymmetrical, and additionally the palatine bones presented themselves. The weight of the woman's brain was 1235 grams.

Among the other skulls listed by the anthropologist was number 274, this also belonged to an epileptic who died at the age of 41. Of mesaticephalic shape, the skull showed the absence of the glenoid dimple in the right region. Among the pithecoid characters he also added protruding eyebrow arches, while the weight of the encephalon was 1335 grams.

The skull number 337 belonged to a woman of Reggio, she had been affected by lipomania and died at the age of 34 years. Brachycephalic in shape, the skull is generally described as very asymmetrical with a remarkable prognathism. In describing the pithecoid character under discussion, Giuffrida reported that instead of the glenoid dimples there were simply two slight imprints. There is no lack of other anthropological anomalies reported by the author as a highly asymmetric mandible as well as the zygomatic arches and the occipital hole was elongated in anteroposterior direction. The weight of the brain was 1069 grams.

The skull number 1205 belonged to a woman from Reggio and was suffering from periodic madness. The shape of the skull was described as follows: plagiocephalic and brachycephalic form. The right glenoid dimple was not bounded anteriorly and the left was limited only by a thin margin. The weight of the brain was 1375 grams.

The next skull considered pithecoid for the description of the character of the glenoid dimples is number 847, belonging to a woman, age not revealed, whose diagnosis was that of pellagrous characterized by a brachycranial form. The glenoid dimples, especially the right one, are not well defined. At the level of the lambdoid suture, the author describes numerous supernumerary bones and the weight of the encephalon is 1250 grams.

The skull number 1081 was of a woman from Reggio, whose clinical history described her as belonging to a neuropathic family suffering from acute delirium. The woman, who died at the age of 62, had a mesaticephalic skull. Both glenoid dimples appeared as a flat surface extending to the rear zygomatic inlets. The weight of the encephalon is 1205 grams.

The next skull, number 1166, of mesaticephalic shape and whose glenoid dimples had anomalies such as poorly marked margins and the left side is covered longitudinally by a bone crest, belonged to a woman who died at the age of thirty-three. The jaw was asymmetrical and the skull was slightly plagiocephaly. The brain's weight was 1315 grams.

The skull number 1123 belonged to a woman with lipomania and a neuropathic family who died at the age of forty-seven. The mesaticephalic skull had a shallow right glenoid dimple and a rough surface in correspondence with the articular tubercles. An asymmetric mandible and an elongated occipital hole were registered by the author. The weight of the encephalon was 1085 grams.

The last skull described, number 841, was that of a woman from Carrara, diagnosed as a maniac and died at the age of 53. She had a brachycephalic skull with an enormously extended and circular right glenoid dimple. The brain's weight was 1180 grams.

According to the author, the fact that the rough surface takes the place of the articular tubercle makes the presence of the glenoid dimple impossible.

The comparison between the presence and absence of the glenoid dimple of the temporal bone between the skulls of the alienated and those of the delinquents (13 out of 1000 in the first and 1 in 25 in the second) was to interpret this morphological feature, link to the low intellect of the people who own it (6-8).

However, he did not give any consideration with regard to the kinds of illness precisely because the cases he analyzed were few. In fact, he recorded only few cases of absence of the glenoid dimples on over a thousand skulls of the insane from the psychiatric collection.

Giuffrida also reports the presence of one of the 25 skulls of delinquents in the psychiatric collection of Reggio presents the absence of the glenoid dimples of the storm.

Another consideration that the author highlighted was the greater presence of this anomalous in the female subjects, therefore believing that the consideration of his colleagues, who said that in the female sex degenerative characters were less present than in men, was wrong.

Discussion

This contribution of a new pithecoid character, or rather the absence of the glenoid dimple of the temporal represents one of the many observational methods of the positivist anthropologists of that time who related anthropological anomalies to psychiatric anomalies (9).

Although Prof. Giuffrida-Ruggeri neither had initiated any form of revolutionary idea nor opened any new chapter, the prestigious Journal *Nature* in his necrology underlined that "his voluminous writings reflect more fully than those of any other writer the anthropological problems discussed by his contemporaries in Europe and America" and "By his death modern anthropology loses one of its most imposing and interesting figures" (10).

From the second half of the nineteenth century, immediately after the development of evolutionary theories, many anthropologists insisted on searching for atavistic and degenerative characters and at times almost excessive, physical characteristics were determined to delineate anomalous personalities.

The resulting achievements of science in the mid-nineteenth century also urged prevailing attention of the positivist anthropologists to the soma as object more easily identifiable, measurable and assessable as part of a rigorous scientific research. By abandoning the interpretative approach of a speculative nature, the identification of deviant forms through anthropometric feedback offers support for criminological theories. However, this approach does not take due account of the experimental verification principle as a certain criterion.

Ruggeri's Giuffrida assessments must therefore be interpreted according to the model of positivism in its most closed phase which penalizes an interpretative approach on the unity of body and psyche, in an orientation that tends to sanction a materialistic vision of human behavior. In this spirit, Pierre Jean Georges Cabanis (1757 - 1808), a well-known French doctor, declared: "The brain secretes thought, just as the liver secretes bile".

The development of research has shown the limitations, illusions and errors of positivist science which, unfortunately, inspired prisons and psychiatric hospitals between the nineteenth and twentieth centuries, to recognize, on the contrary, the profound impact of the "environmental" component in the psychic joint.

For many decades, medicine has abandoned a vision of science anchored to rigid ethno-morphological parameters, typical of positivist thought at the end of the 1800s, to adhere to a holistic and non-sectarian approach.

Even the "evidence-based medicine" (EBM) itself is today subjected to severe critical analysis when it apodictically claims to deduce the clinical decision from the value of statistical-epidemiological evidence (11).

Certainly, these critical observations do not imply the rejection of the value of scientific evidence or, even less, of the usefulness of EBM, they simply remind us to have caution in their use. This is in order not to slip into the dangerous pitfalls of scientism or dogmatism, by taking due account of that reference to the limits of science invoked and theorized by the great scientists of the past and present from Pascal to Godel (12, 13).

To think that a certain anomaly can be correlated with a certain disturbance is a gross limit. The specific feature observed by Giuffrida in thirteen skulls of alienated people kept at the Craniological Museum of the Psychiatric Institute of Reggio-Emilia, is part of the natural variability of human and animal anatomical structures and it has no meaning. As the Lombrosian idea of a "reverse evolution", that is, of the re-emergence of ancestral characters in modern men, is completely without foundation.

