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Knowledge of the history of medicine helps to humanize care

The suggestions made by medical historians are essential today in the challenge of humanizing the treatment. It is not just about models of health organization, instead it seems rather necessary to intervene on the human qualities of women and men of medicine. It is necessary to stimulate an effort of intelligence, a control of thought to make sure that it does not always rest in the sure conformism of protocols and guidelines, as proposed today by the clinic. The current biomedicine, very different from the medicine that was studied and practiced half a century ago, with so many unexpected and astonishing novelties, acts in a revolutionary scientific moment, also addressing bioethical problems. To use it consciously, it is necessary to exercise critical thinking, without resting in the conformism of simple respect for the guidelines protocols. It is therefore not necessary to recall the history of the first approaches of medicine based on evidences as an emerging paradigm of the practice, as the best way for a good clinic, a medicine that affirmed a methodological conception according to strict rationality, that was based on the use of the evidence provided by controlled clinical trials. There is a so-called “pyramid” of evidences, from which guidelines and recommendations are generated. Nevertheless, from the beginning, one could read the provisionality of the meaning of evidence which is valid only in the case of “current evidence” and we know that what is effective today will not be tomorrow. We cannot hinge in evidence-based medicine without considering it within a medical theory. In addition, reflecting on the theory that we will see, a part of medicine has always wondered how to designate the disease, clarify and classify it. And we will see how it was fed the doubt that the idea of diagnosis is really the signifying concept of a rational medicine. The classification of diseases, aimed at the identification of classes of sick individuals, was an ambitious program that appeared in the medicine of two centuries ago in an attempt to recognize, through the symptoms of the truths or constant entities, the classified diseases. The seed thrown by Morgagni in 1761 struggled for fifty years grow, but when it did become a lush tree that in 1819 presented the first true symbol of the new internal clinic with Laennec. The disease was affirmed in the meaning of the pathological changes of the organs, describable and measurable on an anatomo-pathological level, with alterations connected to functioning and the localistic model, made historically dominant, which has since provided our peculiar clinical perspective. Delivered to the archives of history, the previous views of the framework understood as general and systemic imbalances of the whole organism, medicine had reached the search for the essence of the diseases (nosology) as unitary entities and their most faithful description (nosography), with a model of diagnostic classification that constituted the conceptual basis of the nineteenth and twentieth century clinic.

But from here on, can we really continue to trust in this model and its meaning? The concept of many different diseases, each with its own autonomous identity, allowed to recognize a phenomenon and explain it with natural laws based on characteristic signs. However, from the beginning, the internal coherence of the model had been questioned by so many variables. Diagnostic systems are artificial constructions that reflect the momentary state of knowledge, largely provisional tools, to be used with caution. They propose catalogs of human infirmities in the form of tables, but in the clinical pictures not everything can be clearly defined or defined with few words and the diagnoses do not always constitute an exact denomination of the known event, nor an explanation. They give reasonable indications of conduct, but their reliability must be checked by catamnesis. It must therefore be

admitted that a slight veil of fiction has deceived the idealization of the diagnosis and its meaning. One wonders if by creating an univocally clinical situation, by classifying it, we allow to avoid misunderstandings and guarantee without doubts the procedure towards the of therapy. The time has not come for the revision of the concept of diagnosis, because the questions on nosology could question the whole conceptual apparatus of medicine, the general laws of the disease and the end of clinical judgment, or rather the clinical reasoning itself. So let us be helped by the knowledge of history. If we identify clinical reasoning with scientific reasoning, we must know the elements that support a theory of right thinking and right action, in recalling the canon of science that binds to the method, to the inductive logic, to the verified data and to theories founded on the data.

And if we explore the complex of mental acts used to go towards the diagnostic definition, we realize a process that formulates hypotheses and conclusions, with objective arguments that are part of rational logic, but also with our subjectivities, fueled by experience. Not much has changed after a hundred years. The diagnostic procedure adapts itself to the scientific paradigm: the input data are observed and standardized to arrive at different concatenations of sets and subsystems that lead to conclusions. But in proceeding there is a tension of comparison between the probabilistic scientific model and an intuitive model.

That is, something is still hidden in the intuition of the individual, never completely eliminated by the doctor's work. The training of Richard Cabot (*The Anatomy of Clinical Judgments*, 1916), made us reflect on the process of clinical diagnosis and note with how much distrust or resistance the doctors tended to avoid the reasoning on the formalization of their mental operations. Because it is true that - when the possibilities for objective observations fail - the diagnosis is something intermediate between the assessment of a situation and a verifiable hypothesis about that situation.

Therefore, it is not secondary to ask how, in medical education, in the student's education and in the continuing education of the doctor, the skills required to master clinical reasoning and to ensure a freer and more open mental attitude in making therapeutic decisions must be cultivated.

In our opinion, the university teaching which instructs the ways in which the signs and symptoms must be collected cannot allow the student to become a doctor without being educated on the history and on the fundamental notions of logic to connect the facts to each other. Therefore, it is necessary that in the medical education teaching Human Sciences becomes more affirmed, label with which today we teach the History of Medicine, Paleopathology and Bioethics, to better prepare the discipline of reasoning and above all to humanize the care.

Giuseppe Armocida

Magic, science and morality in renaissance humanist medicine and psychiatry

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Abstract. This work has the main purpose to show Neoplatonist and magical-hermetic influences on the non-linear and complex pathway leading the nascent scientific psychiatry's philosophy and practice towards its more mature developments, throughout an excursus from Cardano et Fracastoro, passing by the breaking point represented by Paracelsus, to Van Helmont, Weyer and Vives. The emphasis is on the fruitful and not-contradictory link between magical and empirical world's vision and the beginning of some innovative good practices, during the Renaissance era, for a modern and ethical conception of Psychiatry. That's why, we will see how Renaissance scientific development, often inspired by Neoplatonist and hermetic philosophy, have allowed the development of a modern conception of the mental patients' conditions and the special care, both pharmacological and moral, that they need.

Key words: history of psychiatry, interpretation of madness, Cardano, treatment of the mentally ill, Fracastoro, Paracelsus

Introduction

The medicine's pathway between ideological conditioning, magic and philosophy

It is known that magic has had a great influence on the modern science's birth, especially with regards to medicine and psychiatry (1-4). The sapiential way, belonging to magic, hermetic and astrological conceptions is the origin of that subsequent and different model of reflection on the nature, owing to scientific cosmology.

In this thought development' process, 1400's and 1500's Neoplatonism had a fundamental role by re-thinking and re-proposing the classical sources (Plotinus, Proclus and Pseudo-Dionysius the Areopagite) in a synthesis with the hermetic, Kabbalistic and astrological tradition.

This philosophical tendency gave to magical-hermetic tradition the function of a radical renewing of the cognitive approach to the reality that founded the

nature's modern science and caused the Aristotelian Scholasticism metaphysical system's and its cosmology crisis (5-6).

The humanist-Renaissance thinking, based on the link between magic and science and on Greek philosophy's revival in a Neoplatonist perspective (with a significant preference for Hermeticism), develops some innovative theories on general medicine and psychiatry.

In early modern philosophy, the great success of the Corpus Hermeticum, the Chaldean Oracles and the Orphic hymns, either attributed to mythical (such as Hermes Trismegistus) or existing (such as Zoroaster and Orpheus) characters, contributed to the spread of these new approaches. One explanation of this naïve, even if widely accredited theory, has been attributed to a lacking philological/historical precision (7). However, this thesis seems partial and reductionist, because it does not consider that Neoplatonism's humanistic interpretation, of whom Marsilius Ficinus is an emblematic figure, is based on a classical Antiquity herit-

age's different interpretation compared to the Scholasticism's one.

In the interpretation of mental disease, the esoteric magical components have played an important role also for their intertwined link with philosophy (8-9). In fact, interest in moral issues has always been important in the history of Psychiatry, not only in the field of medical deontology which began with the Greek medicine, from Hippocrates to Galen, but also in close reference to the specificities of the mental disease compared to organic syndromes (10-14). The first fundamental historic mention of a close connection between psychiatry and morality can be found in the Christian thought that, in contrast to the classical tradition, offers a demonological interpretation of mental disease, strictly connected with the witches' concept of sin and evil (15). This interpretation of mental disease (whose traces are found already in Patristic sources), had the widest possible dissemination and success in humanistic heyday with the *Malleus maleficarum* which abandons the Scholasticism's tradition's multifactorial approach.

With Sprenger and Kramer we assist to the mental disorder's shifting from the medical pathology's field to the moral theology's theoretical framework, as a supernatural phenomenon (16). That turning point, marked by the intrusiveness of theological influences, explains Psychiatry's delay, not only compared to astronomy and physics, but also to biology and medicine, in the use of the experimental method and in the acquisition of a truly scientific structure. Anyway, the intrusion of sin's and guilt's concepts will affect Psychiatry also in later times, as in the romantic age (with Heihroth and Ideler and even with Kant in its *Pragmatic Anthropology*).

In fact, the *Malleus Maleficarum* differs from the concept expressed by St. Albertus Magnus and St. Thomas who, while giving credit to stars' and demons' influences, tended to identify a psychological-moral component in the mental disorder's outbreak. The oscillation between the Christian concept of soul's spirituality and those of Aristotelian *synol* and *entelechy* has a real, strong impact on this conciliation between natural and supernatural origin. Consequently, the mental disorder may be related to many factors: body's changes (with vegetative and psychic soul's involvement), pas-

sional excesses, astral influences, Evil's interventions. In this perspective astrology takes a more metaphysical-cosmological aspect rather than magical (17).

Before the *Malleus Maleficarum*, some other mental disease's interpretative theories referenced to Greek and Arab medicine, astrological beliefs, ethical concepts about the relationship passions-reason and, finally, but in a lesser extent, to demonology (18-20). This allows us to understand the clear distinction between medicine and psychiatry in relation to the progressive detachment from classical somatic and genetic explanation (expressed in Hippocrates essay on the sacred disease where epilepsy is due to a brain *noxa* and not to a diabolical possession), in favour to the ethical and theological explanation.

However, the *Malleus maleficarum* is not a return to Scholasticism, but an emphasis on theological issues, considered apart from their theoretical foundations. This rigid and dogmatic religious connotation explained the trials and the convictions against mental patients accused of witchcraft and satanic relationships, thus determining a persecutory involution and an inhuman treatment of madness.

Sprenger and Kramer show, however, some remarkable observations and descriptions skills of psychotic symptoms. The second part of the *Malleus Maleficarum* represents a unique model of psychiatric semiotics whose accuracy is not influenced, in its formal aspect, by symptoms' supernatural interpretation.

The *Malleus Maleficarum*, whose influence, for historical and political reasons, was enormous and endorsed by the ecclesiastical authority, promoted by the Bull of Innocent VIII, *Summis desiderantes affectibus* (21), was therefore an obligatory reference for the doctors-philosophers of the Renaissance who faced the problem of mental disease (16).

From conjunction to disjunction from esoteric magic-components: from Cardano to Fracastoro

In the pathway from magic to science, Girolamo Cardano has assumed an important role, sometimes underestimated (22-23).

The generic and exclusive attribution of this philosopher to the Plotinus-Proclus-Ficino magical tradition's line is quite reductive. This physician-philoso-

pher's thinking is not so oriented to magic's ontological bases, but to the acknowledgment of the esoteric and initiatory knowledge's primacy which makes a doctor a magician and a philosopher (24).

Cardano attributed to himself magical and supernatural powers as it believes that the practice of medicine, in its highest expression, is the exclusive privilege of those who own extraordinary tools for understanding and action. His brilliant career has certainly helped to confirm this conviction. It is true that Cardano had a good diagnostical and therapeutic ability on himself (as it appears in the *De vita propria liber*, 1576) and on his patients as well. His medical achievements are probably partially due to his strong persuasive and empathetic skill, in addition to a great capacity of taking the ill person in charge, which, in contemporary bioethics, is called "therapeutic alliance".

Cardano natural magic anticipates and prepares the way for the new science of nature, with a mix of scientific thought and superstition, already freed by the Scholasticism's philosophical and theological influences. Thus, magic takes, in his thought, a cathartic function against metaphysical intrusions and becomes a bridge towards the experimental observation's model of the scientific revolution.

It should also be pointed out that Cardano's supernatural is not a theological but an anthropological category, in the context of the reality's cosmological conception, freed by the classic medieval sources. He deals with Psychiatry, even if marginally, but his interest in psychic phenomena has a psychological angle rather than medical. Cardano analyses some developmental troubles, he notes (like Della Porta) the different characters with regards to their somatic correlations and addresses also, albeit in a summary way, mental hygiene problems (25).

He can be considered a physiognomy's precursor, discipline that will have significant developments thanks to Lavater, Goethe, Herder, Bell, Carus, Gall, Wundt, Darwin, Maan, Morselli. It is also worthy to mention his courageous defence of mental patients in the name of a strong ethical necessity. In fact, by claiming their human dignity, he harshly and unreservedly condemns the persecutions and the mistreatments mental patients were subjected, as well as social, ethical and religious stigma.

Cardano, telling the story of sixty young orphan girls, that "in one night gave signs of being possessed by the Evil" offers a naturalistic explanation by suspecting some fumes' influences of the place and the water that "mute humours", or the mutual suggestion within a closed community where dialogue lapses into monologue (22).

In his work *De rationali curandi ratione* (1562) he mentioned that even exorcisms could induce positive expectations and improve patients' conditions. In his thought emerges, then, a first rudimentary formulation of the placebo effect's concept (26).

The Girolamo Fracastoro position represents a tentative to go beyond the connection between magic and science (27). His thought, entirely freed from both the supernatural and hermetic-initiatory knowledge, is quite different from the view of Ficino, Pico della Mirandola, Agrippa Nettesheim Port and Cardano himself (28). The naturalistic approach of this philosopher is very close to the initial and first modern scientific medicine's phase. However, his philosophical and non-experimental conception of medicine does not allow us to consider him rightfully a "scientist".

In his essay *De sympathia et antipathia rerum* we can find the theoretical foundation of contagion's etiopathogenetic concept (in *De contagione et contagiosis morbis et curatione*) referring to the Democritus' and, especially, Empedocles' theories. He repurposes an atomistic cosmology that explains every natural event, even those concerning the living beings, through the mechanism of the contact and the attraction and repulsion categories, respectively for similar and dissimilar. This philosophical conception allows him to explain the origin of diseases like a contagion in the human body caused by the "*seminaria*" or "pathological seeds". Fracastoro distances himself from Galen's humoral theory, by proposing an aetiology, exogenous and non-endogenous, determined by dynamic agents and transmissible agents from things to man and from man to man.

Although the source of *seminaria* concept is mostly in Democritus works and maybe in Lucretius's ones, Fracastoro attributes to them more biological than physical characters, such as a certain vital activity and procreative function. His view may be an anticipation, albeit vague, of the modern microbiology, very

distant from Lucretius', Terentius Varro's and Hildegard of Bingen's thinking (27).

He takes this renewal way with few or no Neoplatonist influences by replacing, as philosophical basis of his medicine, a materialistic approach referring to Democritus and Lucretius (29).

The break with tradition: Paracelsus

Paracelsus gave a very significant contribution to medicine and psychiatry evolution (30-31). His magical and astrological beliefs are a symbolic representation of theoretical models of high critical value, which allow a strong and revolutionary beginning of an authentic scientist approach.

He has a philosophical and methodological way of thinking aiming to identify in a cosmological perspective the scientific research's foundation. That is a concept based on the link and unity between man and nature, in line with the *copula mundi* Ficino's concept, which anticipates intuitions that will be developed later by Mesmer and the romantic medicine (32). In this perspective should be precisely understood the meaning of *archeus*, vital force inherent in every natural entity whose it rules life and growth. *Archeus* concept has a double cosmological and medical significance: under the first aspect is a reality's organicist conception (which is the true meaning of natural magic); under the second aspect is a methodological tool that, starting by the uniqueness of living beings, helps to explain the specificity of diseases. Paracelsus, therefore, refers to Hippocrates and Hippocratic tradition which, in his view, had been misinterpreted by Galen and Avicenna (33).

Certainly, in this so singular author, relevant scientific and modern intuitions coexist with some esoteric components. Alchemy, that Paracelsus enthusiastically practises, is not, in his view, the legendary production of gold and silver from base metals, but the science of transformation from rough metals into different and useful products. In this perspective, there is no concession to superstition or supernatural and thaumaturgical factors, but the only recognition of nature's transformation faculty. One of magic's significations is the dynamic character of reality related to handling and pragmatic skills which are the highest expression of

human life. Of course, this implies the attribution of this special expertise to the wise-magician, in the line of initiatory tradition and, also, its translation into a symbolic language (32).

Paracelsus, then, conveyed new ideas within an old frame. Certainly, his undeniable genius, which gave fundamental contributions to medicine's progress, takes advantages, sometimes, of an excesses' predilection. But this does not justify, although it makes it understandable, the charlatanism's accusation and his thought's depreciation, expressed against him by Kepler, Bacon, Hoyle and Bayle: accusation and depreciation that have been inhibiting for a long time a balanced critical and historical judgement (34).

As a further confirmation of the compatibility between magic and science in Paracelsus and, even if to a lesser extent, in Cardano and Cornelius Agrippa (*De occulta philosophia*, 1510) as well, it should also be remembered that natural magic was an alternative to black magic and a weapon to counter the theological supernatural's intrusiveness (35-36). Agrippa 1913; Peterson, 2003). Natural magic played, therefore, a privileged role against superstition and obscurantism, in favour of the rising scientific perspective. Paracelsus, by rejecting the principle of authority (as well as Galen and Avicenna) and by proclaiming himself the true heir of Hippocrates, replaces the humoral theory by a medical model based on chemistry, both in the physiological-pathological and clinical-therapeutic aspects (37). The health or disease conditions do not depend, therefore, on crisis or dyscrasia situations, on temperance or imbalance due to body's humours' (blood, phlegm, yellow bile, black bile) excess or defect, but on a proportionate relationship in the human body, conceived as a chemical system, between mercury, sulphur and salt.

The contribution of Paracelsus represents a revolutionary turning point in medicine, following three fundamental perspectives.

The first is the organic and dynamic unity of man and nature, which implies between them a reciprocal and interactive interventions' exchange, not only limited to the astral influence on the human world. The second perspective is the rejection of traditional, classical-medieval theory on the four elements, constitutive of the material world (air, water, earth and

fire) and on their correlative qualities (cold, wet, dry, hot) referring to body substances' changing states and conditions such as salty and sour. The same primordial elements (salt, sulphur and mercury) are characterised by their inherent qualitative features of solidity, combustibility and fluidity.

The third perspective represents a significant turning point in the anthropological and cosmological field aimed to endorse a dynamic functionalism of qualities' combination and transformation, which contrasts with the substantialist ontology marked by the traditional medicine's strong static nature.

On this theoretical basis, Paracelsus, despite of what was prescribed by contemporary pharmacopoeia, uses mineral and non-organic drugs (both of animal and vegetable origin) for therapeutic purposes. His etiopathogenetic attributes an interactive character, inside the human body, to salt, sulphur and mercury; this interaction has different modes, levels and quantities, which determinate the diseases typology and their development. And that is precisely the origin of the thesis on the diseases' and their remedies' specificity.

Paracelsus believes that diseases' aetiology comes from external agents with their own ontological consistency. Unlike Fracastoro, he does not confer them a biological nature and that is why he cannot be considered a modern microbiology's precursor. He also makes a different assessment on these factors' aggressiveness; he thus hypothesises their partial synergy with environmental conditions. These agents' influence is neither unique nor isolated, nor it works one-way on a passive substrate. Their influence is combined with the astral plane's one, the environment and the endogenous reactions that interact with quantitative and qualitative ratios of sulphur, mercury and salt, and salt and acid. Therefore, this concept, even if very influenced by philosophical assumptions, is a modern medical pathology's precursor factor. The Paracelsus disinterest for anatomy reveals his dogmatic assumptions to the detriment of an experimental knowledge. Paracelsus did not take advantage of the anatomical studies' fundamental progress, already started, in his time, with Mondino, Alberto the Bajaj and Guy de Chauliac, with Leonardo, Marcantonio Della Torre, Paolo Antonio Benivieni, Alessandro Achillini, Alessandro Benedetti, Berengario da Carpi, Charles Esti-

enne and especially with Vesalius. Paracelsus justifies his anatomy' rejection, arguing that the knowledge of human body's organs, in both their physiological and pathological conditions, did not require direct observation by the autopsy, but only a cosmological approach including all the connections between macrocosm and microcosm and the astral influences.

Thus, we can see that in Paracelsus' thought coexist lights and shadows: on one side, he appears extraordinarily modern, on the other one, he is still closely conditioned by invasive and pervasive philosophical theories, trespassing their legitimate competence's area and by esoteric, initiatory suggestions. Anyway, it would be unfair to ignore his thought's incidence and fruitfulness in the modern science's birth, where Neoplatonism and Hermeticism played an extremely important role.

Furthermore, it is undeniable the outstanding Paracelsus contribution as the founder of iatrochemistry (opposed to iatromechanical, coming from Descartes, Borelli, Bellini, Baglivi and Malpighi mechanicism), which brilliantly anticipates, although mainly as intuitions, modern physiology and biochemistry.

Also, regarding the mental disease, the contribution of Paracelsus is relevant (38). First, he reiterates, its pathological nature and entrusts the doctor with the sole responsibility for diagnosis and therapy. Concerning the clinical frameworks, his observations are accurate, even if they reflect traditional psychopathological theories. His studies on clinical melancholy are quite interesting.

Paracelsus conceives the mental disease, which is not, in his vision, a demonic possession or a supernatural phenomenon, as a very peculiar disease, compared to organic syndromes. This disease, even in the context of a biochemical aetiology, entails troubles and *spiritus vitae* alterations, especially with regards to its main negative outcome: the loss or, rather, the subtraction of the reason. In fact, even though Paracelsus written texts on this matter are quite rare and ambiguous, it is still possible to suggest a holistic interpretation, especially if we consider that the *spiritus* (concept deduced, by a tortuous, exegetical path, from Erasistratus, Galen, Ficino, and Telesio) is a kind of mediator and intermediary factor between soma and psyche sensorial and cognitive functions. Paracelsus gives this concept

the same meaning as Ficino does, not without a strong and sometimes ambiguous oscillation between bodily and spiritual nature, with a certain predominance for the latter. Only with Descartes, in fact, the *spiritus* is conceived in neurophysiological terms, in the context of a mechanistic theory (which will be retaken later by Willis through his thesis on vital spirits' motion abnormality as psychopathological phenomena's cause). This conceptual-semantic change is thus one of the main reasons for the divide or, at least, the independence between psychiatry and neurology, which was typical of the sixteenth and seventeenth centuries and which will contribute to implicate a delay, on the side of the psychiatry if compared to medicine, in the choice of the biological model (39).

But, despite these uncertainties and obstacles resulting from philosophical presuppositions that prevent Paracelsus psychopathological theories to achieve an appropriate scientific maturity, we must acknowledge his merit of strongly fighting the demonological beliefs and implementing therapeutic interventions for mental patients. Besides, Paracelsus doesn't merely and generically proclaim that crazy people should be treated, but also specifies several therapeutic indications according with his convictions in the medical field. In the psychological and psychopathological fields, Paracelsus remarks, even if they are not expressed in a systematic and rigorous way, are however several and important, especially about developmental mental health; in fact, he truly understood, even not without some shadows, the opportunity of psychotherapeutic interventions not only to cure, but also to prevent mental disorders. Paracelsus was also an irreducible opponent of witches' persecution, so that he become a victim himself of his anti-demonological polemics.

The legacy of Paracelsus

Paracelsus iatrochemical orientation will be systematically developed by Van Helmont who, however, differs from Paracelsus whose he integrates the fundamental concepts by integrating them with others thesis from different sources (40). Also, in Helmont Platonic influence is present, although in its strictly cosmological and philosophical dimension, without any esoteric and hermetic subjects (41). There is no

doubt that *archeus* is a Paracelsus concept, which also refers to Ficino, whether it is intended as world soul (and therefore spiritual substance), or whether it refers to the *spiritus*, (material substance, although very thin and almost aeriform).

Van Helmont thought is quite ambiguous between these two meanings. Its categorical interpretation's oscillations may be due to two reasons: the first concerns an essentially monist conception of reality, inherited from some Neoplatonist sources; the second is connected to the importance of cosmological-anthropological category of *spiritus*, which has a long and complicated historic path from Erasistratus, Galen, Cardano, Ficino, Telesio, Bacon, and Descartes.

The most reliable hypothesis, to interpret Van Helmont thought in an historically and philological correct way, is the existence of a structural and irreversible oscillation between tradition and modernity and between his need of consistency with the early philosophical sources and an initial scientific vision of human nature.

Another convergence, even with a fundamental difference, with Paracelsus concerns the exogenous, etiopathogenetic theory. In Van Helmont thought, in fact, external agents are linked in a synergic way with the *archei* inside the different organs. This theory is therefore compatible with the multifactorial criterion, always in the only context of chemical processes.

Even if in iatrochemical line, Van Helmont differs from Paracelsus, not only for denying the absolute correspondence of macrocosm and microcosm constituent elements but also for imaging water (and not sulphur, mercury and salt) as the elementary substance and principle of everything formation and transformation.

About medical pathology, Van Helmont identifies diseases cause in the fermentation process and provides chemical drugs for certain pathological forms.

Contemporary and follower of Van Helmont was Sylvius, who practiced anatomical research and constant clinical activity, also encouraging drugs chemical preparation (42-43). Besides, he developed the concept of fermentation, extending it not only to the pathological phenomena, but also to all those that occur in nature. Even Willis, one of seventeenth century biggest medical and anatomic pathology doctor, adheres

to the iatrochemical orientation, as well as Sylvius, and attributes to fermentation a crucial role in biological field (44).

With G. E. Stahl iatrochemistry theory is proposed again within a systematic conception of medicine which recoups the philosophical category of the soul, as it appears in the classical, Platonic and Aristotelian tradition. In Stahl vision, in fact, the soul is body's unifying and regulatory principle and the condition of all physiological movements and their balance which cause diseases when compromised (45).

Is properly with Weyer, Agrippa's student, that a genuinely scientific Psychiatry may be born (46). His *De praestigiis dei* represents a strong refutation of the *Malleus Maleficarum*, through the systematic translation into psychotic symptoms of all those behaviours deemed as witches and demons' actions (47). Thus, a theological and supernatural-based perspective's radical overturning takes place, in favour of a medical vision, based on diagnostics in matter of pathology, limited to the field of purely natural events, and psychic anomalies and deviations.

Mental patient's defence and protection are no longer exclusively the competence of the ethical and social field, like in Vives, but they mainly concern the related medical issues. We may therefore affirm that the Weyer Psychiatry's vision is genuinely scientific since it is medical psychiatry. This seems indisputable, though his medical psychopathology's bases are still traditional, with some references to Galen humoral theory and a limited influence of Paracelsus iatrochemistry as well.

His most original contribution regards the clinical field and especially semiotics and nosology. Weyer really shows his knowledge on melancholy disorder, not only as we find it in Aretaeus of Cappadocia, Sorano of Ephesus and Galen descriptions, but also in Paracelsus etiological interpretations. He also deals with hallucinations and delirious ideas, by elaborating clinical patterns of organic mental disorders induced by psychoactive substances (belladonna, opium, hashish, etc.) and of paranoid disorders, by an expert analysis of nightmares, hysterical manifestations and psychic contagion.

Particularly interesting are his studies on some mental disorders' sexual origin; it is noteworthy that

he tackles the sexuality's issues from a medical point of view, without moralistic attitudes, but with a neutral, no-judgmental biological and naturalistic description.

Another fundamental aspect of his modernity is the critical caution in using a priori theoretical models and his predilection for the empirical observation. For these reasons Weyer stands out from Cardano, Agrippa and the hermetic-magical Renaissance tradition, to align himself in absolute coherence with the scientific revolution of Copernicus, Kepler and Galileo, whose he shares the paradigm.

Vives has a far more complex and articulated personality. He contributed through many sparkling ideas to Psychiatry's scientific development, even if some historians (notably Zilboorg) overestimated him, amplifying his ideas' speculative meaning and originality (48-49). Vives was not a radical innovator, as Paracelsus had been and Weyer will be. He did an intelligent compendium of the most advanced opinions circulating in Europe during the first half of the 16th century. He is opposed to Scholasticism as an abstract and academic knowledge, in the name of a strong necessity of concreteness, of culture divulgation, interest to the human world in the ethical-social-religious angle, as well as a high sensitivity for pedagogical and psychological issues.

Like Agrippa, also Vives refuses the misogyny of his time, mainly present in some theological environments and he deals with women education in a systematic way. The work that directly concerns mental disease's issues is the *De subventionem pauperum* (48). In the third chapter, he tackles the patients' conditions, unhappy dispossessed because of the with the treatment or non-treatment reserved for them by the society of the time. His perspective is not medical but ethical and social and is animated by an ardent, religious philanthropy. Vives, more than with disease, deals with sick people's physical and psychological suffering and, to soothe it, he lists several sanitary and moral precepts on nutrition, and hospitals' cleanliness and requirements (50-51).

Vives also takes care of mental patients, but not from a psychopathological point of view, but in a medical deontology perspective. He makes a list of some tutelary regulations on mental health such as the prompt diagnosis and prognosis at the time of the admission,

a dutiful compassion for the patients, the avoidance of mockery and provocative attitudes against them, as well as the respect for their human dignity.

Conclusions

From this historical path emerges the gradual process towards a genuinely scientific conception of medicine and psychiatry. This innovative process is however in continuity and not in opposition with philosophical, theological and, initially, even magical-hermetic issues. Therefore, this gradual emancipation from the parascientific influences may represent the fundamental premise to the development of a high-level critical approach towards all somatic and psychic disorders' issues, without quitting a marked, philosophical interpretative frame.

References

- Sarton G. Introduction to the History of Science (1). Baltimore: Williams and Wilkins; 1974.
- Butterfield H. The Origins of Modern Science 1300-1800. New York: Macmillan; 1952.
- Thorndike L. History of Magic & Experimental Science (8). New York: Columbia University Press; 1958.
- Fitzharris LA. Magic, mysticism, and modern medicine: the influence of alchemy on seventeenth-century England. A thesis paper submitted to the faculty in candidacy for an honors bachelors of arts degree. Department of history. Illinois: Wesleyan University; 2004.
- Megone C. Aristotle's Function Argument and the Concept of Mental Illness. *Philosophy, Psychiatry, & Psychology* 1998; 5(3): 187-201.
- Lamont J. Fall and Rise of Aristotelian Metaphysics in the Philosophy of Science. *Sci & Ed* 2009; 18: 861-84.
- Burns D. The Chaldean Oracles of Zoroaster, Hekate's couch, and Platonic orientalism in Psellos and Plethon. *Artes* 2006; 6(2): 158-79.
- Lanternari V. *Medicina, Magia, Religioni, Valori*. Napoli: Liguori Editore; 1994.
- Van der Eijk P. *Medicine and Philosophy in Classical Antiquity*. Cambridge: Cambridge University Press; 2005.
- King LS. The transformation of Galenism. Debus AG (Ed.) *Medicine in Seventeenth Century England*. Berkeley: University of California Press; 1974.
- Wakefield JC. The concept of mental disorder: on the boundary between biological facts and social value. *Am Psychol* 1992; 47(3): 373-88.
- Thumiger C. A History of the Mind and Mental Health in Classical Greek Medical Thought. *Hist Psych* 2018; doi: 10.1177/0957154X18793592.
- Majeron M. The meaning of Madness in ancient Greek culture from Homer to Hippocrates and Plato. *Med Histor* 2017; 1(2): 65-76.
- Bizzotto J. The hypothesis on the presence of entheogens in the Eleusinian Mysteries. *Med Histor* 2018; 2(2): 85-93.
- Dionisi A. Il linguaggio magico e linguaggio sacro: evocazione ed alienazione. Bartocci G (Ed.) *Psicopatologia, cultura e dimensioni del sacro*. Roma: Edizioni Unversitarie Romane; 1994.
- Sprenger J, Kramer H. *The Malleus Maleficarum*. London: The Folio; 1968.
- Mercier CA. *Astrology in medicine. The Fitzpatrick lectures delivered before the Royal College of Physicians*. Cambridge: John Clay MA at the University Press; 1914.
- Marketos SG. *Medicine, Magic and religion in ancient Greece*. *Humane Medicine* 1992; 8(1): 41-4.
- Tzeferakos G, Douzenis A. Sacred psychiatry in ancient Greece. *Ann Gen Psychiatr* 2014; 13: 11.
- Thumiger C. *A History of the Mind and Mental Health in Classical Antiquity*. Cambridge: Cambridge University press; 2017.
- Kors AC, Peters E. *Witchcraft in Europe, 400-1700: A Documentary History*. Philadelphia: University of Pennsylvania press; 2001; pp. 177-80.
- Bonuzzi L. *Psicopatologia e criminalità. L'itinerario italiano* <http://www.psychiatryonline.it/node/2418>; 2012.
- Simili A. Il pensiero di Gerolamo Cardano nella psichiatria, nell'antropologia criminale e nella sociologia. *Min Med* 1968; 59(16): 874-84.
- Ayala NI. The influence of Plotinus on Marsilio Ficino's doctrine of the hierarchy of being. A Thesis submitted to the Faculty of The Dorothy F. Schmidt College of Arts and Letters in Partial Fulfillment of the Requirements for the Degree of Master of Arts. Florida Boca Raton: Florida Atlantic University; 2011.
- Wallace ER, Gach J. *History of Psychiatry and Medical Psychology*. New York: Springer; 2008.
- Mantovani V. *Vita di Girolamo Cardano*. Milano: Sonzogno; 1821.
- Castiglioni A. Gerolamo Fracastoro e la dottrina del contagium vivum. *Gesnerus. Swiss Journal of the history of medicine and sciences* 1951; 8: 52-65.
- Pastore A, Peruzzi E. *Girolamo Fracastoro fra medicina, filosofia e scienze delle natura*. Firenze: Leo S. Olschki; 2006.
- Ahonen M. *Mental Disorders in Ancient Philosophy*. Heidelberg: Springer; 2014.
- Webster C. *From Paracelsus to Newton: Magic and Making of Modern Sciences*. Cambridge: Cambridge University Press; 1980.
- Mora G. Paracelsus' psychiatry: on the occasion of the 400th anniversary of his book "Diseases that deprive man of his reason" (1567). *Am J Psychiatry* 1967; 124(6): 803-14.

32. Schott H. The role of imagination in modern medicine. *Berichte zur Wissenschaftsgeschichte* 2004; 27(2): 99-108.
 33. Walter P Paracelsus. *An introduction to Philosophical Medicine in the Era of the Renaissance*. Liestal: Ludin AG; 1958.
 34. Vickers B. *Occult and Scientific Mentalities in the Renaissance*. Cambridge: Cambridge University Press; 1984.
 35. Agrippa CE. *The philosophy of natural magic*. Chicago: The de Laurence Company; 1913.
 36. Peterson JH (Translate) Agrippa. Heinrich Cornelius "Three Books of Occult Philosophy." Twilit Grotto: Esoteric Archives. CD-ROM. Joseph H. Peterson; 2003.
 37. Siddiqui MA, Mehta NJ, Khan IA. Paracelsus: the Hippocrates of the Renaissance. *J Med Biogr* 2003; 11: 78-80.
 38. Midelforth HCE. The anthropological roots of Paracelsus's psychiatry. *Medizinhistorisches J* 1981; 16: 67-77.
 39. Pai-Dhungat JV, Parikh F. Paracelsus (1493-1541). *J Ass Phys India* 2015; 63(3): 28.
 40. Pagel W. *From Paracelsus to Van Helmont*. Winder M (Ed.) *Studies in Renaissance medicine and science*. London: Variorum Reprints; 1986.
 41. Hoff HE. Nicolaus of Cusa, van Helmont, and Boyle: The First Experiment of the Renaissance in Quantitative Biology and Medicine. *J Hist Med All Sci* 1964; 19(2): 99-117.
 42. Hofer JCF. *Histoire de la chimie depuis les temps les plus reculés jusqu'à notre époque*. Paris: Hachette; 1843.
 43. Lindemann M. *Medicine and Society in Early Modern Europe*. Cambridge: Cambridge University Press; 2010.
 44. Willis T. *Pharmaceutice Rationalis*. Oxford: E Theatro Sheldoniano; 1674.
 45. Hélène M. La philosophie de la matière chez Stahl et ses disciples. *Isis* 1926; 8: 427-64.
 46. Meyer T. Weyer, Johann. A cura di Traugott B (Ed). *Biographisch-Bibliographisches Kirchenlexikon* 2002; 20: 1537-44.
 47. Weyer J. *De praestigiis daemonum, et incantationibus, ac veneficiis, libri V. Auctore Ioanne Wiero Medico. Totius operis argumentum in Praefatione comperies*. Basileae: per Ioannem Oporinum; 1563.
 48. Del Nero V. Juan Luis Vives, L'aiuto ai poveri. *De subventione pauperum*. Pisa-Roma: Fabrizio Serra; 2008.
 49. Martini M, Gorini I, Licata M, De Stefano F, Schiavone M, Ciliberti R. Ethical aspects of medical thought on the madness in the enlightenment. *Acta Med Hist Adr* 2016; 14(1): 73-80.
 50. Busfield J. *Mental illness*. Oxford: Polity Press; 2011.
 51. Greenfield S. *The private Life of Brain*. London: Penguin Books; 2000.
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Nietzsche's illness diagnosis issues: a review of his clinical records and some recent hypotheses

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Abstract. A notorious episode took place in Turin in January, 1889: Nietzsche's mental breakdown. That very occurrence marks the start of the hospitalization of the philosopher in mental institutions: accompanied by his friend Franz Overbeck, he first went to Basel where he stayed only for a week (from the 10th to the 17th of January, 1889); he was then taken by his mother to Jena where he actually stayed for more than a year (from January 18th, 1889 to March 24th, 1890). The article will focus on the philosopher's diagnosis starting from his clinical records, passing through the hypotheses of his contemporaries, until some recent ones. The aim will be to overcome manichean and univocal positions both of madness and illness.

Key words: Nietzsche, clinical records, mental health hospital, psychiatry, diagnosis

The 1889 mental breakdown

Nietzsche life was not particularly relevant from a clinical psychiatry perspective because the philosopher was never a diligent patient of hospitals or institutions/communities specialized in mental health care. He was hospitalized only after the first true psychotic episode of his life which, as it is well-known, evolved into progressive paralysis lasting about ten years and ending with a series of strokes and ultimately death.

This notorious episode took place in Turin in January, 1889 and, even for those who do not deal with philosophy, it became the defining moment of the madness increasingly affecting the philosopher from Röcken. It was concurrent with the issuance of the so-called Madness Letters, written during the first half of January of the same year and sent to the philosopher's friends and acquaintances; in these letters, which he signed "Dionysus" or "The Crucified One", he bragged about the absolute preeminence of his position in determining world's future history (1).

When talking about of the above breakdown in Turin, what comes to mind is the often told tale in

which Nietzsche embraced a horse that a coachman was flogging. The episode has more the taste of an anecdote rather than a real event supported by a concrete set of evidence; in any case, what is clear is that, on that very day, Nietzsche collapsed (maybe because he fainted) on the steps of Carlo Alberto Square in the centre of Turin, not far from his landlords' newsstand, Mr. and Mrs. Fino (2, 3).

That very occurrence marks the start of the hospitalization of the philosopher in mental institutions: accompanied by his friend Franz Overbeck, he first went to Basel where he stayed only for a week (from the 10th to the 17th of January, 1889); he was then taken by his mother to Jena where he actually stayed for more than a year (from January 18th, 1889 to March 24th, 1890) (4).

These two stays (the second closely following the first) represent the sole contact of Nietzsche with mental health hospitals: in fact, he had no prior psychotic episodes and would not have any in the future. In psychiatric terms, it is possible to argue that the philosopher had a first psychotic episode when he was 44 years old, and then went into remission and was discharged one year and two months thereafter.

It was not exactly a remission since he subsequently became ill with an organic disease which affected mental faculties and motor functions putting him in a progressive vegetative state.

However, at the age of 44, Nietzsche had already written all his books; indeed, his last work, *Ecce Homo* written in Turin, may be considered his testament.

The period spent in mental health hospitals became the eloquent episode in the existence of the philosopher, especially for those who study his biography (and we know that, in his thinking, biography and work are closely related), paying attention to the resulting demarcation: before the recovery, there is a Nietzsche who writes; after the recovery, during the ten years between his discharge and his death, there is a Nietzsche who stops writing, progressively stops discussing and does not advance the themes he introduced in his works. Most significantly, looking at someone who was accustomed to write almost every day and who did so as early as he became able to do it (and the evidence lies in posthumous written pieces, letters and further, by all the body of work showing intellectual activity that didn't become part of his formally published works) it is almost as if, after 1889, there is no firsthand written record of Friedrich Nietzsche.

Vicissitudes of clinical records

The clinical records of the German philosopher were at the center of peculiar events: the ones concerning his short recovery in Basel were found buried inside the general clinical records (belonging to the hospital) of Jena thanks to a copy that was transcribed upon the arrival of the philosopher at the second hospital (4).

Then, in 1914, after Nietzsche death, the then-director of the mental health hospital in Jena, Otto Binswanger (Ludwing Binswagner's uncle) informed the philosopher's sister, Elisabeth Förster-Nietzsche, that her brother's records had been stolen; the director added that he would have prevented their publication himself. As a matter of fact, those records included the anamnesis and the diary of Nietzsche daily activities and behaviors while in the institution, with details that would not have benefited his person, both as a philosopher and a man.

Instead, in 1929, just after Otto Binswanger death, Erich Podach, an ethnologist and literary man who had studied Nietzsche, published the clinical records of Jena in a Berlin newspaper which was nationally distributed with the title "The last battle of Friedrich Nietzsche" (4): the die was cast, everyone became aware of which battles the philosopher had fought with his mental disorder while in the asylum in Jena; to make matters worse, since Podach had omitted, without saying it, parts of the clinical records (the more intimate ones), a psychiatrist (Wilhelm Lange-Eichbaum) protested, declaring the publication unscientific and asked for a re-publication, this time including the missing parts.

This record was a copy of the original, which was still in Jena under close watch. The copy was found inside the records of another patient and then, the successor of Binswanger, Hand Berger, with no noble purposes, provided the records to the editor of the Berlin newspaper who, in turn, gave them to Podach so that he could publish an article. Finally, the original records were delivered sealed to the Thuringia State archives, in Weimar, on November 22, 1929. Today, the records, as well as the Basel medical records, are safely kept in Nietzsche's archive in Weimar (4).

The relevance of studies on Nietzsche's clinical records

At this point, it is necessary to wonder about the value of studying such clinical records from an historical perspective (for the history of psychiatry), from a biographical viewpoint (as they concern Nietzsche's biography) and also from a clinical perspective as they pertain to the definition of a diagnosis, to the extent that outlining a diagnosis might be a useful operation in the specific case of Friedrich Nietzsche.

Starting with the historical point of view, we may see that the records did not have any exceptional relevance since they tell about the day to day routine in mental health hospitals with no extraordinary findings: according to what was written, the operating procedures for patient treatment are limited to the administration of sleeping pills, tranquillizers and mercury-based rubs; in his case, the therapy was therefore exclusively phar-

macological (or proto-pharmacological) and did not include forceful physical restriction nor any kind of electroshock therapy. There is also no indication that Nietzsche was a particularly violent or uncontrollable patient. After all, as Mario Augusto Maieron recently wrote: “too often patients got better *in spite of the treatment* and that, if this were not so, medicine would be long dead and could in no way have survived” (5).

When it comes to the biographical perspective, the records do fill, even if partially, the historical period during which the philosopher did not leave us any written evidence; or better, such records worked as a point of conjunction, as underlined above, between, on the one hand, the Nietzsche who was actively writing, the Nietzsche of the aphorisms and of the works in which such aphorisms may be found, but also the Nietzsche of the so called posthumous fragments which remained unpublished and did not appear in any of his publications; and finally the Nietzsche of some letters - another significant source - rich of clues as to the development of the philosopher thoughts over time; on the other hand, such records were a point of conjunction with the voiceless Nietzsche of whom we do not have any firsthand evidence and who lived the last ten years of his life in a tragic state of regression, becoming progressively paralyzed and silent.

The problems with the diagnosis

The diagnosis proposed in the clinical records at the moment of the philosopher discharge from both hospitals is one of progressive paralysis caused either by a genetic factor or by third-stage syphilis condition. In the case of an effective infection, the immediate question to elucidate would be the reason for such a long latency (more than twenty years) between the moment he contracted the disease and the onset of the physical symptoms of paralysis. That is, if we subscribe to the idea that the disease was contracted in a brothel in Colonia in 1865; a fact however, that Paul Deussen, a friend of the philosopher, would refute.

Furthermore, we should emphasize that Nietzsche had been suffering for a long time, that is, since his late teens, from a range of ailments, some debilitating such as migraine, eye pain, tiredness, which were never for-

mally diagnosed: he himself did not know what was the cause of his sufferings which predated the alleged syphilis infection; in any case, he remained troubled by his certainty to have inherited a predisposition for degenerative diseases of the nervous system from his father.

However, if his paralysis was associated with his father's genetic heritage - Nietzsche's father died of encephalomalacia following a fall - we wonder whether it would be even conceivable to inherit a pathology that began after an accidental event; presumably, the dynamics of the event was reported incorrectly, or perhaps, these speculations were only his sister's. It appears more likely that his father's fall was the consequence of a neurodegenerative ongoing process, akin to what happened to Nietzsche, forty years later.

Besides this dual hypothesis found in the clinical records, many other hypotheses were spread in those days, especially from a non-specialist side: his sister, for example, believed that Nietzsche's decline was determined by the use of chloral hydrate, a sedative that her brother used in order to sleep better and to wake up with a clear mind for his writing activities. Elisabeth also states that the philosopher preferred this substance to opioids because the latter induced a state of confusion when he woke up in the morning. It is also important to clarify that chloral too, especially when taken in doses higher than customary, caused some level of deficiency to cognitive abilities; indeed, when Nietzsche woke up and felt abnormal, he always went through his morning notes again during the afternoon in order to ascertain that he hadn't written any disconnected or delirious sentences (2). Furthermore, it should be noted that, when he was hospitalized in Jena, he was treated with chloral in massive doses. If this substance had negatively influenced the state of his nervous system, his recovery in Jena would have not improved his condition but worsen it.

Finally, during one of his conversations with Nietzsche's mother (it is not clear whether he did so in order to give rise to the mother's opinion on the matter) Otto Binswanger himself, director of the mental health hospital, despite having confirmed the diagnosis of progressive paralysis, expressed the idea that an over-excitement of cerebral nerves was the cause of the psychophysical state of the philosopher; in his opinion,

it was a process that had been in evolution for a long time (6). According to this hypothesis, which was certainly not reported in any clinical paper, it is possible to infer the origin of all the theories, flourishing even today, which considered Nietzsche's philosophy and the intellectual effort spent proclaiming it, as the cause of his mental decline.

Instead, among the hypothesis that have emerged more recently, based exclusively on data contained in the written evidence, *in primis* in the clinical records mentioned earlier, it is possible to find a meningioma (7); a premature frontotemporal dementia (probably inherited) (8); a genetic cerebral arteriopathy (CADASIL), which was inherited from the father and which may then justify Nietzsche clinical case and the disease that had affected his father (9); a mitochondrial encephalomyopathy (MELAS), typically hereditary on the mother's side and which may not be appropriate in this instance because the philosopher's mother had never suffered from any kind of illness until her death in 1897 (10); but, in our case, given the lack of instrumental analysis confirming one of the above hypotheses, a metabolic illness could be a possibility too.

Perhaps there may not be an exhaustive clinical diagnosis for the case of Nietzsche because no organic pathology may explain such a complex clinical case: there is no doubt that Nietzsche suffered from one or more organic pathological conditions but they should be seen as concurrent causes of the insanity that he is so routinely credited with.

The importance of lifelong illness

As reported in his own works, Nietzsche's illness had an extreme importance in his life but not only because of the ailments that affected and tortured him, preventing him from continuing his intellectual activity; indeed, more appropriately, it was important because he felt that being ill made him more acutely aware of his own existence and also in his perception of the themes he explored throughout his works, themes that both skeptics and epigones of the philosopher from Röcken keep on questioning, but also respectable scholars and philosophers, among them, the French philosopher Gilles Deleuze.

In this respect, in 1886, in the Preface of the second edition of the *Gay Science* Nietzsche argues: "And as for sickness: are we not almost tempted to ask whether we could get along without it? Only great pain is the ultimate liberator of the spirit (...). Only great pain, the long, slow pain that takes its time—on which we are burned, as it were, with green wood—compels us philosophers to descend into our ultimate depths and to put aside all trust (...), things in which formerly we may have found our humanity. I doubt that such pain makes us "better"; but I know that it makes us more *profound*" (11).

This shows how he did not believe that he would have become the person he was without the occurrence of illness both as a sting and as a vision challenge. Being ill, living throughout the illness, one's vision becomes acute, the self becomes less naïve in understanding existence, and, at the same time turns more docile, less reactive. In the above Preface, the philosopher showed how a certain kind of limitation of physical performance, a certain state of denial of illness, gave life to all those philosophies which considered the Other world, that is, "a world behind the world", "a world beyond" as the real essence of what existed and, as such, the only place for human happiness; metaphysics itself would be a philosophy born from a misunderstanding of the body (12); such an explanation does not seem erroneous to us, even though today, paradoxically, scholars consider concepts such as the eternal return as a "misinterpretation of insanity", that is, nothing more than the subjective perception of an hallucination (13).

Nietzsche himself did not believe that he might reach the pinnacle of his thinking without the help of illness, without an illness seen at same time as riverbank and as a force capable of breaking the riverbank; whereas experts, on the other hand, consider illness as a pathological state which, through acute episodes or chronic ones, invalidate normal daily activities, and doing so, test their resistance.

In 1888, one year before Nietzsche physical and cognitive collapse and before the "insanity letters" he also wrote "This young boy is becoming pale and withered prematurely. His friends say: the reason for that condition is this or that disease. I say: the fact that he got sick, that he did not fight his illness was already the consequence of an impoverished life" (14); it is a sen-

tence dictated by an extreme mindfulness, which might become useful today too, by granting a subjective component to every illness: illness itself was already there waiting for him, either because of an hereditary disposition, a subjective conformation, accidental events in his life, or because of all these aspects; and as long as he managed to resist it, illness triggered some attacks, but then stopped; when the philosopher became not longer capable of shielding himself from it, illness overwhelmed him: consciously or unconsciously, Nietzsche surrendered; surrendering was not necessarily a *cupio dissolvi*; on the contrary, it represented more the signal of an abandonment to life and to what life may have planned for the individual. The so called impoverished life mentioned by Nietzsche might restore the lost prosperity thanks to the very illness. All this may sound devious and bizarre to the extent that one embraces the rationale of “health at all cost”, and it may be difficult to conceive a similar twist in today’s society of “wellbeing”.