The approach to the bio-psycho-social model has also determined the overcoming of the biological reductionism of mental illness, typical of the classical German medical-organic model, focused on the psychophysical deficit of the individual ("*all mental illnesses are brain diseases*", using the emblematic definition of Griesinger) (14). This different reference model, attentive to the interaction between biological and psychological, psychosocial and environmental singular components, today solicits a different and more complex interpretation of the person and, also, of the individual deviant acts that requires an open and multidisciplinary interpretative methodology (15).

Even the same paradigm of "rigidity" and "static" of the brain, based on the progressive decrease of neurons, has now been abandoned. In fact, research has shown that cognitive modifiability and brain plasticity are conditions that are not limited only to the early stages of childhood, but characterize the entire life cycle of man, in relation to different experiences and different stimuli, including environmental stimuli (16, 17). Even if the precise mechanisms of plasticity are not yet completely understood, it turns out that experiential factors model the neural circuits underlying social and emotional behavior.

Moreover, if it is widely proven that traumatic events "leave marks" on the emotional circuits of the brain, it has also been shown that other situations, such as pregnancy, stimulate the proliferation of dendritic spines and synapses (18, 19).

In addition, it is useful to point out that on the basis of the growing evidence on the modulation of gene expression, through "epigenetic" processes, the attention of scholars has focused precisely on these mechanisms and on the role they can play in the development of behavior.

In the (re)discovery of the complexity and multiplicity of the various variables involved, clinicians today criticize, to an ever-greater extent, a certain rigid

cognitive approach of pathology based exclusively on statistical evidence, to rehabilitate the observational-empirical criteria, intuitions, sensitivities and individual clinical experience. The concept, nowadays increasingly widespread, of "complex sick" expresses the need for the clinician to maintain his role as a wise reasoner and interpreter, with respect to an only aseptic adherence to scientific-experimental evidence.

In the analysis of Giuffrida's study we cannot forget the limited knowledge of the time. Today we know that the temporomandibular articulation is a complex joint, with significant intra- and inter-individual variability and only the recent use of computerized tomography has allowed for more reliable measurements to be performed (20).

Furthermore, in a critical reading of this historical work, a considerable limit is represented by the extreme variety of psychiatric pathologies by Giuffrida Ruggeri in a common morphological anomaly, psychiatric disorders are totally different from one another: from mental retardation to circular madness. The association between the anomaly and a specific disorder is very small and in the world of evidence-based medicine, this deficiency is really a hazard.

Conclusions

The analysis of a historical article on the correlation between morphological character and intellectual deficiencies brings out the never-quarreled controversy between determinists and indeterminists.

The lack of understanding of the complexity of man and also of the circularity of the outcomes of the various mechanisms of action of the various determinants, underlying human actions, are certainly some fundamental limits of positivist thought.

However You always learn from history (20-22). History teaches us that science and its certainties are always in constant evolution. The scientific results, even the most innovative and seductive ones, must always be carefully weighed and subjected to rigorous critical and logical scrutiny.

Even after a century, the errors of Giuffrida and his time must be present when we risk moving from somatic to genetic determinism or when evaluating the weight of the environment in comparison with that of DNA. Similarly, we must bear in mind the naive nineteenth-century belief that we can draw conclusions on the functioning of human behavior starting from formalin skulls and brains when we interpret brain images obtained with cutting-edge technologies such as functional magnetic resonance imaging or positron emission tomography.

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Correspondence:
Rosagemma Ciliberti
Section of Forensic Medicine and Bioethics, Department of Health Sciences, University of Genoa
Via De Toni 12, 16132, Genoa, Italy
E-mail: rosellaciliberti@yahoo.it

Toward the valorization of our anthropological and paleopathological heritage. The musealization of the osteoarchaeological contexts

Marta Licata, Omar Larentis, Paola Badino, Roberta Fusco, Chiara Tesi

Centre of Research in Osteoarchaeology and Paleopathology, Department of Biotechnology and Life Sciences, University of Insubria, Varese, Italy

Abstract. The musealization of the osteological finds inside the archaeological context is a proposal of our Center of Research and concerns the enhancement and promotion of the archaeological heritage of our territory. The creation of Laboratories of Physical Anthropology and Paleopathology ,set up directly on the archaeological sites of necropolis once the anthropological study is completed, will realize a visibility of its operation, proposing precisely the restoration and museum display of the osteoarchaeological finding. The project will activate local development processes that will improve tourist attraction of the archaeological site and implement strategies that integrate the site with other resources and socio-economic structure of the area.

Key words: musealization of the osteological finds, archaeological heritage, Laboratories of Physical Anthropology and Paleopathology

The study of our anthropological heritage represents an important tool to activate development processes in several cultural fields. We really need to be aware of it.

The model of research that some centers are adopting, such as the setting up of anthropology laboratories in *situ*, represents a significant starting point in this sense. We know the importance of the results obtained by the analysis of human remains, but now, we want to stimulate the valorization of anthropological finds within cultural heritage (1). In fact, osteoarchaeology deals with the study of bone remains from archaeological excavations, with the reconstitution of ancient demographics being one of the main objectives. The "biomedical narrative" of the populations of the past is thus added today to traditional historical sources, consequently increasing our knowledge of the people who have inhabited the same spaces before us. Experts (paleopathologists, anthropologists and archaeologists) have always emphasized the bivalent nature of osteoarchaeological research, which on the one hand enriches the knowledge of living conditions; on the other hand it can play a significant role in the etiological investigation of some pathologies whose origin is still obscure today (2-4).

The study experiences carried out to date show us how the osteoarcheological discipline can also be included in the field of cultural heritage, not only as investigative research but also as a proactive tool that collects, restores, protects and enhances human remains understood as anthropological finds which are also intended to museum display.

In particular, by showing the proposal of our project regarding the valorization of archaeological heritage of Valcuvia and that could be summarized with the title *The creation of archaeological itinerary from the museum of three medieval cemetery areas of Valcuvia*, we want to increase the awareness that all anthropological fields can receive great interest also outside of the academic world.