Still, in the *Gay Science*, aphorism 120, Nietzsche affirms that we should walk away from the idea that there is health and illness which are the same for everyone; the concept of illness might depend on aims, needs and purposes that every individual intends to fulfill; therefore, what becomes illness for someone may be functional or favorable for another (15): it is surprising that similar words are not only extremely actual today but also vastly unheard by the medical community as a whole, obstinately fighting for an abstract and impersonal concept of “health”, which must be achieved independently from subjective needs; moreover, health must be also preserved in a preventive way, through invasive approaches or with the help of devices, instruments, tests and other forms of investigation potentially harmful and having the sole purpose of diagnosing at the earliest or for preventing the patient from getting worse, or to avoid recurrence, inevitably weakening the body itself.

The problem with distinguishing insanity and organic illness

Nietzsche’s death marked the beginning of a major debate aimed at defining whether he was insane or

not. The purpose of such a “diagnosis” was to discredit or validate his philosophy, considered inconvenient on many fronts.

It was inconvenient because of the Nazi tendencies - introduced by his sister Elisabeth Förster-Nietzsche and Peter Gast - appearing in some of his fragments; independently from that, it was inconvenient for the revolutionary ideas (not so much in regards to politics, but more so due to his ethical, theoretical and scientific vision of the world) that his philosophy supported; in the final analysis, the same effect is constantly observable even today since we are a long way from assimilating them.

Was this a philosophy originating from an individual affected by a degenerative illness of the right orbitofrontal cortex (8), or by an hereditary cerebral arteriopathy (9) or an hallucinatory philosophy born from a manic-depressive psychosis (13)?

Early on, Nietzsche’s sister became a supporter of the opposite faction, which considered Nietzsche philosophy the product of a totally sane mind (so much so that Nietzsche’s mental breakdown as well as his recovery and his successive paralysis were determined by just the abuse of chloral hydrate).

Was it a healthy mind with an “organic accident” or an organically sick mind since childhood? Or even, was it a mind experiencing psychotic delirium with pathological accidents added successively and not necessarily related to each other?

These are manichean and univocal positions which turn out to be extremely reductive, or worse, approximate; it is in fact impossible to reduce a thought system, especially one as wide and complex as Nietzsche’s, to a pathology or a psychotic episode.

Was Nietzsche’s case in the middle, a position resulting from different causes, where the claims of the body are not opposed to the claims of the mind and where a psychosis, be it caused by brain malfunction or by innate positioning towards the world-environment, does not reduce the validity of a thinking full of intuitions but also of lucid considerations on the development of society, science and ethics?

And, in the same way, might Nietzsche’s insanity, or to use the notion of the psychoanalyst Jacques Lacan, him belonging to the “psychotic order”, has always characterized him, not as a handicap but, on the

contrary, as an additional *quid*, a peculiarity allowing him the use of special glasses capable of seeing and predicting the dynamics of human nature in his time and in the future?

An individual structured that way, to whom access to the symbolic order was precluded during childhood (16) or, to say it differently, at the point of transition from babbling to proper articulation of words having a concrete meaning, could not have found a link in the confusion of words, setting himself up as a central pivot around which he made everyone rotate as if by virtue of a gravitational pull so that he would be thrown into the world of language without any fixed reference points (arbitrary or conventional) helping to distinguish significant and signification. Would a person structured in such a way have any *extra moenia* faculty of vision of the world of phantasmatic constructions?

Indeed, in Lacan clinical approach, an individual structured in such fashion could experience psychotic episodes only under certain conditions, but not necessarily and in Nietzsche case, we know that process was accelerated by concurrent physiological causes.

Why should anyone portray Nietzsche's philosophy as purely hallucinatory or purely healthy, and consider organic factors as the major causes of his breakdown in Turin, as well as the last ten years of his life when he endured a progressive paralysis?

Nietzsche was not a "normal" person. He was not normal like those who opposed him and would then feel free to brand him and his philosophy as extravagant, nor with respect of those who emulated him and who wanted his madness to be the incarnation of his philosophy or as the consequence of the philosophy itself, so acute and futuristic.

Once again, these positions appear simplistic. If we believe that Nietzsche was leaning toward insanity, even when it was still hidden, it is because we see the ripples caused by early manifestations, and we read about these in his works which is where he expressed his vision and control of life the most.

In fact, either he had always been insane, or he had never been and it was only a cognitive/metabolic misunderstanding.

Indeed, as Lacan wrote: "Nobody goes crazy by choice" (17), that is, a certain inscription/placement already existed to start with.

If here we want to support the psychotic inscription of the Röcken philosopher, we should do so very differently than Eva Cybulska: the bolder ideas in his works (God's death, the over-man and the eternal return) do not call into question an hallucinated position made of his intimate feelings and sufferings (13), which are extremely subjective and self-referential; on the contrary, according to our view, his position has broken the protective screens of the artificial and phantasmatic superstructure which allow people to stand on their feet, despite the fundamental insanity of such occurrence: as a matter of fact the occurrence is certainly not structured as a religion, science or morals get defined and, sometimes, imposed in Nietzsche's time; the existence of a fundamental chaos at the base of the matter is proved for example by the advances in quantum mechanics and the study of subatomic particles.

On the other hand, alignment with this position becomes proper when we want to argue against Nietzsche mental breakdown described as a mere organic accident, syphilis, a simple metabolic syndrome, a neoplasia or arteriopathy, or a mere genetic disease. All these accidents, taken as a single cause, would minimize and destroy the efforts spent throughout a life devoted to outline a philosophy that today is still considered in absolute terms as one of the most acute and unsurpassed, thanks also to its opponents.

As a whole, Nietzsche's work is characterized by a great lucidity and acuity towards the society and culture of his time; however, differently from Eva Cybulska, we do not accept that his most figurative ideas (God death, the Over Man and the Eternal Return) are hallucinatory phenomena, even if they seem to be more intuitions than full blown concepts developed and built over time; in the same way, we do not subscribe to the idea that the works where those concepts are introduced belong to poetry and not philosophy. The history of literature is full of philosophical poetry, and the same is true for the history of science which has a wealth of intuitions, which later evolved into important scientific theories.

There is little doubt today that the concepts mentioned above are not assimilated by our contemporaries, but it is also evident how the seeds of such concepts have grown in the direction of groundbreaking

scientific and philosophical research; moreover they appear to be in perfect harmony with thought models which are very distant from the Occidental one and this occurrence doesn't make them less authentic.

Moreover, even strictly looking at the philosophical field, it is obvious how "God Death" does not merely concern the religious field; instead, it revolves around beliefs that are at the foundation of classical science (the pre-quantum science) and that are becoming dimmer even if they have not reached common sense level; we consider obvious that the "Over Man" is not the founder of a purged race, devoted to violence (8), but a subjective approach which has paid its dues to a past dominated by guilt and shame, but has to be careful not to fall on the opposite side (the cancellation of ethics and modesty); finally, we retain obvious how the "Eternal Return" is not a simple temporal or cosmological conception, but rather firstly an ethical one. Misinterpreting all these instances, we might consider them as poetic-psychotic visions which would be irrelevant for the history of philosophy; on the other hand it might be possible to confront all these instances with Nietzsche's inability to interact with women or to face practical tasks in everyday life (18), as if the fact of having planned a future direction for humanity might go hand in hand with the behavior of a clever charmer.

In conclusion, we quote the description written by Franz Overbeck when, on January 8th, 1889 he came to visit his friend Friedrich after having himself gotten an "insanity letter", our last piece of evidence stating once more the extreme consistency between existence, life, philosophy and illness, so deeply weaved into the works of the German philosopher: "He finds him in a state (with bouts of ecstasy and euphoria) similar to the one that Nietzsche himself described in the first chapter of *The Birth of Tragedy*: «Singing and dancing, man expresses himself as a member of a higher community: he has forgotten how to walk and talk and is on the verge of flying up into the air as he dances» (19).

References

1. Pozzoli C. Nietzsche nei ricordi e nelle testimonianze dei contemporanei. Milano: BUR 1990; 125.
2. Förster-Nietzsche E. Die Krankheit Friedrich Nietzsches, Zukunft 8; 1900.
3. Förster-Nietzsche E. Die Zeit von Nietzsches Erkrankung bis zu seinem Tode. In: Cohn P. (Ed.) Um Nietzsches Untergang. Hannover: Morris; 1931.
4. Volz PD. Nietzsche im Labyrinth seiner Krankheit. Eine medizinisch-biographische Untersuchung. Würzburg: Königshausen & Neumann: 1990.
5. Maieron MA. On the hellebore trail an anthropological research into madness. *Med Histor* 2018; 2(1): 5-18.
6. Pozzoli C. Nietzsche nei ricordi e nelle testimonianze dei contemporanei. Milano: BUR 1990; 389.
7. Saks L. What Was the Cause of Nietzsche's Dementia? *J Med Biogr* 2003; 11(1): 47-54.
8. Milanese P.G. Il caso Nietzsche. *Conf Cephalal et Neurol* 2012; 21: 3.
9. Hemelsoet D. Hemelsoet K. Devreese D. The neurological illness of Friedrich Nietzsche. *Acta Neurol Belg* 2008; 108(1): 9-16.
10. Koszka C. Friedrich Nietzsche (1844-1900): A classical case of mitochondrial encephalomyopathy with lactic acidosis and stroke-like episodes (MELAS) syndrome. *J Med Biogr* 2009; 17 (3): 161-4.
11. Nietzsche F. *La gaia scienza e Idilli di Messina*. Milano: Adelphi 1965; 32.
12. Nietzsche F. *La gaia scienza e Idilli di Messina*. Milano: Adelphi 1965; 30.
13. Cybulska E.M. Were Nietzsche's Cardinal Ideas – Delusions? *IPJP* 2008; 8: 1-13.
14. Pozzoli C. Nietzsche nei ricordi e nelle testimonianze dei contemporanei. Milano: BUR 1990; 23.
15. Nietzsche F. *La gaia scienza e Idilli di Messina*. Milano: Adelphi 1965; 158-9.
16. Lacan J. Discorso sulla causalità psichica in: *Scritti*. Torino: Einaudi 1974.
17. Lacan J. Discorso sulla causalità psichica in: *Scritti*. Torino: Einaudi 1974; 170.
18. Verrecchia A. *La catastrofe di Nietzsche a Torino*. Torino: Einaudi 1978.
19. Overbeck F. *Erinnerungen an Friedrich Nietzsche*. Berlino: Neue Rundschau 1906; 17.

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1978-2018. The Basaglia Law forty years after

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Abstract. Forty years after the Law 180 gives the author an opportunity to speak about the changes brought about in psychiatry since 1978 and to assess psychiatry today, in its organisation, expertise, epistemological references, clinical expressions and operative methods in addition to its critical issues.

Key words: Law 180, Franco Basaglia, psychiatric renewal, reorganisation of Mental Health Services, sector psychiatry, community psychiatry, residential psychiatry

The Law 180, known as the Basaglia Law, is forty years old.

It is the law that sanctioned the closing of mental asylums, the conclusion of a period, defined by Edoardo Balduzzi as “the years of Italian psychiatry”, that go from 1964 to 1978 (1), in which the reform movement was developed and completely modified the prerequisites of care and assistance for persons with psychic disturbances that were put into practice in the years to come.

Alberta Basaglia, psychologist and vice president of the Basaglia Foundation, remembering her father in one of the numerous interviews granted on this occasion, underlined his great merit, besides the organizational aspects of psychiatry, was that of restoring dignity to those who had been marginalized and excluded.

Franco Basaglia who, in the Padua University Clinic where he had initially worked, was known as “the philosopher”, had his cultural roots in phenomenology and more specifically in the anthropophenomenology of Ludwig Binswanger (and in Italy that of Danilo Cagnello). They considered mental disturbances, apart from the health-illness antinomies, as aspects of human presence, creating the prerequisites for a radical change in the methods of their confrontation compared to the where and how that positivistic medicine, born at the end of the 18th century, had con-

fined them, and earlier still, as remembered by Michel Foucault, placed them as diseases of the soul, fruit of insane passions, in the category of vices (2).

Not only Binswanger however.

Other phenomenologists such as Edmund Husserl, with his epoché, Martin Heidegger between phenomenology and existentialism, Eugène Minkowski with his ideas of time, of Bergsonian derivation and lived time and Jean Paul Sartre with *Being and Nothingness*, had influenced his thoughts. His merit, however, lies not only in his original re-elaborations of philosophic conceptualizations, but also in having brought concreteness from a practical point of view to his ideas concerning his experiences above all in Gorizia and Trieste and his battle against the mental asylum which, during the Seventies of the last century together with MAI (the Anti Institutional Movement), had become the dominating theme of the reform movement expressed by official psychiatry and its associations.

This is perfectly summed up in the conclusion given in Wikipedia on his thoughts and way of conducting psychiatry

[...] keep listening and divest yourself of every certainty, [...] make a suspension, an epoché, of all the sclerotic categories, in order to let the patient have his say (3).

The Law 180 represented the conclusion of his battles, it was not, however, his law, even though he accepted to give it his name.

In parliamentary circles it was a preview of a law then under discussion in National Health Service institutions that also included psychiatry. This had been promoted by the psychiatrist Bruno Orsini, a Demo Christian M.P. to avoid holding a referendum proposed by the Radicals for the repeal of the 1904 law on mental hospitals that, if rejected, would have proved a disaster for the reform projects that would have been difficult to remediate. It was in fact a compromise between those (SIP – Italian Society of Psychiatry – and AMOPI – Association of Italian Psychiatric Hospital Doctors-) who intended to eliminate the psychiatric hospitals by setting upwards inside General hospitals and those (MAI – Anit-Institution Movement – Democratic Psychiatry) who retained even these were unnecessary (4).

The law, as far as the closure of asylums was concerned, coincided with the ideas of Basaglia. He retained, however, that placing psychiatry inside hospitals and the same National Health Service was somewhat mystifying, because it tended to reattribute psychiatric suffering to illness, in a naturalist and positivistic sense, negating the work accomplished to give it a social dimension, both in an anthropological and sociogenetic sense.

This has been expertly documented in *Conversations concerning the Law 180*, that Basaglia published in 1980 not long before his death (5).

The 180, however, although giving only very limited indications on psychiatric reorganization, brought to an end not only a period of certain treatment methods for persons with serious psychic disturbances but, compared to the 1904 Law, it completely modified the approach and herewith lies its revolutionary character.

In fact, the 1904 Law, for involuntary commitment, dealt primarily with the social problem of “dangerous to oneself and others” and “public scandal”. Hospitalization, temporary for the first thirty days, for the purpose of checking the mental disturbances, cause of behavioural disorders and their persistence, and the “definitive commitment” were not the responsibility of the patient’s psychiatrist but of a judge who gave authorization with a sentence issued in the Council

Chamber, which also involved loss of civil rights and registration in a special judicial register. The sentence could be modified only by another sentence and the problem of the treatment was secondary. It had become relevant for the progress in the therapies made for some disturbances above all from the Twenties onwards, but it only had an effect on legislation with the Law 431 in 1968 that allowed for voluntary hospitalization “for findings and treatment” without the legal effects that were in act for authorized admissions.

The 180 instead cancelled all the legislations set out in the 1904 Law and always considered the psychic disturbance as a problem of the person, while laying down certain principles of reference for the treatment.

The subject on the findings and the compulsory health treatments with ample guarantees on times and methods for the persons involved (six articles) was explained in greater detail.

Other matters concern hospital psychiatry, with the creation of *Psychiatric Services for Diagnosis and Treatment (SPDC)* in general hospitals which were equipped with a very limited number of beds, intended to manage only extremely critical situations, regarded as coordinated and integrated with territorial Psychiatric Services and Mental Hygiene that were, however only generically indicated. Competence for the organization of the entire sector, which up to then had come under the auspices of the Provinces, on the basis of the 1865 Law, made just after the Unification of Italy, was assigned to the Regions. The final articles refer, as mentioned, to the repeal of the 1904 Law, some articles of the Penal and Civil Code and the law on active and passive voting rights, indications on a transitory phase for patients in psychiatric hospitals and on the expertise of the psychiatrists and their various qualifications.

Apart from considerations on the law itself, speaking about the 180 forty years after its enactment signifies above all talking about how the change in psychiatry has taken place and what psychiatry is like today, not only its organisation, that is affected by several regional legislations, but also its skills, its doctrinal references, its clinical expressions and ways of working. It signifies speaking about those persistent criticisms and precariousness and how, in recent years, society has changed, in its culture, symbolic expressions, its reference values and how this has effected not only the

behaviour of persons but also the ways of expressing their conditions of malaise.

As far as the organisation of Psychiatric Services is concerned my point of reference is the Lombardy region and in particular the province of Varese.

It is, in a general sense, still that which was defined in the Eighties and Nineties and, as far as residential structures are concerned in the following decade too, with some important modifications due to the reorganization of the Regional Health Services which came into effect with the 1997 Law 31 and from the norms and guidelines of the long term regional planning that specifically concerned both territorial and residential psychiatry.

Monocentrism, represented by Varese's psychiatric hospital where territorial services had been adopted almost immediately after its opening in 1939, as the last of the psychiatric hospitals to be built in Italy, and considerably increased under the direction of Edoardo Balduzzi and later under Carlo Romerio, was, from 1981, taken over by the UOP (Psychiatric Operative Units). These were responsible for several USSLS (*Local Social-Health Units*), authorities that came into existence with the application of the Law 833/1978, instituted by the National Health Service.

Initially, the activation of the Hospital Services for Diagnosis and Treatment (SPDC) in the general hospitals expressly provided for by art. 6 in the Law 180, which still retained ties of dependence to the Psychiatric Hospital Management in its transitory phase where new admissions, however, had been blocked, concerned the hospitals in Varese and Busto Arsizio.

In 1981, roughly about the same period that the Psychiatric Operative Units (UOP) were put into practice, a third service was also activated, the Verbano Psychiatric Operative Unit, with Hospital Services for Diagnosis and Treatment (SPDC) in Cittiglio and subsequently, in 1996 UOPs in Gallarate and Saronno.

Every UOP had a Hospital Service and at least one CPS in each USSL under its jurisdiction. On the basis of regional laws, during the second half of the eighties, in Varese in 1986, the first residential structures came into being: the CRT (*Residential Centres for psychiatric therapies and rehabilitation*).

In the following decade, with the application of the 1992-93 ministerial decrees modifying the

833/1978, the Lombardy region under the 1997 regional law 31/1997 introduced, as previously mentioned, profound changes in the operational procedures of the entire health sector. These separated the programming and control, assigned to new institutions, the ASL (*Local Health Authorities*) with a wider territorial responsibility compared to the USSL, often coinciding with the provinces, from those providing specialist services, in which also included were those provided by the UOP, which came under the responsibility of the general hospitals (AO: *Azienda Ospedaliera -Hospital Authority*)

At the same time, the USSL were abolished, with the creation of the *Departments of Mental Health* (DSM) including one or more UOP and relationships between the ASL-DSM and DSM-UOP were defined.

The DSM is the organism that includes all the structures in any given territory and their job is to take charge, in terms of coordination and planning, of the care, assistance and safeguarding of mental health.

At the end of the nineties, in order to cope with the requirements derived from the definitive closure of the psychiatric hospitals (1999), that had retained a temporary role for patients who could not be discharged, without however the possibility of admitting new patients and those with chronic diseases, the *Residential Communities* came into being. These were structures managed directly by the Health Services or by private accredited facilities that the Region then decided to further differentiate, according to the purpose (mainly rehabilitation or assistance), the intensity (high or low) of the interventions necessary relating to the type of patients admitted, with differentiations concerning the organogram of the personnel, their working hours and also the payments to the hospital in relation to the length of hospitalization.

The Nineties also saw the arrival of *Day Centres*. These, too, were run by the Health Services or by private accredited facilities followed by the latest opened in 2009, the *Light Residency*, another form of residential care with both low protection and cost that provided solutions for individual patients or small groups, with only limited support from health professionals, to achieve greater autonomy. It should provide a bridge between the Communities and the recuperation of

complete autonomy but for some patients it can also be a long-term solution.

Recently, further modifications to the Lombardy legislation for improvements in function and cost/benefit ratio, have led to mergers of the ASL and AO and broadened the scope of the DSM.

From the mergers of the ASL of Varese and Como came the ATS Insubria (Insubrian Agency for the Safeguarding of Health, while the Varese AO has become ASST - Sette Laghi; Seven Lakes Social-Health) and includes the hospitals in Varese, Tradate, Luino, and Cuasso al Monte while the Mental Health Departments in the province have been reduced from three to two, and have acquired the responsibility for Ser.T. (Drug Addiction Service).

The Law 180, with its drastic reduction in beds, reserved for the management of critical situations has also considerably modified the way many pathologies are managed that in the past had the psychiatric hospital as a reference for both short term and long term care. Drug addiction alone, in that period, mainly due to alcoholism, amounted to 25% of total admissions and came under the auspices of the newly formed SerT (Drug Addiction Service). Psycho-organic pathologies, outcomes of ageing, dementias, in their various etiopathogenesis and some confusion and amnesia syndromes, which made up 23-24% of total admissions, were dealt with by other Health or Welfare Services (6).

Apart from competency on pathologies, the move to centralize assistance to the Psycho-Social Centres, leaving the hospital to deal with only extremely critical situations, also considerably modified the approach to the various conditions of psychic suffering. In addition to psychopharmacological therapies, individual or group psychological and psychosocial treatments have assumed increasing relevance and it has finally been possible to introduce a form of rehabilitation with the purpose of social reintegration.

The CPS, besides clinical activities, has also taken on a central role in integrated assistance. This was thanks to the multi-professionalism of the operational team, becoming part of a wide network of social assistance within the community, while broadening the scope of their activities, in collaboration with others (Public entities, associations, individuals) who are interested in programmes of prevention and initiatives

concerning the modification of cultural aspects and prejudices. These had been the causes of social exclusion and marginalization of which the mental hospital had been an emblematic expression that had affected and even now still affects persons with psychic disturbances.

I have given a broad description of this in various chapters of my previous publications (7).

Over the years psychiatry has however seen a marked change in the clinical outcomes that have remained within its competence and the onset, for a variety of reasons, of new pathologies.

The nosodromia of psychosis besides changes brought about by various pharmacological, psychological and social approaches has been considerably influenced, in cases that once would have been long-term hospitalization and institutionalisation, with the exception of critical situations, by management in out-patients' or day-care centres.

Many are the considerations that can be put forward concerning treatments in residential structures but these will be the subject of future analysis.

Over the years it has also been possible to ascertain the emergence of new clinical forms of psychic distress with a considerable increase, particularly among the young, in personality disorders, the result of changes that have taken place in society in recent years.

Above all changes have occurred in reference values, the concept and types of the family, the approach to sexuality, the relationship between children and parents often disturbed, adulterated or absent, the entrance age and ways of carrying out job activities, the age of reaching psychological and economic autonomy and also, in certain situations, changes determined by the migration of persons from other ethnic cultures. All of this has led to the appearance or accentuation of various forms of dependency not just on substances with easy suggestibility, but conditions of low self esteem and loneliness or vice-versa dangerous aggression, the search for affirmation or compensation often through abnormal methods and a rejection of rules, all conditions that facilitate the emergence of genetic or epigenetic fragility.

These phenomena have been particularly exacerbated in the last two decades but they had already begun to manifest themselves previously. In fact, during the Fifties, the World Health Organisation had, quite rightly, when redefining the concept of illness, that had

historically been interpreted preternatural and later naturalistic, underlined the importance of social cultural factors in its aetiology, specifying, as remembered by Gilberto Corbellini, that the processes can depend on genetic and epigenetic alterations but that these

operate within ever-changing contexts; therefore the same causes give rise to different clinical forms on the basis of the life experiences of each person affected. This would suggest that the concept of illness must take into consideration both evolutionary and functional factors and the burden of individual experience within a determined social-cultural context. (8)

In the second half of the last century, when compared to a previously long period, psychiatry had radically changed its epistemological references and its *modus operandi* even if it is true to say that this had begun before the 180, the law itself made many of these changes unavoidable.

The crisis in biological psychiatry and the problem of ethics for the care and assistance of persons with psychiatric disturbances was born, as previously mentioned, with the conceptualization of Ludwig Binswange and phenomenological philosophy (Husserl and Heidegger in particular) that permitted overcoming the exclusion that even Freud and Jaspers had maintained with regard to psychotics. The former due to retaining them unsuitable for the transfert, the latter because of his ideas of conceptualizations of incomprehensibility and not participation, genetic misunderstanding concerning deliriums, not participation for the supposed inability of psychotics to internalize the experiences of others.

Biological psychiatry that was itself, in many respects, a hypothesis devoid of significant scientific validations, was replaced by psychological psychiatry, or rather many kinds of psychological psychiatry with reference to meta-psychological hypotheses even though not scientific and, for this reason in fact, long rejected by official psychiatry that was anchored to the hypotheses which had as its reference the concept of disease expressed by Giambattista Morgagni.

The references were initially Freud, the psychoanalysis and its metapsychology, born at the end of '800

and the many other metapsychologies later developed inside and outside of this (Alfred Adler, Gustav Jung, Melania Klein, Heinz Hartmann and later Jacques Lacan, to name just a few of the most important authors and founders of schools of thought) (10). It was only after the mid 20th century that they were accepted into official psychiatry, even though it is only correct to remember previous experiences such as those of the American psychiatrist Henry Sullivan (in the Thirties and Forties) with his *The Interpersonal Theory of Psychiatry* and his attempts to extend forms of treatment inspired by psychoanalysis to schizophrenia and those of the French Paul C. Racamier and George Daumézou (in the Fifties) with their *Institutional Psychotherapy*.

In the second half of the twentieth century, however, other types of psychological psychiatry with reference to metapsychology came into being. These were founded on other aspects of mental activity, the principles of which were *Cognitivism* (Aaron Beck) and the *Relational-Systemic theory* (Gregory Bateson) and were often the doctrinal reference for activities emerging in the newly adopted facilities after the 180.

Also to be remembered is *Social Psychiatry* that came into being at the same time and which was not so much an alternative to other procedures but rather an integration and completion of them.

It may be said that its theory is independent of the causes of mental illness that can be social, psychological or biological

for persons with these disturbances, it is the environment of the community where they live that must become therapeutic so that they can find conditions of equilibrium and the possibility to recuperate and reintegrate into society. (11)

However, just when biological psychiatry, which all in all had not gone beyond the asylum and shock therapy, seemed to be completely unsuccessful, an event contrary to the evolutionary trend in new concepts and therapeutic practices suddenly brought it back to life. This event was the birth of psychopharmacology.

This created problems from an epistemological point of view, not so much for social psychiatry, but for psychological psychiatry and of compatibility and

coherence between psychotherapy and pharmacological therapy.

They were ideological problems and derived, for psychological psychiatry, from the conviction and alleged self-sufficiency of their theoretical approaches. This was the topic of debates and meetings that landed on the pages of the psychiatric section of the Medical-Surgical Encyclopaedias (Jean Guyotat and M. Marie-Cardin). (12)

The diverse positions taken went from an alleged incompatibility, to the acceptance of their synergy, with a yes or no separation of competence between the psychotherapist and the psychiatrist.

Psychopharmacology represented a considerable step forward in the treatment of psychosis. However, it also had the merit, due to the understanding of brain physiology, of furthering considerable development in the knowledge of neurotransmissions and of providing a relevant contribution to the development of neuroscience, which had become, after long-term neglect, one of the most advanced sectors of bio-medical research. The interest in this aspect of scientific research, which is by its nature multidisciplinary, involved, as far as mental activity is concerned, above all neuropsychology and philosophy, with Philosophy of Mind that attained its own autonomy both in research and teaching.

As for neuropsychology, which has become, thanks to new investigation techniques such as fMRI, PET and many others, in all respects, an experimental science, it has been able to achieve innovative results, not only on neurobiological correlations of cognitive processes (Elkonoon Goldberg) (13) but also on affectivity and decisional processes (Joseph Le Doux) (14), (Antonio Damasio) (15), even managing to render the study of consciousness an autonomous experimental science (Stanislas Dehaene) (16), something considered unthinkable until not long ago, for its non-reducible subjectivity.

Psychiatry, although involved in biological aspects under its jurisdiction, did not play a significant role in the development of neuroscience, maintaining a distant and sometimes suspicious position, closed in a *de facto* dualism. And that, as I have previously said,

for various reasons, that on the one hand, has its own prerequisites in the different ways of pro-

posing itself, quite rightly defended, when compared to other clinical disciplines, in the relationship to the sick, that favours inter-subjectivity rather than objectivity of the empiric sciences [and somatic medicine], and on the other hand because, after the divorce from neurology, which only came about fifty years ago, the prefix neuro- is frequently seen as a threat to one's own identity and autonomy and as a dangerous return to impositions that are too biological and reductionist. (17)

In effect, however, the enormous progress attained in neuroscience in the physiology of the brain, is opening up a new phase in the history of psychiatric doctrine.

After an extended biological period characterized by the equating of mental disturbances to somatic illnesses such as diseases of the brain and a second period during the Sixties of the last century, with the many types of psychological psychiatry born, in contrast to previous psychiatry, referring to the numerous forms of metapsychology previously mentioned, a third period is now emerging characterized by a newly-found non-divisive psychosomatic unity, which evaluates biological, psychological and social aspects, thereby giving them a scientific validation that the doctrine of the previous periods did not have or had only partially.

And this also provides confirmation concerning the mind-brain relationship, of the monistic hypothesis from which differs only slightly the latest dualism of Karl Popper and John Eccles (18) who with the acceptance of evolutionism and neo-emergentism recognizes the causal link between mental activity and neurobiological substrate, placing both in a naturalism with the same laws.

The effects of the Law 180 that most underline what it was and what it provoked in psychiatry, more than in specific indications on its organisation, lie in the fact that they sanctioned the end of an era and determined the beginning of something new and completely different.

The period of psychiatric renewal, which goes from 1963-64 to 1978, had seen two opposite schools of thought. One that was prevalent for about ten years which had as its reference the French experience of

Sector psychiatrists, considered the problem of eliminating the psychiatric hospital as a goal to be reached gradually and had even inspired a bill, the Balconi bill of 1965 (19) that had aroused great expectations but had in fact never materialised. The other, more political and revolutionary became dominant in 1972 onwards, backed by Basaglia and the MAI (Anti-Institutional Movement) that proposed as a single objective the closure of psychiatric hospitals, considered anachronistic, ethically unacceptable and anti-therapeutic, in spite of the changes brought about by the 1968 Law 431 (Mariotti Law) that had permitted voluntary admissions for medical examinations and treatment, abolished judicial registers, introduced by the Rocco code in 1930 and defined some standards for the organograms and organisation of psychiatric hospitals.

As ideological references, in their most radical expressions, it had the denial theories (Thomas Szasz) or in any case interpretations of mental disturbances that placed them more in an anthropological and sociological category than a medical one.

Both these schools of thought, however, were well aware of the ethical problem of the brutality of institutionalization, expressed by deportation, social exclusion, isolation and a life style that left little or no space for personal choices, naturalness and privacy.

Sector Psychiatry, born in France in the Forties with the conceptualisations of Lucien Bonnafé who, considering the internment of mental health patients as “primitive”, had proposed a welfare policy that would place an emphasis on the natural and social environment they had come from, which would favour their recovery. It was not, as some had thought, a merely organisational proposal but a bona fide ideology with the aim of eliminating the asylum.

Bonnafé's ideas had been put into practice in a pilot scheme carried out from 1954 in the XIII district by Philippe Paumelle, Serge Lebovici and René Diatkine and in 1960 Sector Psychiatry was made official in France with acts and directives of the Ministry of Health.

Its innovative significance is perfectly expressed in some keywords:

- *Territory* (or rather area or sector) to underline the shift of centrality in the care and assistance of persons suffering from psychiatric distur-

bances from the hospital to the territory and the competence of the team;

- *Multi-professional team* because the needs of the patients, multiple and complex and not only clinical, cannot be tackled with only a traditional doctor-patient relationship;
- *Taking charge* because these needs must not be just highlighted and analysed but managed directly and professionally;
- *Therapeutic continuity*, with a single hospital and territorial team to indicate the uniqueness of the therapeutic and care relationship, necessary for solving one of the most important problems of psychotic conditions, the difficulty of creating and maintaining meaningful relationships.

During those years there were various experiences of Sector Psychiatry or at least the start of territorial activity and among these the most important was that in Varese, which extended over the entire province. The promoter was Edoardo Balduzzi, during his direction of the psychiatric hospital from 1964 to 1968.

Because of his knowledge and rapport with French psychiatry and the “Sector” ideology he became, in those years, the guiding light.

Despite the friendship between Balduzzi and Basaglia, confrontations on the experiences that they had both encountered materialized in meetings in Varese and Gorizia, when in 1972 the climate changed and references to Sector were suddenly abandoned and experiences and renewal programmes, as they were not aimed at an immediate closure of the hospitals, were considered to be in collusion with the asylum.

History, in recounting these experiences in the decades to come has, generally speaking, has been none too kind.

Only in recent years has there been a reconsideration of that time as being, in fact, an experience that had anticipated that which is or would like to be psychiatry today: a psychiatry that in its relationship with society has built or is endeavouring to build, albeit with regional and area diversities, its new paradigms.

It may therefore be said that with the 180 Sector Psychiatry and Balduzzi both gained a victory. It was

in a different name, less technical but emotionally more captivating, *community psychiatry*. Some

wordings at that time found a more precise and accurate conceptualisation, other things have also changed. For example, better clarified was the role of psychiatry within the social framework with the evaluation of other subjects: the families, associations, single persons or groups in civil society, that operationally, in fact, often acquire greater relevance than the Health Services themselves. Better specified also was the concept of culture, in its values and symbolic expressions, positive and negative, for the effects and the relapses on distress and psychic disturbances. The concept of taking charge has been extended, although technically it still predominantly bears professional references, socially it should however be much broader. The roots of all this nevertheless lie in the keywords of those bygone years: *territory, multi-professional team, therapeutic continuity, taking charge*, and in those of phenomenological derivation of *relationships* and *intersubjectivity*. (20)

In perfect continuity with his previous experience during the Sixties and Seventies a further contribution made by Balduzzi to the renewal of psychiatry and in this case also to the implementation of the 180, was the proposal, in 1986, for the setting up of a working group in the Provincial Administration under the acronym of GLP (Psychiatric Working Group, later modified to an extended expression, Provincial Working Group for Mental Health).

The GLP, that two years ago completed thirty years of activity, is both unique and exemplary in Italy because it has signified a different way of practising psychiatry. It is a working group open to Health Service operators, family associations and volunteers and persons who for various reasons are interested in psychiatric renewal in which, without any hierarchical and operative constraints and without subtracting anything from the institutional competences and relations with the individual UOP interact with the territory, compare evaluations, suggestions, proposals and initiatives.

One of the problems that psychiatry had to face in its reorganisation after the 180 was that of finding the right connections in the territory for introducing itself into the network of various social and health agencies,

coming out of an isolation that had concerned not only the patients, and the ability to influence those complex prejudices and cultural aspects of society that had determined and determine even today stigma, exclusion and isolation.

In fact, the asylum besides being a physical place is also a mental category whose virtual walls are much more difficult to break down and this group has made a significant contribution to dealing with this problem.

The most important leverage in this was the alliance of the Health Services with family members and their associations, not only for reciprocal comprehension but for doing things together, comparing assessments, aims and programmes with interventions, outside the specific competences of the Health Services and institutional technical meetings, that have, however, proved to be invaluable for the results that they have achieved.

This alliance proved useful to the associations themselves, that thanks to the initiative of a Varese journalist, Lisetta Buzzi Reschini, founded the COPASaM (Provincial Coordination of Associations for Mental Health). This too was both unique and exemplary and it gave the family associations and volunteers the possibility of creating a partnership with the Institutions, otherwise impossible for separate associations.

It was, however, an important conquest for the Health Services as well and a highly effective way of influencing society and its culture.

Many were the initiatives put into effect that should be remembered: interventions in the schools and in public demonstrations, raising awareness in Government Bodies and public and private structures, activities for the patients themselves and the promotion and their participation first hand in formulating programmes and activities that concerned them. (21)

Present day psychiatry, all things considered, presents precarious and critical aspects above all evident, albeit with pros and cons, in the new residencies.

This is how Armocida summed up the situation a few years ago:

If unexpectedly, in the singular political and cultural atmosphere of 1978, the law came into force that suppressed psychiatric hospitals by substitut-

ing them with treatment of the patient in his own familiar and social environment, after thirty-five years the “credibility” in long-term care has returned. [...] If we take a look at where psychiatrists and patients are today we can realise that the manifestations of the revolution, together with the fantasies of those who were enlightened with the idea of being able to renounce places of “segregation”, no longer have the same voice as in the past. Perhaps psychiatrists have changed their ways and are no longer in the blaring positions that had led them forcibly to the Law 180. While asylums have now been dissolved, many comments are possible, but it must be recognised that the same outsourced assistance that worried psychiatrists in the past, knows moments of undeniable fortuity allowing a certain amount of flexibility in terms of healthcare solutions. (22)

The way in which the problem of chronic care has been tackled, for which these structures are destined, is in effect full of ambiguity in the way it has been evaluated and for the uncertainties and errors in how the solutions have been determined. The concept of chronicity, as far as psychosis is concerned, is the example of ambiguity because besides the clinical criteria all too often ideological prejudices are also expressed. Residency in psychiatric mental institutions was intended for the persistence of symptoms above all if these were expressed with behavioural disorders and the incorrect assumption that an ordered lifestyle away from family or pathogenic environments contributed to their improvement. The new residencies, on the other hand, are derived from a declared emphasis on the disability aspect and rehabilitation as its declared motive, failing to mention instead a negative prognostic judgement as far as recovery or precarious and difficult existential situations are concerned.

The problem of severely ill patients with persistent symptomatology applies not only to Italy. Even advanced legislation such as that in France in 2005 speaks about psychic handicap as equivalent to persistent chronicity and of Treatment Units as organisational solutions for difficult patients.

The region of Lombardy, as previously mentioned, had foreseen, as residential structures, first the CRT,

then Therapeutic Communities highly differentiated by type with a further form of low protective residency: light residency. This complex legislation in Lombardy would seem to be an optimal method for giving adequate and diverse solutions to the various needs of the users while also paying attention to the cost/benefit ratio. In reality, however, this has not been so. The criticisms that can be made are multiple and regard both the legal aspects and the management. To indicate just a few: Therapies conditioned by different types of communities on the basis of the intensity of the intervention and the conditions of the patient foresee a complete resetting and restarting instead of an indispensable continuity in the therapy in patients that already have difficulty establishing meaningful relationships; the time constraints penalizing the length of rehabilitation make it easier to fall into welfare categories; the lack of territorial restriction in the choice of the community, even though allowing in its activities interventions aimed at maintenance and a recovery of “ability”, makes it more difficult or even impossible to programme social inclusion, partial and gradual experiences of autonomy are in conflict with the regulations concerning the running of the Communities. Ample arguments can be made for each and every case.

This is the conclusion I had reached, speaking about this problem in one of my earlier publications:

In therapeutic communities the inadequate investigation into the problems connected to persistent chronicity of severe psychic patients, all too often collocate these persons in a dimension that is almost exclusively assistive, proposing many of the objectives that are characteristic of the asylum: marginalisation, exclusion, in many cases deportation, difficulties, obstacles and renunciation of projects leading to even partial recovery. The improved quality of life and the attention that most of these institutions reserve for restoring abilities, or at least for maintaining them, does not modify judgement, particularly if the assessment is prospective. The low turnover, the result of experiences that come about simply from the changeover from one community to another or for not renewing the programme already initiated, without having obtained results

from programmes and treatments carried out, also paves the way for other effects, already seen in the asylum or as a consequence of their closure without taking adequate account of the real needs of the patients: the progressive number of patients deposited in this area or on the contrary situations of abandonment. However, it is not fair to paint everyone with the same brush and it is necessary to evaluate situations that due to their initiatives are of a less negative prospective, [...] the consideration that may be made is that this is one aspect of the psychic health organisation that is already present to some extent and could later have even further regressive developments, surreptitiously proposing exactly what the 180 wanted to finally eliminate. (23)

This is a short excerpt from an article by Francesco Cro, psychiatrist and coordinator of the DSM in Viterbo, in the publication *Mente e Cervello* (Mind and Brain) (magazine associated to *Le Scienze*) in June 2014, that deals with the same subject from a more general point of view.

Closure of the asylums, but perhaps it is not enough. The Italian psychiatric legislation concerning the closure of the asylums represented an original experiment, viewed from abroad favourably or critically, but in any case with interest [...] however numerous residential structures still remain throughout the country, in which patients are accommodated in the long term and therefore the problem of chronicity and institutionalization remains unsolved [...] Simply abolishing the asylums by law is not sufficient, therefore, to tear the patients away from containment structures and reintroduce them into society. Research coordinated by Stefan Priebe, lecturer in social psychiatry at the London School of Medicine, has drawn attention to the risk of an increase in admittance to residential structures that is underway in six European countries that had, on the contrary, set up reform programmes to “deinstitutionalize” – Great Britain, Germany, Italy, Holland, Spain and Sweden. Italy and Holland. Holland, especially, had shown an increase

in places in [...] protected structures superior to the decrease in places in asylums, while the prison population, that often has to take in persons with psychic problems, has increased in all of these six countries. (24)

And this also has had objective confirmation in the province of Varese. (25) Problems however also exist in territorial psychiatry, even where it has been possible to evolve into *community psychiatry*, which represents the real aspect of innovation compared to the past.

Some are problems that exist not only in psychiatry but all branches of medicine, particularly in recent years. The excessive bureaucracy that concerns all facets of activity and therapeutic interventions, developed for control purposes, after dividing the organisation into Authorities that programme, authorize and quantify economically the health services and other Authorities that put them into practice in their institutions, has ended up privileging merely documentary formalities, taking up a considerable part of the operators' time (particularly those with responsibility), subtracting it from clinical activities. The reduction in health costs in certain sectors has often penalized staffing and reduced activity resources that in psychiatry have concerned above all rehabilitation.

And the effects of these two problems are summed together.

The other aspect, above all for psychiatry, concerns the number of beds in the SPDC. Those foreseen are roughly 1/10.000 inhabitants, in the province of Varese 75 for a population of approximately 850.000 inhabitants (data from 2015), slightly fewer than what there should be.

This sometimes makes admissions precarious with temporary recovery outside the area and, due to necessity, discharges are often hurried which only facilitates subsequent re-admissions.

The conclusions to be reached in judgement of the 180 and what has happened after its activation should therefore necessarily be noted. On the one hand its ideological and symbolic significance means that its relevance remains unchanged: it is a divide that marks a “before and after” and the ‘after’ has opened up completely new horizons, shifting the centrality of psychiatric intervention to the needs of the persons and re-

storing their dignity rather than, improperly, to that of society. On the other hand, due to later developments, that have seen delays, criticisms and diversity from area to area but have also had to come out of utopia and come to terms with the clinical reality, often not easy, with the evolving of scientific knowledge and the changes in society and its culture, we can say that it is a law where everyone has come out on top.

Basaglia and the Anti Institutional Movement (MAI) have gained, with the destruction of the asylum that as it was before will never surface again; Balduzzi, too, that with his Sector anticipated *community psychiatry* which is the concrete alternative to previous institutional solutions; psychiatry, also, as a discipline of medical-biological naturalism that neuroscience and psycho-pharmacology have validated with their scientific evidence and finally the asylum itself that at times is re-proposed disguised in other shapes and sizes.

The last words on this subject go to Armocida, resuming the previously mentioned text:

In a highly complex horizon, among so many differences, many of the past uncertainties remain and the opportunity cannot be missed for renewing the importance of some concepts of timeless value.

Psychiatrists follow their path like explorers who continually circumnavigate their destination, they get nearer, sense that they are close but caught between transformations and contradictions, understand all too well that the spaciousness of thought is often in contrast with the desperate straits of everyday clinical life [...] Following a natural evolution, many significant ideas of the past have lost importance in the interests, culture and professional life of psychiatrists, in repeatedly veering backwards and forwards that often, even in recent history, has led to correcting and modifying the objectives. We can but reflect and take awareness of this. (26)

References

- Balduzzi E. L'albero della cuccagna. 1964-1978. Gli anni della psichiatria italiana. Novara: Grafema s.r.l.; 2004.
- Foucault M. Storia della follia nell'età classica. Milano: Rizzoli; 1977.
- Voce Franco Basaglia, available from: https://it.wikipedia.org/wiki/Franco_Basaglia
- Armocida G. Società e assistenza psichiatrica. Aspetti della sua evoluzione nel '900. L'istituzionalizzazione, il suo superamento e la territorializzazione dei servizi. In: Maieron MA. (Ed.) Il matto dei tarocchi, Alice e il Piccolo Principe. La follia come diversità nella cultura e nella società. Milano-Udine: Mimesis; 2013.
- Omnis L, Lo Russo G. Dove va la psichiatria? Pareri a confronto su salute mentale e manicomi dopo la nuova legge. Milano: Feltrinelli; 1980.
- Maieron MA, Banfi F, Giacomini L. L'ospedalizzazione psichiatrica dal territorio della USSL 3. Considerazioni e raffronti tra i ricoveri in ospedale psichiatrico e nel servizio di diagnosi e cura dell'Ospedale di Circolo di Varese negli anni 70-71 e 80-81. Bollettino del Consiglio dei Sanitari dell'Ospedale Regionale di Varese 1982; 7-8: 23-36.
- Vender S. Società e assistenza psichiatrica. Aspetti della sua evoluzione nel '900. Malattia mentale e stigma. In: Maieron MA. Il matto dei tarocchi, Alice e il Piccolo Principe. La follia come diversità nella cultura e nella società. Milano-Udine: Mimesis; 2013: 125-41.
- Maieron MA, Armocida G. Storia, cronaca e personaggi della psichiatria varesina. Milano-Udine: Mimesis; 2015.
- Corbellini G. Malattia. In: Dizionario di Medicina, Treccani; 2010. Available from: http://www.treccani.it/enciclopedia/malattia-storia-delle-idee-di-malattia_%28Dizionario-di-Medicina%29/
- Babini VP. Liberi tutti. Manicomi e psichiatri in Italia. Una storia del Novecento. Bologna: Il Mulino; 2009: 178.
- Maieron MA. Pagine sparse di uno psichiatra. Milano-Udine: Mimesis; 2017.
- Guyotat J, Marie-Cardin M. Médicaments psychotropes et psychotérapies. Encyclopedie medico-chirurgicale; 1975.
- Goldberg E. La sinfonia del cervello. Milano: Salani; 2010.
- Le Doux J. Il cervello emotivo. Alle origini delle emozioni. Milano: Baldini e Castoldi; 2003.
- Damasio R. L'errore di Cartesio. Emozione, ragione e cervello. Milano: Adelphi; 1995.
- Dehaene S. Coscienza e cervello. Come i neuroni codificano il pensiero. Milano: Cortina; 2014.
- Maieron MA. C'era una volta...un re! Intorno alla mente tra neuroscienze, filosofia, arte e letteratura. Milano-Udine: Mimesis; 2012.
- Popper K, Eccles J. L'io e il suo cervello. Dialoghi aperti tra Popper ed Eccles. Roma: Armando; 1981.
- Maieron MA. L'esperienza del GLP. In: Maieron MA. Il matto dei tarocchi, Alice e il Piccolo Principe. La follia come diversità nella cultura e nella società. Milano-Udine: Mimesis; 2013: 173-93.
- Reschini LB. Le associazioni dei familiari. In: Maieron MA. Il matto dei tarocchi, Alice e il Piccolo Principe. La follia come diversità nella cultura e nella società. Milano-Udine: Mimesis; 2013: 156-67.

21. Iannella G, Cantarelli C. I gruppi di auto-aiuto. In Maieron MA. Il matto dei tarocchi, Alice e il Piccolo Principe. La follia come diversità nella cultura e nella società. Milano-Udine: Mimesis; 2013.
22. Maieron MA, Armocida G. Storia, cronaca e personaggi della psichiatria varesina. Milano-Udine: Mimesis; 2015: 211-53.
23. Cro F. Salute mentale: l'Italia e le altre. L'incontro sul territorio con il paziente è cruciale per ridurre il rischio di ricadute e favorire l'inserimento sociale. Ecco come sono

organizzati i servizi sanitari psichiatrici in Italia e nel resto d'Europa. *Mente e Cervello*; 2014; 114:75

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Bodies for science. The display of human statues for educational purposes

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Abstract. Every time von Hagens’ plastinated bodies are exposed, they cause polemics, controversies and an inevitable echo in the media. It is not clear whether what raises greater scandal and ethical doubts is the exposure of real bodies, corpses for anatomical demonstration, or the fact that the Body Worlds Exhibition attracts crowds of visitors, resulting in huge financial revenues. Contextualized within the history of medicine, if it were only the display of “prepared” corpses to be called into question, the issue should not cause outcry, as we are merely in the presence of the latest technique, plastination, in the long evolution of medical and anatomical teaching. Such statues, created in anatomical cabinets, were used in the past as a compendium for courses of anatomical studies. The bodies were prepared using complex techniques, treated with great care and postured as if they were “alive” in order to make them more understandable and effective for teaching. A related theme - with important ethical implications - is how these bodies were made available to anatomical institutes. In Britain there was the very interesting case of Jeremy Bentham (1748-1832), father of utilitarianism: he donated his body for research purposes and display. This philosopher was ahead of his time not only regarding the display of bodies for scientific purposes, but also the formula for the donation of bodies to science, now the only really viable solution for the use of the human body in educational and scientific settings.

Key words: medical education, human body exposition, anatomy

Introduction

Every time the plastinated bodies created by the German doctor Gunther von Hagens have been put on public display, since 1995, they have caused polemics, controversies and an inevitable echo in the media.

It is not clear whether what raises greater scandal and ethical doubts is the exposure of real bodies, corpses for anatomical demonstration, or the fact that the Body Worlds travelling exhibition attracts crowds of visitors – according to recent estimates more than 47 million people – making use of means of communication and advertising and earning huge commercial revenues, to become the most-visited exhibition in history.

Contextualized within the history of medicine, if it were only the display of “prepared” corpses to be called into question, the issue should not cause outcry,

as we are merely in the presence of the latest technique, plastination, in the long evolution of medical and anatomical teaching which, since the 17th century, has attempted to represent the “human machine” not only through tables and drawings, but also using natural and artificial models.

The von Hagens exhibition displays statues created from corpses using a technique invented in 1977, which substitutes blood and other natural fluids with polymer and silicone. The technique substitutes fluids and biological tissues with plastic substances in a series of steps, in order to create models that do not decompose (1).