Three sites of Valcuvia are included in this project: Saint Agostine in Caravate, San Biagio in Cittiglio

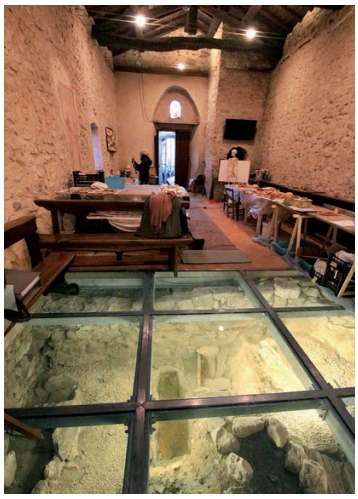

Figure 1. Laboratory of Physical Anthropology and Paleopathology

and Saint Eusebio and Antonio in Azzio. All three archaeological contexts have preserved funerary areas, inside and outside the churches. Actually, the cemetery areas under archaeological investigations have allowed us to set up a laboratory for the study of the human remains inside the churches or in other covered spaces close by. It is clear that, also during the study phase, these spaces acquires "archaeological value" and become "sites of interest". Starting from these considerations, we also proposed to transform these sites into *osteoarchaeological museums*, or museum of cemetery areas, in which to realize the valorization of funerary spaces and also the osteological finds directly inside the churches annexed. Indeed, especially for the strong thematic and territorial links of these sites, it is also envisaged the creation of archaeological itinerary under three thematic lines: *Christianity and rituals in medieval and post-medieval times in Valcuvi*a, *Christian art in Valcuvia in medieval and post medieval times* and *The ancient populations of Valcuvia*.

We believe that the musealization of the osteological finds inside the sites can solve many questions related to the display of human remains in museums from a purely archaeological and an ethical point of view (4). Under the archaeological profile, the possibility to preserve human remains close by to the place of the recovery assists in not decontextualizing the finds. From the ethical point of view, the preservation of the human remains inside the sacred place in which the deceased was buried could solve, in part, the remonstration moved by some groups that see an outrage in the exhumation of human remains from the burial site.

In our project, we are sure that the anthropological study of human remains will also develop the inclusion of these archaeological sites within the museum circuits of the Lombardy region.

In fact, the study of osteoarchaeological sample, especially through a great attention to deep demographical, pathological, ritual aspects (5), will guarantee the realization of the archaeological itinerary, which will include also a theme of the "*History of population through human remains*".

Muzealization of osteoarchaeological context will activate development processes that will improve tourist attraction of the archaeological site and implement strategies that integrate the site with other resources and socio-economic structure of the area.

With archaeobiology, we have a tool to spread the human experience of encient populations. Through the exhibition of human death, through the museum display of human remains, funerary objects, tombs and in general the sacred funerary context, it is possible to raise awareness of the historical knowledge of our past.

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Correspondence:
Omar Larentis
Centre of Research in Osteoarchaeology and Paleopathology, Department of Biotechnology and Life Sciences, University of Insubria, Varese, Italy
E-mail: olarentis@studenti.uninsubria.it

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Albert R. Jonsen: one of the most important pioneers of Bioethics and Clinical Ethics. An historical portrait

Silvia Siano

PhD in Medicine and Human Sciences, Centre for Clinical Ethics, Department of Biotechnology and Life Sciences, University of Insubria, Varese, Italy

Abstract. Starting from his most significant books "The Birth of Bioethics", "The Abuse of Casuistry", and "Clinical Ethics", the articles aims to trace a short but exhaustive historical-scientific itinerary on the work of Albert R. Jonsen, who is considered one of the "Founding Fathers" of contemporary Bioethics and Clinical Ethics. The outlined biographical path outlined serves as a guide to the reflection on the peculiar characteristics of the first true clinical bioethicist, really in contact with patients and health care professionals. Furthermore, the essay offers an overview on his most significant contribution in the history of bioethical thought: the definition of the Neocasistic method in Clinical Ethics.

Key words: Albert R. Jonsen, bioethics, clinical ethics, casuistry, medical ethics

Introduction

Starting from the analysis of Albert R. Jonsen's main text "The Birth of Bioethics" (1), our work aims to outline the history of clinical ethics by focusing on the personal and professional path of one of the main authors of contemporary Bioethics.

A.R Jonsen's main contribution to clinical ethics is the development of a specific *method of analysis of cases* and ethical issues of biomedicine. Therefore, focusing on his work is highly important for those who are involved in Clinical Bioethics.

Moreover, this topic should be interesting for those who deal with the History of Medicine, Bioethics, and, expecially, Clinical ethics "at the bedside of the patient". In fact, a precise reference to the "practical" treatment of the ethical problems generated by contemporary techno-scientific development always emerges from Jonsen's production.

Jonsen's relationship with Medicine cannot be separated from a careful analysis of his academic and personal biography. In fact, his thought has been influenced by "fatal" meetings both with prominent theologians, philosophers and jurists interested in moral issues brought by technological and scientific progress, and with doctors who are sensitive to ethical aspects connected with their daily activity.

Thanks to these meetings, he started to deal with the moral problems bounded up with Biomedicine and the concreteness of medical practice, both at a more general level, through his work with government commissions, and from a specific point of view, through the exercise, initially "pioneering", of ethical advice - clinical real within the hospital wards.

Albert R. Jonsen is universally considered one of the "fathers" of American Bioethics and the main promoter, together with his colleague Stephen Toulmin (2), of the recovery of the *Neocasistic method* as a model of approach to ethical reasoning in the clinical field.

This work consists of a thorough examination ofI the theoretical path offered by the main author and

advocate of Neocastics. Throught Jonsen's reference texts the research outlines the fundamental aspects of the origin and development of his model and of the consequent interpretation given to ethical issues meant as subject of investigation of Bioethics as a discipline.

The general profile of the Author wants to focus on Jonsen as *clinical bioethicist*, on his role as a pioneer and active player in the development of Bioethics. In this way, Bioethics can be regarded as a science with an autonomous status and its own fields of investigation.

Albert R. Jonsen, bioethicist in "The Birth of Bioethics"

Albert Jonsen (3) is currently co-director of the Program of Medicine and Human Values at the California Medical Center in San Francisco. He is also Emeritus Professor of Ethics and Medicine at the Faculty of Medicine at the University of Washington, where he was Director of the Department of History of Medicine and Ethics from 1987 to 1999.

His text, *The Birth of Bioethics*, begins with a short overview on his personal history. It is indeed very interesting to see which biographical and academic aspects are considered by Jonsen himself as those that led him to approach Clinical Ethics. Great contributions came both from the accurate theological-philosophical knowledge acquired over time, and by acquired over time, but also by p meetings and collaborations with other scholars, who often suggested new and additional ideas for research.

At the age of 18, feeling called to the Catholic priesthood, he entered the Jesuit seminary at the Gonzaga University of Spokane, Washington, and the Santa Clara University of California (4).

After having obtained the Master's Degree in Philosophy, with a study on Aristotle, Thomas Aquinas and Maritain, he taught Philosophy at the same Jesuit College for 3 years, as he went on with his theological studies.