First formaldehyde is injected into the body through the arteries; later water and soluble fats are melted away by immersing the body in an acetone bath; the substances are then substituted with resins and elastomers, such as silicon rubber and epoxy res-

in, through vacuum-forced impregnation, to then be polymerized by the action of gas, light or heat. This latter phase allows the statues to be placed into the desired pose, as well as obtaining elasticity and durability. Once the process is complete, the end result is anatomical statues frozen in the middle of everyday actions, such as running or dancing, with an overall effect that seems to nod in the direction of contemporary art exhibitions, combining and overlapping the feelings of unease and repulsion that the corpses may generate with feelings of wonder and curiosity towards the strange “object” one observes.

Body Worlds therefore purports to represent a great innovation in the field of contemporary scientific exhibitions, but perhaps it is not that at all, if we examine these statues in the context of the history of medicine and of traditional anatomical museums which the exhibition knowingly and explicitly references (2). In analysing the exhibition, from some points of view we might consider it to be more of a ‘revival’ than something truly original, though without a doubt it has the merit of drawing broader public attention to anatomy. Indeed, the most innovative aspect of Body Worlds, apart from the techniques used, is certainly linked to the methods of promotion, communication and marketing which, employed in a globalized world, have allowed interest in anatomy and the wonders of the human body (an interest that was probably never wholly dormant) to re-emerge. It attracts huge numbers of people, each no doubt with their own different motivations, in what is the largest-ever operation in medical/anatomical education for the broader public.

Medical anatomical museums, both university-based and otherwise, that are often closed or inaccessible, without adequate captions and explanatory texts, are at present unable to carry out this function.

Teaching models

Dissection was the first means by which the human body was investigated and displayed, including to laypeople. Exemplary cases of public dissections took place from the Middle Ages on, such as that conducted by Mondino de’ Liuzzi (1275-1326), or those held in the 16th century beginning with Andrea Vesalio (1514-1564). Just such a public demonstration was

admirably recorded on canvas by Rembrandt amid the light and shade of his *The Anatomoy Lesson of Doctor Nicolaes Tulp* (1632).

Alongside the dissections, however, means were sought by which to preserve bodies for scientific purposes, with a view to making the entire system of the living being both visible and durable. Every anatomical discovery was to be documented and if possible “fixed” from life to make it visible to future generations. The goal was, therefore, to make natural preparations so that the human body might be open to examination in a permanent manner. Such preparations necessarily went beyond mere skeletons, which by their very nature were easily preserved, to include whole human corpses, their skin and outer tissues removed to reveal their innermost secrets (3, 4).

The first to make the creation of natural human statues possible was the naturalist Jan Swammerdam (1637-1680), who first used arterial injections using a method that he published in 1672 in the compendium *Miraculum naturae, sive, Uteri muliebris fabrica* (5).

However it was Frederik Ruysch (1638-1731), a professor of anatomy in Amsterdam, who perfected the technique of injecting liquid wax. He was able to highlight the finest branchings of the circulatory system, creating the “mummies” made famous by Leopardi in his *Operette morali*. He created *tableaux* composed of human and animal remains. In these compositions, such as the *mountains of the vanities*, he artfully placed the skeletons of fetuses upon mountains made up of apparent mineral and vegetable conglomerates, which were in reality parts of arteries injected with wax that were made to seem like corals, with kidney and gallstones in place of rocks. The little fetuses were in poses and attitudes which recalled the theatrical spirit and sense of “wonder” of the 17th century (6). It was only natural that the taste for *Vanitas* themes, common in Dutch still lifes of the time, should be reflected in the compositions of Ruysch’s anatomical collection. The fetuses looked animated, and held evocative objects in their hands, such as a sickle, a pearl necklace, or a handkerchief to cry into (in reality made of human tissue). This represented the *miseria hominum* in the classic iconographies of the *memento mori*, where skulls and precious objects are depicted side by side to symbolize the fleeting nature of the mundane.

This display technique, which was meant to make a naturally macabre subject more pleasing, combines coreographic intent with explicit pedagogical and moralistic function, becoming a benchmark for later anatomical museums.

The true turning point towards new collections for teaching purposes was the collections of the Hunter brothers, William (1718-1782) and John (1728-1793). They prepared human corpses using paints, resins, waxes and mercury and began gathering collection that would be useful for their teaching activity. Together they created two important private collections, later to be bought respectively by the University of Glasgow and the Royal College of Surgeons.

Inspired by the Hunter collections, one of the greatest creators of anatomical preparations of all time created his own collection: Honoré Fragonard (1732-1799), cousin of the painter Jean-Honoré Fragonard, surgeon and professor first at the veterinary school of Alfort and later at the veterinary school of Paris. He created thousands of anatomical preparations, including the statues that were to become famous as *les écorchés* (lit. ‘the flayed’). Made for teaching purposes for the veterinary school of Alfort – under the direction of Claude Bourgelat – the statues known as the “Man with a Mandible” and the “Horseman of the Apocalypse” betray their creator’s ambition to be considered also as works of art. When he came into conflict with Bourgelat, Fragonard was dismissed from the school at Alfort and began to work privately as a creator of anatomical preparations, crafting works for many existing cabinets. He was able to make a small fortune, finding a rich market for his works among collectors of “worldly curiosities”. The school at Alfort fell into decline during the revolutionary period, but Fragonard sought to promote his dream of creating a national school of anatomy in line with his enlightenment convictions, which he expressed in a 1792 report to the legislative assembly. This report, in the context of an organisational project for public education laid out by Condorcet, proposed the creation of “a cabinet in which all the wise men of Europe may find all the anatomical disciplines, be they human or veterinary, in the highest degree of perfection possible, in order to advance such discoveries as are useful to our suffering human kind, and with which national professors may

guide their pupils in the study of the bodies of living beings” (7). In his intentions, his expertise in this field would therefore have been useful for the good of the Nation, although he did not disdain to put his artistic human statues to far more commercial ends.

Antonio Scarpa (1752-1832) visited William Hunter, in order to perfect his mercury injections technique, which he brought to full fruition in Pavia in an anatomical museum almost entirely made up of natural preparations, with human statues of admirable complexity and elegance, with the sole and exclusive end of improving the effectiveness of his teaching activities (Fig. 1).

The museum of Pavia, first begun by Giacomo Rezia upon the request of Pietro Moscati, came to completion with the arrival as Chair of Anatomy of Scarpa, who immediately made one of the goals of his tenure the desire to carry out practical teaching activity that should not be limited to dissection alone, but should include the creation of anatomical preparations.

His interest in the creation of the most complete anatomical collection possible was immediately evi-



Figure 1. Angiological anatomical statues (18th century), Anatomical Museum of the University of Pavia.

dent: his inaugural address as the Chair of Anatomy, *On the necessity of perfecting preparation methods* (8), left no doubt as to the matter.

In this oration he illustrated his teaching methods, which were no longer to be centred around frontal instruction, but rather around a long series of anatomical demonstrations aimed at illustrating the topographical relations between tissues and organs, with particular regard to physiology and an introduction to surgery. The students were to recreate the most important preparations in the dissection rooms, with a view to acquiring objective cognition based on experience.

Going into detail concerning the methods used for creating individual preparations, he gave particular attention to the representation of the circulatory system, mentioning Ruysch and Albino's beautiful preparations, but criticising them because in his opinion they were made more to elegantly adorn cabinets than to contribute new scientific knowledge.

He also criticised some of the preparation methods of the time, abhorring as "utterly flawed" the habit of creating artery (and also nerve) trees removed from the body and laid out on boards. He instead proposed a "more advantageous and more perfect" method of making them useful for teaching purposes, which consisted of separating first muscles and then viscera from the vessels, preparing them separately, and then putting the injected vessels back in place "in their natural line of flow, allowing the ordinary bone structure to be of support to them" (8). He therefore essentially blazed a trail toward the creation, for his cabinet, of whole angiological statues, which were soon to be created. The statues dating back to the time of Scarpa that are still conserved today at the Anatomical Museum of Pavia – in the Institute of Human Anatomy – are included in the Angiology section with the following caption: "Whole dry corpses, injected and prepared (statues)" (9). The didactic intent was to follow the arterial or venous tree in all of its principal branches throughout a whole body.

These statues, as is the case of all the preparations present in the Museum, were to serve as compendiums for the teaching of anatomy, not only because they were carefully observed during the theory lessons, but also because creating such preparations was a useful exercise for future doctors and surgeons, in line with

the indications of the Study and Discipline Plan of the University of Pavia.

The preparations therefore had a two-fold didactic function: on the one hand they helped train the hands of surgeons and make them steady in the creation of preparations, and make them familiar with the inside of the human body and all of its vital systems. On the other hand, the best preparations might be put on display in the Museum, becoming in turn tangible benchmark models that students and, occasionally, the broader public might consult. Occasional openings for students and for the public had an important pedagogical role, leading to contact with a broader public and progress in medical science, and helping to rid the population of superstitions, charlatans and faith-healers (10).

Anatomical preparations and statues filled Italian and European anatomical cabinets from the 18th century onwards, at first often as a result of private initiative, but ever more frequently, from the turn of the 19th century onwards, they came to be a fundamental part of the educational policies of governments and academic institutions, who saw museums as places in which culture was to be put on display and where Enlightenment and, later, Positivist ideas were to be showcased.

Other Italian museums, apart from those of Pavia, feature anatomical statues, above all in the Angiology sections, as is the case of the Anatomical Museum of Pisa, founded in 1832 by Tommaso Biancini, where the angiological statues for the demonstration of the circulation of blood vessels are conserved (11). In the Anatomical Museum of Naples, where the collection of dry preparations includes 417 pieces, two desiccated bodies with injected vascular trees are on display. The first is seated upon a wooden pedestal in a classic statuary pose, while the second is standing and displays the whole, interwoven complexity of the blood vessels, injected with two differently coloured substances in order to differentiate between arteries and veins.

Using art to change meaning

As previously mentioned, the bodies were not only prepared using complex and jealously guarded techniques, but continued to be placed in "animated" poses, remaining within the tradition started by Ruysch, in order to make them more understandable and effective

from the teaching point of view. The poses portraying wonder, melancholy, or inspired by celebrated works of art were intended to produce a change in meaning, transforming “macabre remains” into objects that were useful to knowledge and worthy of display.

For Scarpa and his contemporaries the desire was to achieve a certain elegance, making the subject “speak”, with the intention, perhaps, of conferring upon it the life it could no longer have. To achieve this result the emotions such as wonder and sadness were attributed to the statues, together with detailed study of artistic poses, making highly cultured reference to the works of Michelangelo, Durer, or Borromini.

Anatomists willingly crossed over in this way into the field of art, and indeed considered themselves artists. Often, in fact, they were also connoisseurs of the Fine Arts. Antonio Scarpa, for example, was the owner of a rich collection of paintings, which were put up for auction upon his death, including works by Mantegna, Perugino and Sodoma (12). William Hunter, too, was a passionate collector of the visual arts. It was only natural, therefore, that in order to make corpses less unpleasant and more presentable, inspiration should be taken from both classical and contemporary art.

The stated desire was that of making each preparation “instructive and elegant”. Where elegance is the fundamental means by which to achieve the end of teaching. In order to illustrate musculature it is certainly better to set a figure in a pose of movement, rather than leave it inert. The pedagogical goal was indeed to reveal the secrets of the living body, rather than investigate or display the dead body.

The concept of elegance referred to a human anatomical preparation may seem to be an oxymoron, but it was in keeping with the spirit of the times, and the enthusiasm that was palpable in the anatomical cabinets, where, from one day to the next, one could easily be involved in sensational new discoveries, which could then be “fixed” in an anatomical preparation. There was the desire to highlight the worth of the difficult techniques and challenging works of anatomists, able to conserve in the most natural possible semblances that which would otherwise soon have been lost. It was all thanks to the expertise, the sensitivity and the culture of the person creating the preparation that this change in meaning could be achieved, transforming “macabre remains” into

objects that were useful to knowledge and worthy of display. The same manner of elegance and artistic references was certainly present also in the development of artificial preparations, in the anatomical models created by the Florentine and Bolognese wax modellers of the 18th and 19th centuries, but in their case the connection was, perhaps, more immediate, because it was art that was offering its services up to science and not science imitating art. For this reason the celebrated anatomical statues of the La Specola laboratory, or those by the Manzolini husband and wife team of Bologna, or by Louis Th. Auzoux, were highly successful, but could never perform the same dual didactic function.

The technical creation of the statues

In order to create natural-looking human statues, “flayed figures”, long and complex artificial processes were necessary. In the cabinets, the anatomists and dissectors were able to create, using techniques that were often kept secret, arterial, venous, neurological and myological statues. Each of the parts were separately prepared and then the whole was reassemble in the most natural way possible, around the skeleton which was in turn adequately prepared.

During the 18th century articles and indeed manuals began to circulate that illustrated the main aspects of these techniques, including the *Antropotomie* by Jean-Joseph Sue and the work of the same title by Pierre Tarin, as well as the articles on the subject by Vicq D’Azir and by Alexander Monro (13). In Italy we find Angelo Dubini’s *Trattato di Antropotomia* (14) which, though a relatively late work, allows us to better understand the techniques and activities of Italian anatomical cabinets in the 18th and 19th centuries, with its reliable, precise content and the breadth of its bibliographical references. In this volume, detailed descriptions of the phases of creations of “arterial statues” can be found. This operation was complex because “it is easily seen how much care and attention is required from dissectors to create a statue in which many objects must be prepared in no longer than eight to ten days after being placed in the conserving solution”, both for “venous statues” and “neurological statues” (14).

Statues were, in any case, relatively rare in museums. The preferred option was the anatomical prepara-

tion, both dry and in liquid, of specific single organs. Statues, given their greater size and complexity, were more difficult to conserve, and always caused more problems for their creators, who were often accused of nefarious activities. These are among the reasons why most have now been lost. An emblematic case is, however, that of England where statues both human and artificial (mostly in wax) were destroyed in Victorian times, because they were considered scandalous. In the 19th century, anatomical demonstrations were ever more focused on the conservation of body parts in liquid, a technique which allowed the preparation to remain more natural. The fame and importance of anatomical museums diminished hand in hand with progress in the fields of photography and radiography, and all but disappeared around the turn of the 20th century, leading to entire collections being all but forgotten.

In 1886, August Wilhelm von Hofmann (1818-1892) discovered formaldehyde, which was soon introduced as the liquid of choice for the conservation of body parts in liquid in anatomical cabinets and institutes. In the 20th century it was to become one of the basic elements of plastination, the technique that has brought anatomical displays back into the limelight through dry-preserved human statues.

Plastination for the teaching and science communication

The Body Worlds exhibition fits perfectly into the historical development briefly outlined in the present article, which made use of corpses and of “transformed” human bodies.

Von Hagens is familiar with the history of anatomy, and the history of anatomical preparations and their creators and, through the continual and insistent use of citations and references to this rich and complex tradition, he willingly places himself within that same history, continuing its development and bringing it to a level of technical perfection hitherto unknown.

The poses and attitudes of von Hagens’ plastinated statues, which are more extreme, contemporary, and linked to modern everyday life – such as the poker players, or the dancing girl or the horse-rider on his horse – can therefore be wholly placed within the tradition of the “pose”, used as a tool for the aesthetic

acceptance of human remains with the intention to achieve didactic goals, aimed however at a far broader public, certainly made up for the most part of laypeople, but far more knowledgeable than the people who visited the exhibitions of the 18th and 19th century.

Furthermore, the exhibition has a higher educational intent, that is not limited to simple awareness of the human body but, as expressed in the presentation: “In addition to organ functions, common diseases are described in an easily understood manner by comparing healthy and affected organs. They show the long-term impact of diseases and addictions, such as tobacco or alcohol consumption, and demonstrate the mechanics of artificial knee and hip joints” (15).

Before hosting the exhibition in Los Angeles, in 2004/5, the California Science Center requested an ethical evaluation, supported by a report made by an external consultant of international reputation.

The conclusions were the following: “The consensus of the Ethics Advisory Committee was that the exhibit has considerable educational value [...] What makes the exhibit so compelling (real bodies in everyday poses) is also what makes it most controversial. Without those very features, the exhibit would not be such a powerful educational experience [...] The plastinates are displayed in the context of science, health and medical education, and create an atmosphere of respect” (16). The report was updated in 2016/7 (17).

The exhibition, regardless of the didactic and pedagogical messages it is intended to transmit, leads to noteworthy ethical questions (18) every time; questions which are themselves part of the history of medicine and anatomy. It is often the way in which the bodies to be made into statues are acquired that is called into question. Von Hagens has been accused – though without any supporting evidence – of using the bodies of Chinese death row convicts in order to create his works. In reality the Institute of Plastination has access to hundreds of bodies that are daily donated for the purposes of plastination, and therefore has no need to procure bodies through other, illicit means. The present article is not the appropriate context in which to go into greater detail concerning this issue, which has important ethical implications, but it is necessary to at least mention it. The diffidence and scepticism on the subject are not entirely without reason, because

at least until the 18th century the bodies of outcasts, criminals condemned to death or even bodies stolen by grave-robbers were indeed used for dissections. With the Enlightenment, in Italy and France, under the guidance of enlightened sovereigns, doctors were able to obtain the bodies they felt were necessary for their work directly from hospitals, with a view to the benefit their work would bring to the greater community and to the cause of public health.

In Great Britain, however, which up until the early 19th century had no laws regarding this type of activity, the terrible case of Burke and Hare occurred (brought to the silver screen by John Landis in the film *Burke & Hare*), in which the West Port murderers provided anatomists with bodies for payment. The case caused a terrible scandal for the British anatomical schools and forced the government to urgently pass an *ad hoc* law, the Anatomy Act.

In this context we find the case of Jeremy Bentham (1748-1832), the founder of modern utilitarianism, who donated his body to his friend, Thomas Southwood Smith, doctor and author of *The Use of the Dead for the Living* (1824), to support the benefits to research of corpses in order to achieve progress in treatment for the living. The body of Bentham was publicly dissected, just before the Anatomy Act of 1832 was passed, and was later put on display at the University College of London (19). With this action the British philosopher proved ahead of his time, not only regarding the display of bodies for scientific purposes, but also the formula for the donation of bodies to science.

The donation of bodies for educational and research purposes, as a voluntary act on the part of the donor, seems to be the only really viable solution for any form of medical anatomical display that might be created today.

References

- Hagens VG. Body Worlds: The Original Exhibition of Real Human Bodies. Nachdruck: Arts & Sciences; 2008.
- Licata M, Gorini I, Iorio S. An osteological museum inside the varesse medical school? A proposal from the medical, anthropological and paleopathological point of view. *Acta Biomed* 2018; 88(4): 510-11.
- Monza F, Licata M. Anatomical Preparations in Museums A Special Category Of Cultural Heritage. *Med Secoli* 2015; 27(2): 615-28.
- Monza F, Badino P, Licata M. Johann Gottlieb Walter (1734-1818) and the technical preparation of bones in an anatomical cabinet in the late eighteenth and nineteenth century. *Acta Med Hist Adriat* 2017; 15(2): 253-60.
- Swammerdam J. *Miraculum naturae, sive, Uteri muliebris fabrica*, Lugduni Batavorum, apud Severinum Mhatthaei. Leiden: Publisher Leiden; 1672.
- Ruyschii F. *Thesaurus Anatomicus Primus*, Amstelodami, apud Janssonio Waesbergios, MDCCXXXIX. 1721.
- Degueurce C. Honoré Fragonard et ses écorchés. *Un anatomiste au Siècle des lumières*. Paris; 2010 pp 147-50.
- Scarpa A. *Opere del Cav. Antonio Scarpa*, prima edizione completa in cinque parti. Tip. Della Speranza; 1838: 537-53.
- Zoja G. *Il Gabinetto di Anatomia Umana*. Pavia: Università di Pavia; 1882: 23-4.
- Carli A. Il valore educativo e la rilevanza formativa dei preparati anatomici tra XVIII e XX secolo. *Alcuni brevi spunti*. *Riv Sto Med* 2010; 1(2):1-10.
- Marinozzi S, Gazzaniga V, Iorio S. The Earliest Blood Transfusions in 17th-Century in Italy (1667-1668). *Transfus Med Rev* 2018; 32 (1): 1-5.
- Momesso S. *La collezione di Antonio Scarpa*. Padua: Edizioni prioritarie; 2007.
- Sue JJ. *Antropotomie ou l'art du disséquer, d'embaumer et de conserver les parties du corps humain, &c., 2° edition revue et considérablement augmentée*. Paris: Cavellier; 1765.
- Dubini A. *Trattato di Antropotomia o dell'arte di eseguire e conservare in cera le preparazioni anatomiche del dottore Angelo Dubini*. Milano: Tipografia di P.A. Molina; 1837.
- Von Hagens G. *Body Worlds: The Original Exhibition of Real Human Bodies*, <https://bodyworlds.com/about/philosophy/>
- California Science Center, *Body Worlds: An Anatomical Exhibition of Real Human Bodies*. Summary of Ethical Review, 2009. https://koerperwelten.de/wp-content/uploads/2017/09/EthicReport_CSC_E_190110.pdf
- California Science Center; *Gunther von Hagens' Body Worlds: Pulse* Summary of Ethical Review Update 2016/2017 <https://bodyworlds.com/wp-content/uploads/2018/04/EthicsReport-CSC-update-2017.pdf>
- Monza F, Licata M. Ethical issues in paleopathological and anthropological research experiences. *Acta Biomed*; 2017; 88(3): 315-8.
- Cassman C, Odergaard N, Powell J. *Human Remains. Guide for Museums and Academic Institutions*. Lanham: Altamira Press; 2008: 262-3.

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The story of a vitamin for bone health that upgraded to hormone for systemic good health

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Abstract. The discovery of Vitamin D is a multi-step history started in 1650 and culminated in 1963 with the determination of its chemical structure. The diffusion of rickets in North Europe and North America was the first reason for experimental studies. Nevertheless, in the last decades new potential actions have been revealed. Besides bone and intestine, the Vitamin D receptors have been demonstrated in different organs such as the brain, prostate, breast, colon, immune system cells, smooth muscle and heart. Not totally fulfilling the criteria of a vitamin, Vitamin D is actually considered a pleiotropic hormone with endocrine and paracrine actions. The current evidences support the role of Vitamin D in skeletal health and suggest that the treatment of Vitamin D deficiency should be desirable to reduce the risk of chronic health diseases.

Key words: Vitamin D, Vitamin D deficiency, bones, metabolic disease, health benefits

Vitamin D: general features

Vitamin D is likely to be one of the oldest existing hormones on the Earth (1). Indeed, Vitamin D photosynthesis has been demonstrated in fossils existing 750 millions years ago (1, 2). In normal physiological condition the activation of Vitamin D is a multistep pathway. All mammals can generate adequate Vitamin D levels through the sunlight activation of 7-dehydrocholesterol in the skin, followed by two hydroxylations in liver (1,25(OH)₂Vitamin D or cholecalciferol) and kidney (calcitriol). Events modifying Ultraviolet B (UVB) wave exposure (e.g. skin hyperpigmentation, sunscreen, zenith angle of the sun) may impair the photosynthesis of pre-Vitamin D (1). As a consequence, Vitamin D deficiency is “epidemic” in most adults, who are not exposed to adequate amount of sunlight (3, 4).

The discovery of the fourth Vitamin: the “Antirachitic Factor”

The word “rickets” first appeared in 1634 when the disease figured in the “Annual Bill of Mortality” of London City (5). In a book published in 1650, Francis Glisson provided the most detailed description of the disease, responsible of bone deformation and fractures in infants and children (5). The raising number of cases in North Europe and America during the Industrial Revolution supported intensive speculations on its pathogenesis and treatment (2).

It was just in 1918-19 that Mellanby conducted conclusive experiments on the role of diet in the etiology and treatment of rickets (6, 7) (Figure 1). He tested 4 diets in a group of puppies, discovering that just rich in fat-soluble Vitamin A food (cod-liver oil, butter, and whole milk) could prevent rickets (6). In

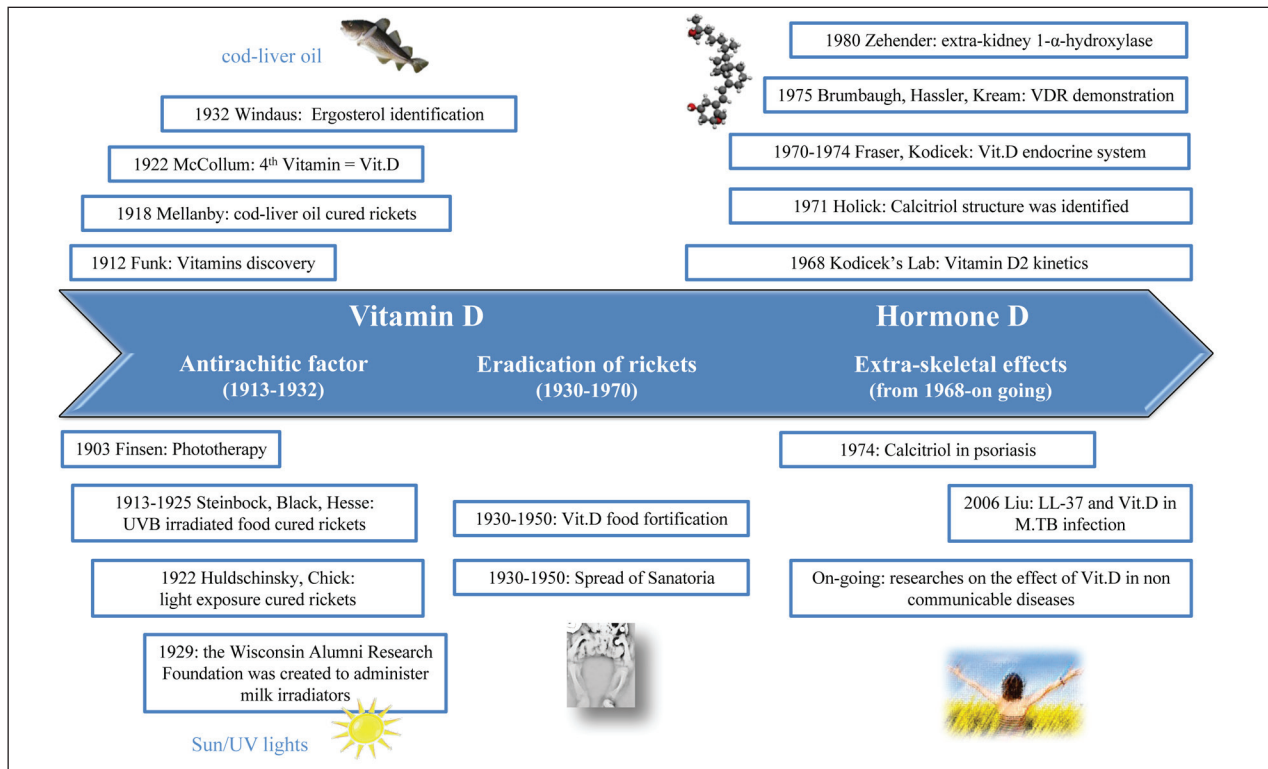


Figure 1. Historical discoveries about Vitamin D, related both to its role in treating rickets and in general health. The diagram is divided in three parts: 1) discovery of a way to prevent and cure rickets, 2) eradication of rickets through food fortification and sun exposure, 3) paracrine/autocrine effects of Vitamin D. M.TB = *Mycobacterium tuberculosis*.

1922 McCollum discerned the real “antirachitic factor”, proving that the inclusion of cod-liver oil in diet could favor bone growth even after denaturalization of Vitamin A (8). McCollum concluded the “antirachitic substance” was distinct from fat-soluble Vitamin A and that its “specific property was to regulate the metabolism of the bones” (8). In the meanwhile, awareness rose on the health benefits of light exposure. It was largely observed that children grew up along the European coasts had healthier skeletal structure than children in towns (2, 3).

Chick and Huldshinsky in 1919 independently demonstrated that rickets could be prevented by lights exposure. This intuition supported the application of Finsen chemical light lamp to treat rickets (2). Accordingly, Steinbock and Blant in 1925 cured rickets irradiating food and recommended food irradiation to enhance the “antirachitic effect” (9). It happens a few years later, in 1928, that the Nobel Prize Windaus identified a plant steroid from ergot able to cure rickets

when irradiated (2) (Figure 1). According to Windaus the steroid isolated from plants was similar to ergosterol isolated in animals (2). The 7-dehydrocholesterol later isolated from the skin, could be transformed in a vitamin by irradiation (10). Since the purified ergosterol was the fourth vitamin discovered, it was called “Vitamin D” (11, 12, 13). The chemical identification of Vitamin D precursor in the skin confirmed the hypothesis of epidermal synthesis (14). Despite these discoveries, rickets cases were increasing. As a result of the long time spent in factories, workers’ exposure to sunlight remained poor. Nevertheless, the use of cod-liver oil was still inadequate (2). From 1930 Phototherapy Spas (Sanatoria) become very popular in Europe and North America (2). Concomitantly, US Government imposed the fortification of food with Vitamin D (initially bread and milk and later also beer) managing to eradicate rickets (2). In the 50s, food fortification was forbidden because of the uncontrolled amount of Vitamin D in milk (2, 5).

Vitamin D and bone metabolism

In 1920 Nicolaysen observed a better absorption of calcium in animals on low-calcium-diet and postulated the existence of an “endogenous factor” able to regulate intestinal calcium absorption (2). Administering known doses of radiolabeled Vitamin D₂, Kodicek provided a better description of the process (15). In 1971, De Luca identified the first active metabolite (1,25(OH)₂Vitamin D₃ or calcitriol) (Figure 2). Interestingly, he found that anephritic animals were unable to produce active Vitamin D metabolites. Some years later, Holick definitely demonstrated that the final activation of Vitamin D took place in the proximal convolute tubule (2). The metabolizing enzyme was discovered to be a 1- α -hydroxylase (CYP27B1) by three different groups (3, 15-19).

Between 1969-1984 it was discovered that most of Vitamin D actions were mediated by the nuclear

Vitamin D Receptor (VDR), whose crystal structure has been recently identified, acting as a ligand-activated transcription factor (2, 20-24).

Boyle and De Luca demonstrated that a low calcium-diet enhances the synthesis of Vitamin D₃, raising serum levels (16). When VDRs were discovered in parathyroid gland, it became clear that Vitamin D₃ could suppress the secretion of Parathyroid hormone (PTH) (16, 25). Vitamin D analogs were formulated for commercialization (16).

Garabedian showed the existence of a feedback mechanism involving serum calcium, Vitamin D and PTH. This system corresponded to Nicolaysen’s endogenous factor (2, 16). Decrease in serum calcium rapidly induced the activation of Vitamin D through PTH secretion, whereas high calcium levels suppressed the conversion of pre-Vitamin D (1, 2). Calcitriol in turn promoted intestinal and renal calcium absorption, enhancing bone resorption and calcium

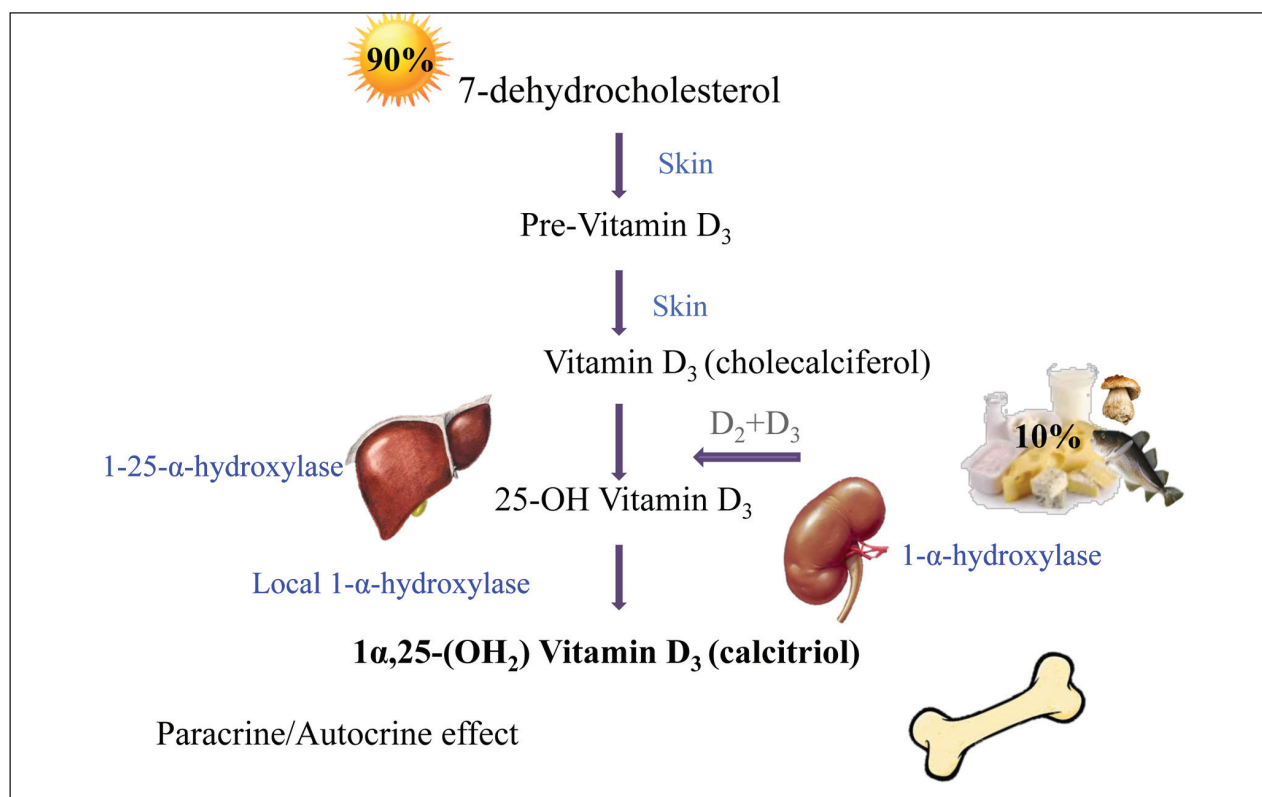


Figure 2. Systemic active Vitamin D (calcitriol) derives from a multistep process of activation (sunlight activation of 7-dehydrocholesterol in the skin, followed by two hydroxylations in liver and kidney). Vitamin D may also be activated locally for paracrine/autocrine function, regulating general health.

freeing (14). Calcitriol together with PTH regulates phosphate levels (Pi) by modulating intestinal and renal Pi reabsorption and bone metabolism (17). As initially demonstrated by Heyman in 1928 (18), up to 30% of Pi is absorbed in intestine (17). According to De Luca experiments on nephrectomized animals the process was mediated by the active metabolite (19).

Extra-skeletal functions

The observation of higher sensitivity to Vitamin D in patients suffering from chronic granulomatous diseases such as sarcoidosis and tuberculosis paved the way for the first experiments on extra-skeletal roles of Vitamin D. In 1982 it was observed that macrophages in the granulomatous tissues convert pre-Vitamin D in calcitriol (3). With the advent of Molecular Biology, transcripts of CYP27B1 and VDR were found in tissues not previously recognized as sites of Vitamin D synthesis (23, 26).

Additionally, it was discovered that VDR was involved in the selective modulation of tissue-specific gene transcription through heterodimerization with retinoid X receptor, recruitment of nuclear proteins and binding to vitamin D response elements (27). It became progressively clear that genetic alterations of VDR affected calcium metabolism, cell proliferation and the immune system (27). By the end of the 90th century, polymorphisms of VDR gene were localized between the 8 and 9 exons by restriction enzymes, and later, applying the sequences approach, new polymorphisms were discovered (27, 28). Actually, polymorphisms in the VDR gene occur frequently, but the significance is not completely understood and it is still object of intensive research.

Osteomalacic myopathy

The initial descriptions of rickets mentioned muscular weakness, especially in children (29, 30). Proximal myopathy with severe muscular impairment has been observed in subjects with severe Vitamin D deficiency (29). The term “osteomalacic myopathy” was definitely coined in 1965 to describe proximal muscular weakness (30).

Lesser severe muscle changes have been observed in mild deficiency (29). Recently, the effect of vitamin D supplementation in deficient athletes or not-athletes returned ambiguous results, being conditioned by basal Vitamin D levels (29, 31). Three recent meta-analysis observed that the beneficial effects of Vitamin D supplementation were higher in elderly subjects, with improvement of balance and muscle function (29, 31, 32). Actually, Vitamin D deficiency is prevalent in institutionalized older subjects and may contribute to the development of age-related sarcopenia and to increase risk of fall. Bischoff-Ferrari demonstrated an impairment of Vitamin D photosynthesis and renal activation with aging (33). Therefore, older people could be more exposed to Vitamin D deficiency and could benefit the most from adequate supplementation (29).

The “bidirectional” relationship between Vitamin D and the skin

The earliest records about the relationship between skin diseases and sun exposure date back to the ancient Egyptians and Indians (34). Surprisingly, more than 3500 years ago, Egyptians treated Vitiligo by associating sunlight exposure and the ingestion of boiled weed (35). In the second Century BC, travelling to Egypt, Hippocrates discovered the beneficial effect of sun. Back to Greece, he recommended the exposure to sunlight for health benefit (34). In 1877, Downs and Blunt demonstrated that light exposure could prevent fungal growth *in vitro*.

In 1985, MacLaughlin reported that psoriatic fibroblasts were partially resistant to the anti-proliferative effects of calcitriol. This finding encouraged to speculate that calcitriol could be effective in the treatment of psoriasis (35). Concomitantly, Morimoto and Kumahara incidentally observed the remission of psoriatic lesions in a patient treated with oral Vitamin D for osteoporosis. Thereafter, they demonstrated that oral treatment with calcitriol could significantly improve psoriasis (35) (Figure 1).

In the last years, numerous studies reported that topical Vitamin D analogs (e.g. calcitriol, calcipotriol, tacalcitol, hexafluoro-1,25-dihydroxyvitamin D₃) are effective and safe in the treatment of psoriasis (35). In

1998 Parsad published effectively combined PUVAol and topical calcipotriol; these findings were confirmed by later studies (36, 38).

Cardiovascular health

The history of the relationship between vitamin D and cardiovascular health is quite recent. In 1981, Robert Scragg (39) first hypothesized that the decrease of cardiovascular disease mortality and morbidity in summer season might be a consequence of cardiovascular-protective effects of vitamin D through a direct action on the platelet, or mediated by a change in calcium metabolism. Over the last three decades the possible role of vitamin D in cardiovascular diseases has become a particularly intriguing topic (40).

Both the enzyme 1-alpha-hydroxylase, and VDR are found in the vessels and in the heart, namely in cardiomyocytes, cardiac fibroblasts, vascular smooth muscle cells, and vascular endothelial cells. This knowledge is derived from experimental models published from the second half of the 80s. Walters and coworkers, in 1986 demonstrated the presence of specific receptors for 1,25-dihydroxyvitamin D₃ in low salt chromatin preparations from normal rat hearts (41). Some years later, Bidmon and coworkers (42) reported that receptors for vitamin D exist in the heart of mice, predominantly in the right atrium. In 2002, Li and coworkers observed that a mouse with a complete deletion of the VDR gene demonstrates both hypertension and cardiac hypertrophy (43). In subsequent years, in particular between 2005 and 2008, a further step forward is derived from studies in knock-out mice for VDR or 1- α -hydroxylase, which suffer from cardiovascular pathologies including arterial hypertension, myocardial hypertrophy and increased thrombogenicity (44, 45, 46). In rat models, it was shown that early life vitamin D deficiency is associated with impaired vascular endothelial and smooth muscle cell function (47). In parallel with experimental animal studies, in 1996 O'Connell and Simpson (48) identified the receptor protein for 1,25(OH)₂D₃ in tissue from two human hearts by using an antibody directed against the recombinant Vitamin D₃ receptor, suggesting a role of Vitamin D in cardiovascular pathophysiology. A few years

later, Somjen and coworkers (44) identified the expression of 25-hydroxyvitamin D₃ – 1-alpha-hydroxylase in human vascular smooth muscle cells and in 2008, Chen and coworkers, reported an increased expression of the Vitamin D receptor in the human hypertrophic heart (45). In addition to the preclinical observations, there are numerous clinical evidences linking Vitamin D to cardiometabolic risk factors and cardiovascular diseases. Since the 1970s, an increasing interest in the relationship between vitamin D and coronary heart disease has emerged. Among the first studies there is a Danish study published in 1978 (46), which found that low Vitamin D levels were significantly associated with angina and myocardial infarction. Low Vitamin D levels were associated with a higher risk of myocardial infarction in the Health Professionals Follow-up Study (47), including 18,225 US men between 1993 and 1999. Data collected from studies performed in the US and Europe between 1970 and 2003 were analyzed in a meta-analysis published in 2012, evaluating the risk of ischemic heart disease and early death. The Authors observed an increasing risk of ischemic heart disease, myocardial infarction, and early death with decreasing plasma 25-hydroxyvitamin D levels (48). In the same years, particularly between 2007 and 2011, interesting epidemiological data were proposed in the literature about the relationship between vitamin D status and blood pressure, based on the NHANES III 1988-1994 (49) and NHANES 2003-2006 (50), showing an inverse association. Furthermore, an inverse association between vitamin D status and risk of incident hypertension was observed in men from the Health Professionals Follow-up Study and in women from the Nurses' Health Study, suggesting a pooled relative risk of 3.18 (51). Furthermore, in hypertensive patients several studies demonstrated a link between low 25 (OH) Vitamin D concentrations and cardiovascular events (52).

When we consider the spectrum of cardiovascular diseases and their risk factors, an analysis of NHANES III 1988-1994 (53) showed that low Vitamin D was associated with cardiovascular diseases and with some risk factors, such as diabetes mellitus, obesity, and hypertriglyceridemia (54). The analysis of data from NHANES 2001-2004 showed a high prevalence of hypovitaminosis D in patients with coronary heart disease and heart failure (55). In 2012 Wang and

coworkers published a meta-analysis of 19 prospective studies in 65,994 individuals, demonstrating a generally linear and inverse association between circulating 25(OH) Vitamin D levels in the range of 20–60 nmol/l and risk of cardiovascular diseases (56).

To date, experimental and clinical data suggest that Vitamin D system may play an important role in the maintenance of cardiovascular health (57), but the causality of the relationship between Vitamin D deficiency and cardiovascular diseases remains to be established. Some, but not all, observational studies in humans provide support for these experimental findings, raising the possibility that Vitamin D or its analogs might prove useful therapeutically in the prevention or treatment of cardiovascular diseases. Larger randomized clinical trials are needed to support the benefits of Vitamin D therapy in managing patients with cardiovascular disease in the clinic. It is desirable that knowledge in this issue will progress in the near future, when the results of two large ongoing studies will be available, the VITAL trial (VITamin D and Omega-3 Trial) (58) and the Vitamin D3-Omega3-Home Exercise-Healthy Ageing and Longevity Trial (59).

Vitamin D and the its relationship with cancer

The first reports indicating a role of Vitamin D in anticancer activity dated on 1981, when Colston et al. demonstrated that the Vitamin D₃ was able to inhibit the growth of melanoma tumor cells *in vitro* (60). Later in that year Abe and his group indicated that calcitriol can induce the differentiation of mouse HL60 leukaemia cells towards the macrophage cell type (61). Then, the antineoplastic effects of Vitamin D₃ have been reported both *in vitro* and *in vivo*, in various malignancies, in particular in breast, prostate and colorectal cancer (62). The first epidemiological report that linked a lack of sunlight exposure to colon cancer risk was in 1980 from Garland et al. for colon cancer (63). Afterwards, other epidemiological studies suggest an inverse correlation between blood Vitamin D₃ levels and increased incidence of several types of cancers, but associations have most consistently been observed for colorectal cancer (64). Since then, several distinct mechanism underlying the anticancer effects

of calcitriol have been elucidated by experimental data, such as: anti-proliferative effects, induction of apoptosis, stimulation of differentiation, anti-inflammatory effects, inhibition of invasion and metastasis and inhibition of angiogenesis in different types of cancers (65). More recently, emerging data from preclinical and some clinical studies seem to suggest that avoiding deficiency and adding vitamin D₃ supplements or analogs might be a way to reduce cancer incidence and improve cancer prognosis and outcome (65). This consideration may also have clinical relevance on anticancer therapies using monoclonal antibodies approach, possibly due to the effects of the Vitamin D₃ on the immune system, through the antibody-dependent cell-mediated cytotoxicity mechanism either on natural killer cells (66, 67) or on macrophages (68).

However, several immune cell types of both innate and adaptive cells, including T cells, express VDR and the key enzyme CYP27B1, that render immune cells able to produce on its own the active form of vitamin, i.e. 1,25(OH)₂D. Furthermore, a growing body of evidence suggests an important immune-modulating role of vitamin D in the T-cell differentiation and their effector functions (69). These mechanisms seem to recapitulate the role of vitamin D₃-VDR interaction in the setting of proper immune cell functions and impeding autoimmune disorder development (70). Finally, recent data seem to postulate a possible role for vitamin D blood serum levels as a predictive element in the immune-checkpoint blockade using anti-CTLA-4, anti-PD-1 and anti-PD-L1 monoclonal antibodies in melanoma metastatic patients, highlighting a potential positive antigen-dependent role of vitamin D in cancer treatments (71).

Conclusion

Progressively it has been acquired that Vitamin D is important for general health (16). Interestingly, besides being essential in skeletal health, Vitamin D plays a role in cellular proliferation, growth and differentiation. Endocrine, paracrine and autocrine functions have been discovered. The history of Vitamin D research, after more than 400 years of research, is definitely not completed.

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References

- Holick MF, Chen TC, Lu Z, Sauter E. Vitamin D and skin physiology: a D-lightful story. *J Bone Miner Res* 2007; 22(suppl. 2): V28-V33.
- DeLuca HF. (Ed.) Vitamin D. In: Feldman D, Pike J W, Bouillon R, Giovannucci E, Goltzman D, Hewison M. Academic Press 2017; 4th Edition (1).
- Holick MF. Evolution and function of vitamin D. *Recent Results Cancer Res* 2003; 164: 3-28.
- Holick MF. Vitamin D deficiency. *N Engl J Med* 2007; 357(3): 266-81.
- O'Riordan JL, Bijvoet OL. Rickets before the discovery of vitamin D. *Bonekey Rep* 2014; 3:478.
- Rajakumar K. Vitamin D, cod-liver oil, sunlight and rickets: a historical perspective. *Paediatrics* 2003; 112(2): e132-5.
- Mellanby E. The part played by an accessory factor in the production of experimental rickets. *J Physiology* 1918; 50: 1915-6.
- McCollum EV, Simmonds N, Becker JE, Shipley PG. An experimental demonstration of the existence of a vitamin which promotes calcium deposition. *J Biochem Chem* 1922; 53: 293-8.
- Steenbock H, Black A. Fat soluble vitamins XVII. The induction of bone promoting and calcifying properties in a ration by exposure to ultraviolet light. *J Biochem Chem* 1924; 61: 405-22.
- Wolf G. The discovery of vitamin D: the contribution of Adolf Windaus. *J Nutr* 2004; 134(6): 1299-302.
- Funk C. The etiology of deficiency diseases. *J State Med* 1912; 20: 341-54.
- Semba RD. The discovery of the Vitamins. *Int J Vitam Nutr Res* 2012; 82(5): 310-5.
- Bill C, Massengale ON, Hickman KCD, Gray EL. A new vitamin D in cod liver oil. *J Biochem Chem* 1938; 126: 241-4.
- Holick MF, MacLaughlin JA, Clark MB, Holick SA, Potts JT Jr, Anderson RR, Blank IH, Parrish JA, Elias P. Photosynthesis of previtamin D3 in human skin and the physiologic consequences. *Science* 1980; 210: 203-5.
- Fraser D, Kodicek K. Unique biosynthesis by kidney of a biological active vitamin D metabolite. *Nature* 1970; 228: 764-6.
- DeLuca HF. History of the discovery of vitamin D and its active metabolites. *Bonekey Rep* 2014; 3: 479.
- Jacquotte G, Unwin RJ. Physiological regulation of phosphate by vitamin D, parathyroid hormone (PTH) and phosphate (Pi). *Pflugers Arch* 2018; Nov 5. doi: 10.1007/s00424-018-2231-z.
- Nikolaysen R, Eeg-Larsen N. Vitamin D and Homones. The Biochemistry and physiology of vitamin D. Academic Press Inc. Publishers New York 1953; 11: 38-42.
- Rizzoli R, Fleisch H, Bonjour JP. Role of 1,25-dihydroxyvitamin D₃ on intestinal phosphate absorption in rats with a normal vitamin D supply. *J Clin Invest* 1977; 639-47.
- Brumbaugh PF, Haussler MR. Specific binding of 1alpha,25-dihydroxycholecalciferol to nuclear components of chick intestine. *J Biol Chem* 1975; 250: 1588-94.
- Lawson DE, Wilson PW. Intranuclear localization and receptor proteins for 1,25-dihydroxycholecalciferol in chick intestine. *Biochem J* 1974; 144: 573-83.
- Haussler MR, Myrte JF, Norman AW. The association of a metabolite of vitamin D3 with intestinal mucosa chromatin, in vivo. *J Biol Chem* 1968; 243: 4055-64.
- Norman AW, Roth J, Orci L. The vitamin D endocrine system: steroid metabolism, hormone receptors and biological response (calcium binding proteins). *Endocr Rev* 1982; 3: 331-66.
- Rochel N, Wurts JM, Mitschler A, Klaholz B, Moras D. The crystal structure of the nuclear receptor for vitamin D bound to its natural ligand. *Mol Cell* 2000; 5(1): 173-9.
- Demay MB, Kiernan MS, DeLuca HF, Kronenberg HM. Sequences in the human parathyroid gene that bind the 1,25-dihydroxyvitamin D3 receptor and mediate transcriptional repression in response to 1,25-dihydroxyvitamin D3. *Proc Nat Acad Sci USA* 1992; 89(17): 8097-101.
- Zehnder D, Bland R, Williams MC, McNinch RW, Howie AJ, Stewart PM, Hewison M. Extrarenal expression of 25-Hydroxyvitamin D(3)-1 alpha-hydroxylase. *J Clin Endocrinol Metab* 2001; 86(2): 888-94.
- Norman AW. Minireview: vitamin D receptor: new assignments for an already busy receptor. *Endocrinology* 2006; 147(12): 5542-8.
- Gross C, Eccleshall TR, Malloy PI, Villa ML, Marcus R, Feldman D. The presence of a polymorphism at the translational initiation site of the vitamin D gene is associated with low bone mineral density in postmenopausal Mexican-American women. *J Bone Miner Res* 1996; 11(12): 1850-5.
- Gunton J, Girgis CM. Vitamin D and muscle. *Bone Rep* 2018; 8: 163-7.
- Dastur DK, Bomi MG, Waia NHDesai MM, Bharucha EP. Nature of muscular change in osteomalacia: light- and electron-microscope observations. *Plates CV-CCII* 1975; 117: 221-8.
- Stockon KA, Mengersen K, Parats JD, Kandiah D, Bennell KL. Effect of vitamin D supplementation on muscle strength: a systematic review and met-analysis. *Osteopors Int* 2011; 22: 859-71.
- Muir SW, Montero Odasso. Effect of vitamin D supplementation on muscle strength, gait and balance in older adults: a systematic review and meta-analysis. *J Am Geriatr Soc* 2011; 59: 2291-300.
- Bischoff-Ferrari HA, Borchers M, Gudat F, Dürmüller U, Stähelin HB, Dick W. Vitamin D receptor expression in human muscle tissue decrease with age. *J Bone Min Res* 2004; 19: 265-9.