He was then ordained in 1962, and his superiors - Jonsen writes -accepted his request to deal with religious Ethics in an ecumenical context. Therefore, in 1967, he obtained a doctorate at the Department of Religious Studies of the University of Yale, with a thesis on "Responsibility in contemporary religious ethics", published in 1971 (5).

Jonsen admits in that period the interaction with his professor of Theology at Yale, James M. Gustafson, constituted his first contact with the themes concerning Bioethics. Gustafson was not only an ecumenical theologian, expert both in Protestant and Catholic Theology, but also one of the first to deal with the cultural context which was emerging along with the progress of the biomedical sciences, with particular interest to genetics and neurosciences (3-6).

In his "The Birth of Bioethics", Jonsen clearly recalls the two crucial "meetings" which led him to deal with bioethical themes. The former was with F. Patrick McKegney, director of the psychiatry department of the Yale-New Haven hospital, the latter with Englebert Dunphy, prominent surgeon at the University of San Francisco. After the presentation of the contents of his PhD thesis, Jonsen was asked by Dr McKegney: "You have read and written everything that exists on this subject, Ethics; why don't you come to the hospital now, so I will show you how ethical problems actually present themselves in concrete reality? Jonsen accepts his proposal and for two months, he followed a sort of "internship" in the hospital where Dr McKegney worked. Thanks to Dr McKegney, the theologian Jonsen had to face the first ethical pratical questions concerning biomedicine. For example, if the "suicide from dialysis" can be considered a suicidal mania, a psychopathology or, given the condition of a long dependence on the aid of a life-saving support, we must consider differently the request made by some patients to "turn the machines off" and to be left to die (3).

Jonsen is thus "forced" to deal with ethical problems connected to dialysis as a life-saving technology and to study the literature on the matter (3). Furthermore, he had to experiment in practice the observation of cases, even throught his actual presence. This will turn out to be a fundamental aspect of all his subsequent professional career.

The meeting with Dr.Dunphy took place in 1969, after a period spent in Paris, where Jonsen studied at Institut Catholique, and in Rome, where he attended the Gregorian University.Back to US, he

was appointed professor of Theology and Moral Philosophy at the University of San Francisco.

Dr. Dunphy invited him to get involved with the ethical problems created by kidney transplantation (7), which included the thorny question of the choice of criteria for proceeding with the allocation of organs. Dunphy asked Jonsen his opinion about the legitimacy and acceptability of the Harvard medical School proposed definition of death (8,9), in relation to the possibility of carrying out or not the kidney transplant. In fact, the University of San Francisco Medical School had constituted an ad hoc committee, to evaluate what was elaborated by the Harvard Commission, and Jonsen agreed to be member of it as a consultant. In this wqy, Jonsen really began to deal with Clinical Ethics.

Jonsen says:-My "internship" with Dr McKegney in the wards of the New Haven Hospital in Yale, my service as a consultant to the Committee on Brain Death at the University of San Francisco have begun my "transformation" *from an ethicist to a bioethicist* (3).

Officially, Jonsen started his career as bioethicist, with a title and a proper salary, back in spring 1972, when Dr. P. R. Lee, Chancellor of the Medical Center of the University of California in San Francisco, invites him to spend a period (which would have lasted a full year) at the new Institute of Public Health, as a "Visiting Professor" (3).

This opportunity was so significant for his training that, as Spinsanti points out (5), it marked a real turning point in Jonsen's professional career. In fact, he had the opportunity to follow the courses of medical students, to be involved in visits, discussion of cases and even autopsies. Furthermore, he had the opportunity to listen, which turned out to be even more important

Not coincidentally, Jonsen summed up his own career as a clinical bioethicist under the programmatic motto "Watching the doctors" (10). By looking at and listening to doctors at work, Jonsen realized that a new way of doing Ethics was necessary, in comparison with the one taught in the faculties of Philosophy or Theology.

He was immediately struck by an aspect that would have played a key-role in the development of his thinking: doctors deal with *cases*, and in each case specific circumstances have a decisive importance. Moreover, speculative and abstract approach seldom matches the way health professionals normally deal with biomedical issues. Therefore if Ethics wants to fulfil the healthcare task, it must be characterized by an academic discipline model and must deal with actual cases.

Thanks to pratical experience, Jonsen also realized that ethical issues have a temporal dimension that is not so evident by considering a situation from a theoretical point of view, circumstances may change as time goes by, even significantly. Jonsen explains that when doctors say: "Let's wait and see", they don't seek an excuse, postponing to avoid facing problems; they are simply recognizing that, with the passing of time, the problem can occupy in a different way.

In the interview given to Spinsanti, Jonsen pointed out that the difference between academical Ethics expert and health professionals lies in way they manage a clinical case: each healthcare intervention the case, involves risks, requires comparative assessment of the benefits. On the other hand, the speculative thinker is not called to get involved with he single case. The Ethics expert who instead accepts to be involved in the clinic aspects has an intermediate position: he is sensitive to the management of the case and must speak the language of the clinicians alongside whom he works, but must avoid abstract discussion or long explanation of the principles, to grasp the significant particularities and characteristic circumstances that specify the present concrete case (10).

At the end of 1972, UCSF School of Medicine Dean Dr. J.R. Krevans, appointed Jonsen associate professor, entrusting him with the chair of Bioethics of the Faculty of Medicine. He taught here until 1987, when he moved to the University of Washington Department of History of Medicine and Ethics of the Faculty of Medicine.

Jonsen joined the clinical staff of the UCSF, as an expert in Ethics with the specific function of consulting ("to be a consultant"), which was a task still to be invented.

He explained that holding the position of professor of Bioethics was equivalent to being considered as "a strange, singular creature", as he was the

first ethicists who joined the Faculty of Medicine. Furthermore, on those times Bioethics did not have an independent status, at the point that the real meaning of the term "Bioethics" was very debated, as it was still object of study (3).

This is the reason why Jonsen is considered one of the "pioneers" of the development of the Bioethics. As he himself points out "I became a bioethicist, when Bioethics was just born" (3).

Along the years he spent as a consultant ethicist, Jonsen developed the conviction that dealing with Clinical Ethics involves assuming indications of content and method requirements that make it profoundly different from that elaborated on the basis of abstract principles, even if of a high ideal profile, as happens in Catholic moral reflection.

Jonsen was also influenced by the case study methodology developed by the Business School of Harvard University, where he attended summer courses organized by Administration and Education programs, drawing the conviction that the case study method was also applicable to Clinical Ethics.

"Clinical Ethics": the Neocasistic method of Clinical Ethics

In 1982, Jonsen published "Clinical Ethics. A pratical Approach to Ethical Decisions in Clinical Medicine" (11), written in collaboration with two other leading scholars, Mark Siegler (12) and William Winslade (13).

It is important to remind that the three authors brought their own professional skills: Siegler as a doctor, Winslade as a lawyer and Jonsen as a theologist.

This work aimed to bring Ethics back into its own context, i.e. the clinical one, offering a method to consider several options in the management of similar problems, which present difficulties both from a clinical and ethical point of view.

The edition we are considering (i.e. the fifth), clearly states that the text is not only meant for clinicians and students who directly deal with the patient, but also for other professionals such as hospital administrators and lawyers, members of institutional Ethics committees, quality control officers, health plan managers. All those, in short, whose work requires an awareness and sensitivity to the issues of clinical practice, and who have the responsibility of preserving the ethical dimension as an essential element to offer a quality health service (14).

According to the proposed method, cases have a key-role: not only border-line cases, which are of course interesting or spectacular, but also those that doctors and health professionals deal with every day in clinical practice.

For this point of view, Clinical Ethics consists in the identification, analysis and solution of moral problems that arise in the care of a patient. In fact, moral concerns cannot be separated from the medical ones. Ethical judgement is not separable from the clinical judgement, indeed, it relies on it (15).

The focus of the book is an attempt to offer a good methodology to examine clinical cases from an ethical point of view. The proposing method aims to help bring out the complex interweaving of ethical, emotional, social and economic elements offered by each case, and that must be accurately taken into account to make a good ethical-clinical decision.

Their attitude is even more explicit when they point out that their work wants to be different from other essays on the same topic. On one hand, many books on Health Ethics analyze several cases by considering classical principles such as respect for autonomy, charity, the principle of non maleficence; on the other hand, other books focus on particular and/or exceptional issues like the suspension of vital support treatments and various types of informed consent.

Jonsen clarifies that applying the neocasistic methodology to approach the moral problems emerging in cases of Clinical Ethics (16) means to conduct in a practical context, the three fundamental "steps" of the *casuistic reasoning*. This was rediscovered in his book analyzing the casuistry tout court in the history of theological-moral thought.

In case reasoning, Jonsen writes that the solutions of analyzed cases are compared with paradigms of similar cases, in which the relationship between the involved moral principles and the individual circumstances suggests the same obvious conclusions. The comparison between similar cases is called reasoning by analogy (16).

The fundamental reference is to the so-called paradigmatic cases, which provide initial presumptive or probable indications. By analyzing similarities and differences with the case under examination, and in the absence of exceptional circumstances, the probable indications acquire conclusive value for the exercise of moral judgment, which takes place by analogy.

Jonsen argues (16) that the reasoning by *analogy* is clearly different from the typical deductive method of the Bioethics of Principles, which proceeds rigidly from the premises to its logical conclusions. Moreover, Jonsen explains that the analogical elements are not concepts, but the features of the actually considered situation.

Given this basic theoretical "premise", in Clinical Ethics Jonsen, Siegler and Winslade presented the neocasistic method applied to Clinical Ethics as consisting, essentially, of three phases in succession:

1. Exposure of the clinical case;
2. Commentary on the case;
3. Moral advice or recommendation.

The exposition of the case must report all the information of the patient's clinical history, starting the main symptoms present, the recent and the remote pathological history, the family and social history, the results of the objective tests carried out, the laboratory data that led to the diagnosis and allowed to formulate an adequate treatment plan. Besides, the examination of the existential, psychological, emotional, socio-cultural conditions of the patient and his or her family are meaningful elements in order to outline clinical path. Of course, the patient's choices should be shared as much as possible.

The second moment is that of the "moral" commentary.

The commentary is based on four categories, four criteria the authors suggest to analyze for each clinical case, especially if it raises some ethical dilemma. In fact, as Jonsen writes, they constitute the load-bearing structure and essential characteristics of the relationship between doctor and patient. Furthermore, they are the key elements of the cases that constitute the "content" of Clinical Ethics (14).

They are:

1. Medical indications;
2. The patient's preferences;
3. Quality of life;
4. Contextual aspects, such as the social, economic, legal and administrative context.

Medical indications: are all information about the diagnosis, prognosis and treatment of the medical problem of the patient. They must be the object of ethical discussion, as they must be considered for their possibility of benefiting the patient and respecting his preferences.

Patient preferences are value judgements expressed by the patient regarding the assessment of the risk/benefits of any medical treatment, They are based on the patient's background regarding personal, religious and moral beliefs.

Quality of life: this criterion refers to the current living conditions of the patient. It concerns both the quality of the current condition and his or her existential condition, i.e. the ethical judgment of the individual about the quality of his or her real psychophysical state.

The contextual aspects are the set of interpersonal relationships, institutional, financial and social situations that can influence positively or negatively the care of the patient. In the same way, the context in which the patient is placed is influenced by the decisions taken by or on the patient. In fact, any decisions that may have a psychological, emotional, financial, legal, scientific, educational or religious impact on others. These aspects must always be examined and evaluated because they could be of crucial importance for the profiling and resolution of the ethical problem emerging from the case (14).

The Authors state that although individual cases may differ from each other, these criteria are always relevant, help to organize the data. At the same time, they draw attention to ethical principles that are appropriate to the specific case, thus "represent a systematic method to identify and analyze ethical problems that occur in clinical medicine".

The four criteria would allow the clinician to understand the connection between ethical principles and the circumstances of the individual clinical case. When it is analyzed, "the different circumstances are placed in all four categories and affect the meaning and relevance of the ethical principles involved" (14).

By examining the four criteria together, clini-

cians can verify how the principles and circumstances, as a whole, define the ethical problem of a specific case and what resolution they suggest. Therefore, the formulation of a good ethical-clinical judgment consists in assessing how ethical principles should be interpreted in the actual situation that occurs in daily practice.

Gracia (15) also points out that these criteria have an explicit reference link with the Belmont Report Principles, as the medical criteria are usually based on the principle of charity, on the patient's preferences over autonomy, on the quality of life over welfare, on the contextual aspects on the principle of justice or social equity.

Jonsen, Siegler and Winslade clearly state that the four criteria can be considered "road signs", which guide the clinician through the complexity of real cases. Thanks to them, healthcare personnel can assess how much a real ethical case falls within the more general understanding of similar situations, and then create an appropriate opinion on it (14).

The four criteria can also be helpful during meeting among operators, patients and families at the time of hospitalization.