34. Jarret P, Scragg R. A short history of phototherapy, vitamin D and skin disease. *Photochem Photobiol Sci* 2017; 16(3): 283-90.
35. Honigsmann H. History of Phototherapy in dermatology. *Photochem Photobiol Sci* 2013; 12(1): 16-21.
36. Mostafa WZ, Hegazy RA. Vitamin D and the skin: Focus on a complex relationship: A review. *J Adv Res* 2015; 6(6): 793-804.
37. Kovacs R. *Electrotherapy and the Elements of Light Therapy*. Philadelphia: Lea & Febiger, 1932.
38. Parsad D, Saini R, Verma N. Combination of PUVA-sol and topical calcipotriol in vitiligo. *Dermatology* 1998; 197(2): 167-70.
39. Scragg R. Seasonality of cardiovascular disease mortality and the possible protective effect of ultra-violet radiation. *Inter J Epidemiol* 1981; 10(4): 337-41.
40. Pilz S, Tomaschitz A, März W, et al. Vitamin D, cardiovascular disease and mortality. *Clin Endocrinol* 2011; 75: 575-84.
41. Walters MR, Wicker DC, Riggle PC. 1,25-Dihydroxyvitamin D3 receptors identified in the rat heart. *J Mol Cell Cardiol* 1986; 18(1): 67-72.
42. Bidmon HJ, Gutkowska J, Murakami R, Stumpf WE. Vitamin D receptor in heart: effects on atrial natriuretic factor. *Experientia* 1991; 47(9): 958-62.
43. Li YC, Kong J, Wei M, Chen ZF, Liu SQ, Cao LP. 1,25-dihydroxyvitamin D3 is a negative endocrine regulator of the renin-angiotensin system. *J Clin Invest* 2002; 110(2): 229-38.
44. Somjen D, Weisman Y, Kohen F, Gayer B, Limor R, Sharon O, Jaccard N, Knoll E, Stern N. 25-hydroxyvitamin D3-1 α -hydroxylase is expressed in human vascular smooth muscle cells and is upregulated by parathyroid hormone and estrogenic compounds. *Circulation* 2005; 111: 1666-71.
45. Chen S, Glenn DJ, Ni W, Grigsby CL, Olsen K, Nishimoto M, Law CS, Gardner DG. Expression of the vitamin D receptor is increased in the hypertrophic heart. *Hypertension* 2008; 52: 1106-12.
46. Lund B, Badskjaer J, Lund B, Soerensen O. Vitamin D and ischaemic heart disease. *Horm Metab Res* 1978; 10(6): 553-6.
47. Giovannucci E, Liu Y, Hollis B, Rimm E. 25-hydroxyvitamin D and risk of myocardial infarction in men: a prospective study. *Arch Intern Med* 2008; 168: 1174-80.
48. Brondum-Jacobsen P, Benn M, Jensen GB, Nordestgaard BG. 25-hydroxyvitamin D levels and risk of ischemic heart disease, myocardial infarction, and early death: population-based study and meta-analyses of 18 and 17 studies. *Arterioscler Thromb Vasc Biol* 2012; 32: 2794-802.
49. Scragg R, Sowers M, Bell C. Serum 25-hydroxyvitamin D, ethnicity, and blood pressure in the Third National Health and Nutrition Examination Survey. *Am J Hypertens* 2007; 20: 713-9.
50. Zhao G, Ford ES, Li C, Kris-Etherton PM, Etherton TD, Balluz LS. Independent associations of serum concentrations of 25-hydroxyvitamin D and parathyroid hormone with blood pressure among US adults. *J Hypertens* 2010; 28: 1821-8.
51. Forman JP, Giovannucci E, Holmes MD, Bischoff-Ferrari HA, Tworoger SS, Willett WC, Curhan GC. Plasma 25-hydroxyvitamin D levels and risk of incident hypertension. *Hypertension* 2007; 49: 1063-9.
52. Wang TJ, Pencina MJ, Booth SL, Jacques PF. Vitamin D deficiency and risk of cardiovascular disease. *Circulation* 2008; 117: 503-11.
53. Kendrick J, Targher G, Smits G, Chonchol M. 25-Hydroxyvitamin D deficiency is independently associated with cardiovascular disease in the Third National Health and Nutrition Examination Survey. *Atherosclerosis* 2009; 205: 255-60.
54. Martini LA, Wood RJ. Vitamin status and the metabolic syndrome. *Nutr Rev* 2006; 64: 479-86.
55. Kim D, Sabour S, Sagar U, Adams S, Whellan DJ. Prevalence of hypovitaminosis D in cardiovascular diseases (from the National Health and Nutrition Examination Survey 2001 to 2004). *Am J Cardiol* 2008; 102: 1540-4.
56. Wang L, Song Y, Manson JAE, Pilz S, März W, Michaëlsen K, Lundqvist A, Jassal SK, Barrett-Connor E, Zhang C, Eaton CB, May HT, Anderson JL, Sesso HD. Circulating of 25-hydroxy-vitamin D and risk of cardiovascular disease: a meta-analysis of prospective studies. *Circ Cardiovasc Qual Outcomes* 2012; 5(6): 819-29.
57. Piantanida E, Gallo D, Veronesi G, Dozio E, Trotti E, Lai A, Ippolito S, Sabatino J, Tanda ML, Toniolo A, Ferrario M, Bartalena L. Cardiometabolic healthy and unhealthy obesity: does vitamin D play a role? *Endocr Connect* 2017; 6: 943-51.
58. Manson JE, Bassuk SS, Lee IM, Cook NR, Christen WG, Bubes VY, Gordon DS, Copeland T, Friedenberg G, D'Agostino DM, Ridge CY, MacFadyen JG, Kalan K, Buring JE. The VITamin D and Omega-3 Trial (VITAL): rationale and design a large randomized controlled trial of vitamin D and marine omega-3 fatty acid supplements for the primary prevention of cancer and cardiovascular disease. *Contemp Clin Trials* 2012; 33(1): 159-71.
59. *CORDIS. DO-Health Report Summary, Universitaet Zuerich, Switzerland, 2017.*
60. Colston K, Colston MJ, Feldman D. 1,25-dihydroxyvitamin D3 and malignant melanoma: the presence of receptors and inhibition of cell growth in culture. *Endocrinology* 1981; 108: 1083-6.
61. Abe E, Miyaura C, Sakagami H, Takeda M, Konno K, Yamazaki T, Yoshiki S, Suda T. Differentiation of mouse myeloid leukemia cells induced by 1 α ,25-dihydroxyvitamin D3. *Proc Nat Acad Sci USA* 1981; 78: 4990-4.
62. Leyssens C, Verlinden L, Verstuyf A. Antineoplastic effects of 1,25(OH)2D3 and its analogs in breast, prostate and colorectal cancer. *Endocr Relat Cancer* 2013; 20: R31-R47.
63. Garland CF, Garland FC. Do sunlight and vitamin D reduce the likelihood of colon cancer? *Intern J Epidemiol* 1980; 9: 227-31.

64. Chung M, Lee J, Terasawa T, Lau J, Trikalinos TA. Vitamin D with or without calcium supplementation for prevention of cancer and fractures: an updated meta-analysis for the U.S. Preventive Services Task Force. *Ann Intern Med* 2011; 155: 827–38.
65. Feldman D, Krishnan AV, Swami S, Giovannucci E, Feldman BJ. The role of vitamin D in reducing cancer risk and progression. *Nat Rev Cancer* 2014; 14(5): 342–57.
66. Bittenbring JT, Neumann F, Altmann B, Takeda M, Konno K, Yamazaki T, Yoshiki S, Suda T. Vitamin D deficiency impairs rituximab-mediated cellular cytotoxicity and outcome of patients with diffuse large B-cell lymphoma treated with but not without rituximab. *J Clin Oncol* 2014; 3(29): 3242–8.
67. Mortara L, Gariboldi MB, Bosi A, Bregni M, Pinotti G, Guasti L, Squizzato A, Noonan DM, Monti E, Campiotti L. Vitamin D Deficiency has a Negative Impact on Cetuximab-Mediated Cellular Cytotoxicity against Human Colon Carcinoma Cells. *Target Oncol* 2018; 13(5): 657–65.
68. Bruns H, Büttner M, Fabri M, Mougiakakos D, Bittenbring JT, Hoffmann MH, Beier F, Pasemann S, Jitschin R, Hofmann AD, Neumann F, Daniel C, Maurberger A, Kempkes B, Amann K, Mackensen A, Gerbitz A. Vitamin D-dependent induction of cathelicidin in human macrophages results in cytotoxicity against high-grade B cell lymphoma. *Sci Transl Med* 2015; 7(282): 282ra47.
69. Kongsbak M, Levring TB, Geisler C, von Essen MR. The vitamin D receptor and T cell function. *Front Immunol* 2013; 4: 148.
70. Mangin M, Sinha R, Fincher K. Inflammation and vitamin D: the infection connection. *Inflamm Res* 2014; 63(10): 803–19.
71. Timmerman D, McEnery-Stonelake M, Joyce CJ, Nambudiri VE, Hodi FS, Claus EB, Ibrahim N, Lin JY. Vitamin D deficiency is associated with a worse prognosis in metastatic melanoma. *Oncotarget* 2016; 8(4): 6873–82.

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A wolf howling at the sun: a historic perspective of actinotherapy in Systemic Lupus Erythematosus

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Abstract. The letter illustrates a particular method of therapy for systemic lupus erythematosus in use at the beginning of the 20th century

Key words: systemic lupus erythematosus, actinotherapy, Moritz Kaposi, Niels Ryberg Finsen

Systemic Lupus Erythematosus -SLE from this point onward- is arguably the most famous disease which takes its name directly from a typically nocturnal animal. SLE was initially considered only a skin disease of purely dermatological matter, and later, only after the second half of 20th century, its systemic character and its relations with connective tissue became clear.

Since the Middle Ages the cutaneous ulcers resembling the ripping-off bites to human skin and flesh by this fierce wild animal were alternatively named *cancer*, and *lupus* with different meanings: while the former -*cancer*- could involve any body tissue or organ, the latter -*lupus*- mostly, or nearly always, referred to a skin ulcerative disease. Intriguingly, SLE was also mistaken for cutaneous tuberculosis- *scrofula*. A non-secondary phenomenon is the link between werewolf imaginary myth (a man turning into a half human-canine being during full-moon nights) and SLE- suffering patients (1).

An intriguing question arise: did medieval physicians understand the connection between sunlight exposure and these dermatological phenomena? It is necessary to wait until Moritz Kaposi (1837 – 1902) and his mentor Ferdinand Ritter von Hebra (1816-1880), who contributed to establish the new ‘Vienna School of Dermatology’, to see a further understanding of this disease. Kaposi not only used the term *lupus erythematosus disseminatus* for the first time in history but also

first described and coined the famous nosographical identity *discoïd lupus* or *fixed lupus* exclusively referring to cutaneous form of the disease. Thus, during the late 19th century the term acquired a twofold meaning: *L. vulgaris*, a form of secondary cutaneous tuberculosis, affecting millions of patients in the urban centers of Europe from ancient times till the antibiotic era and, *Systemic L. erythematosus*, -SLE- a chronic inflammatory autoimmune disease of the connective tissue (2).

On the basis of these discoveries and a more modern classification, along with the ongoing technical and scientific discoveries, new therapies established, such as physical therapies: actinotherapy -or phototherapy- saw a growing interest in the scientific community especially applied to dermatology and this new approach rapidly spread across Italy. Many medical textbooks published in this period mention this specific form of therapy. For example, Niels Ryberg Finsen (1860-1904, Nobel prize for Medicine in 1903) studies on the properties of actinic light and its “*exciting*” and “*bactericidal*” properties were popular within Italian doctors. However, Finsen asserted the use of concentrated actinic light to cure a broader spectrum of diseases including “*superficial, parasitic, localized*” pathologies (3).

In SLE actinotherapy was used in addition to classic medical therapies, including the administration of arsenic, phosphorus, iodine, sulfur, ammonia, phenic acid, lactic acid, tar, mercuric chloride, resor-

cinol and other ointments. Scarification was indeed a common procedure (4).

A typical "radiotherapy" session was carried out using a "Crookes tube" for 10 minutes every other day with local cutaneous application of electrical high frequencies via a condensing electrode.

On the other hand, Finsen therapy used concentrated light beams and was also very popular in *lupus vulgaris* treatment, since it was reported to be "extremely effective" (4, 5).

These results of efficacy must take into account that they were used to treat both SLE and also tubercular cutaneous forms.

It's peculiar to mention that nowadays sunlight exposure is considered potentially harmful, since approximately two-thirds of SLE suffering patients experience marked photosensitivity. This condition is such a common feature of the disease that was included in the historical ACR '97 classification of SLE (6).

However, it is interesting to note that between the late 19th and early 20th centuries, physical therapy with light contributed to the therapeutic practice of the period.

References

1. Smith CD, Cyr M. The history of lupus erythematosus. From Hippocrates to Osler. *Rheum Dis Clin North Am* 1988; 14(1):1-14.
2. Hebra F, Kaposi M. On Diseases of the Skin Including the Exanthemata. (Tay W, ed.). London: The New Sydenham Society; 1875.
3. Bellini A. Luce e salute. Fototerapia. Radioterapia. Milano: Ulrico Hoepli; 1903.
4. Franceschini G. Le malattie della pelle. Milano: Ulrico Hoepli; 1908.
5. Bocciardo AD. Eletticità Medica. Milano: Ulrico Hoepli; 1904.
6. Update of the 1982 American College of Rheumatology Revised Criteria for Classification of Systemic Lupus Erythematosus.

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The “Mummy of Erba”: A study proposal for the analysis of a mummified Egyptian specimen

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Abstract. The so-called “Mummy of Erba” is an Egyptian specimen housed in the Civic Museum of Erba, consisting of three embalmed parts, a head, a left hand and a foot. As intact contexts, mummies allow to conduct comprehensive studies on all the preserved tissues, offering the possibility to analyze them through the non-invasive Radiodiagnostic methods, without proceeding to the unwrapping. The study we present is a proposal to analyze the mummy with a multidisciplinary approach, in order to acquire anthropological, paleopathological, archaeometric and archaeological data on this preserved specimen. Finally, this contribution is aimed at exposing all the provided methodologies with a view to conducting a complete analysis of the sample.

Key words: Egypt, mummy, computed tomography, anthropology, paleopathology

Three Egyptian mummified human remains that are exposed in the Civic Museum of Erba (Lombardy, northern Italy), were originally donated by the Marquis Francesco Majnoni d'Intignano who bought them during his stay in Cairo as the General Consul of Italy (1). The specimen consists of a head (Fig. 1), a left hand and a foot (Fig. 2).

The head is in a bad state of preservation in some portions of the cranial cap, the bandages have been destroyed and it has skeletonized, the second and third fingers are missing on the foot, while the conditions of conservation of the hand are good.

On the foot, adherent to the bandages, there are some blue Faience tubes, a particular type of vitreous material, which was part of an ancient funeral net. Nets like this, were used on a mummy to protect it and guarantee its survival forever. This custom appeared in the XXI dynasty but it is attested with particular frequency during the XXVI dynasty and it seems to continue until the Ptolemaic period (2).

In the present state of knowledge, it is difficult to establish if the three mummified anatomical parts belong to the same individual. The mummy was already fragmented and deprived of the body when it arrived in Italy, maybe due to transport needs, to historical events, or the outcome of an embalming that had not perfectly succeeded.

Starting from the early 1900s, following the discovery of a large quantity of mummies it was understood the importance of them for the purposes of medical research (3). Sir A. Ruffer was among the first doctors to analyze samples of mummified soft tissues looking for traces of infectious diseases.

Mummified specimens, by natural or artificial processes, are very significant in the paleopathological field, due to the conservation of most body parts and of the otherwise deperible tissues, enabling complete studies on intact biological contexts. These evidences represent unique examples in the archaeological perspective, because they retain evident and detectable



Figure 1. Frontal view of the embalmed head. It is observed the preservation of the upper facial bandages and the uncovering of the cranial cap.



Figure 2. Lateral view of the left foot. Blue Faience tubes are visible on the dorsal portion of the wrappings.

traces of the processes to which they had been subjected to. As intact contexts, mummies allow us to conduct comprehensive studies on all the preserved evidence. Numerous research on mummified samples has already been conducted all over the world in the past and

recently, providing a wide scientific literature of comparison for the techniques and methods of study (4, 5).

In this letter, we propose the multidisciplinary analysis of the specimen of the Mummy of Erba.

Here, we expose our purpose to first conduct the radiographic and tomographic studies on these evidences in order to analyze the internal features, obtain 3D reconstructions and detailed images of the covered surfaces and a wide number of subtle slices of the specimen, avoiding the issue of destruction and loss of the evidences, which would otherwise arise due to an invasive process of study (6). Then, our aim is to provide anthropological data of the mummified remains, determining the sex and the age-at-death of the individual and its pathological conditions, proceeding to a generic identification through the reconstruction of the biological profile (7). Detection of pathologies is allowed by the imaging of the bone surfaces and preserved tissues and through the multi-slice tomographic procedure. In summary, the major goal of CT-scan procedures is, as stated by Mininberg (8), the possibility to “unwrap” the mummies without actually unwrapping them.

Interesting for the reconstruction of embalming techniques is the possibility to visualize the cranial cavity, the eventual breakage of ethmoid bone and ex-cerebration marks. Other possible applications of the tomographic unwrapping are also the identification and facial reconstruction through the determination of the shape of the skull (9).

Firstly, an external morphological evaluation of the mummy has been conducted by the authors, in order to provide some information on the conservation status, the pattern of wrappings and the preservation of tissues. Other data concerning the internal cavities and the eventual presence of embalming-related substances, such as fillings in the orbits and the mouth cavity, will be collected after the complete radiographic study.

Histological analysis is useful to assess the preservation status of the sample, the diagenesis processes, the eventual fungal growths and bacterial damage; moreover this analysis is needed to study in depth eventual pathologies of the tissues noticed during the study (10). For a better comprehension of the chronology we propose the ^{14}C analysis in order to assign the sample a more reliable absolute date.

Finally, we believe that the study we are proposing will allow us to describe, in detail, the remains from Erba, in order to catalogue and insert them into the literature about Egyptian mummified specimens stored in Italian museums and to provide anthropological data on an adjunctive evidence of the ancient process of mummification.

References

1. Inventario Reperti, Civico Museo di Erba, E 421 Mummia
2. Engelbach R. *Introduction to Egyptian Archaeology*. Cairo: Institut Français d'Archéologie Orientale; 1946.
3. Grilletto R. *Il mistero delle mummie: dall'antichità ai nostri giorni attraverso il tempo e lo spazio*. Roma: Newton & Compton; 2005.
4. Nystrom KC, Tilley L. Mummy studies and the bioarchaeology of care. *Int J Paleopathol* 2018. doi: 10.1016/j.ijpp.2018.06.004.
5. Licata M, Tosi A, Larentis O, Rossetti C, Iorio S, Pinto A. Radiology of Mummies. *Semin Ultrasound CT MR* 2018. doi: org/10.1053/j.sult.2018.10.016.
6. Cesarani F, Martina MC, Ferraris A, Grilletto R, Boano R, Marochetti EF, Donadoni AM, Gandini G. Whole-Body Three-Dimensional Multidetector CT of 13 Egyptian Human Mummies. *AJR Am J Roentgenol* 2003; 80(3): 597-606.
7. Licata M, Borgo M, Armocida G, Nicosia L, Ferioli E. New paleoradiological investigations of ancient human remains from North West Lombardy archaeological excavations. *Skeletal Radiol* 2016; 45(3): 323-31.
8. Mininberg DT. The Museum's Mummies: An Inside View. *Neurosurgery* 2001; 49(1): 8.
9. Cesarani F, Martina MC, Grilletto R, Boano R, Roveri AMD, Capussotto V, Giuliano A, Celia M, Gandini G. Facial Reconstruction of a Wrapped Egyptian Mummy Using MDCT. *Am J Roentgenol* 2004; 183(3):755-8.
10. Giuffra V, Pangoli D, Cosmacini P, Caramella D, Silvano F, Fornaciari G, Ciranni R. Paleopathological evaluation and radiological study of 46 Egyptian mummified specimens in Italian Museums. *Egitto e Vicino Oriente* 2009; 3: 121-55.

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Ethical implications of genetic susceptibility testing: NeuroGenEthics and the “Angelina Jolie effect”

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Abstract. An increasing interest in genetics of aggressive behavior has developed in literature over time and specifically regarding genes involved in dopaminergic and serotonergic systems, sex steroids and glucocorticoids. The same could be said for mood and anxiety disorders, psychosis, schizophrenia syndromes and anti-social and criminal behavior. This has led to the idea that it was possible to make genetic tests applicable in psychiatry with the ability to define a risk profile. However, the results obtained to date are mostly contradictory, un-replicable and lack standardized protocols and the legal frames are not clear. The results found were that there wasn't a simple mendelian transmission or connection of a few genes. Today, we have to overcome the genetic determinism and generalize it in an interdisciplinary perspective without neglecting the ethical, legal and social issues and without slipping into a sort of “Angelina Jolie effect”.

Key words: neurogenetics, predictive testing, vulnerability, un-patients, criminal trial

Introduction

The belief that behavioral traits are transmitted from one generation to the other is very old (1). Aspects of human personality such as intelligence, extroversion and introversion, social or antisocial behavior, substance abuse, the constant search for new sensations, are some of the topics of greatest interest and the object of study of behavioral genetics (2). The recent development of innovative methods of molecular biology has led to the sequencing of the human genome and has opened up the study of the molecular basis of behavior (3). Furthermore, the question of what are the components of the hereditary behavior was very controversial, due to its heavy social and political implications. In the early twentieth century, when genetics as a science was still in its infancy, there has been a rush to attribute all human traits, including complex types of personalities and even socioeconomic status, to the effects of individual genes which are inherited according to a mendelian model; this extremist position of absolute determinism fueled the eugenics movement

aimed at the genetic improvement of the human species (4). In the second half of the century, however, there has been a net change as a result of several factors: the specific criticisms of the new results obtained by some geneticists, the birth of the modern social sciences and the aversion for the implementation of the ideology of eugenics (5). In any case, after years in which prevailed the tendency to avoid this kind of study, in many states, research about correlations between genetics and personality, genetics and antisocial behavior and crime are increasing.

Some research centers are able to predict, assessing the personal genetic profile, the degree of stress tolerance, the threshold for depression and pathological anxiety, the threshold of tolerance to exposure to psychological trauma (6-8). The results of these genetic experiments can spread the notion that behavior, including that of man, is genetically determined. Unfortunately, the media often report titles such as “Discovered the homosexuality gene”, “Identified the gene of enterprising”, “Found the gene for depression” and so on (9, 10). These three cited examples, which cor-

respond to real cases ended up in the newspapers, have been blatantly denied, as well as many others.

Over the last 20 years, literature has been developing an increasing interest about genetics of impulsive-aggressive behaviors, especially related to genetic variants on key neuromodulators involved in the control of aggression (serotonin, dopamine, sex steroids, glucocorticoids and arginine vasopressin), which represent possible biological markers of predisposition toward criminal and violent behavior (11).

Starting from this scenery, came up the idea that it was possible to carry out genetics tests, applicable for example in forensic psychiatry able to establish a genetic risk profile that could represent an objective test and also influence imputability (12).

Several studies have been conducted in this field, but results were mostly contradictory or not replicated. It should also be said that, for mood and anxiety disorders, as well as for most common psychosis and schizophrenic syndrome, a simple Mendelian transmission was not found or related to a few limited genes that play a primary role (13).

The technical impossibility to decode a single complex phenotype is particularly evident when considering the study of brain function, one of the most fascinating topics since it is involved in the connections between body and mind, between material structure and abstract reasoning, between genetically determined cellular composition and environmental influences (14).

On the basis of these considerations, the Working Group of Forensic Genetics of the Italian Society of Human Genetics at the present time, does not recognize a scientific validity in the use of genetic testing for susceptibility to behavioral traits in any way, and especially so in the complex and delicate context of forensic genetics. It is believed that these tests are not useful, scientifically invalid and unfit to achieve the purposes for which they are executed (15). An integrated approach including biological, psychological and social variables seems more appropriate, although the relative contribution of the above mentioned factors and the most appropriate methodology for their investigation are still subject to debate (16). In the outlined framework, one question arises: What role should be taken by medicine? Is there a conflict of values if we

consider, on one side the principle of autonomy of the patient and on the other, the principle of beneficence and justice peculiar of medicine?

Social and Ethical implications

The bioethicist George Annas in 2000 imagined that the decoding of the human genome identified the DNA molecule in a sort of medical records (17). He had also anticipated that, before reaching that goal, it would be necessary to answer some basic questions, including: who is authorized to create the ‘CD’, which contains the genetic information? Who keeps it? Who controls the use? In that way, the ‘CD’ may be treated as sensitive medical information. Eighteen years after that prediction, this scenario seems at hand.