The essay is then divided into four chapters, each of which explores a criterion through the definition of the main related bioethical concepts that may affect it. The volume then illustrates typical cases in which the specific criterion plays a decisive role and, finally, critically examines the arguments commonly offered to solve the problem.

The four clinical cases used in the text as main examples are patients who have been given the fictitious names of Mr. Cure, Mrs. Care, Mrs. Comfort and Mr. Cope (11). Of course, the names have been chosen to suggest some typical aspects of their health condition. In this way, the reader can find the additional variables that allow to consider the elements that are introduced to express a possible ethical assessment of the problems arisen by the considered situation. For example, the case of Mrs. Care allows the authors both to ethically analyze the problem of care for the final patient and to define when a medical intervention can be considered futile in medicine. In this case, the Authors point out that the woman is in the condition of being close to the end. The "physiological futility", compared to her clinical condition, would be a sufficient ethical reason for the doctor to propose the suspension of all interventions, except those that provide some relief to the patient.

Just to better explain, if we consider the Italian debate, the proposed solution could be regarded as too extreme, Nevertheless, we should focus on the adopted methodology, which provides the most exhaustive presentation of the typical case and which can thus offer a broader reading of the several ethical issues that a specific case can introduce.

Finally, the third methodological "step" is the real moral advice. Gracia (15) states that is the most problematic aspect, because advising on the importance of facts, opinions and circumstances from the ethical point of view is very demanding.

According to the Authors, ethical priority should be ideally given to the preferences of the patient, followed by medical indications. If, for any reason, the patient's preferences are unknown (e.g. in the case of the vegetative state) and medical indications are not so clear, it would be necessary to resort to the other two criteria and even to change the order of priority. However, the text also aims to "set out the way in which this order can be altered in particular cases, so that the factors that we have placed at the bottom (quality of life, contextual factors) are of the greatest importance" (15).

Through the use of the proposed method, it is thus possible to determine evaluative judgements, clarifying whether a fact should be considered relevant, important or decisive.

Relevant simply means that a consideration plays a role in the deliberation of an ethical problem: therefore, it should not be discarded as "inadmissible evidence" (...)

If a consideration is relevant, it may have varying degrees of importance. Its greater or lesser importance can sometimes be assessed intuitively. If not, it will be necessary a careful analysis of the reasons for or against. (…) After a careful analysis of its implications and of other values, an important consideration can be finally considered decisive when the scale decides in favour of a particular choice.

A consideration is said decisive when, after having analyzed all the other relevant and important

considerations, it turns out to be of greater importance.

Of course, what is to be considered decisive is debatable, but we believe that in many clinical situations a wider consensus can be achieved through the careful analysis of relevant and important considerations (15).

The Authors are thus able to clarify the meaning of descriptive terms by defining the concept of "permission" and "mandatory" in relation to practical actions that may or may not be implemented in clinical reality.

An action is allowed when, after a sufficient analysis, it is not possible to find decisive considerations. The alternatives of choice will be offered by the important considerations, in which case the choice of the person cannot be forced towards one or the other of the alternatives. When there is a decisive condition in favour of the alternative, we consider that this alternative is compulsory. Therefore, we seem to be allowed to detach a person in a permanent vegetative state from the respirator. And it is compulsory, in our opinion, to respect the refusal of treatment (except for very concrete circumstances) of a patient who is competent or capable of understanding and wanting (15).

The same curator of the Italian edition of the text, A.G. Spagnolo, points out that " you can not help but appreciate the methodological aspect, more than the content of the specific decisions, which is the main merit of the work. Even wisdom and common sense emerge from the majority of the proposed conclusions, which do not come from pre-established ideologies, but from the actual analysis of the case, where the direct and empathetic involvement of the Authors always emerges" (14).

Spagnolo hopes that the clinicians read the whole essay in order to acquire a good understanding of the method, before adopting it for the management of their clinical cases. He adds that, as far as Italian Bioethics is concerned, the text is both a useful aid for Bioethics teaching in the Faculty of Medicine and Surgery and to Health Professions and as a methodological tool for ethics committees and for ethical advisors who will deal with ethical advice in clinical practice (17-9).

Conclusion

In short, our analysis aim to prove that A. R, Jonsen's contribution has been fundamental to point out the need clinical bioethicists in health care structures. In fact, bioethicists can complement and support the task of healthcare personnel, thanks not only to philosophical skills and to the knowledge od a solid *methodology* but also to the attention to the variability of real cases. This would allow a high standard patient care, which is not only desirable, but possible.

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Correspondence:
Silvia Siano
Medicine and Human Sciences, Centre for Clinical Ethics
Department of Biotechnology and Life Sciences
University of Insubria, Varese, Italy
E-mail: silvia.siano8380@gmail.com

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Meaning and role of medical deontology today

Mario Picozzi
Director Center for Clinical Ethics, University of Insubria, Varese, Italy

Abstract. Today we need to redefine deontology and specifically medical deontology to better clarify its meaning and consequently its role. This is a pressing task as deontology risks seriously to become marginal, being squeezed between law and bioethics. There are elements that delineate the deontological profile in a unique and original way. Starting from these elements, we will also illustrate some practical aspects.

Key words: deontology, medical profession, bioethics, law, informed consent, advance directives

Introduction

Today deontology and specifically medical deontology needs to be reinvented to better define its meaning and consequently its role. This is a pressing task as deontology risks seriously to become marginal while being squeezed between law and bioethics.

To fully understand the specific role of deontology and to explain its peculiarities, we must start from the notion of ethos and therefore of professional ethos.

General profile

The role of culture in defining a person's identity

The culture in which we live and act builds our own identity.

Culture represents forms of good life and models that have settled over time which offer a person the sense, the meaning, the reason to spend his life.

Culture has forged its reference criteria and praises - or blames - human behaviors accordingly.

Culture constitutes the ethos within which a specific community recognizes itself. Consequently, ethos is ethically connoted (1).

Each individual will evaluate culture critically and might eventually reject it but nobody will ever be able to avoid a real confrontation with it.

The cultural story of a people or a community evolves over time.

It is never final and settled; instead, it represents the effort of a group of people to answer new social questions and dilemmas and to understand here and now the reasons to engage one's freedom.

Good life forms necessarily have a practical structure.

When and if necessary, a community comes to establish binding legal rules and standards effective for all its members; their purpose is to preserve those shared principles and grounds, while defending and clarifying them.

Cultural mediation becomes necessary to legislate, especially if there are issues at stake that touch fundamental values, such as life.

The notion of profession

The word *profession* derives from the verb *profiteor* (2) which means *to say openly, to confess, to profess, to engage, to promise, to declare publicly* (3). All these meanings reveal the abundance and complexity of the term; therefore, we need to pay duly attention to each of them (4).

First, we can affirm that the practice of a profession involves a public commitment to certain values

(5) along with their accomplishment in precise ways (6), making the knowledge and technical skills an expression of those very same values.

Each profession presents these characteristics:

1. a systematic and unitary set of theories and knowledge;
2. an institutional body, independent from the state and economic powers, exclusively controls and verifies the exercise of these knowledge and skills, establishes the conditions and purposes of the professional activity, and at the same time has the right and duty to judge its members, both technically and ethically. This body, public guarantor of the entire professional category, defines the social, cultural, economic and political aspects of the profession itself;
3. a public procedure of admission and formation of its members;
4. an ethical code that defines an ideal model of services and performances rendered to third parties;
5. the personal autonomy of each individual member in the exercise of the profession, in compliance with the established professional standards and applicable laws (7, 8).

The profession is a stable structure, morally defined, necessary for the solidity of a society (9).

This perspective recalls the idea, typical of the medieval Christian civilization, that each entity, social or individual, grounded and found its justification within a pre-established order and culture, contributing within its competence, to the realization of the common good.

Society is similar to a body, in which a reality, corporation or individual subject, like a single organ, performs a well-defined function for the good of the entire body (10).

In the Christian vision, God established the scheme of things and the profession is a pertinent response to His call, as real vocation.

In that context, there was unity between public and private life because autonomy, specific competence and moral principles - determining both professional and ordinary existence - were essential elements of every profession, required for the realization of the superior good of society.

Many have criticized this interpretation. Does it still make sense to talk about a "professional ideal" and to devote reflection and attention from both a theoretical point of view and practical commitment? (10).

Historically the phenomenon of the industrialization criticized a lot the concept of profession (10): the notion of work focuses on the performance and functional character of acting towards a purpose in which a person is completely alien.

They talked about the "proletarianization" of the professions: the individual operator loses control over his own activity, while the bureaucratic-administrative and economic aspects guide and determine his actions. The professional loses his autonomy, hetero-directed by forces unrelated to his specific work context (11).

From a theoretical point of view, the liberalist and the Marxist perspectives formalized the decline of the idea of profession: for the former, the profession is a distorting and restraining element in the development of the free market and a serious impediment to its full affirmation. For the second, the appeal to professional deontology represents an undue privilege and an unacceptable exploitation by professionals towards society. The eighties, with the swirling development of technical-scientific progress, represent the crucial moment for the notion of profession. The scientific progress was expected to bring together civil progress and human promotion automatically.

The ethical and deontological questions had no longer space nor meaning within this perspective: the duty was to create externally the best conditions for the affirmation of the technique; the rest would have happened by itself. These favorable conditions could materialize either with the full accomplishment of the free market or with massive state planning. This confidence in scientific progress has shown all its limitations, due to the concerns expressed both on a social level and in personal experiences (10).

The professional relationship is structured "in the form of rigid regulations and a person does not have significant power to modify them. However, from a moral point of view these are all 'neutral' regulations... We must keep moral and religious beliefs out of the professional relationship. In this sense, the professional relationship realizes the characteristic of each commercial relationship" (12).

The medical profession

The story of medicine in recent decades is emblematic.

The increased knowledge and technical skills led people to mistrust medicine more and more. Medicine offers new chances every day and one of the effect is to reduce the confidence towards the doctor. At the same time, the notions of authority and monopoly are harshly criticized (5).

This growing distance between doctor and patient seriously threatens the foundations of the medical art and cannot be adequately relieved by the market (with the risk of an economic reduction of the medical activity) nor by the public administration (exposed to the risk of excessive bureaucracy). The notion of profession represents not only the decisive element to overcome the current crisis of medicine, but also the essential tool to realize its authentic meaning (13). "The technical-scientific component is certainly essential to modern medicine and is integrated to orientate and give dignity to medicine: not only in objective terms - as an activity in the service of the common good - but also at a personal level... Considered in its original sense, the profession asks to be experienced as a cause worthy of personal dedication, capable of shaping and unifying the spiritual identity of those who practice it, being a concrete determination of what gives meaning to human life" (10).

Professional ethos and notion of deontology

If we assert "the decisive role of personal responsibility and the importance of subjective attitudes that build the character, the mentality, the personality and the conscience of the individual" (10) we can define deontology as the ethos of medical profession, i.e. the discipline which formalizes good ethical practices inside and outside the medical profession.

Through these practices, the doctor will recognize examples of "good doctors" whose former actions will positively motivate and lead his practical choices (14).

At the same time, those good ethical practices will ground practical mediations for (new) laws on health and life that will bind all citizens and not only doctors.

In this perspective, we realize that deontology bridges the gap between ethics and law (15). Deontology stands up for the doctor's conscience and the formation of the law, but ethics and law will not overwhelm deontology.

We cannot recognize the role of deontology if we claim its independence from law and ethics; on the contrary, we can gather the role of deontology only when we affirm the mutual dependence among deontology, law and ethics.

Only in this way, deontology will overcome the poor notion that defines deontology as a label or a list of good manners or - worse - flattening it on the technical-scientific profile of medical action.

The investigative and morally connoted character of deontology contributes to define the conscience of the doctor (16) avoiding any form of arbitrariness, while creating the conditions to make laws, in which it will be possible to recognize oneself even starting from different moral assumptions.

Therefore, we will avoid the frequent accusation that deontological knowledge is directed from the outside and just takes note of what is sanctioned by law (17).

The professional ethos, in analogy to what happens for the culture of a society, is not something solid and immutable (18), but evolves over time, taking into account both social changes and pluralism itself present in the medical class (19). This brings up the matter of the purposes of medicine. Medicine is an integral part of a society and therefore must take charge of the ends and values that individuals and society propose. At the same time, the doctor's action remains centered on the treatment activity exercised in some concrete forms that translate the interpersonal character of the medical action, without being overwhelmed by the institutional dimensions (20). In other words, "the impersonal and institutional dynamics of the contract must be combined with the personal logic of the trust-based care pact, so that the exercise of medicine does not become a mere professional work performance, but contributes to the well-being of the person within the right institutions (21).

Characterizing elements of medical deontology

If we analyze the practical forms, the ethos, within which the medical profession takes shape and manifests itself, we realize that there are elements that

define the deontological profile in a unique and original way.

We propose two elements, which we believe are particularly significant and consistent with what we have supported so far.