Not only the goal to reduce the cost of the human genome sequencing and thus to make it available has been reached, but more importantly, the techniques able to process large-scale biological samples are now available in many laboratories and so citizens are under the increasing pressure by an “health market”, which emphasizes the predictive and preventive potential of these analysis.

The ethical issues that are pointed out in predictive genetic tests are framed under normal procedures of medical ethics: protection and autonomy of the person undergoing the test, privacy and confidentiality, the share of the genetic information with at risk relatives, fairness (equity) and non-discrimination. These arguments are widely debated during studies on the applications of clinical genetics, forming the core of the bioethical reflection (18, 19).

When (and if) Genetic testing should be offered

Genetic tests are heterogeneous. In medical practice, they are mainly used with diagnostic purposes. The diagnostic tests are performed on people who have, or are suspected of having, a particular disease; attempting to resolve the question is whether the patient has or has not a specific disease (20). Genetic tests are instead classified as pre-symptomatic, when they identify the risk of developing a disease in the future in a person not suffering at the time of the analysis and who belongs to a family in which one or more in-

dividuals have a late-onset disease. A pathological result of the analysis indicates that the person is likely to develop the disease at some point in his life, if he lives long enough (eg. Huntington's disease) (21). Finally, the predictive genetic tests covering many common diseases, in which the risk of disease is increased or reduced, but with a level of accuracy much lower than that of other genetic tests (eg. ApoE4 and Alzheimer's disease) (22).

It is widely believed that the increasing knowledge about the human genome can determine an indiscriminate spread of these genetic testing often without a required medical application. A genetic test should allow individuals and their families to identify, understand, and especially checking out their risk of contracting certain diseases. The challenge is to ensure that genetic tests are offered in the most effective and fair way with high quality standards. This can be achieved only if genetic tests are considered as an integrated service, and not just as an activity of the laboratory. The gap between the diagnostic and therapeutic capacity should never be forgotten in the case of the development and application of a genetic test. The ability to predict that an individual will get sick or, still in perfect health, is predisposed to contracting the disease, especially when there is no therapeutic treatment or prevention, may result in a high cost in terms of psychological and social implications and create particular problems of an ethical and legal (23).

Genetic testing and the "Direct To Consumer" medicine

Over recent years the widespread use of Internet and web search engine, led to the emergence and flourishing expansion of a market based on the commercialization of "Direct To Consumer" (DTC) genetic testing. A dozen of sites can be found through Internet, that sell the whole entire analysis of the genome (23 andMe, DeCODE Me, etc.) or targeted analysis on the study of susceptibility to complex diseases such as the psychiatric ones (DNA Direct, Direct Health Test).

More and more people will have free access to genetic testing of any kind, without a close medical supervision, and will have a large amount of information about their health status, without having the right

tools to interpret and manage and with the lack of guarantee on the respect of the privacy regarding own data. The field of genetic tests sold directly to consumers, is the subject matter of a heated debate for more than fifteen years: dating back to 2003, the first survey on DTC tests, was conducted by the British Human Genetics Commission (HGC) (24).

Since then the situation has not changed with regard to the regulation of this business: there aren't clear laws in many European countries, and in some countries do not even exist guidelines (25). In the last years the caution indication for these initiatives, has not been able to curb the marketing of predictive or susceptibility tests, which are often no scientific validated and which are offered outside protocols and standards with which the medicine should be approached with the diagnostic and technological innovations.

Despite the controversies in the USA, the first test to detect genetic tendency to mental illness is already on the market. It's called Psynome, it costs \$ 750 and one can simply order it on the Internet (26, 27). The kit to collect the saliva sample, on which the test will be performed, directly arrives at home; it only takes a drop to reveal if in the DNA are present genetic variants associated with the risk of developing bipolar disorder, a disease that dangerously alters the mood mechanisms and affects on 1% of the adult population. John Kelsoe, a geneticist at the University of California and father of Psynome, argues that the test will help physicians and patients, dramatically reducing the time required for diagnosis of the disease, which now takes an average of seven years. By analyzing the DNA of hundreds of families, Kelsoe found that when two particular gene variants are present in the Gkr3gene, the risk of developing the disease could double. The conditional tense, however, is a must, because, as the American geneticist Francis Collins, head of the Human Genome Project, told to the magazine 'Science' (28) it is not shown which genes are actually involved in bipolar disorder, which is considered a complex disease, where environmental factors affect genetic ones.

The increasing availability of these tests directly accessible to the consumer, outside of strict medical supervision, makes imperative for professionals to continuously update on the types of tests on the market, on the possible applications in the health field, on

the potential and limitations related to genetic testing, and on the interpretation of the results. DNA testing is not a game or a curiosity, but a tool of science still evolving, to which approach, with a serious health motivation and with the help of a geneticist or physician.

Genetic Counseling and Informed Consent

In the case of predictive genetic tests, ensure a high quality service means also taking care and worrying about the social and psychological effects associated to them. Special attention should be placed in communication, as giving a clear information on the service, but also on the interpretation of the results through proper counseling. All National, European and International documents offering Recommendations and Guide Lines on genetic counseling, consider it indispensable and even imperative, either before or after testing, especially in the case of pre-symptomatic, susceptibility or probability tests (29). It will, increasingly respond to people who want to know their susceptibility or resistance to multi factorial diseases or their suitability for certain treatments. It will not, therefore provide a “certain” risk in relation to a specific disease, but to be able to communicate very complex concepts about the nature of “probability” in the information of this type of tests.

Similarly to what observed for the susceptibility testing related to pathological phenotypes, the test prediction of human impulsive-aggressive behavior suffer the same limits, with particular reference to the positive and negative predictive values as well as those relating to the specificity and sensitivity. Important questions are about how much genetic counseling is necessary for the user to understand these concepts and what may be the best strategies to communicate (30).

The exercise of self-determination, that is true, both in the decision to be tested and even to escape from it, however, is not devoid of effects, to evaluate with full responsibility. First of all it involves rights: who decides to be tested, has the right to receive and exchange data acquired freely, without pressure, to ascertain the truthfulness of the information concerning the analyzes performed on his body, to choose which information can be spread to others and to exercise the “right not to know”.

However, there are also duties. Who decide to take the test might reflect on some personal effects related to the outcome of these tests such as severe depression after the unveiling of predisposing to progressive diseases, anxiety and conflict between acceptance / refusal to change lifestyle as a preventive measure, awareness of the procreative risks and the effect on other family members.

Therefore, the consulting service offered to the individual must encourage his self-awareness so that he becomes able of taking decisions accepting the related psychological and social implications.

The consent act, following the genetic counseling, it's the documentation of the received information and testimonial of the positive determination of the subject to undergo a genetic test (31); informed consent is defined only when the person has received, in an appropriate manner, all the relevant information and is therefore in a position to understand the risks, benefits, limitations and the ethical, social and psychological implications related to genetic tests and so the multidisciplinary of competence is very significant.

The access to results and the psychological impact

The psychological repercussions of the individual who is undergoing genetic susceptibility testing, and consequently of his family, is a fundamental chapter that requires special attention. The emotional consequences that the result of a genetic test could generate, is sometimes difficult to manage (32). The discovery of an average risk of contracting certain disease, for some people is better than living with stress and anxiety caused by ignorance. One might have the feeling that the information could be useful because that means one can try to do anything possible to prevent, restrict or delay its onset. For others could be like discovering to have already a disease and that may cause the feeling of being alone, anxious, frustrated, and maybe feel ashamed.

To perceive themselves, and to be perceived by others, as people “at risk”, and therefore as different compared to common expectations of “normality”, can indeed influence the development of the sense of self and self-esteem; in fact the certainties of social acceptability are increasingly dependent from the adaptation

to a dominant model of physical and mental health efficiency (33).

Discrimination and Stigma

Genetic information are sensitive data, thus require that the fullest protection of safety and confidentiality of the treatment are to be given, this is foreseen from the privacy policy and from a relational point of view, based on the principle of confidentiality. Currently the greater dissemination of medical information between multiple parties did increase in public opinion, the fear of being subjected to discrimination as a result of broader knowledge of their genetic condition which has not opposed a more accurate confidentiality of the data. The rejection of discriminatory behavior based on the genetic profile is now widely shared on both legal and ethical (34). In practice, however, is still a concept that suffers from exceptions and different interpretation, especially in the context of work activities and, in certain circumstances in insurance, industry and business.

Especially in countries with a liberal economy, episodes of “working selection”, of “scholarship selection” and of “failure to progress in career and in leadership roles of greater responsibility”, were observed on the basis of genetic evaluations mainly related to susceptibility testing of organic disease, but also to aptitude genetic test for psychological and psychiatric disorders.

In the insurance sector, the situation is even more complex, however, the question about the lack of insurance coverage for health or life does not arise in Europe and in those states that have adopted systems of universal coverage of health risks. A monitoring on European regulations shows that only Italy (35, 36), France, Belgium and Denmark have the statutory prohibition on the use of genetic testing in the conclusion of insurance. Other countries have chosen or a moratorium path (Finland and Germany) or a limited use strictly related to the thresholds value of insurance (England, Holland, Switzerland, Sweden).

Beyond what may be the discrimination by an insurance point of view, disciplinable in different ways, there are other forms of discrimination and stigmatization more subtle and, unfortunately, quite common in the social life and more complex to eliminate. Along-

side the non-discrimination, has recently appeared the no-stigma principle that does not necessarily affect the exercise of an individual right resolving in a psychological attitude of hostility or discomfort towards those who are perceived as “different”. The “DNA mystique” is likely to be harbinger of the deplorable forms of classification and of “social control” which could result in selective drifts and “politics of exclusion” in many context of social life (37).

“Un-patients”

For a long time medicine has been a primarily “palliative” function in respect of the patient, for whom he had little healing resources to offer. With the development of scientific medicine, major diagnostic and therapeutic advances have made possible not only to better understand the disease, but also to treat it more effectively trying to intervene in its early stages. The additional step was even more ambitious: to identify the “potential disease”. The Angelina Jolie’s choice to have both breasts removed because carrier of gene variant Brca-1 which greatly increases (over 80%) the risk of developing an aggressive and often fatal breast cancer, caused a stir and created great confusion (38), such as the decision of a British manager to have his prostate removed for the same reason (39).

Nowadays this excess of knowledge is likely to create more doubts than certainties. The “certainty language” is not commonly used in medicine, instead, the “probability language” is the most used one. Even predictive medicine, in the presence of specific genes that predispose to cancer or the onset of severe neurodegenerative diseases simply expresses the high possibility that these pathological conditions develop in that individual, not that the disease will manifest itself certainly. Is that an aid to health or an obstacle to a quiet and peaceful existence? The risk is to make life medicalized, making feel sick who is actually healthy.

These conditions emphasize how the new reality of predictive genetic testing might undermine the concepts of health and illness, therapy, and doctor-patient relationship.

The “un-patients” are a new class of people within medicine: they are not “patients” in the classic sense, since they do not show symptoms and signs; they are

people who share genetic predispositions and who might live in the expectation of the hypothetical appearance of any sign of disease, who organize their lives according to the medical examinations or laboratory tests, and who end up feeling sick or even develop psychosomatic symptoms.

Genetic vulnerability and criminal trial

Giving excessive importance to these biological characteristics can lead, following a consequential logic, (slippery slope theory) (40), to the predetermination of future ways of behaving of the individual, to the point of justifying the application of preventive measures, in order to reduce the risk of deviance of those who, following this address would be considered predestined, according to a probability calculus, to express an impulsive-aggressive attitude. From a criminal justice system, related to the commission of an offense, one might lead to a preventive model that, regardless an unlawful conduct, would legitimize the compression of personal freedom only for the presence in the DNA of the suspected person, of peculiar properties predisposing to violence and crime, which would open the way to selective scenarios of Lombrosian memory (41). The knowledge of the genetic correlation between aggressive and impulsive behaviors are progressively and dramatically increasing, but not as they are increasing regulatory and legal frames within which these data and knowledge must enter. It is conceivable that the defense lawyers will ride this evidence to subtract the defendants from legal liability, as it is conceivable to fall deviant behavior in terms of a state of disease, genetically determined. The magistrate then, will face with new situations for which, he may not be called to order a prison sentence, but the obligation of therapy that would prevent further criminal conduct (42).

Conclusions

The issue discussed in this dissertation is rather complex and a quick analysis of the literature allows to assert the following propositions: heredity varies depending on disorders; in spite of the obvious genetic basis of common forms of psychopathology, it must be

remembered that inheritance is not synonymous with inevitability, given that even the most heritable disorders can improve with psychological treatments; the interplay between genes is important. The simple heredity of a liability gene or the exposition to momentary events often don't leads to mental illness. Genes and environment influence each other; the results of molecular genetics are contradictory. No clear consensus on the location of putative genes for the development of defined psychiatric disorders has been revealed. These data highlight the limits of current psychiatric diagnostic phenotypes in relation to genetic analysis and show that the use of genetic testing on a clinical level does not offer relevant information. In particular, the assessment of social dangerousness is a psychiatric clinical evaluation with relevant consequences on the prognosis. Genetic analysis for its current structural characteristics and for the information that can now provide, it is not able to take into account the dynamic, evolutionary and transformative aspects inherent the complex notion psychiatric social dangerousness.

All this aspects, in conclusion, can generate: risky short-circuits (defensive forensic psychiatry); reduction in the accuracy of clinical assessment; aggravation of social stigma and consequent worsening of prognosis (circular causality); flattening of forensic psychopathology research on existing case law. It must therefore be cautious in the use of genetic data, which will undoubtedly require a wider statistical validation and a more precise definition of their validity and explanatory.

We are in front of two principles: the first is the autonomy of the individual, the second is the role of Medicine.

On one hand the autonomy of the individual who – whereas duly informed – is in a position to choose whether and when undergo a genetic test, undertaking the responsibilities of his own choice.

On the other hand the role of Medicine, which has its own values besides values conveyed by the community. Medicine must decide if and in which conditions some treatments may to be available. Medicine also responds to the principle of beneficence and the principle of justice, since – to avoid any discrimination or inequality, some form of public intervention is definitely required.

At present, it seems that the first principle has wide relevance and is broadly considered while the second is not thoroughly studied nor considered. Moreover it's Medicine itself – in the sense of social entity – that is still too weak and unable to take accountability for those crucial decisions.

Indeed, it is Medicine which needs to create those boundaries of legitimacy for certain interventions, boundaries within which the independent choice of the individual may unfold. We will then be able to avoid an anachronistic paternalism but at the same time we'll be finally able to safeguard beneficence and to promote justice.

References

- Galton F. *Hereditary Genius*. London: Macmillan; 1869.
- Flint J, Monaco AP. Focus on behavioral genetics. *Eur J Hum Genet* 2006; 14: 647-8.
- Venter C, Adams MD, Myers EW, Li PW, Mural RJ, Sutton GG, Smith HO, Yandel M, Evans CA, Holt RA, Gocayne JD, Zhu X. The Sequence of the Human Genome. *Science* 2001; 291:1304-51.
- Galton F. Eugenics: Its Definition, Scope, and Aims. *Am J Sociol* 1904; 10(1): 82.
- Foster MW, Royal CDM, Sharp RR. The routinization of genomics and genetics: implications for ethical practices. *J Med Ethics* 2006; 32: 635-8.
- Morley KI, Hall WD, Carter L. Genetic screening for susceptibility to depression: can we and should we? *Aust N Z J Psychiatry* 2004; 38: 73-80.
- Mitchell Pb, Meiser B, Fellerton J, Donald J, Wilhelm K, Schofield PR. Predictive and diagnostic genetic testing in psychiatry. *Clin Lab Med* 2010; 30(4): 829-46.
- Rukenstein M. Keeping data alive: talking DTC genetic testing. *Information, Communication & Society* 2017; 20(7): 1021-39.
- Smerecnik J. Lay responses to health messages about the genetic risk factors for salt sensitivity: do mass media genetic health messages result in genetic determinism? *Psychol Health Med* 2010; 15(4): 386-93.
- Domaradzki J. Behavioral genetics in Polish print news media between 2000 and 2014. *Psychiatr Pol* 2016; 50(6): 1251-71.
- Pavlov KA, Chistiakov DA, Chekhonin VP. Genetic determinants of aggression and impulsivity in humans. *J Appl Genet* 2012; 53(1): 61-82.
- Tatarelli R, Del Casale A, Tatarelli C, Serata D, Rapinesi C, Sani G, Kotwalidis GD, Girardi P. Behavioral genetics and criminal responsibility at the courtroom. *Forensic Sci Int* 2014; 31(237C): 40-5.
- Cross-Disorder Group of the Psychiatric Genomics Consortium, Genetic Risk Outcome of Psychosis (GROUP) Consortium. Identification of risk loci with shared effects on five major psychiatric disorders: a genome-wide analysis. *Lancet* 2013; 381(9875): 1371-9.
- Chalmers DJ. How can we construct a science of consciousness? *Ann N Y Acad Sci* 2013;1303: 25-35.
- Gruppo di Lavoro SIGU. Osservazioni sulla validità ed utilità dei test genetici di suscettibilità del comportamento umano e violento in ambito forense (2013) <https://www.sigu.net/show/attivita/5/1/genetici>. Access made on 28-07-2018.
- Documento del gruppo misto Comitato Nazionale per la Bioetica e CNBBSV. Test genetici di suscettibilità e medicina personalizzata (2010) http://presidenza.governo.it/biotecnologie/documenti/Test_genetici.pdf. Access made on 28-07-2018.
- Annas GJ. The Man on the Moon, Immortality, and Other Millennial Myths: The Prospects and Perils of Human Genetic Engineering. *Emory Law J* 2000; 49(3): 753-82.
- Nuffield Council on Bioethics. *Mental Disorders and Genetics: The Ethical Context* (1998) http://www.nuffieldbioethics.org/go/ourwork/mentaldisorders/publication_300.html. Access made on 28-07-2018.
- Battistuzzi L, Ciliberti R, Forzano F, De Stefano F. Regulating the communication of genetic risk information: the Italian legal approach to questions of confidentiality and disclosure. *Clin Genet* 2012; 82(3): 205-9.
- Basehore MJ, Friez MJ. Molecular analysis of fragile X syndrome. *Curr Protoc Hum Genet* 2014; 21: 80.
- Duyao M, Ambrose C, Myers R, Novelletto A, Persichetti F, Frontali M, Folstein S, Ross C, Franz M, Abbot M. Trinucleotide repeat length instability and age of onset in Huntington's disease. *Nature Genet* 1993; 4: 387-92.
- Argyri L, Dafnis I, Theodossiou TA, Gantz D, Stratikos E, Chroni A. Molecular basis for increased risk for late-onset Alzheimer disease due to the naturally occurring L28P mutation in apolipoprotein E4. *J Biol Chem* 2014; 289(18): 12931-45.
- Bortolotti L, Widdows H. The right not to know: the case of psychiatric disorders. *J Med Ethics* 2011; 37(11): 673-6.
- Howard HC, Borry P. Survey of European clinical geneticists on awareness, experiences and attitudes towards direct-to-consumer genetic testing. *Genome Med* 2013; 5(5): 45.
- Kalokairinou L, et al. Legislation of direct-to-consumer genetic testing in Europe: a fragmented regulatory landscape. *J Community Genet* 2018; 9: 117-32.
- Psynomics - Genomics For The New Psychiatry <http://www.psynomics.com/>. Access made on 28-07-2018.
- Mitchell PB, et al. Predictive and diagnostic genetic testing in psychiatry. *Clin Lab Med* 2010; 30(4): 829-46
- Collins F. Francis Collins interview. Departing U.S. genome institute director takes stock of personalized medicine. Interview by Jocelyn Kaiser. *Science* 2008; 320(5881): 1272.
- Rantanen E, Hietala M, Kristoffersson U, Nippert I, Schmidtke J, Sequeiros J. What is ideal genetic counselling? A survey of current international guidelines. *Eur J Hum Genet* 2008; 16(4): 445-52.

30. Roberts JS, Uhlmann WR. Genetic susceptibility testing for neurodegenerative diseases: ethical and practice issues. *Prog Neurobiol* 2013; 110: 89-101.
31. Dinwiddie SH, Hoop J, Gershon ES. Ethical issues in the use of genetic information. *Int Rev Psychiatry* 2004; 16: 320-28.
32. Broadstock M, Michie S, Marteau T. Psychological consequences of predictive genetic testing: a systematic review. *Eur J Hum Genet* 2000; 8(10): 731-8.
33. Chatterjee A. The ethics of neuroenhancement. *Handb Clin Neurol* 2013; 118: 323-34.
34. National Human Genome Research Institute. The Genetic Information Nondiscrimination Act of 2008. In <https://www.genome.gov/27568492/the-genetic-information-nondiscrimination-act-of-2008/> (Access made on 28-07-2018).
35. Documento del gruppo misto Comitato Nazionale per la Bioetica e CNBBSV. Test genetici e assicurazioni (2008). In http://www.governo.it/bioetica/gruppo_misto/test_genetici_assicurazioni_1.pdf. Access made on 28-07-2018.
36. Godard B, et al Genetic information and testing in insurance and employment: Technical, social and ethical issues. *Eur J Hum Genet* 2004; 11 Suppl 2: S123-42.
37. Ashkenas J. The DNA mystique: The gene as a cultural icon. *Am J Hum Genet* 1997; 60(1): 248.
38. Sirohi B, Sinha N, Goel NS, Badwe RA. Angelina's choice: private decision, public impact. *Indian J Med Ethics* 2014; 11(1): 34-5.
39. James PA, Mitchell G, Bogwitz M, Lindeman GJ. The Angelina Jolie effect. *Med J Aust* 2013; 18(10): 646.
40. Oakley J, Cocking D. Consequentialism, complacency, and slippery slope arguments. *Theor Med Bioeth* 2005; 26(3): 227-39.
41. Cannavacci, M. La genetica del crimine – Lombroso aveva ragione (2006) <http://www.poliziaedemocrazia.it/live/index.php?domain=archivio&action=articolo&idArticolo=1217>. Access made on 28-07-2018.
42. Appelbaum PS, Scurich N, Raad R. Effects of Behavioral Genetic Evidence on Perceptions of Criminal Responsibility and Appropriate Punishment. *Psychol Public Policy Law* 2015; 21(2):134-44.

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B O O K R E V I E W S

Giampiero Pasero, *Una piccola storia dell'aspirina*, Edizioni Clinical and Experimental Rheumatology, Ospedaletto (Pisa) 2018, pp. 44

Special limited edition, that the Author dedicates to his friends, colleagues and students on the occasion of his ninetyeth birthday.

A quick search for the word “aspirin” in *PubMed* portal produces over 63,000 results. This number is certainly huge, but very low when compared to the number of tablets produced and consumed. In fact, it is estimated that 10^{18} aspirin tablets have been taken over the last 100 years.

Such a number is really difficult to imagine, but it reflects the spreading and use of a drug about which thousands of pages in the History of Medicine have been written. Giampiero Pasero – former professor of Medical Pathology and Rheumatology – goes through these same pages in his captivating work *A Little History of Aspirin*.

The use of salicylates has indeed an ancient origin: Sumerians, Egyptians, Greeks and Romans used willow leaves infusions against fever and pain. Further on, the ingenuity of father Edward Stone opens the path for a “systematic” use of drugs based on salicylates: in 1757, while on a walk, father Stone tasted willow bark and found it bitter like the cinchona bark. He hypothesized, by analogy, that it could be equally useful in fighting diseases such as malarial fever. Stone then began to treat his patients suffering from fever (malarial or not) with willow bark based drugs. In 1763 he communicated his findings to the *Royal Society* and soon the antipyretic effect was confirmed by the medical community. The Italians Rigatelli and Fontana, in 1824, extracted the first samples of active substance from willow bark – even though the final isolation of the powerful therapeutic substance called *salicin* took place in 1827 by Johann Andreas Büchner. Salicylic

anhydride was extracted in 1831 and salicylic acid, in 1835. In 1844, salicylic acid was extracted from willow bark, but also meadowsweet flower and gaultheria oil. A few years later, in 1853, salicylic acid was synthesized by Henri Gerland and in 1859 a synthesis of acetylsalicylic acid was obtained by Hermann Von Gilm (maybe by Charles Frédéric Gerhardt in 1853). Since 1874 salicylates were officially used for the symptomatic treatment of acute rheumatism and the following year they were proposed for treating also chronic rheumatism and gout.

In the 90s of the 19th century, thanks to the collaboration of Arthur Eichengrün, Felix Hoffmann and Thomas Dreser, a series of fortunate circumstances led to the final synthesis of stable and pure acetylsalicylic acid on the 10th August 1897 and its registration by Bayer, as Aspirin, on February 1899. From then until the introduction of cortisone and NSAIDs at the end of the 40s of the 20th century, Aspirin prevailed as the most common anti-rheumatic drug in the market. It is indeed an extraordinary drug: it reduces fever, pain, inflammation and, obviously, acute articular rheumatism.

When progress in pharmacology produced new drugs for Rheumatology (but not only) and Aspirin lost ground, acetylsalicylic acid, thanks to the ingenuity of Lawrence Craven in 1948, began to be proposed for anti-thrombotic prophylaxis, thus effectively opening the path for myocardial infarction prevention.

This drug, as Prof. Pasero explains, still hides many resources, including some important opportunities for preventing dementia and some forms of cancer (colorectal carcinoma).

This is the compelling and still to be discovered “great little” story, of a drug that we daily use in clinical practice and that, let’s not forget, arrived even to the moon.

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