The first characterizing element is the relationship profile.

The doctor-patient relationship is the necessary and favorable form that makes the healing action practicable.

At the beginning of their relationship, the doctor and the patient do not know which treatment will be suitable: first, they must get involved personally and go beyond technical aspects so that together they can trace a way towards a shared choice. In this relationship, both parts have something to say: if not, they cannot make a shared choice. We all agree that at the end of the day, the last word belongs to the patient. However, this does not mean that penultimate words are useless (22). In a relationship, all subject' identities are involved: this applies also to doctor and patient who are involved as individuals besides their respective competence. The doctor cannot reduce his role to a qualified technician, and the patient cannot delegate a decision in which his future is at stake (23).

The second characterizing element is the mutual trust (24).This relationship requires mutual trust. Taking care is possible only if one trusts the other and vice versa. The doctor has confidence that his patient will do what they agreed and the patient trusts that the doctor will always stand by his side. This is why medicine is never just a contract. If you switch from faith to test, trust will be lost and the relationship will finish.

Practical implications

Now let us try to apply this specific notion of deontology to two related topics. The first is the matter of informed consent (25). Starting from the assumption that a decision is possible thanks to a relationship, deontology becomes the custodian and guarantor of this relationship. The final decision depends on the autonomy of the subjects and on their free moral responsibility: it is their relationship - deontologically granted – which makes this decision possible. This same relationship creates the conditions for a legal formulation, as demonstrated by the law (26) recently approved in Italy about the consent and advance directives (27).
The other issue concerns advance directives. The law requires a written formulation; however, people often express their preferences orally to beloved or friends; in these cases, deontology must ensure the respectful translation of the patients' wills.

Conclusion

We have tried to identify the peculiar characteristics of deontology in the current context, defining its specific and necessary role. The next task is to verify if and how we can apply this model to the different matters which compose the medical deontological code.

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Correspondence:
Mario Picozzi
Director Center for Clinical Ethics
Insubria University, Varese, Italy
E-mail: mario.picozzi@uninsubria.it

Human sciences?

Lorenzo M. Capasso

MIUR, USR Abruzzo, Chieti; National Commission on "Professional, Health, Environment and Economic development" National Federation of Medical Boards (FNOMCeO), Rome, Italy; [3]Chieti Provincial Medical Board, Via Spezioli, 31 – 66100 Chieti lorenzo.capasso@istruzione.it

Abstract. This paper is in response to the Editorial by Professor Armocida about the theme of Human Sciences in medical education (Medical Humanities). The author thinks that this is a central topic and he reckons that all the involved subjects must gain consideration and be part of the medical curriculum in order to improve and widen not only the knowledges of undergraduate students, but also their skills. The author concludes suggesting a strong shift in medical education, promoting the introduction of a curriculum including medical humanities at the expenses of clinical subjects and to move practical training from hospitals to territorial services in order to learn how to face chronicity, comorbidity and disability.

Key words: Medical Education, Medical Humanities, Italy, Public Health

I read with great interest and with a certain satisfaction the editorial published in the last number of the journal. First, let me thank *Medicina Historica* and in particular Professor Armocida for having opened such a crucial debate on a scientific journal, overtaking the dark silence on this matter in the Italian academic panorama.

The theme of Human Sciences in medical education (Medical Humanities) is a central topic, the lack of such a mixture of knowledge has a serious impact on both clinical practice and research, and of course it resonates and self-perpetuates in teaching, generating new physicians devoid of these fundamental knowledges and skills.

As a member of the Monitoring Center for Young Professionals of the National Federation of Medical Boards (FNOMCeO), I had the possibility to study the problem of medical education, and this issue was one of the key points. In Italy we are living hard times with regards to medical malpractice, and international literature widely demonstrated that improving the relationship with patients strongly decreases disputes. FNOMCeO hold a National Conference (*Formazione e accesso al lavoro. Innovare per garantire il futuro della professione*, Bari June 13-14th 2014) and published a monographic book (1) on these themes; in these occasions, both the vice-president of the Federation (Dr. Maurizio Benato) and I highlighted as human sciences represent the core of such an improvement of medical education. Among the subjects that should be included in Medical Humanities, we ought to consider:

- History of Medicine
- Psychology in Medicine
- Sociology in Medicine
- Communication studies
- Bioethics
- Health Laws
- Physician-patient relationship
- Team working and leadership in Medicine

All these subjects must gain consideration and be part of the medical curriculum in order not only to have physicians that acquired these knowledges, but that have actually developed the related skills.

Practical and basic knowledge that lacks completely in medical education (except from some, just one University as far as I know) is a class of "Introduction to professional practice". In this class students are expected to learn basic skills related to their, upcoming, professional life. I am talking about: Medical Board requirements and functions, Medical Ethical code, Medical pensions system, but also very practical things as how to release a bill or which are the possible classifications and roles of a physician in the National Health System. The Monitoring Center for Young Professionals draw up a guide for young physicians (2) freely downloadable from FNOMCeO's web page. A good moment to introduce and teach these themes could also be (instead of the sixth year of Medical school) the three month of post-graduation training, which is compulsory in order to undergo the so called "State Exam" (Medical license), but, once again this period is under University organization.

After these fundamental considerations I have to say that I completely agree with professor Armocida about the role of History of Medicine Professors (MED/02 scientific sector) that cannot absolutely bear all these courses and deal with all these different subjects. Anyway, I think that the only way to address these problems, that deals with future healthcare in Italy and its quality and sustainability, is to let Medical History Professors lead the Medical Humanities group of subjects. I really do think that they are the only ones that can face this task, because they have the most humanistic approach and culture among medical professors, because they do be part of medical schools and medical departments and because they can lead a team of teachers (not necessary of medical formation) in order to clarify the target of their teaching work. Of course, I must conclude that University, each single seat and the system in the whole, should accept these innovations and understand that its role is to train physicians, and not to maintain themselves and a sort of lobby-style consortium. This strong shift deals with the introduction of a medical humanities curriculum at the expenses of clinical subjects and to shift practical training from hospitals to territorial services in order to face chronicity, comorbidity and disability. If we do not act this way, we are just training young dinosaurs, linked to a healthcare that has no reason to exist anymore, just because it does not meet population need and it is not sustainable any after. Are these challenges within reach of Italian University? Of course, they are, it is just a matter of will…

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Correspondence:
Lorenzo Capasso
Chieti Provincial Medical Board
Via Spezioli, 31 - 66100, Chieti
E-mail: lorenzo.capasso@istruzione.it